

Numerical investigation of data-driven dynamical brain models with application to inter-individual variability

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Eidesstattliche Erklärung

Ich versichere an Eides Statt, dass die Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist. Die Dissertation hat in gleicher oder ähnlicher Form bislang keiner anderen Prüfungsbehörde vorgelegen.

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Summary

Mathematical optimization problems play a decisive role in various domains of the economy, health, and research. Examples include business modeling for profit maximization or minimization problems in engineering and design. The health sector considers mathematical simulations for optimizing the effects of personalized therapies. In particular, human brain research utilizes mathematical models to replicate measured data of brain activity as closely as possible. Such an investigation of brain dynamics has received new perspectives following the shift of neuroimaging research towards the so-called resting-state activity. It describes the constantly ongoing mental processes in the absence of any behavioral task. In the most common approach, the temporal fluctuations of blood oxygenation level-dependent (BOLD) signals of the brain at rest are measured by functional magnetic resonance imaging (fMRI). This process allows for the computation of functional connectivity (FC). It is reflected by a matrix containing the cross-correlations between the corresponding BOLD signals. Resting-state FC is deemed to represent the intrinsic functional organization of the brain. However, the mechanisms underlying the emergence of specific functional patterns in the brain remain vague. The approach described in this thesis builds personalized models of brain activity in terms of FC upon empirical structural data of the brain. To this end, the brain is subdivided into a set of distinct regions according to a given brain atlas. While the regions serve as nodes of the model network, the edges are defined by the empirical structural connectivity (SC) which represents anatomical connections between brain regions extracted from diffusion-weighted MRI (dwMRI). The network nodes are equipped with coupled stochastic differential equations (SDEs) whose solutions provide a simulation of the corresponding brain regions' mean BOLD signals.

In my PhD project, I addressed the optimization problem of approximating those model parameters that maximize the correlation between empirically measured and model-simulated FC for individual subjects. This is termed model fitting or model validation. The non-convexity and non-differentiability of the multimodal objective functions prevents the application of gradient and quasi-Newton methods. I therefore tested four direct, i.e., derivative-free search algorithms and compared their performance across subjects with one another and with the results of a dense grid search (GS) in two- and three-dimensional model parameter spaces (study 1). Having identified two most efficient methods, I proceeded to optimization problems with up to 103 free parameters, where I studied the reliability of the results and their potential utility in a classification task (study 2). I eventually participated in the development of a workflow leading from raw MRI data towards model-based predictions of human behavior and phenotypes (study 3).

The considered derivative-free search schemes were the Nelder-Mead Algorithm (NMA), Particle Swarm Optimization (PSO), the Covariance Matrix Adaptation Evolution Strategy (CMAES) and Bayesian Optimization (BO). Study 1 revealed that CMAES and BO provide the most favorable tradeoff between the required computational resources and the robustness against local optima in low-dimensional parameter spaces. The results of study 2 showed advantages of high-dimensional model fitting for a classification task, but also highlighted the need for adequate solution selection strategies in cases of several near-optimal parameter values. Study 3 demonstrated how the incorporation of model simulation results can enhance the prediction quality of behavioral traits and phenotypical characteristics in comparison to empirical data alone. In summary, the presented studies showed the indispensability of well-conceived parameter optimization strategies for simulations of human brain activity and subsequent investigations of inter-individual variability.

To better bond with the interested reader, I will henceforth use the collective “we”.

List of abbreviations

ARD	Automatic relevance determination
BO	Bayesian Optimization
BOLD	Blood oxygenation level-dependent
BW model	Balloon-Windkessel model
CMAES	Covariance Matrix Adaptation Evolution Strategy
CR	Confound removal
CV	Cross-validation
DTI	Diffusion tensor imaging
dwMRI	Diffusion-weighted magnetic resonance imaging
EEG	Electroencephalography
eFC, empFC	Empirical functional connectivity
EM method	Euler-Maruyama method
EPSP	Excitatory postsynaptic potential
ES, es	Effect size
FC	Functional connectivity
fMRI	Functional magnetic resonance imaging
GM	Gray matter
GOF, GoF	Goodness-of-fit
GP	Gaussian Process
GS	Grid search
HCP	Human Connectome Project
HH model	Hodgkin-Huxley model
HO0Thr	Harvard-Oxford atlas with 0% threshold
ICC	Intraclass correlation coefficient
IPSP	Inhibitory postsynaptic potential
IQR	Interquartile range
JR model	Jansen-Rit model
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
NMA	Nelder-Mead Algorithm
ODE	Ordinary differential equation
PCA	Principal component analysis
PSO	Particle Swarm Optimization
qm	Quadratic mean
ROI	Region of interest
SC	Structural connectivity
Sch100	Schaefer atlas with 100 regions
SDE	Stochastic differential equation
sFC, simFC	Simulated functional connectivity
SHAP	Shapley additive explanation
WBT	Whole-brain tractography
WC model	Wilson-Cowan model
WM	White matter
WW model	Wong-Wang model

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0 Overview

The human brain is undoubtedly one of the most complex creations of nature. In the thesis at hand, we focus on the dynamical modeling of *whole-brain activity*. We use principles from the field of mathematical optimization in order to design precise simulation models that aid in explaining the sophisticated phenomena observed in *neuroscience*. The term *neuroscience* describes the scientific discipline of studying the nervous system of human beings and animals. Our brain is a crucial part of the nervous system as it coordinates the processing of sensory input (e.g., hearing, seeing or smelling) with subsequent reactions. To do so, the brain transmits signals among different areas in itself and, along the nervous system, to different parts of our body. Mathematical whole-brain models, which feature a set of tunable model parameters, try to replicate the measured brain activity. Ideally, the model output matches the empirical data as closely as possible in terms of a given similarity measure. In this context, simulations can reveal distinct patterns which are not directly observable in empirical measurements. Combining neuroscience with mathematical expertise therefore bears great potential for rendering the data obtained from brain scans more interpretable. It can be helpful for the identification of brain abnormalities and early disease detection. Further, it may shed light on potential links between an individual's brain and behavior as well as on the presence of inter-individual differences. However, the underlying search for optimal model parameters is not trivial. On the contrary, it is a non-differentiable, non-convex optimization problem that manifests itself by computational burdens, several near-optimal solutions and the virtual lack of exact ground truth values. This PhD thesis was conceived with the goal to develop and suggest efficient workflows to cope with these issues.

In the included publications, i.e., study 1 ([Wischnewski et al., 2022](#)), study 2 ([Wischnewski et al., 2025](#)) and study 3 ([Jung et al., 2025](#)), we will encounter terms and expressions that do not belong to the standard vocabulary of mathematics. We thus start by providing some background knowledge necessary for understanding the topics and challenges addressed in this thesis. Chapter 1 covers important principles towards a mathematical representation of the brain as a network as used in the later chapters. We highlight the importance of a dimensionality reduction, describe structural and functional properties revealed in brain scans, and summarize some common preprocessing steps for raw data. In chapter 2, we outline the concept of stochastic differential equations which constitute the heart of the dynamical whole-brain models considered in this thesis. We explain the calculus of stochastic integration and discuss the role of noise in the derivation of numerical solution strategies. Chapter 3 is devoted to a description of common mathematical models of whole-brain activity and the applicability of derivative-free optimization algorithms for the model fitting to empirical data. In chapter 4, we elucidate the aims of this thesis before we present the three included studies in the chapters 5, 6 and 7. We close with an overarching discussion of the results in chapter 8.

1 Measuring the human brain

First of all, it is important to explain how current research tries to analyze the brain and to specify what we mean when we speak about *whole-brain activity*. In an organ that features up to 100 billion cells in total, a description of the entirety of all possible connections and interactions is neither possible nor expedient. A common approach is therefore to perform a dimensionality reduction. This is typically done with help of a so-called *brain atlas* or *brain parcellation* (Eickhoff et al., 2018). It subdivides the brain into a tractable number $N \in \mathbb{N}$ of *regions of interest* (ROIs). There exist various brain atlases, all of which have their own characteristics, underlying rationales and *granularities*, i.e., numbers of brain regions. While many atlases are targeted at the *cerebral cortex*, the outer layer of neural tissue that contains the largest agglomeration of neurons in the nervous system, others also include deeper layers with subcortical areas or even the entire brain (Eickhoff et al., 2018). We will elaborate on the atlases considered in this thesis in subchapter 1.2.

With the subdivision of the brain into distinct regions, we have laid the basis for deeper analyses. In neuroscience, especially the mathematical part of it, it is common to pursue a network approach [Figure 1] and treat the brain as an undirected graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ with sets of vertices $\mathcal{V} = \{1, \dots, N\}$ and weighted edges

$$\mathcal{E} = \{w_{ij} \in \mathbb{R} \mid i, j \in \mathcal{V}\}. \quad (1)$$

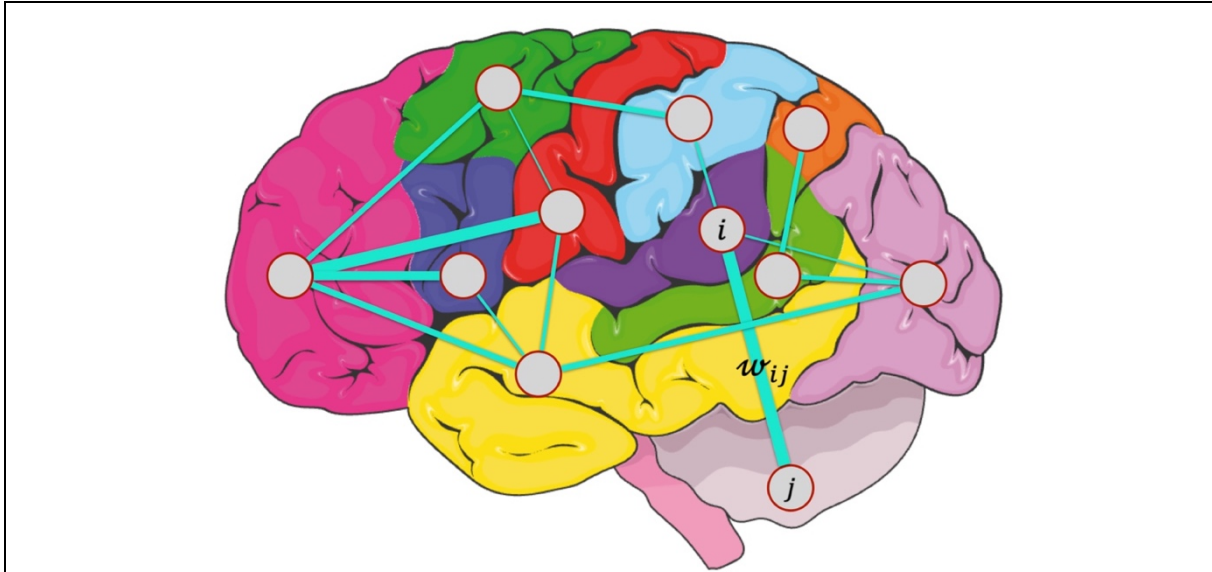


Figure 1: Simplified network illustration of the brain. Color-coded brain regions are represented by network vertices shown as gray circles with red contours. Turquoise lines indicate the connecting edges in between. The thickness of the turquoise lines reflects the strength or weight of the corresponding connections. One exemplary connection between the brain regions i and j is labeled with w_{ij} . The brain shape used in this figure has been adapted from Servier Medical Art (<https://smart.servier.com>), licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

We interpret the brain regions defined by a given atlas as the vertices, or nodes, of the network. For the connecting edges in between, we consider two types of connectivities in their corresponding matrix representations. These are related to the structure and

function of the brain, whereby the completeness of all connections is typically referred to as the structural and functional *connectome*, respectively ([Sporns et al., 2005](#)). In the following, we will describe how brain scans via *magnetic resonance imaging* (MRI) lead to the extraction of the mentioned properties from both the structural and functional perspective.

1.1 Magnetic resonance imaging (MRI)

MRI belongs to the most popular imaging techniques in neuroscience and modern medicine. It is common clinical practice nowadays to acquire MR images of several parts of the body (e.g., heart, kidneys, knees) in order to identify damages or diseases and design a suited therapy ([Hashemi et al., 2010](#)). Its main advantages are its non-invasiveness, meaning that no tracers or contrast agents need to be inserted or injected into the body as in, e.g., *positron emission tomography* (PET), and the fact that it copes without any potentially harmful radiation as present in, e.g., X-rays used for *computed tomography* (CT). Additionally, there is no need to change the position of the human subject during the scan as MRI can collect and visualize data about the relevant tissue from the axial, sagittal and coronal plane. The technique of MRI is further able to generate different types of contrast in the images, so-called *weightings* ([Mori & Barker, 1999](#)). For the investigation of **brain structure** that is relevant in this thesis, two such facets of MRI are important: the T_1 -*weighted* MRI and the *diffusion-weighted* MRI (dwMRI).

When a human is lying in an MRI scanner, a strong magnetic field is imposed. Intensities of around 3 Tesla are typically used ([Smith et al., 2024](#); [Van Essen et al., 2013](#)). Variations of the magnetic field excite the water molecules in the brain or, more precisely, the positively charged hydrogen protons within the water. In this setting, T_1 -weighted imaging is a technique with a relatively high-resolution depiction of the brain anatomy. It reflects differences in the interaction of water molecules with surrounding tissues and reveals a strong contrast between *gray* and *white matter* (GM and WM, respectively) ([Smith et al., 2024](#)). GM forms the cerebral cortex, i.e., the outer tissue layer on the surface of the brain which contains the majority of neural cell bodies. In living tissue, such concentrations of neurons have a pink color that fades to gray after death (therefore *gray* matter). WM in turn describes the component of the brain embodying bundled nerve fibers called *axons* which interconnect the neurons. dwMRI is a technique for their estimation and tracking. The fibers are encased by *myelin*, a membrane of lipids and proteins that separates the axons from the outer environment (referred to as *extracellular matrix*). Myelin typically has a white color, and its function is to accelerate the signal transmission between neurons along the axons.

In the following sections, we elaborate on selected properties of MRI based on the associated literature.

1.1.1 T_1 -weighted MRI

As indicated before, a strong magnetic field is imposed in an MRI scanner. It influences the originally random orientation of the protons in the water molecules and prompts their alignment ([Pooley, 2005](#)). During an MRI scan, this uniform orientation is temporarily perturbed by the introduction of high-frequency pulses, after which the protons start to realign again. For a better understanding, it may be helpful to have the following toy example in mind: Let us assume that we spin and throw a small gyroscope. Thanks to the energy that we invested with our fingers, the gyroscope spins around its axis, while its peak points straight upwards. Repeating this procedure with more gyroscopes will give us a set of objects, whose orientations are in alignment, i.e., their peaks all point upwards. The gyroscopes can now be interpreted as protons in the water molecules ([Mori & Barker,](#)

[1999](#)). Their aligned orientation is determined by the magnetic field, as if the gyroscopes were uniformly surrounded by magnets that keep them spinning and ensure the upward orientation of their peaks. In case of no friction, gravity and other inhibiting forces, the gyroscopes will continue spinning and maintain their orientation. This scenario can be achieved for the protons during the MRI scan when a strong and homogeneous magnetic field is upheld. However, this approach would not yield the desired information about the brain anatomy. The truly relevant phenomena occur when the magnetic field is perturbed by external forces. In our toy example, this may, for instance, correspond to the force of gravity that acts on the spinning gyroscopes. These will eventually start to falter or, physically speaking, *precess*, which tilts their axes and induces deviations on the peaks' orientations. Such time-dependent deviations are measurable in the xy -plane (*transverse components*, reflect the new sideward orientation of the peak) as well as along the z -axis (*longitudinal component*, reflects the loss of height of the peak when it does not point upwards). In MRI scans, a series of electric high-frequency pulses fulfills the role of, e.g., gravity in the toy example. An important difference is however given by the fact that the pulses only cause a temporal loss of alignment of the protons in the molecules. In other words, after the pulses, i.e., when gravity is "turned off" again, the protons begin to realign their orientations due to the magnetic field, which is still active (as if the gyroscopes would recover from gravity and strive to reach their upward orientation again). During this returning process, electric voltage is generated and detected as signal in MRI scans.

To illustrate the described concepts, we have a look at the early formulations from the 1940s ([Bloch, 1946](#)). In his work, Bloch proposed to describe the mean orientation of protons in a magnetic field with help of a vector

$$M = M(t) = \begin{pmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{pmatrix} \in \mathbb{R}^3,$$

where $t \geq 0$ denotes the time. The scenario of spinning gyroscopes that are not perturbed by any external forces corresponds to

$$\begin{aligned} M_x(t) &= M_y(t) = 0, \\ M_z(t) &= M_0 \in \mathbb{R} \quad \forall t \geq 0 \end{aligned}$$

for the transverse and longitudinal components, respectively. This means that there is no sideward deviation from the peak's upward orientation [**Figure 2**].

In case of a constant perturbation that does not allow for a return to the desired equilibrium state of alignment, the equations read

$$\begin{aligned} M_x(t) &= a \cos(\omega t), \\ M_y(t) &= a \sin(\omega t), \\ M_z(t) &= M_0 - \varepsilon \quad \forall t \geq 0, \end{aligned}$$

where $\omega \in [0, 2\pi]$ is an angular spinning frequency and $a > 0$ is a scaling factor. It follows from the equations that the peak of the gyroscope rotates on a circle with radius a in the xy -plane, while resting at a given height $M_0 - \varepsilon$ in z -direction [**Figure 2**]. We note that $M_0 - \varepsilon < M_0$ due to $\varepsilon > 0$.

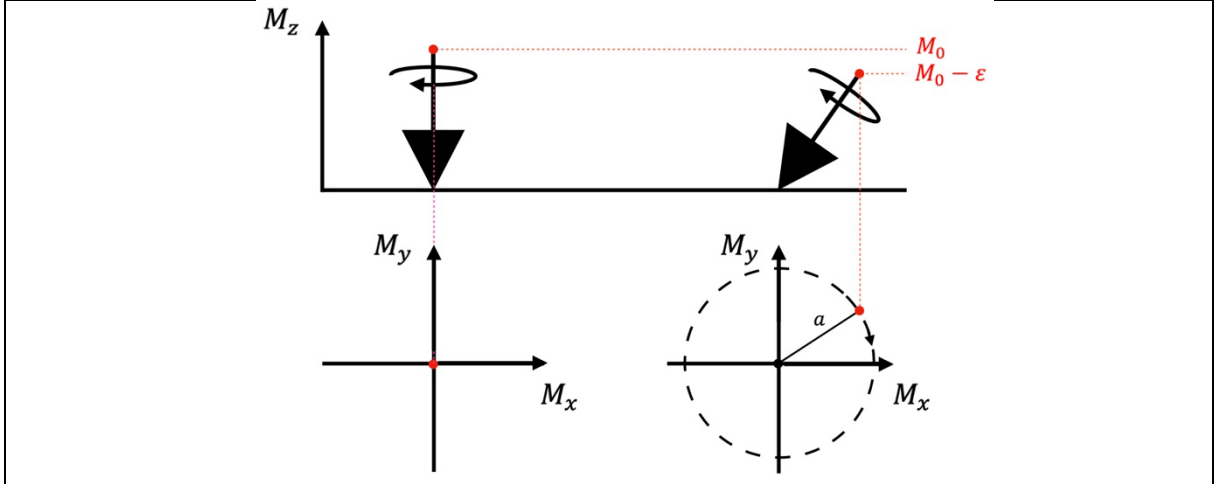


Figure 2: Toy example of spinning gyroscopes as proxies for protons in water molecules during a magnetic resonance imaging scan. The upper row shows the longitudinal component z , while the lower row depicts the transverse components x, y . On the left-hand side, the gyroscope spins around its axis with its peak (indicated in red color) pointing straight upwards. The right-hand side reflects the situation following a perturbation of the magnetic field. A sideward deviation with tilted gyroscope axis in z -direction and a rotation of the peak on a circle with radius a in the xy -plane are illustrated.

Ultimately, the following equations describe the return to the equilibrium state in the magnetic field when external pulses and forces are turned off:

$$\begin{aligned} M_x(t) &= a \exp\left(-\frac{t}{T_2}\right) \cos(\omega t), \\ M_y(t) &= a \exp\left(-\frac{t}{T_2}\right) \sin(\omega t), \\ M_z(t) &= M_0 \left(1 - \exp\left(-\frac{t}{T_1}\right)\right). \end{aligned}$$

$T_1, T_2 > 0$ are so-called *relaxation times*. We note for the transverse components

$$M_x(t), M_y(t) \rightarrow 0 \text{ for } t \rightarrow \infty$$

and for the longitudinal component

$$M_z(t) \rightarrow M_0 \text{ for } t \rightarrow \infty,$$

meaning that the initial state will be restored eventually. It has become common practice in MRI to define T_1 as the time required for the longitudinal component M_z to increase from $M_z(0) = 0$ (corresponding to an axis tilted by 90°) to $M_z(T_1) = M_0 \left(1 - \frac{1}{e}\right)$, which is around 63% of its maximum value M_0 .

For the transverse components, T_2 is defined as the time needed for $\left\| \begin{pmatrix} M_x(0) \\ M_y(0) \end{pmatrix} \right\|_2 = a$ to

decay to $\left\| \begin{pmatrix} M_x(T_2) \\ M_y(T_2) \end{pmatrix} \right\|_2 = \frac{a}{e}$, which is around 37% of the maximal sideward deviation a . In

line with that, T_1 is often referred to as the relaxation time related to the recovery of magnetization in z -direction, while T_2 is referred to as the relaxation time related to the

loss of magnetization in the xy -plane ([Bitar et al., 2006](#); [Damadian, 1971](#); [Smith et al., 2024](#)).

Brain research makes use of the fact that water protons have characteristic MRI properties depending on their physical and chemical environment ([Mori & Barker, 1999](#)). This allows for a distinction between different tissue types based on the described relaxation process. Following the external pulses, a series of brain images in form of different slices across time is recorded. The relaxation process is then analyzed for every considered *voxel*, i.e., the smallest voluminal element $vox \in \mathbb{R}^3$, cf. *pixel* in $\mathbb{R}^2$. A progressing relaxation is displayed in color using a grayscale of signal intensity information. The observed signal intensities and corresponding relaxation times are then compared with known tissue-specific time constants $T_1 = T_1(\text{tissue})$ and $T_2 = T_2(\text{tissue})$. There is a considerable difference between T_1 (GM) and T_1 (WM) as well as between fluid and solid substances, for instance ([Bojorquez et al., 2017](#); [Bottomley et al., 1984](#); [Stanisz et al., 2005](#)). Consequently, the T_1 -weighted brain images provide a strong signal contrast between GM and WM ([Damadian, 1971](#)). They are therefore particularly suited for the detection of specific parts or areas of the brain during anatomical analyses. In the studies explained in this thesis, T_1 -weighted imaging serves the purpose of identifying the GM in brain regions defined by the utilized brain atlas for a given subject. This technique usually provides a clean and undistorted image of the whole brain ([Ombao, 2016](#)). The related T_2 -weighted imaging technique is particularly suited for detecting agglomerations of water and potential brain lesions as it has advantages in identifying T_2 -dependent properties of interacting water molecules ([Smith et al., 2024](#)). In the presented studies, however, we worked with T_1 -weighted images as we were primarily interested in a good differentiation of ROIs.

1.1.2 Diffusion-weighted MRI (dwMRI)

The second considered modality for structural brain analyses, dwMRI, offers a way to describe the connections between brain regions. It tracks the diffusion process of water molecules along nerve fibers ([Mori & Barker, 1999](#)). Diffusion describes the process of a random particle movement without any external influence, cf. *Brownian motion* ([Bechinger et al., 2016](#)). Particles dispersed in a fluid, i.e., a liquid or gas, randomly collide with the surrounding atoms and molecules of the fluid and thereby perform arbitrary location changes ([Allen & Tildesley, 2017](#)). This phenomenon usually leads to a balanced concentration of particles in any substance as the particles *diffuse* from areas with higher concentrations to those with lower ones and finally approach a uniform concentration for $t \rightarrow \infty$. Brain research is focused on the interactions with molecular obstacles during the diffusion process. More precisely, dwMRI measures the ability of water molecules to move within the anatomical constraints of their local tissue environment. While this technique is less suited for GM identification, it is nowadays the most powerful tool for the non-invasive approximation of bundled nerve fibers in WM which connect individual ROIs ([Jones & Cercignani, 2010](#); [Le Bihan et al., 2001](#)).

The concept of dwMRI is based on the same principles as T_1 -weighted MRI, where the effects of a temporal perturbation of a magnetic field on protons in water molecules are analyzed. There are, however, decisive differences in the application.

First, it plays a role in which “direction” the magnetic field is disrupted. Coming back to the previous toy example of spinning gyroscopes, gravity would indicate an external force perturbing the system from above. Sudden gusts of wind in turn might reflect sideward or oblique influences on the orientation of the gyroscopes. In dwMRI, such directed inhomogeneities of the magnetic field are achieved via electrical pulses that are referred

to as *(pulsed) field gradients* ([Mori & Barker, 1999](#)) or *diffusion-phase-encoding gradients* $g \in \mathbb{R}^3$ ([Jones et al., 2013](#); [Le Bihan et al., 1986](#)). They cause momentary alterations of the magnetic field strength in a predefined direction g ([Elster, 1993](#); [Markl & Leupold, 2012](#)).

Second, we do not measure the time needed for recovery from the external perturbation but look at the signal attenuation between two measurements instead. The underlying idea is the following: After an initial pulse that we may call the *tagging pulse* for simplicity, the realignment of the water molecules in a given voxel will induce a voltage. We treat it as the initial signal of amplitude $S_0 \in \mathbb{R}$. Simply speaking, the molecules exposed to this initial pulse were “tagged”. They will show different spatial characteristics with respect to additional pulses than those molecules that diffuse into the given voxel afterwards. The subsequent application of a field gradient along a given direction g will therefore generate another signal, which is based on the “tagged” molecules in the given voxel. As this signal will have an amplitude lower than S_0 , it can be treated as a correlate of the motion of particles diffusing along the direction or axis specified by g ([Jones et al., 2013](#)). The particles having left the considered voxel via diffusion in the direction of g will no longer contribute to the signal and thereby cause an attenuation. This way, dwMRI enables the visualization of location changes along a specified axis. We note here that the MRI scan does not accelerate or interfere with the diffusion process as such. The latter remains independent of the magnetic field ([Le Bihan et al., 2001](#)).

An important underlying assumption in dwMRI is that the diffusion along the direction of the nerve fibers is less restricted by anatomical barriers and therefore happens faster than in an orthogonal direction, for instance ([Jones et al., 2013](#)). The mentioned loss of signal amplitude due to diffusion in the direction of g can be described by the *Stejskal-Tanner equation* ([Jones & Cercignani, 2010](#); [Mori & Barker, 1999](#); [Stejskal & Tanner, 1965](#)):

$$S(g) = S_0 \exp(-bg^T D g),$$

where $S_0 \in \mathbb{R}$ and $S(g) \in \mathbb{R}$ reflect the signal amplitude before and after the gradient pulse application, respectively. The so-called b -value

$$b := \gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right)$$

is derived from the (constant) particle-specific *gyromagnetic ratio* $\gamma \in \mathbb{R}$, the strength $G \in \mathbb{R}$ and the duration $\delta > 0$ of gradient pulses as well as the diffusion time $\Delta \in \mathbb{R}$, i.e., the time that water molecules are allowed to diffuse between two pulses ([Jones et al., 2013](#)). We have $\delta < 3\Delta$. The matrix

$$D \in \mathbb{R}^{3 \times 3}, \text{ where } D = D^T \succcurlyeq 0,$$

i.e., symmetric and positive-semidefinite, denotes the so-called *diffusion tensor*. It is the most important object when estimating the apparent diffusion in a specified direction $g \in \mathbb{R}^3$.

From the presented equations, it can easily be seen that the signal attenuation due to diffusion along the direction of g follows an exponential decay depending on the b -value and the diffusion tensor D . So, the extent of signal decay increases with an increasing gradient strength and also depends on the diffusion constants of water molecules in the brain ([Mori & Barker, 1999](#)).

Due to its symmetry, D contains six unknown entries, making it necessary to perform diffusion-weighted measurements in at least six different directions $g \in \mathbb{R}^3$ in addition to an unweighted one for reference. As g and b are fixed beforehand and S_0 as well as $S(g)$ are known after the measurement, a voxel-wise $D = D_{vox}$ can be estimated from a series of diffusion-weighted images. The described dwMRI technique is therefore also referred to as *diffusion tensor imaging* (DTI).

Due to the presence of noise artifacts and other errors in the measurements, it is common to apply many more gradient directions (50-90, see (Smith et al., 2024; Van Essen et al., 2013)) than only the mandatory six. Further, as the signal attenuation also depends on the gradient strength and duration, two or three different b -values, so-called *shells*, are usually tested (Smith et al., 2024; Van Essen et al., 2013). This leads to a more accurate description of the apparent molecular diffusion and its directionality. Finally, the unknown entries of D are estimated via least squares approximation methods (Jones & Cercignani, 2010). The basic assumption of DTI is that the direction of the longest distance covered via diffusion reflects the course of the nerve fibers between neurons.

Once a matrix $D = D_{vox}$ is approximated for every voxel vox , it is typically diagonalized in order to extract its eigenvalues $\lambda_i^{vox} \geq 0$ and eigenvectors $v_i^{vox} \in \mathbb{R}^3$, $i \in \{1, 2, 3\}$. The vector v_i^{vox} belonging to $\max_{i \in \{1, 2, 3\}} \lambda_i^{vox}$ is supposed to indicate the main fiber orientation in the considered voxel, i.e., the way where the diffusion of water molecules faces the fewest obstacles. Having knowledge about this direction at each voxel is crucial for reconstructing the most probable course of axons across multiple images of brain slices (Mori & Barker, 1999).

It must be kept in mind, however, that even the resolution of around 1 mm of dwMRI/DTI cannot capture all present axons, whose diameter is in the range of micrometers. The estimated quantities can therefore only be interpreted as approximations of the mean value of the diffusion, mainly influenced by the largest axonal bundles (Jones et al., 2013). Current methods compute trajectories through the acquired data, for which it is believed that a large portion of the nerve fibers runs nearly in parallel (Jones et al., 2013).

Another challenge is given by the possibility of crossing fibers, where DTI has shown weaknesses (Maier-Hein et al., 2017; Neher et al., 2015). Here, even more advanced approaches within the scope of dwMRI such as *diffusion spectrum imaging* (DSI) may provide a more realistic description of axonal bundles (Wedeen et al., 2005; Wedeen et al., 2008). Still, in a recent DTI-related animal study, it has been shown that, given an appropriate data preprocessing strategy, the *false positive rate*

$$FPR = \frac{FP^+}{TN^- + FP^+} = \frac{FP^+}{N^-},$$

where FP^+ , TN^- and N^- denote the number of false positives, true negatives and total negatives, respectively, can range around only 5% (Maffei et al., 2022). This means that there is a low risk of erroneously detecting fiber sections in voxels where none are present. Further, it promotes DTI as a suited, non-invasive technique to approximate the course of nerve fibers in the human brain nowadays.

1.1.3 Structural connectivity (SC)

Based on the acquired dwMRI data and the reconstructed matrices D_{vox} , probabilistic *tractography* algorithms estimate the presence of interregional fiber connections in the brain ([Jeurissen et al., 2019](#); [Tournier et al., 2009](#)). These methods require the user to specify a total number of so-called *streamlines*, which represent the most reasonable proxy for the true nerve fibers in the brain. For every considered seed region of the brain, the algorithms use the available dwMRI data to compute the most probable distribution of streamline connections to a given target region or voxel ([Behrens et al., 2003](#)). Between 10 000 and 10 000 000 streamlines are suggested in the literature ([Jung et al., 2021](#)). The result of this procedure is a *whole-brain tractography* (WBT). It can be interpreted as a map of the brain showing its regions together with the respective connections among them.

Two matrices for further analysis are derived from this outcome [**Figure 3**]. The first one is the matrix $SC \in \mathbb{R}^{N \times N}$ of streamline counts. Its entries SC_{ij} show how many connections the tractography algorithm has assigned to any pair of ROIs $i, j \in \{1, \dots, N\}$. We have

$$SC = SC^T, \text{ diag}(SC) = 0 \in \mathbb{R}^N.$$

The diagonal reflects self-connections of individual brain regions. It is set to zero on purpose. Although a given region defined under a selected brain parcellation may show anatomical connections to itself, the corresponding non-zero diagonal elements would induce unwanted self-couplings in the considered models of whole-brain activity. More precisely, they would cause a (time-delayed) interaction of a region with itself. This might distort the simulated dynamics, as such self-couplings and intrinsic activities are usually accounted for by the local dynamics of the model and its associated model parameters. Consequently, the diagonal elements are set to zero, and focus is put on the off-diagonal elements describing connections between different brain regions. Due to the symmetry of SC , these can be considered for the upper triangular part only.

The second matrix, $PL \in \mathbb{R}^{N \times N}$, describes the average path length of the streamlines connecting two regions. Here we also have

$$PL = PL^T, \text{ diag}(PL) = 0 \in \mathbb{R}^N,$$

following the same argumentation as above. To ensure comparability between subjects in subsequent applications, both matrices are typically divided by their respective mean value. SC and PL constitute the *structural connectivity* in the brain, commonly referred to as SC. Unless indicated otherwise, we will summarize both matrices under this umbrella term and explicitly refer to SC and PL only where it is reasonable.

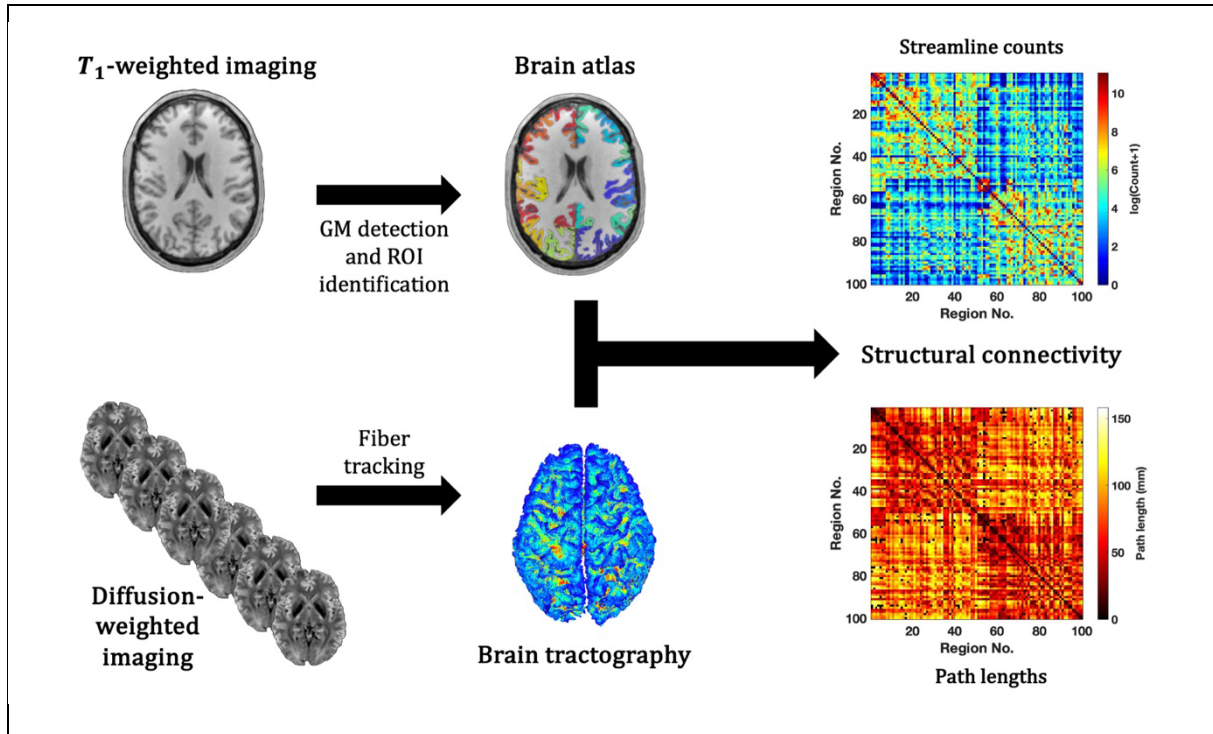


Figure 3: Schematic overview of structural connectivity extraction from magnetic resonance imaging. T_1 -weighted images of the brain are used to identify gray matter (GM) which is assigned to specific regions of interest (ROIs) as given by the considered brain atlas. Diffusion-weighted imaging visualizes the diffusion of water molecules along nerve fibers. The process is tracked to derive a whole-brain tractography. It shows the connecting pathways between areas. Together with the spatial delineation of brain regions in an atlas, the structural connectivity matrices of streamline counts and average path lengths are derived from the mentioned scanning modalities.

1.1.4 Functional MRI (fMRI) and blood oxygenation level-dependent (BOLD) signals

Besides the highlighted methods for analyzing the anatomical structure of the brain, there are also suited approaches to investigate the **brain function** with its related activation patterns. In this setting, *functional* MRI (fMRI) is a useful technique. It detects changes in the cerebral blood flow and thereby allows researchers to draw conclusions about spontaneous brain activity. The most popular approach towards fMRI works with the *blood oxygenation level-dependent* (BOLD) contrast which reflects the relative change in the ratio of *oxygenated* to *deoxygenated hemoglobin* in the blood ([Siero et al., 2013](#)). Hemoglobin is the primary ingredient of red blood cells, so-called *erythrocytes*. It is a protein compound that contains a high amount of iron, thereby giving the blood its characteristic red color. Oxygenated hemoglobin, called *oxyhemoglobin*, is generated when the heart pumps fresh blood from the lungs to the body. It is important for supplying living tissue with the necessary oxygen. After releasing molecular oxygen to the tissue, the blood will contain a higher fraction of deoxygenated hemoglobin, called *deoxyhemoglobin*. Hemoglobin can therefore be interpreted as a conveyor belt for oxygen in the human body ([Scholander, 1960](#)).

The biological principle underlying the concept of BOLD imaging is the following: When the brain consumes energy in form of oxygen, the local ratio of oxyhemoglobin to deoxyhemoglobin will change, causing fluctuations of the BOLD signal. More precisely, *firing neurons*, i.e., active neurons that generate electrical signals, show an increased need for oxygen, which is served by a temporal expansion of the nearest blood vessels. This augments the inflow rate of fresh blood to the active brain regions despite an unaltered

blood pressure from the heart. Accordingly, other, non-active regions receive less fresh blood and therefore less oxyhemoglobin. Since oxyhemoglobin and deoxyhemoglobin differ in their magnetic susceptibility and recovery rate, fMRI via BOLD imaging is able to capture changes in the blood flow and oxygenation level and thereby indicates which parts of the brain are activated ([Ogawa et al., 1990](#)). The phenomenon of a link between neural activity and increased cerebral blood flow is referred to as the *neurovascular coupling* ([Phillips et al., 2016](#); [Soares et al., 2016](#)). Oxygenated hemoglobin causes stronger BOLD signals, while deoxygenated hemoglobin leads to weaker BOLD signals.

In summary, BOLD fMRI analyzes changes in the blood oxygenation levels presumably caused by neural firing, but it does not measure the behavior of the neurons as such. BOLD signals can thus be described as an *indirect* measurement of neural activation, which provides a proxy measure for regional brain activity.

While BOLD fMRI is characterized by a comparably low temporal resolution that cannot capture the fast dynamics of neural firing, it distinguishes itself by being a non-invasive technique with a typical spatial resolution of around 2-3 mm that procures *in vivo* function information of the brain under normal physiological conditions ([Ogawa et al., 1990](#); [Smith et al., 2024](#)).

By sampling the relative BOLD signal changes at regular time steps of less than one second, time series of brain activity are obtained. Typically, the signals extracted from all voxels belonging to a particular brain region are averaged in order to generate one time series per brain region. Such data reflecting brain activation patterns can basically be collected under two experimentally different conditions, namely during *cognitive task performance* or during the so-called *resting-state*. Both task-based and resting-state fMRI yield specific insights into the function of the human brain ([Biswal et al., 1995](#)).

In the former setting, the subjects are instructed to perform a cognitive or behavioral task while being in the MRI scanner. The collected BOLD signals are compared between performing and pausing intervals as well as across tasks to infer insights about the involvement of certain brain regions in particular task executions. In the latter scenario in turn, the participants are left to relax in the scanner and think for themselves about nothing particular ([Buckner et al., 2008](#)). The resting-state condition measures the spontaneous brain activity in the absence of any tasks and may thus unveil important details about the intrinsic organization of the human brain ([Fox & Raichle, 2007](#)). Further, it can be used to study large-scale brain networks associated with character traits and behavioral performances ([Fox & Raichle, 2007](#)). It has been shown that there is an increase of only 5% in energy consumption of brain activity if compared between rest and task executions ([Raichle, 2010](#)), which stresses the functional importance of the persistently ongoing mental processes in the absence of specific cognitive loads. In fact, resting-state activity has been regarded primarily as noise or meaningless background activity long before the early 1990s ([Pinneo, 1966](#)). Only the groundbreaking work by Biswal and colleagues revealed strong and meaningful interdependencies between the spontaneous BOLD signal fluctuations ([Biswal et al., 1995](#)). Ever since then, the resting-state condition has enjoyed increasing popularity and belongs to the most commonly applied settings in brain research nowadays. The fact that participants only have to lie awake in the scanner with their eyes closed or fixated on a specific point, has simplified the data acquisition across subjects with different age, cultural background and other demographic characteristics, and led to more generalizable results after all ([Biswal, 2012](#)).

1.1.5 Functional connectivity (FC)

From a mathematical point of view, it is desirable to extract some quantity or object from the observed brain activity that can be used for further analyses, similar as the matrices of SC. Here, it has become common practice to compute the temporal correlation between the BOLD signal time series of different brain regions ([van den Heuvel & Hulshoff Pol, 2010](#)). To this end, we summarize the values of signal intensities

$$\text{BOLD}_{i,t_k} := \text{BOLD}_{i,k} \text{ and } \text{BOLD}_{j,t_k} := \text{BOLD}_{j,k}$$

for two brain regions $i, j \in \{1, \dots, N\}$ at time points $t_k, k \in \{0, \dots, n\}, n \in \mathbb{N}$, via

$$\text{BOLD}_i := (\text{BOLD}_{i,k})_{k \in \{0, \dots, n\}} \text{ and } \text{BOLD}_j := (\text{BOLD}_{j,k})_{k \in \{0, \dots, n\}}.$$

Given such vectors $\text{BOLD}_i, \text{BOLD}_j \in \mathbb{R}^{n+1}$, the (*sample*) *Pearson correlation coefficient* $r \in [-1, 1]$ is calculated as

$$r := r(\text{BOLD}_i, \text{BOLD}_j) := \frac{\sum_{k=0}^n ((\text{BOLD}_{i,k} - \overline{\text{BOLD}}_i)(\text{BOLD}_{j,k} - \overline{\text{BOLD}}_j))}{\sqrt{\sum_{k=0}^n (\text{BOLD}_{i,k} - \overline{\text{BOLD}}_i)^2} \sqrt{\sum_{k=0}^n (\text{BOLD}_{j,k} - \overline{\text{BOLD}}_j)^2}}, \quad (2)$$

where $\overline{\text{BOLD}}_i := \frac{1}{n+1} \sum_{k=0}^n \text{BOLD}_{i,k}$ and $\overline{\text{BOLD}}_j := \frac{1}{n+1} \sum_{k=0}^n \text{BOLD}_{j,k}$ denote the average BOLD signal of brain region i and j , respectively. The Pearson correlation coefficient is a statistical measure that captures the extent of linear relationships between two datasets, here the BOLD signal time series. Matrix data can be vectorized accordingly. We stress that Eq. (2) describes the Pearson correlation coefficient for two samples, which is considered throughout this thesis. In a stochastic sense, the mentioned signal intensities could also be interpreted as realizations of two random variables I, J . The corresponding *population Pearson correlation coefficient* $\rho \in [-1, 1]$ would then equal their covariance divided by the product of their standard deviations, i.e.,

$$\rho(I, J) = \frac{\text{Cov}(I, J)}{\sigma_I \sigma_J}.$$

Functional connectivity (FC) in the brain is defined as the connectivity between spatially distant brain regions that share functional properties expressed via temporal co-activations ([Friston et al., 1993](#); [Park & Friston, 2013](#); [van den Heuvel & Hulshoff Pol, 2010](#)). Similar as for SC, a matrix $FC \in \mathbb{R}^{N \times N}$ is derived from the measurements by computing the sample correlation coefficients across all possible pairs of brain regions [Figure 4], i.e.,

$$FC_{ij} = r(\text{BOLD}_i, \text{BOLD}_j) \quad \forall i, j \in \{1, \dots, N\}. \quad (3)$$

We have $FC = FC^T$ and set $\text{diag}(FC) = 0 \in \mathbb{R}^N$. Due to the definition of the Pearson correlation coefficient, all diagonal elements originally equal one. Such uniform self-correlations however do not contain any useful information for explorations of subject-specific activity patterns and investigations of inter-individual variability. These are usually carried out on the off-diagonal elements (of the upper triangular parts, using the symmetry of FC). That is why the diagonal elements can be set to zero, which ensures

consistency with the SC matrices and allows for effective comparisons between SC and FC in terms of graph-theoretical measures, for example.

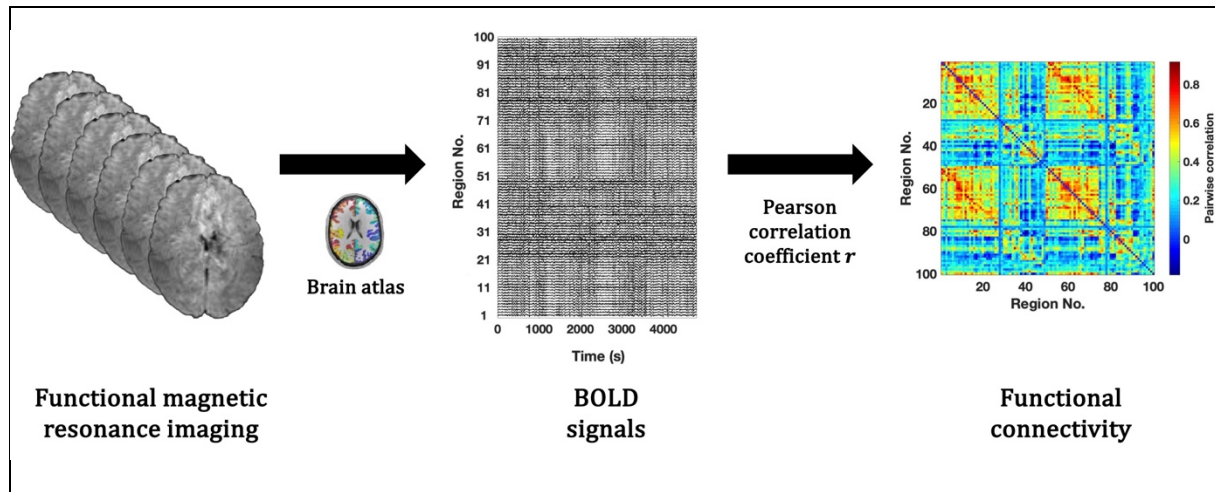


Figure 4: Schematic overview of functional connectivity extraction from magnetic resonance imaging. Functional brain recordings across time allow for the derivation of blood oxygenation level-dependent (BOLD) signals for every brain region as defined by the considered atlas. A subsequent calculation of the pairwise Pearson correlation coefficients among all measured signal time series yields the matrix of functional connectivity.

Resting-state FC is deemed to reflect the intrinsic functional organization of the human brain by measuring the temporal co-activation patterns of different brain areas. This approach is frequently used for several kinds of group analyses across multiple brains focusing on trait characteristics and behavioral performances, for example ([Fox & Raichle, 2007](#)). Moreover, it has been shown that SC and FC, i.e., structural (anatomical) and functional connections, respectively, are no mutual indicators: Brain regions do not have to be structurally connected to share a common function, and structural connections do not necessarily signify a functional link ([Honey et al., 2009](#); [Koch et al., 2002](#)). Such observations motivate the question about the details of this complex relationship. As we will see in chapter 3, dynamical whole-brain models provide a means to study the interplay between brain structure (SC) and function (FC). This is of particular interest since brain abnormalities and disorders like schizophrenia and autism may be the result of an altered connectivity between brain regions ([Bullmore & Sporns, 2012](#); [Karbowski, 2014](#)).

1.1.6 Preprocessing

Our preceding formulations may have evoked the impression that it is relatively easy and straightforward to extract reliable information about the human brain structure and function from MRI scans. In reality, however, the way from MRI data acquisition to the matrix representation of SC and FC contains many important preprocessing steps. The issue of an adequate preprocessing of raw data is a research topic on its own, being beyond the scope of this thesis. In this section, we throw only a short glance at some key aspects of the workflow, frequently used software packages and popular databases.

When a human undergoes an MRI scan, the brain is usually recorded via more than one imaging modality, meaning that, for example, diffusion-weighted, T_1 -weighted and functional MRIs are all acquired during consecutive sessions of roughly 10-20 minutes.

This means that for every weighting type, an image series across time and brain slices is obtained. It is captured along a given *phase-encoding direction*, e.g., from left to right. An immediate problem results from the fact that the images of brain slices are recorded sequentially, which means that they do not reflect exactly the same moment of measurement time t . Imagine, for simplicity, a scanner with low spatial resolution that can generate pictures of only three brain slices denoted by B_i , $i \in \{1,2,3\}$. The time between two recordings shall be denoted by Δt . Ideally, researchers would like to measure the entire brain at time t , i.e., $B_i(t)$, and then investigate the changes for $B_i(t + k\Delta t)$, $k \in \mathbb{N}$. In practice, however, they obtain an image sequence like

$$B_1(t), B_2(t + \Delta t), B_3(t + 2\Delta t), B_1(t + 3\Delta t), \dots$$

This is where the concept of *slice timing correction* comes in ([Henson et al., 1999](#); [Poldrack et al., 2011](#)). In order to account for the differences in timing, a reference slice B_j with fixed $j \in \{1,2,3\}$ is typically selected and studied over time, while the data for the remaining slices B_i ($i \neq j$) and time points are estimated via interpolation ([Poldrack et al., 2011](#)).

Another challenge results from possible head movements by the subject during the scanning session, which can distort the measured signals. This issue may also be tackled by realigning the images in the time series to a reference image ([Poldrack et al., 2011](#)). As the subject's head does not change its size and shape, *motion correction* or *realignment* is usually performed via rotation and translation of the voxel coordinates in the distorted image, together with the measured signal intensities, i.e.,

$$(vox, S) = ((x, y, z)^T, S) \in \mathbb{R}^3 \times \mathbb{R},$$

towards those in the reference image. Their eventual overlap may not be ideal due to noise, for example, which makes further interpolations for the actual signal intensities necessary ([Poldrack et al., 2011](#)). The software tools *Statistical Parametric Mapping* (SPM, ([Penny et al., 2007](#))) or *FreeSurfer* ([Fischl, 2012](#)) may be used for motion correction in raw MRIs, for instance. Additionally, a technique referred to as *Independent Component Analysis* (ICA) has proven very powerful for artifact detection, especially in fMRI data ([Griffanti et al., 2014](#); [Poldrack et al., 2011](#)). Its superiority to standard motion correction approaches results from the fact that it decomposes the data into independent components and thereby identifies unwanted noise components based on a variety of spatial and temporal features ([Tohka et al., 2008](#)). The *FMRIB Software Library* (FSL, ([Jenkinson et al., 2012](#))) contains a robust toolbox for ICA, called *FMRIB's X-noiseifier* (FIX, ([Salimi-Khorshidi et al., 2014](#))). It is frequently used for the removal of motion artifacts as well as other, more sophisticated noise perturbations in functional data preprocessing.

Two additional noteworthy techniques are termed *bias field correction* and *intensity normalization*. The former eliminates broad variations in signal intensity, especially in T_1 -weighted images, caused by proton excitation inhomogeneities in the head ([Poldrack et al., 2011](#); [Sled & Pike, 1998](#)). The latter performs a rescaling of signal intensities to common reference values in order to account for variations introduced by different scanners, sites and scanning techniques. *Advanced Normalization Tools* (ANTs, ([Tustison et al., 2010](#))), *MRtrix3* ([Tournier et al., 2019](#)) and FreeSurfer are suited for bias field correction and intensity normalization to give a few examples.

In section 1.1.1, we mentioned that T_1 -weighted images provide a pronounced contrast between GM and WM, i.e., between the tissue types containing the majority of neural cell bodies and the bundled nerve fibers connecting them, respectively. While this is true, there are, however, also other tissue types such as the *cranial bone*, and body fluids such as *cerebrospinal fluid* (CSF) that feature their own characteristic relaxation times and therefore signal intensities. Their presence complicates a direct identification of GM and WM. Further, the MRIs can be noisy (cf. motion correction), and some voxels may contain more than one tissue type, leading to overlapping signals and the so-called *partial volume effect* ([Poldrack et al., 2011](#)). Consequently, *tissue segmentation*, i.e., the accurate categorization of brain tissue into separate compartments like GM, WM and CSF constitutes one of the most sophisticated tasks in MRI preprocessing pipelines. Modern software tools like FreeSurfer, FSL or SPM determine a “prior probability” that a selected voxel most likely contains GM or WM by considering probabilistic brain maps of tissue types ([Poldrack et al., 2011](#)). Combining such probabilities with the acquired data allows for a more effective identification of the present tissue type. In this way, even voxels with identical signal values can be assigned to different tissue types ([Ashburner & Friston, 2005](#); [Poldrack et al., 2011](#)). A proper tissue segmentation is crucial, particularly for the WBT computation, as, for instance, the tractography algorithms included in MRtrix3 rely on anatomical information that should be as precise as possible ([Maffei et al., 2022](#)).

Ultimately, we want to address the topic of *intersubject registration*, also referred to as *spatial normalization*, which is of utmost importance in MRI data preprocessing. When we overlay the image series obtained for different brain slices with a three-dimensional coordinate system (e.g., $\mathbb{R}^3$), we can effectively describe the location of specific structures or ROIs for a given human subject. This initial coordinate system used for the images acquired directly from an MRI scanner is typically referred to as the *native (subject) space* ([Poldrack et al., 2011](#)). It is helpful for the localization of tumors, for instance, and the planning of a subsequent brain surgery. However, many neuroscientific research questions are not limited to understanding the brain of a single subject only but aim at comparisons between subjects. The goal is to derive more general claims that apply to broader parts of the population ([Poldrack et al., 2011](#)). This calls for a common reference coordinate space to which the data of different subjects, or different scans of the same subject, can be *warped* for comparison. For this purpose, researchers from the *Montreal Neurological Institute* (MNI) have processed and averaged the MRI data from hundreds of subjects and developed a common template, the so-called *MNI standard space* ([Brett et al., 2002](#); [Collins et al., 1995](#)). The biological plausibility of this coordinate system is regularly reviewed and kept up-to-date based on the current state of the art.

In view of distinct individual brains in the population and subjects’ varying head positions in the scanner, the MNI space has become the default means for result reporting in brain MRI. It can be interpreted as a map of a standard brain in a common coordinate system with predefined origin. This tool enables the localization of region or tissue boundaries in the scale of millimeters. Importantly, it also allows for efficient comparisons between individual brains as the data from the native subject spaces can be transformed to the MNI standard space, where they are mutually aligned. To this end, suitable mappings $a: \mathbb{R}^3 \rightarrow \mathbb{R}^3$ are applied to the voxel coordinates $vox = (x, y, z)^T$ in the native space to transfer them to the MNI standard space, for instance, via translation, rotation or scaling. This process is referred to as *intersubject registration* or *spatial normalization*. Apt software tools are FreeSurfer and FSL, for example.

To ensure within-subject consistency, it is crucial to align the functional brain images with the anatomical ones for a given subject. Typically, the fMRI data are registered to the subject's high-resolution anatomical image (e.g., T_1), a process which is known as *co-registration* in the literature ([Poldrack et al., 2011](#)).

A brain atlas can then be interpreted as a mask or template that assigns the voxel coordinates of the MNI standard space to particular brain regions ([Fischl et al., 2004](#)). This allows for analyses on the group level. If desired, back-transformations to the native subject space allow for the detection and visualization of ROIs in individual brains.

While some researchers acquire their own MRI data suited for the planned analyses and research questions, others resort to public databases. These often include MRIs of several modalities combined with demographic information as well as evaluations of questionnaires and scores related to personality traits for several hundreds of subjects. Some of these popular data repositories are the *Human Connectome Project* (HCP, ([Van Essen et al., 2013](#))), the *UK Biobank* ([Smith et al., 2024](#)), the *1000BRAINS* study ([Caspers et al., 2014](#)) and the *Rockland* sample of the *Enhanced Nathan Kline Institute* ([Nooner et al., 2012](#)).

1.2 Brain atlases considered in this thesis

As we already implied in the beginning of chapter 1, a brain atlas or brain parcellation serves as a tool to reduce the feature dimensionality during the analysis of neuroimaging data. It can be interpreted as a biologically informed data reduction strategy to condense the data of a myriad of voxels into a manageable set of brain regions or *parcels* ([Eickhoff et al., 2018](#)). As summarized by Eickhoff and colleagues ([Eickhoff et al., 2018](#)), there are three major criteria that need to be fulfilled in order to define a brain region, namely a specific microscopic structure, shared functional properties and a distinct connectivity profile to other regions. The fundamental idea of a brain parcellation is to identify components that are internally homogeneous with respect to a particular neurobiological measure but that are different from one another in this matter ([Eickhoff et al., 2018](#)). Typical markers may therefore be the thickness of some tissue layers on the cerebral cortex, the extent of the fiber bundle myelination or the functional signal responses to external stimulation ([Eickhoff et al., 2018](#)). In this setting, local and global partitioning approaches have proven useful to delineate distinct parts of the brain. While the former methods consist of boundary mapping strategies that aim to detect the most abrupt spatial changes in the considered marker ([Barnes et al., 2010](#); [Cohen et al., 2008](#); [Eickhoff et al., 2018](#); [Nelson et al., 2010](#)), the latter methods include clustering and factorization algorithms which group the voxels according to their (dis)similarity regarding the marker ([Eickhoff et al., 2018](#); [Orban et al., 2015](#); [Sotiras et al., 2015](#); [Yang et al., 2016](#)).

In sum, a brain parcellation can be considered a procedure of assigning every voxel of the MRIs to a specific brain region based on properties related to the structure, function and connectivity profile. There is no gold-standard parcellation technique, and the lack of a biological ground truth renders any questions about the attributes such as the number of parcels in the “true” or “best” atlas purely speculative. The most suited representation of the data is specific to the data at hand and to the very purpose of the representation ([Eickhoff et al., 2018](#)).

We considered two paradigmatically distinct brain atlases in the studies making up this thesis: The Harvard-Oxford atlas ([Desikan et al., 2006](#)) and the Schaefer atlas ([Schaefer et al., 2018](#)).

The Harvard-Oxford atlas is inspired by the macrostructural (i.e., structure recognizable without visual aids) organization of the brain surface ([Jenkinson et al., 2012](#)). It was derived from T_1 -weighted MRIs of 37 healthy individuals aged between 18 and 50 years. The images had been visually inspected and individually processed at the *Harvard Center for Morphometric Analysis* at Massachusetts General Hospital in Boston, USA using both manual and semi-automated labeling tools ([Fischl et al., 2004](#)). Afterwards, the data had been incorporated into the software tool FSL developed at the University of Oxford, UK ([Jenkinson et al., 2012](#)). The result is an atlas that parcellates the cortex into $N = 96$ brain regions (48 per hemisphere) based on anatomical criteria such as the presence of sulci and gyri on the cortical surface ([Makris et al., 2006](#)). All these regions had been identified in all 37 brains, but their size and exact location on the cortex could vary from subject to subject. Therefore, there exist several variations of the Harvard-Oxford atlas, where the number of included voxels per brain region may vary considerably, while the total number of ROIs tends to remain constant. The underlying principle is the following: After processing the data from the given MRIs, every considered voxel possessed a distinct probability to belong to a particular brain region, resulting in 96 probabilities per voxel. These voxel-wise probability vectors were inspected for their maxima which were subsequently compared to specific thresholds. There are multiple such *maximal probability thresholds* between 0% and 45% which define the different variants of the Harvard-Oxford atlas and must be exceeded in order for a voxel to be counted to a particular brain region. In case of a 0% threshold, a voxel was immediately assigned to the ROI for which it showed the highest probability. If the maximal probability did not exceed the considered threshold (e.g., 45%), such a voxel was not added to any brain region (which is why the total number of ROIs might be lower for higher thresholds). In sum, higher thresholds indicate stricter inclusion criteria and therefore smaller region sizes ([Fischl et al., 2002](#); [Popovych et al., 2021](#)). We consider the most relaxed version of the Harvard-Oxford atlas. It features a probability threshold of 0%, i.e., the largest region sizes if measured in the number of voxels per region.

The second parcellation under deliberation is the Schaefer atlas. It primarily differs from the Harvard-Oxford atlas to the effect that it is not based on anatomical brain imaging data but on functional measurements. Indeed, its design is inspired by the resting-state fMRI data of 1489 healthy individuals aged between 18 and 35 years ([Schaefer et al., 2018](#)). During its derivation, local boundary detection methods were blended with clustering strategies – a combination deemed advantageous and promising for the development of future brain parcellations ([Eickhoff et al., 2018](#)). The Schaefer atlas subdivides the cerebral cortex into distinct regions that show a high homogeneity in terms of their resting-state FC profiles. Abrupt changes across close locations determine the region boundaries ([Cohen et al., 2008](#)), which thereby preserve a neurobiological meaningfulness and simultaneously maintain the connectional homogeneity within every ROI ([Schaefer et al., 2018](#)). There exist different variants of the Schaefer atlas that parcellate the brain into, among others, $N = 100$, 200 or even 1000 ROIs. Here, the number of voxels included in every region decreases for a higher resolution, i.e., higher N . We worked with the parcellation featuring $N = 100$ ROIs in the studies presented in this thesis.

Our atlas selection allowed for effective comparisons between two paradigmatically different parcellation approaches (anatomical vs. functional) sharing a similar number of brain regions (96 vs. 100) and the highest number of voxels per region for the respective approach (0% threshold for Harvard-Oxford vs. $N = 100$ for Schaefer). This can be

transferred to the application of whole-brain models (see chapter 3) with regional model parameters for optimization. Importantly, the similarity in region number reflects two model parameter spaces of comparable dimension ($\mathbb{R}^{96}$ vs. $\mathbb{R}^{103}$), for which the fitting quality as well as other result properties may be investigated and compared. All in all, brain parcellations appear fundamental for decoding the human brain as they may procure crucial insights into the organizational principles of the brain structure, function and connectivity ([Eickhoff et al., 2018](#); [Passingham et al., 2002](#)).

2 Stochastic differential equations (SDEs)

In the previous chapter, we illustrated the critical steps from MRI scans towards a matrix representation of the brain network in terms of atlas-based SC and FC. Now we elaborate on the theoretical background of mathematical modeling in neuroscience. We describe the general shape of the considered model equations and explain numerical solution strategies. This provides necessary knowledge for the development of mathematical models, where the extracted matrices of SC are incorporated, and the FC matrices serve as a benchmark to assess the quality of the model output.

Dynamical whole-brain models simulate the temporal development of a given quantity of interest like, for example, a BOLD signal or an electric current over a relevant interval of time. Most models are derived from *ordinary differential equations* (ODEs) that, together with given initial conditions, are solved numerically due to lacking knowledge about an analytical solution. A challenge is often given by the presence of delays in the ODEs, meaning that the derivative of the unknown function at a certain time may depend on the values of the function at previous times. In such cases, an *initial function* (instead of a mere initial value) has to be specified, which describes the behavior of the system prior to the prescribed starting time ([Myshkis, 1955](#)). In addition, the considered ODEs do not only contain deterministic functions and their respective derivatives but also random noise perturbations. Such *stochastic differential equations* (SDEs) are ubiquitous in the field of simulative studies of natural phenomena, where the stochasticity adds an element of realistic uncertainty to the equations. The fields of application range from physical experiments on random particle movements to analyses of unforeseen prize fluctuations in financial markets. In physical explorations of the population dynamics of active particles like bacteria in a liquid, for example, researchers initially disregard the exact properties of the solvent and approximate them via random stochastic terms ([Bechinger et al., 2016](#); [Burrage et al., 2004](#)). This way, the computational cost reduces considerably, and focus can be put on the actual behavior of the particles in the solvent, which reflects the phenomenon of interest in such applications. Similar approaches are utilized to simulate prize fluctuations ([Higham, 2001](#)). Simply speaking, noise terms in SDEs reflect complicated, unforeseen and sometimes unpredictable external influences on a given system, while noise-free ODEs often represent idealized scenarios ([Burrage et al., 2004](#)).

2.1 White noise and Wiener processes

Stochastic perturbations are commonly modeled by *white noise*, a discrete signal which we can interpret as a sequence of samples of uncorrelated random variables with expected value zero and finite variance ([Marmarelis, 2004](#)). Independent and identically distributed random variables are the simplest representation of white noise ([Stein, 1999](#)). It is often generated by normally distributed random variables (*Gaussian white noise*), but can also be obtained from other probability distributions such as a uniform distribution with zero mean, for instance ([Vicsek et al., 1995](#)). To provide a proper mathematical formulation, we elaborate on the concept of *Wiener processes* which play an important role for the definition of white noise.

Given a sample space Ω and $T > 0$, a standard Wiener process $\{W(t) \mid t \in [0, T]\}$ is a family of time-dependent random variables $W_t := W(t)$, $W_t: \Omega \rightarrow \mathbb{R}$, with the following properties ([Higham, 2001](#); [Kloeden & Platen, 1993](#)):

- 1) Initial condition
 $W_0 = 0$ almost surely, i.e., with probability one, (4)

- 2) Gaussian increments
 For $\Delta t > 0$: $\Delta W_t := W_{t+\Delta t} - W_t = \sqrt{\Delta t} G_t$, where $G_t \sim \mathcal{N}_{0,1}$ or,
 equivalently, $W_{t+\Delta t} = W_t + \Delta W_t$, where $\Delta W_t \sim \mathcal{N}_{0,\Delta t}$, (5)

- 3) Non-overlapping increment independence
 For $0 \leq s < t < u < v \leq T$: $W_t - W_s$ and $W_v - W_u$ are independent. (6)

Since W_t is a random variable for every $t \in [0, T]$, we ought to write $W_t(\omega)$ (instead of W_t) with $\omega \in \Omega$ being an event in the underlying sample space Ω . For any fixed $\omega \in \Omega$, $\{W_t(\omega) \mid t \in [0, T]\}$ is then one *path* of the Wiener process, while for any fixed t , $W_t(\omega)$ is a *realization* of the Wiener process at time t . For the sake of convenience, we will however omit the use of ω wherever possible and thereby stick to the common habit in probability theory. A standard Wiener process is often referred to as Brownian motion (cf. section 1.1.2) ([Higham, 2001](#); [Kloeden & Platen, 1993](#)). White noise has been described as its temporal derivative although such a quantity does not exist in a strict mathematical sense, see below.

From condition 2) it follows that ΔW_t is not proportional to Δt in the limit $\Delta t \rightarrow 0$ ([Allen & Tildesley, 2017](#)). This is related to the concept of timescale separation derived from the *fluctuation-dissipation theorem* studied under the *Langevin equation*. Simply speaking, the theory states that the retained variables in a differential equation change much more slowly than those replaced by stochastic terms, see ([Allen & Tildesley, 2017](#); [Wischniewski, 2019](#)) for more detailed explanations. The Gaussian increments further indicate that the paths of a Wiener process manifest an unbounded variation on any finite interval in $\mathbb{R}_{\geq 0}$, i.e.,

$$\sup \left\{ \sum_{i=0}^{n-1} |W_{t_{i+1}}(\omega) - W_{t_i}(\omega)| \right\} = \infty, \quad (7)$$

where the supremum is taken over all subdivisions $0 \leq t_0 \leq t_1 \leq \dots \leq t_n = T$ of $[t_0, T]$ with $n \in \mathbb{N}$ ([Fahrmeir, 1976](#); [Kloeden, 2011](#); [Kloeden & Platen, 1993](#)). This means that, in general, a Wiener process, or Brownian motion, is nowhere differentiable, i.e., an expression such as $\frac{d}{dt} W_t(\omega)$ is not well-defined ([Higham, 2001](#)). Still, it has become common practice among researchers from other disciplines than mathematics to formally write

$$“\eta_t(\omega) = \frac{d}{dt} W_t(\omega)”$$

to denote white (Gaussian) noise. They intend to describe a stochastic process, where all $\eta_t := \eta(t)$ are independent and $\mathcal{N}_{0,1}$ -distributed random variables ([Kloeden, 2011](#)). Accordingly, the dynamical whole-brain models considered in this thesis can generally be described by SDEs of the following type:

$$\dot{X}(t) = \frac{d}{dt} X(t) = f(t, X(t)) + g(t, X(t)) \eta_t, \quad t \in [t_0, T], \quad (8)$$

$$X(t_0) = X_{t_0}. \quad (9)$$

$X_t := X(t)$ denotes the value of the considered quantity of interest at time t . It is to be treated as a random variable $X_t: \Omega \rightarrow \mathbb{R}$ for each t , whose initial value, strictly speaking also a random variable, is given by $X_{t_0}, t_0 \geq 0$ ([Higham, 2001](#)). We disregard the presence of delays in the models for the moment so as not to introduce two sophisticated concepts simultaneously. For the general understanding of SDEs, delays do not play a role and will therefore be addressed in more detail later in section 3.3.2. The smooth functions $f, g: [t_0, T] \times \mathbb{R} \rightarrow \mathbb{R}$, sometimes referred to as *coefficients* ([Kloeden & Platen, 1993](#)), describe the deterministic *drift* and the *amplitude* of stochastic perturbations, respectively. The latter term is also referred to as *diffusion coefficient* in the literature, but we will omit this expression to prevent misunderstandings related to the diffusion of water molecules in the brain described in section 1.1.2. Finally, “ $\eta_t = \frac{d}{dt} W_t$ ” reflects the random noise term.

We stress that Eq. (8) must be regarded in a purely symbolic sense. It offers the convenience of describing the problem at hand in terms of a differential equation, but it is unsuited for further mathematical interpretations, in particular for the derivation of numerical integration schemes for approximating a solution. Analogues of Eq. (8) will be referred to as *symbolic* in subsequent chapters. Note that we adapted the style of Eq. (8) in the publications ([Jung et al., 2025](#); [Wischniewski et al., 2022](#); [Wischniewski et al., 2025](#)) presented in this thesis to follow the literature.

On the way to a valid formulation of the given SDE, both sides of Eq. (8) are multiplied by dt :

$$dX_t = f(t, X_t) dt + g(t, X_t) dW_t. \quad (10)$$

This formulation may be treated in a generalized sense of differentials and serves as an abbreviation of the following *integral equation* ([Fahrmeir, 1976](#); [Kloeden & Platen, 1992](#)) obtained via an integration over $[t_0, t]$:

$$\begin{aligned} \int_{t_0}^t 1 dX_s &= \int_{t_0}^t f(s, X_s) ds + \int_{t_0}^t g(s, X_s) dW_s \\ \Leftrightarrow X_t - X_{t_0} &= \int_{t_0}^t f(s, X_s) ds + \int_{t_0}^t g(s, X_s) dW_s \\ \Leftrightarrow X_t &= X_{t_0} + \int_{t_0}^t f(s, X_s) ds + \int_{t_0}^t g(s, X_s) dW_s. \end{aligned} \quad (11)$$

Equation (11) is a proper formulation of the condition that a solution of Eq. (8) must satisfy. We repeat that X_{t_0} is a random variable, which, nevertheless may be constant almost surely. Equally, X_t is a random variable for all $t \in [t_0, T]$ as indicated above. In terms of the theory of SDEs, a solution X_t further satisfies $\mathbb{E}[X_t^2] < \infty$, is independent of the increments ΔW_t of the Wiener process, while every path $t \mapsto X_t(\omega)$ is continuous in t ([Kloeden, 2011](#)). It has been shown that under certain conditions for the initial value, and continuous functions f and g for the drift and noise amplitude, respectively, the existence and uniqueness (see below) of such a solution X_t is guaranteed ([Arnold, 1974](#); [Liptser & Shiryaev, 1977](#)).

Precisely, these conditions can be formulated as follows ([Burrage et al., 2004](#); [Fahrmeir, 1976](#); [Kloeden & Platen, 1992](#); [Kloeden, 2011](#); [Rümelin, 1982](#)):

There exists $L > 0$, such that for all $(t, x), (t, y) \in [t_0, T] \times \mathbb{R}$

1) Lipschitz condition

$$|f(t, x) - f(t, y)| + |g(t, x) - g(t, y)| \leq L |x - y|, \quad (12)$$

2) Linear growth condition

$$|f(t, x)|^2 + |g(t, x)|^2 \leq L^2 (1 + |x|^2), \quad (13)$$

3) Initial value condition

$$\mathbb{E}[X_{t_0}^2] < \infty \text{ and the increments } \Delta W_t \text{ are independent of } X_{t_0}. \quad (14)$$

The uniqueness of the solution is to be understood in terms of *path-wise uniqueness*, meaning that if X_t and Y_t are two solutions of the SDE, we have

$$\sup_{t \in [t_0, T]} \{|X_t(\omega) - Y_t(\omega)|\} = 0 \text{ almost surely,}$$

i.e., with probability one ([Burrage et al., 2004](#)). As we will see in section 3.3.2, the conditions 1) - 3), adapted to the delay case ([Yin & Gan, 2015](#)), are fulfilled for the SDEs of the whole-brain model that was considered in the publications presented in this thesis.

2.2 Stochastic integrals

Before we proceed to the numerical approximation of a solution, we emphasize that the interpretation of the SDE Eq. (8) in its integral form given by Eq. (11) is not straightforward. While

$$\int_{t_0}^t f(s, X_s) ds$$

is a usual Riemann integral over the realizations of X_s for any given path

$$\{X_s(\omega) \mid s \in [t_0, T]\},$$

the integral

$$\int_{t_0}^t g(s, X_s) dW_s$$

is to be taken with respect to Brownian motion ([Burrage et al., 2004](#); [Higham, 2001](#)). It may seem intuitive and reasonable to apply the so-called *Riemann-Stieltjes integral* here, which constitutes a generalization of the classical Riemann integral ([Kloeden & Platen, 1992](#)):

Given a subdivision $0 \leq t_0 \leq t_1 \leq \dots \leq t_n = T$ of $[t_0, T]$, $n \in \mathbb{N}$, a (for simplicity) continuous function $\varphi: [t_0, T] \rightarrow \mathbb{R}$, called *integrand*, and a function $\psi: [t_0, T] \rightarrow \mathbb{R}$ of bounded variation, called *integrator*, the Riemann-Stieltjes integral can be defined as

$$\int_{t_0}^T \varphi(t) d\psi(t) = \lim_{n \rightarrow \infty} \sum_{i=0}^{n-1} \varphi(\tau_i) (\psi(t_{i+1}) - \psi(t_i)) \quad (15)$$

for any $\tau_i \in [t_i, t_{i+1}]$, where the limit implies

$$\Delta t_i^{(n)} := (t_{i+1} - t_i) \xrightarrow{n \rightarrow \infty} 0 \quad \forall i \in \{0, \dots, n-1\}.$$

This definition resembles the approximation of an integral $\int_{t_0}^T \varphi(t) dt$ by Riemann sums of the type

$$\sum_{i=0}^{n-1} \varphi(t_i) \Delta t_i^{(n)} \quad \text{or} \quad \sum_{i=0}^{n-1} \varphi(t_{i+1}) \Delta t_i^{(n)},$$

where $\Delta t_i^{(n)}$ had been replaced by the increments of ψ ([Higham, 2001](#)).

However, we know that the paths of a Wiener process are not of bounded variation, see Eq. (7). This means that if we set $\psi(t) = W_t$ in Eq. (15), the second factor in the sum on the right-hand side would in general not approach zero for $n \rightarrow \infty$, unlike $\Delta t_i^{(n)}$ in the classical Riemann integral. Consequently, a further adaptation of the notion of stochastic integrals is necessary.

Two well-established approaches for this endeavor are given by the so-called *stochastic Itô integral* and the *stochastic Stratonovich integral* ([Kloeden & Platen, 1992](#); [Kloeden, 2011](#)). Both variants are essentially related in their derivation but require particular attention due to their differing output. Integrals computed with respect to a Wiener process, i.e., a family of random variables, are supposed to be random variables themselves ([Mannella, 2002](#)). That is why an adequate definition of convergence in a probabilistic sense was required to design stochastic integrals emerging as the limit of their approximating sums. The theories both by Itô and Stratonovich resort to *convergence in the quadratic mean* (qm) here, meaning that a sequence of random variables $\{X^n\}_{n \in \mathbb{N}_0}$ (the superscript denotes an index) approaches another random variable $\bar{X}$ if the expected value of their quadratic difference converges to zero, formally

$$X^n \xrightarrow{n \rightarrow \infty} \bar{X} \text{ [qm]}, \text{ if } \mathbb{E}[|X^n - \bar{X}|^2] \xrightarrow{n \rightarrow \infty} 0. \quad (16)$$

Based on that, for a function $\varphi: [t_0, T] \rightarrow \mathbb{R}$, or, more generally, for $\varphi: [t_0, T] \times \mathbb{R} \rightarrow \mathbb{R}$ that additionally depends on the random variable X_t , the stochastic integral taken over a Wiener process W_t , i.e.,

$$I(\varphi) := \int_{t_0}^T \varphi(t, X_t) dW_t$$

is defined as the qm-limit of the approximating sum

$$I_{n,\tau}(\varphi) := \sum_{i=0}^{n-1} \varphi(\tau_i, X_{\tau_i})(W_{t_{i+1}} - W_{t_i})$$

for any subdivision $0 \leq t_0 \leq t_1 \leq \dots \leq t_n = T$ of $[t_0, T]$, where

$$\Delta t^{(n)} := \max_{i \in \{0, \dots, n-1\}} (t_{i+1} - t_i) \xrightarrow{n \rightarrow \infty} 0.$$

For simplicity, we will focus on equidistant subdivisions from now on, so that

$$\Delta t_i^{(n)} = \Delta t^{(n)} \quad \forall i \in \{0, \dots, n-1\}.$$

In addition, we will not always indicate the dependence on n in $\Delta t^{(n)}$ and write Δt instead. $\tau_i \in [t_i, t_{i+1}]$ in the argument of φ remains variable and can be expressed as

$$\tau_i = \tau_i(\lambda) = \lambda t_{i+1} + (1 - \lambda) t_i, \quad \lambda \in [0,1]. \quad (17)$$

([Burrage et al., 2004](#)). It has been documented that, if

- 1) $\varphi_t = \varphi(t, \cdot)$ as a measurable random variable satisfies $\mathbb{E}[\varphi_t^2] < \infty \quad \forall t \in [t_0, T]$,
- 2) $t \mapsto \varphi_t$ is continuous on $[t_0, T]$ almost surely, i.e., for all paths $t \mapsto \varphi_t(\omega)$,
- 3) φ_t and ΔW_t are independent $\forall t \in [t_0, T]$,

then the limit $I(\varphi)$ does not depend on the selected subdivision of $[t_0, T]$ (but on the selection of τ_i) and it further satisfies

$$\begin{aligned} \lim_{n \rightarrow \infty} \mathbb{E} \left[|I_{n,\tau}(\varphi) - I(\varphi)|^2 \right] &= 0 \\ \Leftrightarrow I_{n,\tau}(\varphi) &\xrightarrow[n \rightarrow \infty]{} I(\varphi) \quad [\text{qm}] \end{aligned}$$

([Burrage et al., 2004](#); [Kloeden & Platen, 1992](#); [Kloeden, 2011](#)). If $\varphi_t \equiv \sigma \in \mathbb{R} \quad \forall t \in [t_0, T]$ almost surely, then the conditions above are trivially fulfilled, for example. This solves the issue of a non-existent limit in the classical sense due to the unbounded variation of the Wiener process in Eq. (7) and clears the way for the following definitions:

For $\lambda = 0$ in Eq. (17), i.e., the left-hand endpoint $\tau_i = t_i$ of each subinterval, the resulting integral

$$\int_{t_0}^T \varphi(t, X_t) dW_t := \lim_{n \rightarrow \infty} \sum_{i=0}^{n-1} \varphi(t_i, X_{t_i}) \underbrace{(W_{t_{i+1}} - W_{t_i})}_{=\Delta W_{t_i}} \quad [\text{qm}] \quad (18)$$

is called the Itô integral.

For $\lambda = \frac{1}{2}$ in Eq. (17), i.e., the midpoint $\tau_i = \frac{t_i + t_{i+1}}{2}$ of each subinterval,

$$\int_{t_0}^T \varphi(t, X_t) \circ dW_t := \lim_{n \rightarrow \infty} \sum_{i=0}^{n-1} \varphi\left(\frac{t_i + t_{i+1}}{2}, X_{\frac{t_i + t_{i+1}}{2}}\right) \underbrace{(W_{t_{i+1}} - W_{t_i})}_{=\Delta W_{t_i}} \quad [\text{qm}] \quad (19)$$

is called the Stratonovich integral ([Burrage et al., 2004](#); [Higham, 2001](#); [Kloeden & Platen, 1992](#); [Kloeden, 2011](#)). Hence, the difference between “ dW_t ” in Eq. (18) and “ $\circ dW_t$ ” in Eq. (19) indicates whether the Itô or Stratonovich integral is referred to.

Both presented approaches offer a way to describe a stochastic integral taken over a random noise variable, here Brownian motion. However, we will see below that the

decision where to evaluate φ plays an important role for subsequent applications of such a stochastic integral. This is a phenomenon that does not occur in the deterministic setting when considering the limit of Riemann sums to define an integral. We will illustrate the role of the argument of φ with help of an example ([Higham, 2001](#); [Kloeden, 2011](#)).

Consider the case where $\varphi(t, X_t) = W_t$ for $t \in [0, T]$ and we want to compute $\int_0^T W_t dW_t$. For any subdivision $0 = t_0 \leq t_1 \leq \dots \leq t_n = n \Delta t = T$, the relevant Itô sum in Eq. (18) reads

$$\begin{aligned}
& \sum_{i=0}^{n-1} W_{t_i} (W_{t_{i+1}} - W_{t_i}) \\
&= \frac{1}{2} \sum_{i=0}^{n-1} 2W_{t_i} (W_{t_{i+1}} - W_{t_i}) \\
&= \frac{1}{2} \sum_{i=0}^{n-1} (2W_{t_i} W_{t_{i+1}} - 2W_{t_i}^2) \\
&= \frac{1}{2} \sum_{i=0}^{n-1} [W_{t_{i+1}}^2 - W_{t_i}^2 - (W_{t_{i+1}}^2 - 2W_{t_i} W_{t_{i+1}} + W_{t_i}^2)] \\
&= \frac{1}{2} \sum_{i=0}^{n-1} [W_{t_{i+1}}^2 - W_{t_i}^2 - (W_{t_{i+1}} - W_{t_i})^2].
\end{aligned}$$

Using the properties of a telescoping series as well as the initial condition (Eq. (4)) of the Wiener process ($W_{t_0} = 0$), the last term can be rewritten to obtain

$$\frac{1}{2} \left(W_{t_n}^2 - \underbrace{W_{t_0}^2}_{=0} - \sum_{i=0}^{n-1} (W_{t_{i+1}} - W_{t_i})^2 \right) = \frac{1}{2} \left(W_T^2 - \sum_{i=0}^{n-1} (W_{t_{i+1}} - W_{t_i})^2 \right) =: S_n.$$

The qm-limit of this expression is $\frac{1}{2} W_T^2 - \frac{1}{2} T$, because we have:

$$\begin{aligned}
& \left| S_n - \left(\frac{1}{2} W_T^2 - \frac{1}{2} T \right) \right|^2 \\
&= \left| \frac{1}{2} W_T^2 - \frac{1}{2} \sum_{i=0}^{n-1} (W_{t_{i+1}} - W_{t_i})^2 - \frac{1}{2} W_T^2 + \frac{1}{2} T \right|^2 \\
&= \left| \frac{1}{2} \left(T - \sum_{i=0}^{n-1} (W_{t_{i+1}} - W_{t_i})^2 \right) \right|^2 = \frac{1}{4} \left| \underbrace{T}_{=n\Delta t} - \sum_{i=0}^{n-1} \Delta W_{t_i}^2 \right|^2 \\
&= \frac{1}{4} \left| \sum_{i=0}^{n-1} (\Delta t - \Delta W_{t_i}^2) \right|^2 =: \frac{1}{4} \left| \sum_{i=0}^{n-1} Z_i \right|^2.
\end{aligned} \tag{20}$$

Using $\Delta W_{t_i} \sim \mathcal{N}_{0, \Delta t}$ from Eq. (5) as well as $\text{Var}(\Delta W_{t_i}) = \mathbb{E}[\Delta W_{t_i}^2] - \mathbb{E}[\Delta W_{t_i}]^2$, we obtain

$$\begin{aligned}
\mathbb{E}[Z_i] &= \mathbb{E}[\Delta t - \Delta W_{t_i}^2] = \mathbb{E}[\Delta t] - \mathbb{E}[\Delta W_{t_i}^2] \\
&= \Delta t - \left(\underbrace{\text{Var}(\Delta W_{t_i})}_{\stackrel{(5)}{=} \Delta t} + \underbrace{\mathbb{E}[\Delta W_{t_i}]^2}_{\stackrel{(5)}{=} 0} \right) = 0
\end{aligned} \tag{21}$$

and

$$\begin{aligned}
\text{Var}(Z_i) &= \mathbb{E}[Z_i^2] - \underbrace{\mathbb{E}[Z_i]^2}_{\stackrel{(21)}{=} 0} = \mathbb{E}[\Delta t^2 - 2\Delta t \Delta W_{t_i}^2 + \Delta W_{t_i}^4] \\
&= \Delta t^2 - 2\Delta t \underbrace{\mathbb{E}[\Delta W_{t_i}^2]}_{\stackrel{(21)}{=} \Delta t} + \mathbb{E}[\Delta W_{t_i}^4] = \Delta t^2 - 2\Delta t^2 + \mathbb{E}[\Delta W_{t_i}^4] \\
&= 2\Delta t^2,
\end{aligned} \tag{22}$$

since $\mathbb{E}[\Delta W_{t_i}^4] = 3\Delta t^2$, because the higher moments of a $\mathcal{N}_{0, \sigma^2}$ -distributed random variable V are generally computed as

$$\mathbb{E}[V^d] = \begin{cases} 1 \cdot 3 \cdot 5 \cdot \dots \cdot (d-1) \cdot \sigma^d, & \text{if } d \text{ even} \\ 0, & \text{if } d \text{ odd} \end{cases}$$

(Kloeden, 2011). So, for $d = 4$ and due to

$$\text{Var}(\Delta W_{t_i}) \stackrel{(5)}{=} \Delta t = \sigma^2 \Leftrightarrow \sigma = \Delta t^{\frac{1}{2}},$$

we have

$$\mathbb{E}[\Delta W_{t_i}^4] = 3\sigma^4 = 3\left(\Delta t^{\frac{1}{2}}\right)^4 = 3\Delta t^2.$$

Since it follows from the independence of ΔW_{t_i} and ΔW_{t_j} for $i \neq j$ (Eq. (6)) that Z_i and Z_j are independent as well, this leads to:

$$\text{Var}\left(\sum_{i=0}^{n-1} Z_i\right) = \sum_{i=0}^{n-1} \text{Var}(Z_i) \stackrel{(22)}{=} \sum_{i=0}^{n-1} 2\Delta t^2 = 2 \sum_{i=0}^{n-1} \left(\frac{T}{n}\right)^2 = 2n \frac{T^2}{n^2} = \frac{2T^2}{n}. \tag{23}$$

By using

$$\begin{aligned}
\text{Var}\left(\sum_{i=0}^{n-1} Z_i\right) &= \mathbb{E}\left[\left(\sum_{i=0}^{n-1} Z_i\right)^2\right] - \underbrace{\mathbb{E}\left[\sum_{i=0}^{n-1} Z_i\right]^2}_{\stackrel{(21)}{=} 0} \\
&\stackrel{(20)}{=} \mathbb{E}\left[\left|\sum_{i=0}^{n-1} (\Delta t - \Delta W_{t_i}^2)\right|^2\right] \stackrel{(20)}{=} 4\mathbb{E}\left[\left|S_N - \left(\frac{1}{2}W_T^2 - \frac{1}{2}T\right)\right|^2\right],
\end{aligned} \tag{24}$$

we finally obtain

$$\mathbb{E} \left[\left| S_N - \left(\frac{1}{2} W_T^2 - \frac{1}{2} T \right) \right|^2 \right] \stackrel{(24)}{=} \frac{1}{4} \text{Var} \left(\sum_{i=0}^{n-1} Z_i \right) \stackrel{(23)}{=} \frac{1}{4} \frac{2T^2}{n} = \frac{T^2}{2n} \xrightarrow{n \rightarrow \infty} 0,$$

meaning

$$\int_0^T W_t dW_t = \frac{1}{2} W_T^2 - \frac{1}{2} T$$

for the Itô integral.

Similarly, it can be shown that

$$\int_0^T W_t \circ dW_t = \frac{1}{2} W_T^2$$

holds for the corresponding Stratonovich integral ([Burrage et al., 2004](#); [Kloeden & Platen, 1992](#); [Kloeden, 2011](#)), see also ([Higham, 2001](#)) for a numerical confirmation. This value shows an analogy to the result obtained for deterministic integrals, where for any differentiable $u: \mathbb{R} \rightarrow \mathbb{R}$ satisfying $u(0) = 0$ (as in Eq. (4) for the Wiener process), we have:

$$\begin{aligned} \int_{u(0)}^{u(T)} u(t) du(t) &= \int_0^T u(t) \frac{du(t)}{dt} dt = \int_0^T u(t) u'(t) dt = \left[\frac{1}{2} u(t)^2 \right]_0^T \\ &= \frac{1}{2} u(T)^2 - \frac{1}{2} \underbrace{u(0)^2}_{=0} = \frac{1}{2} u(T)^2. \end{aligned}$$

In summary, the two stochastic sums in Eq. (18) and (19) differ markedly in their qm-limit, revealing a considerable difference between deterministic and stochastic integration ([Higham, 2001](#)). This implies that a given SDE can have different solutions if interpreted either in the sense of Itô or in the sense of Stratonovich. Now the natural question arises how to deal with such a result.

2.2.1 Itô or Stratonovich?

It is known that the Stratonovich integral follows the rules of deterministic calculus, making it more suitable for computing an explicit solution of a given SDE ([Burrage et al., 2004](#); [Kloeden, 2011](#); [Kloeden & Platen, 1993](#)). The Itô integral in turn has many useful properties (such as an expected value of zero) that render it adequate for deriving upper estimates needed for proving related theorems ([Kloeden & Platen, 1992](#); [Kloeden, 2011](#)). Fortunately, there exists a relatively simple formula that allows users to transform an SDE from Itô to Stratonovich sense and vice versa:

Given an Itô SDE in the form of Eq. (10), i.e.,

$$dX_t = f(t, X_t) dt + g(t, X_t) dW_t,$$

the drift modification

$$\underline{f}(t, x) := f(t, x) - \frac{1}{2} g(t, x) \frac{\partial}{\partial x} g(t, x) \quad (25)$$

ensures that Eq. (10) in Itô sense and the following Stratonovich SDE

$$dX_t = \underline{f}(t, X_t) dt + g(t, X_t) \circ dW_t$$

have the same solution ([Burrage et al., 2004](#); [Fahrmeir, 1976](#); [Higham, 2001](#); [Kloeden & Platen, 1992](#); [Kloeden, 2011](#); [Rümelin, 1982](#)). Before illustrating such a transformation with help of another example, we highlight that the formula in Eq. (25) is derived from the *stochastic chain rule*, also known as *Itô's lemma*, which reveals a considerable abnormality of stochastic calculus:

Consider first the (deterministic) ODE

$$\varphi'(t) = f(t, \varphi(t)), \quad (26)$$

where the functions $\varphi: [t_0, T] \rightarrow \mathbb{R}$ and $f: [t_0, T] \times \mathbb{R} \rightarrow \mathbb{R}$ are sufficiently smooth. The chain rule, or, better, the total derivative then yields:

$$\begin{aligned} \varphi''(t) &= \frac{d}{dt} f(t, \varphi(t)) = \frac{\partial}{\partial t} f(t, \varphi(t)) + \frac{\partial}{\partial \varphi} f(t, \varphi(t)) \underbrace{\frac{d}{dt} \varphi(t)}_{=\varphi'(t)} \\ &\stackrel{(26)}{=} \frac{\partial}{\partial t} f(t, \varphi(t)) + \frac{\partial}{\partial \varphi} f(t, \varphi(t)) f(t, \varphi(t)) \\ \Rightarrow df(t, \varphi(t)) &= \left(\frac{\partial}{\partial t} f(t, \varphi(t)) + \frac{\partial}{\partial \varphi} f(t, \varphi(t)) f(t, \varphi(t)) \right) dt. \end{aligned}$$

Now consider again Eq. (10)

$$dX_t = \underbrace{f(t, X_t) dt + g(t, X_t) dW_t}_{=: U(t, X_t) dt},$$

where we can apply this procedure in an analogous sense to some $Y_t := U(t, X_t)$ with sufficiently smooth $U: [t_0, T] \times \mathbb{R} \rightarrow \mathbb{R}$:

$$\begin{aligned} dY_t &= dU(t, X_t) = \left(\frac{\partial}{\partial t} U(t, X_t) + \frac{\partial}{\partial x} U(t, X_t) \frac{dX_t}{dt} \right) dt \\ &= \frac{\partial}{\partial t} U(t, X_t) dt + \frac{\partial}{\partial x} U(t, X_t) dX_t \\ &\stackrel{(10)}{=} \frac{\partial}{\partial t} U(t, X_t) dt + \frac{\partial}{\partial x} U(t, X_t) (f(t, X_t) dt + g(t, X_t) dW_t) \\ &= \left(\frac{\partial}{\partial t} U(t, X_t) + \frac{\partial}{\partial x} U(t, X_t) f(t, X_t) \right) dt + \frac{\partial}{\partial x} U(t, X_t) g(t, X_t) dW_t \\ &=: \underline{L}^0 U(t, X_t) dt + \underline{L}^1 U(t, X_t) dW_t \end{aligned} \quad (27)$$

Intuitively, this seems reasonable and appears as a straightforward generalization of the chain rule to stochastic calculus. However, a formula like

$$dY_t = \underline{L}^0 U(t, X_t) dt + \underline{L}^1 U(t, X_t) \circ dW_t$$

is valid only for the Stratonovich integral ([Kloeden, 2011](#)). Itô presented the stochastic chain rule in a different way ([Itô, 1951](#)). For an SDE in the form of Eq. (10) interpreted in Itô sense and some general $Y_t = U(t, X_t)$ not necessarily defined as above, the differential dY_t is given as:

$$\begin{aligned} dY_t &= \left(\frac{\partial}{\partial t} U(t, X_t) + \frac{\partial}{\partial x} U(t, X_t) f(t, X_t) + \frac{1}{2} g(t, X_t)^2 \frac{\partial^2}{\partial x^2} U(t, X_t) \right) dt \\ &\quad + \frac{\partial}{\partial x} U(t, X_t) g(t, X_t) dW_t \\ &=: L^0 U(t, X_t) dt + L^1 U(t, X_t) dW_t. \end{aligned} \tag{28}$$

So, compared to the deterministic setting as well as the Stratonovich case, an additional term occurs in L^0 . Roughly speaking, it results from a Taylor series expansion of the term

$$\Delta Y := U(t + \Delta t, X_{t+\Delta t}) - U(t, X_t)$$

combined with some properties of the Wiener process such as $\mathbb{E}[\Delta W_t^2] \stackrel{(21)}{=} \Delta t$. These lead to the remainder $\frac{1}{2} g(t, X_t)^2 \frac{\partial^2}{\partial x^2} U(t, X_t)$ in Eq. (28), whereas other terms of higher order disappear in the qm-limit ([Itô, 1951](#); [Kloeden & Platen, 1992](#); [Kloeden, 2011](#)).

We stress that this chapter is intended to provide a survey and general understanding of the numerical handling of differential equations with noise terms. Since it is not the main topic of this thesis and of the presented publications, we will not go into the details required to prove the claims of Itô's lemma (Eq. (28)) and the related statements. A full coverage of these elements goes beyond the scope of this work, which in fact focuses on SDEs with noise types, where Itô and Stratonovich solutions coincide, see later below. The interested reader is referred to the provided citations for further information about the technical details.

As a practical example, we will illustrate the effect of either calculus on solving the SDE

$$\begin{aligned} dX_t &= a X_t dt + b X_t \circ dW_t, \\ X_0 &> 0 \text{ almost surely,} \end{aligned}$$

where $t \in [0, T]$ and $a, b \in \mathbb{R}$, i.e., $f(t, x) = ax$ and $g(t, x) = bx$ in Eq. (10). It describes the so-called *geometric Brownian motion* and is frequently used as a model of stock price behavior in financial mathematics ([Higham, 2001](#); [Hull, 2021](#)). Interpreted in the sense of Stratonovich, we can solve it like a deterministic equation:

$$\begin{aligned} dX_t &= a X_t dt + b X_t \circ dW_t \\ \Rightarrow \frac{1}{X_t} dX_t &= a dt + b \circ dW_t \end{aligned}$$

$$\begin{aligned}
\Rightarrow \int_0^t \frac{1}{X_s} dX_s &= \int_0^t a ds + \int_0^t b \circ dW_s \quad (\text{Stratonovich only!}) \\
\stackrel{(19)}{\Rightarrow} [\ln(X_s)]_0^t &= [as]_0^t + b \left(W_t - \underbrace{W_0}_{=0} \right) \\
\Rightarrow \ln(X_t) - \ln(X_0) &= at + bW_t \\
\Rightarrow \ln\left(\frac{X_t}{X_0}\right) &= at + bW_t \\
\Rightarrow X_t &= X_0 \exp(at + bW_t).
\end{aligned}$$

We have two options to solve the equation

$$\begin{aligned}
dX_t &= a X_t dt + b X_t dW_t, \\
X_0 &> 0 \text{ almost surely}
\end{aligned}$$

in the sense of Itô now. The first ansatz is given by a drift modification according to Eq. (25) and a resulting transformation into a Stratonovich SDE. With f and g from above, we obtain

$$\underline{f}(t, x) = f(t, x) - \frac{1}{2} g(t, x) \frac{\partial}{\partial x} g(t, x) = ax - \frac{1}{2} b^2 x. \quad (29)$$

The resulting Stratonovich SDE

$$dX_t = \underline{f}(t, X_t) dt + g(t, X_t) \circ dW_t = \left(a - \frac{1}{2} b^2\right) X_t dt + b X_t \circ dW_t \quad (30)$$

can then be solved analogously by means of deterministic calculus:

$$\begin{aligned}
\frac{1}{X_t} dX_t &= \left(a - \frac{1}{2} b^2\right) dt + b \circ dW_t \\
\Rightarrow \int_0^t \frac{1}{X_s} dX_s &= \int_0^t \left(a - \frac{1}{2} b^2\right) ds + \int_0^t b \circ dW_s \\
\stackrel{(19)}{\Rightarrow} [\ln(X_s)]_0^t &= \left[\left(a - \frac{1}{2} b^2\right) s\right]_0^t + b \left(W_t - \underbrace{W_0}_{=0}\right) \\
\Rightarrow \ln\left(\frac{X_t}{X_0}\right) &= \left(a - \frac{1}{2} b^2\right) t + bW_t \\
\Rightarrow X_t &= X_0 \exp\left(\left(a - \frac{1}{2} b^2\right) t + bW_t\right).
\end{aligned}$$

This shows that an SDE with the same coefficients has different solutions in general when interpreted as either an Itô or a Stratonovich SDE.

Alternatively, the Stratonovich transformation can be omitted in favor of Itô's lemma (Eq. (28)). We therefore apply an exponential approach and define

$$Y_t := U(t, X_t) := \ln(X_t), \text{ i.e., } U(t, x) = \ln(x).$$

It follows that

$$\frac{\partial}{\partial t} U(t, x) = 0, \quad \frac{\partial}{\partial x} U(t, x) = \frac{1}{x} \quad \text{and} \quad \frac{\partial^2}{\partial x^2} U(t, x) = -\frac{1}{x^2}.$$

With f and g from above, Itô's lemma (Eq. (28)) then yields

$$\begin{aligned} L^0 U(t, x) &= \frac{\partial}{\partial t} U(t, X_t) + \frac{\partial}{\partial x} U(t, X_t) f(t, X_t) + \frac{1}{2} g(t, X_t)^2 \frac{\partial^2}{\partial x^2} U(t, X_t) \\ &= 0 + \frac{1}{x} ax + \frac{1}{2} b^2 x^2 \left(-\frac{1}{x^2} \right) = a - \frac{1}{2} b^2, \\ L^1 U(t, x) &= \frac{\partial}{\partial x} U(t, X_t) g(t, X_t) = \frac{1}{x} bx = b, \end{aligned}$$

so that

$$dY_t = L^0 U(t, X_t) dt + L^1 U(t, X_t) dW_t = \left(a - \frac{1}{2} b^2 \right) dt + b dW_t. \quad (31)$$

Note that we had also obtained the term $a - \frac{1}{2} b^2$ after applying the Stratonovich drift modification in Eq. (29) and (30).

After using Itô's lemma (Eq. (28)), we are allowed to apply the integral to Eq. (31), which can be solved easily then:

$$\begin{aligned} \int_0^t 1 dY_s &= \int_0^t \left(a - \frac{1}{2} b^2 \right) ds + \int_0^t b dW_s \\ \stackrel{(18)}{\implies} Y_t - Y_0 &= \left(a - \frac{1}{2} b^2 \right) t + b \left(W_t - \underbrace{W_0}_{=0} \right) \\ \implies \ln(X_t) - \ln(X_0) &= \left(a - \frac{1}{2} b^2 \right) t + b W_t \\ \implies X_t &= X_0 \exp \left(\left(a - \frac{1}{2} b^2 \right) t + b W_t \right). \end{aligned}$$

This is of course the same result that we obtained when transforming the Itô SDE to a Stratonovich SDE in Eq. (30).

We conclude that the integral formulation by Itô and Stratonovich must be handled with care. An SDE can have different solutions depending on the selected concept. While both representations have their advantages, as stated above, integrating an SDE given in Itô form is not as intuitive as integrating a Stratonovich SDE, where the rules of deterministic calculus apply immediately. However, we have seen ways to transform the two types into each other, assuring that the computed solutions are consistent.

By default and if no further information is provided, an SDE is typically treated in the sense of Itô (Kloeden & Pearson, 1977). When aiming to solve such an SDE, the drift must either be modified to apply deterministic integration tricks, or Itô's lemma must be

applied to derive a hopefully easily solvable equivalent, as we have seen in the example of geometric Brownian motion. The existence and uniqueness theorem based on the conditions listed in Eq. (12)-(14) holds for either of the presented concepts.

Both the Itô and Stratonovich integral coincide if

$$\frac{\partial}{\partial x} g(t, x) = 0 \quad \forall (t, x) \in [t_0, T] \times \mathbb{R} \quad (32)$$

in the SDE Eq. (10). This follows directly from $\underline{f} = f$ in the Stratonovich drift transformation (Eq. (25)). Such a noise perturbation is called *additive noise*. Otherwise, it is referred to as *multiplicative noise* (Burrage et al., 2004; Fahrmeir, 1976; Kloeden & Platen, 1992; Kloeden, 2011; Kloeden & Platen, 1993).

In the dynamical whole-brain models considered in this thesis, the noise will always be additive. Additive noise frequently arises from fluctuations in experimental data but can also be observed in blood clotting systems and in the field of cellular energetics, for instance (Burrage et al., 2004; Fogelson, 1984; Veuthey & Stucki, 1987). We will however not exclude multiplicative noise in the following sections as this more general case plays a decisive role in the design of numerical methods for solving SDEs. Such approximative methods are needed, because explicitly solvable SDEs are rare in practical applications (Kloeden & Platen, 1993).

2.3 Numerical procedures for solving SDEs

We now proceed to the description of numerical methods for approximating moments and sample paths, or *trajectories*, of solutions to SDEs. The key technique to derive such schemes is often a Taylor series expansion of the exact solution with a corresponding truncation after a given order. However, the stochasticity in the SDEs and their solutions prevents an immediate application of the deterministic notions of stability, consistency and convergence. In search for other, noise-adapted definitions, we describe two concepts of convergence for numerical SDE solvers. We further discuss the role of Itô's lemma for the derivation of numerical methods, of which we present a few examples. Concrete stability analyses on SDEs and related method comparisons are beyond the scope of this thesis and can be found elsewhere (Acebrón et al., 2005; Higham, 2001).

2.3.1 Strong and weak convergence

There are two important definitions that apply to numerical solutions of SDEs: *strong* and *weak convergence*. Assume we are searching for the solution $X_t = X(t)$, $t \in [t_0, T]$, of an SDE in form of Eq. (10). The domain may be discretized via $0 \leq t_0 \leq t_1 \leq \dots \leq t_n = T$, such that

$$t_k = t_0 + k \Delta t \quad \forall k \in \{0, \dots, n\}$$

and $n \in \mathbb{N}$. Further assume that the numerical approximation of X_{t_k} is denoted by $\tilde{X}_k$. A numerical method is then said to have *strong order of convergence* equal to $\gamma > 0$ if

$$\exists C > 0, \text{ such that } \mathbb{E}[|\tilde{X}_k - X_{t_k}|] \leq C \Delta t^\gamma \quad \forall t_k \in [t_0, T]. \quad (33)$$

It is said to have *weak order of convergence* equal to $\beta > 0$ if for any polynomial P

$$\exists C_P > 0, \text{ such that } |\mathbb{E}[P(\tilde{X}_k)] - \mathbb{E}[P(X_{t_k})]| \leq C_P \Delta t^\beta \quad \forall t_k \in [t_0, T] \quad (34)$$

([Burrage et al., 2004](#); [Higham, 2001](#); [Kloeden & Platen, 1992](#); [Kloeden, 2011](#); [Kloeden & Platen, 1993](#)). While strong convergence is inferred from the mean of the errors, weak convergence is based on the error of the means, making it a weaker condition ([Higham, 2001](#); [Kloeden, 2011](#)). Indeed, recalling that every path $t \mapsto X_t(\omega)$ is continuous in t (see subchapter 2.1), we infer that the codomain of X can be written as

$$X_{[t_0, T]} = \left[\min_{t \in [t_0, T]} \{X_t\}, \max_{t \in [t_0, T]} \{X_t\} \right] =: [a, b]. \quad (35)$$

Since $P \in C^\infty[a, b]$ holds for every polynomial P , its derivative P' is also continuous and therefore bounded in $[a, b]$, i.e.,

$$\exists L_P > 0, \text{ such that } \|P'\|_{\infty, [a, b]} < L_P.$$

This gives

$$|P(x) - P(y)| < L_P |x - y| \quad \forall x, y \in [a, b] \quad (36)$$

by virtue of the *mean value theorem*. Consequently, the error of the means (weak convergence, Eq. (34)) is bounded by the mean of the errors (strong convergence, Eq. (33)):

$$\begin{aligned} |\mathbb{E}[P(\tilde{X}_k)] - \mathbb{E}[P(X_{t_k})]| &= |\mathbb{E}[P(\tilde{X}_k) - P(X_{t_k})]| \leq \mathbb{E}[|P(\tilde{X}_k) - P(X_{t_k})|] \\ &\stackrel{(36)}{<} \mathbb{E}[L_P |\tilde{X}_k - X_{t_k}|] = L_P \mathbb{E}[|\tilde{X}_k - X_{t_k}|], \end{aligned} \quad (37)$$

indicating that strong convergence implies weak convergence, whereas the opposite is not true in general ([Kloeden, 2011](#)). Note that we implicitly assumed that the approximation satisfies $\tilde{X}_k < \infty \quad \forall k \in \{0, \dots, n\}$ and that without loss of generality

$$\tilde{a} := \min_{k \in \{0, \dots, n\}} \tilde{X}_k > a \quad \text{and} \quad \tilde{b} := \max_{k \in \{0, \dots, n\}} \tilde{X}_k < b,$$

so that Eq. (36) can be applied in Eq. (37). Otherwise, the interval $[a, b]$ in Eq. (35) would have to be modified accordingly, leaving the central assertion inviolate.

Strong or *path-wise solutions* are required in applications where it is crucial that the trajectories of the numerical approximations are close, in a strong sense, to those of the exact solution of a given SDE ([Burrage et al., 2004](#); [Higham, 2001](#)). Such direct simulations of solution paths play an important role for testing statistical estimators and for studying the simultaneous motion of ensembles of particles via probabilistic models ([Burrage et al., 2004](#); [Kloeden & Platen, 1993](#)). The fields of applicability range from theoretical considerations of stochastic flows on topological manifolds like spheres or tori ([Baxendale, 1986](#); [Carverhill et al., 1986](#)) over physical phase transitions and synchronization patterns ([Lythe, 1995](#); [Popovych et al., 2013](#)) to biologically motivated population dynamics in brain models ([Burrage et al., 2004](#); [Kuske, 2000](#); [Popovych et al.,](#)

[2019](#)). All these models have in common that the behavior of every single considered unit like, e.g., an oscillator or a molecule, can have significant influence on the population dynamics. This underscores the need for strong numerical solutions.

In other scientific contexts, however, only qualitative information about the solution is of interest. This includes ensemble averages, expected values or higher moments as well as other characteristics. In financial mathematics, for instance, averaged reactions to price fluctuations on an economic market can be of high relevance ([Higham, 2001](#); [Hull, 2021](#)). It may suffice in such scenarios to approximate a probabilistic quantity such as $\mathbb{E}[P(X_T)]$ induced by the solution X of an SDE at the end time T for certain types of functions denoted by P ([Kloeden & Platen, 1993](#)).

In sum, numerical methods guaranteeing strong convergence are needed for problems involving direct simulations, where individual trajectories of, for example, a brain region's activity, can provide important insights into the collective behavior ([Burrage et al., 2004](#)). Weak convergence in turn often relates to the mean of the solution and can be applied for generating frequency histograms or computing moments, i.e., when less strict conditions are imposed on a numerical approximation. The final choice depends on the problem at hand and the disciplinary requirements of the analyses that a scientist wants to conduct. In the next section, we will describe a few numerical procedures suited for solving the SDEs considered in the publications included in this thesis. We will also briefly allude to the fact that the application of numerical methods for strong solutions is more expensive from a computational point of view. It requires the calculation of stochastic integrals, which may be approximated when using methods for weak solutions ([Burrage et al., 2004](#); [Kloeden & Platen, 1993](#)).

2.3.2 Examples of numerical solvers

A common way to derive numerical schemes for solving SDEs is to truncate a (stochastic) Taylor series expansion after a certain order as in the deterministic setting. The most prominent example of the latter scenario is the *Euler method*. Given a deterministic initial value problem originating from Eq. (26), i.e.,

$$\begin{aligned}\varphi'(t) &= f(t, \varphi(t)), \\ \varphi(t_0) &= \varphi_0 \in \mathbb{R},\end{aligned}$$

it can be derived from considering the corresponding integral equation

$$\varphi(t) = \varphi_0 + \int_{t_0}^t f(s, \varphi(s)) ds, \text{ where } t \in [t_0, T]. \quad (38)$$

Equation (38) also holds on every subinterval $[t_k, t_{k+1}] \subseteq [t_0, T]$, meaning that

$$\varphi(t_{k+1}) = \varphi(t_k) + \int_{t_k}^{t_{k+1}} f(s, \varphi(s)) ds.$$

By fixing the argument of f at $s = t_k$ (as in a trivial Taylor series around $s = t_k$ with only one summand), we obtain the approximation

$$\begin{aligned}\varphi(t_{k+1}) &\approx \varphi(t_k) + \int_{t_k}^{t_{k+1}} f(t_k, \varphi(t_k)) ds = \varphi(t_k) + f(t_k, \varphi(t_k)) \int_{t_k}^{t_{k+1}} 1 ds \\ &= \varphi(t_k) + f(t_k, \varphi(t_k)) (t_{k+1} - t_k) = \varphi(t_k) + f(t_k, \varphi(t_k)) \Delta t,\end{aligned}$$

which describes the well-known *Euler method*

$$\tilde{X}_{k+1} = \tilde{X}_k + f(t_k, \tilde{X}_k) \Delta t, \quad (39)$$

a first order scheme in the deterministic setting. The same approach can be pursued for the stochastic initial value problem resulting from Eq. (10), i.e.,

$$\begin{aligned}dX_t &= f(t, X_t) dt + g(t, X_t) dW_t, \\ X(t_0) &= X_{t_0}.\end{aligned}$$

Analogously, the integral equation Eq. (11)

$$X_t = X_{t_0} + \int_{t_0}^t f(s, X_s) ds + \int_{t_0}^t g(s, X_s) dW_s.$$

also holds on $[t_k, t_{k+1}]$, i.e.,

$$X_{t_{k+1}} = X_{t_k} + \int_{t_k}^{t_{k+1}} f(s, X_s) ds + \int_{t_k}^{t_{k+1}} g(s, X_s) dW_s.$$

Fixing the arguments of both f and g at $s = t_k$ yields the approximation

$$\begin{aligned}X_{t_{k+1}} &\approx X_{t_k} + \int_{t_k}^{t_{k+1}} f(t_k, X_{t_k}) ds + \int_{t_k}^{t_{k+1}} g(t_k, X_{t_k}) dW_s \\ &= X_{t_k} + f(t_k, X_{t_k}) \int_{t_k}^{t_{k+1}} 1 ds + g(t_k, X_{t_k}) \int_{t_k}^{t_{k+1}} 1 dW_s \\ &= X_{t_k} + f(t_k, X_{t_k})(t_{k+1} - t_k) + g(t_k, X_{t_k})(W_{t_{k+1}} - W_{t_k}) \\ &= X_{t_k} + f(t_k, X_{t_k}) \Delta t + g(t_k, X_{t_k}) \Delta W_{t_k},\end{aligned}$$

where $\Delta W_{t_k} \sim \mathcal{N}_{0, \Delta t}$ according to Eq. (5) (Higham, 2001; Kloeden, 2011). On a computer, it is implemented as

$$\tilde{X}_{k+1} = \tilde{X}_k + f(t_k, \tilde{X}_k) \Delta t + g(t_k, \tilde{X}_k) \sqrt{\Delta t} \eta_{t_k}, \quad (40)$$

where $\eta_{t_k} \sim \mathcal{N}_{0,1}$ is obtained from a random number generator. This is possible since

$$\text{Var}(aX) = a^2 \text{Var}(X) \quad \forall a \in \mathbb{R}$$

holds for any random variable X , so that $\sqrt{\Delta t} \eta_{t_k} \sim \mathcal{N}_{0, \Delta t}$. Equation (40) describes the stochastic generalization of the Euler scheme (Eq. (39)) introduced in the 1950s

([Maruyama, 1955](#)). It is also referred to as the *Euler-Maruyama (EM) method* ([Burrage et al., 2004](#); [Higham, 2001](#)).

We recall that for every time point t_k , the solution X_{t_k} and the approximation $\tilde{X}_k$ are random variables, and that the implementation of the described procedure leads, strictly speaking, to an approximation $\tilde{X}_k(\omega)$ of $X_{t_k}(\omega)$, which is taken from one possible path

$$\{X_t(\omega) \mid t \in [t_0, T]\}, \quad \omega \in \Omega,$$

of the solution.

The EM method reaches an order of $\gamma = \frac{1}{2}$ and $\beta = 1$ for strong and weak convergence, respectively ([Burrage et al., 2004](#); [Fahrmeir, 1976](#); [Kloeden & Platen, 1992](#); [Kloeden, 2011](#); [Kloeden & Platen, 1993](#); [Rümelin, 1982](#)). Looking into the provided references and those therein, the interested reader will find the following: When deriving the (strong) convergence order of a numerical method for SDEs, many authors do not immediately show that $\mathbb{E}[|\tilde{X}_k - X_{t_k}|] \leq C \Delta t^\gamma$ (Eq. (33)) holds, but instead prove that $\mathbb{E}[|\tilde{X}_k - X_{t_k}|^2]$ is bounded by some power of the time step Δt . This detour via qm-convergence (Eq. (16)) has proven practical for confirming upper bounds and can easily be related to the original definition of strong convergence (Eq. (33)) with help of the *Cauchy-Schwarz (CS) inequality*:

$$\begin{aligned} \mathbb{E}[|\tilde{X}_k - X_{t_k}|] &= |\mathbb{E}[|\tilde{X}_k - X_{t_k}|]| \leq_{\text{CS}} \left(\mathbb{E}[|\tilde{X}_k - X_{t_k}|^2] \right)^{\frac{1}{2}} \underbrace{(\mathbb{E}[1^2])^{\frac{1}{2}}}_{=1} \\ &\Rightarrow (\mathbb{E}[|\tilde{X}_k - X_{t_k}|])^2 = |\mathbb{E}[|\tilde{X}_k - X_{t_k}|]|^2 \leq \mathbb{E}[|\tilde{X}_k - X_{t_k}|^2] \end{aligned}$$

([Kloeden, 2011](#)). We stress that in the general case, where no further information about the drift f and amplitude g is given, the strong order $\gamma = \frac{1}{2}$ for the EM method is lower than for its deterministic counterpart (Eq. (39)). However, it can be improved by retaining more terms in the Taylor expansion as done for the so-called *Milstein method*, for example ([Mil'shtejn, 1975](#)). It can be derived as follows ([Kloeden, 2011](#)): Consider an SDE in integral form (Eq. (11)), i.e.,

$$X_t = X_{t_0} + \int_{t_0}^t f(s, X_s) ds + \int_{t_0}^t g(s, X_s) dW_s,$$

and Itô's lemma (Eq. (28))

$$dY_t = dU(t, X_t) = L^0 U(t, X_t) dt + L^1 U(t, X_t) dW_t$$

for some $Y_t := U(t, X_t)$ with $U: [t_0, T] \times \mathbb{R} \rightarrow \mathbb{R}$, $U \in C^2([t_0, T] \times \mathbb{R})$. We recall that

$$L^0 U(t, X_t) = \frac{\partial}{\partial t} U(t, X_t) + \frac{\partial}{\partial x} U(t, X_t) f(t, X_t) + \frac{1}{2} g(t, X_t)^2 \frac{\partial^2}{\partial x^2} U(t, X_t),$$

$$L^1 U(t, X_t) = \frac{\partial}{\partial x} U(t, X_t) g(t, X_t).$$

The corresponding integral form of Itô's lemma (Eq. (28)) reads

$$U(t, X_t) = U(t_0, X_{t_0}) + \int_{t_0}^t L^0 U(s, X_s) ds + \int_{t_0}^t L^1 U(s, X_s) dW_s. \quad (41)$$

This equation holds in particular if we set $U = f$:

$$\begin{aligned} f(t, X_t) &= f(t_0, X_{t_0}) + \int_{t_0}^t L^0 f(s, X_s) ds + \int_{t_0}^t L^1 f(s, X_s) dW_s \\ \Rightarrow \int_{t_0}^t f(s, X_s) ds &= \int_{t_0}^t \left(f(t_0, X_{t_0}) + \int_{t_0}^s L^0 f(\tau, X_\tau) d\tau + \int_{t_0}^s L^1 f(\tau, X_\tau) dW_\tau \right) ds. \end{aligned} \quad (42)$$

Similarly, we can also set $U = g$:

$$\begin{aligned} g(t, X_t) &= g(t_0, X_{t_0}) + \int_{t_0}^t L^0 g(s, X_s) ds + \int_{t_0}^t L^1 g(s, X_s) dW_s \\ \Rightarrow \int_{t_0}^t g(s, X_s) dW_s &= \int_{t_0}^t \left(g(t_0, X_{t_0}) + \int_{t_0}^s L^0 g(\tau, X_\tau) d\tau + \int_{t_0}^s L^1 g(\tau, X_\tau) dW_\tau \right) dW_s. \end{aligned} \quad (43)$$

Inserting the results from Eq. (42) and (43) into the SDE in integral form (Eq. (11)), we obtain

$$\begin{aligned} X_t &= X_{t_0} + f(t_0, X_{t_0}) \int_{t_0}^t 1 ds + g(t_0, X_{t_0}) \int_{t_0}^t 1 dW_s \\ &\quad + \int_{t_0}^t \int_{t_0}^s L^0 f(\tau, X_\tau) d\tau ds + \int_{t_0}^t \int_{t_0}^s L^1 f(\tau, X_\tau) dW_\tau ds \\ &\quad + \int_{t_0}^t \int_{t_0}^s L^0 g(\tau, X_\tau) d\tau dW_s + \int_{t_0}^t \int_{t_0}^s L^1 g(\tau, X_\tau) dW_\tau dW_s. \end{aligned} \quad (44)$$

Retaining the first three summands of this expansion leads to the EM method (Eq. (40)). The double-integrals can be regarded as remainders. In principle, all of them could be treated as starting points for further expansions now. The Milstein method, for instance, focuses on the purely stochastic double-integral

$$\int_{t_0}^t \int_{t_0}^s L^1 g(\tau, X_\tau) dW_\tau dW_s.$$

Setting $U = L^1 g = \frac{\partial}{\partial x} g$ in Eq. (41), we obtain

$$L^1 g(t, X_t) = L^1 g(t_0, X_{t_0}) + \int_{t_0}^t L^0 L^1 g(s, X_s) ds + \int_{t_0}^t L^1 L^1 g(s, X_s) dW_s \quad (45)$$

for the integrand.

With this, the purely stochastic double-integral can be expressed as

$$\begin{aligned}
& \int_{t_0}^t \int_{t_0}^s L^1 g(\tau, X_\tau) dW_\tau dW_s \\
& \stackrel{(45)}{=} \int_{t_0}^t \int_{t_0}^s \left(L^1 g(t_0, X_{t_0}) + \int_{t_0}^\tau L^0 L^1 g(\rho, X_\rho) d\rho + \int_{t_0}^\tau L^1 L^1 g(\rho, X_\rho) dW_\rho \right) dW_\tau dW_s \\
& = L^1 g(t_0, X_{t_0}) \int_{t_0}^t \int_{t_0}^s 1 dW_\tau dW_s + \int_{t_0}^t \int_{t_0}^s \int_{t_0}^\tau L^0 L^1 g(\rho, X_\rho) d\rho dW_\tau dW_s \\
& \quad + \int_{t_0}^t \int_{t_0}^s \int_{t_0}^\tau L^1 L^1 g(\rho, X_\rho) dW_\rho dW_\tau dW_s, \tag{46}
\end{aligned}$$

where the remainders feature even three integrals. Inserting the last expression from Eq. (46) into Eq. (44) yields

$$\begin{aligned}
X_t &= X_{t_0} + f(t_0, X_{t_0}) \int_{t_0}^t 1 ds + g(t_0, X_{t_0}) \int_{t_0}^t 1 dW_s + L^1 g(t_0, X_{t_0}) \int_{t_0}^t \int_{t_0}^s 1 dW_\tau dW_s \\
& \quad + \int_{t_0}^t \int_{t_0}^s L^0 f(\tau, X_\tau) d\tau ds + \int_{t_0}^t \int_{t_0}^s L^1 f(\tau, X_\tau) dW_\tau ds \\
& \quad + \int_{t_0}^t \int_{t_0}^s L^0 g(\tau, X_\tau) d\tau dW_s + \int_{t_0}^t \int_{t_0}^s \int_{t_0}^\tau L^0 L^1 g(\rho, X_\rho) d\rho dW_\tau dW_s \\
& \quad + \int_{t_0}^t \int_{t_0}^s \int_{t_0}^\tau L^1 L^1 g(\rho, X_\rho) dW_\rho dW_\tau dW_s,
\end{aligned}$$

where the first four summands are kept to define the Milstein method ([Kloeden & Platen, 1992](#); [Mil'shtejn, 1975](#)). It can be shown that the included double-integral can be expressed as

$$\int_{t_0}^t \int_{t_0}^s 1 dW_\tau dW_s = \frac{1}{2} (\Delta W_t^2 - \Delta t)$$

([Kloeden, 2011](#)), so that the updating rule for the Milstein method reads

$$\begin{aligned}
& \tilde{X}_{k+1} \\
& = \tilde{X}_k + f(t_k, \tilde{X}_k) \Delta t + g(t_k, \tilde{X}_k) \Delta W_{t_k} + \frac{1}{2} L^1 g(t_k, \tilde{X}_k) (\Delta W_{t_k}^2 - \Delta t) \\
& = \tilde{X}_k + f(t_k, \tilde{X}_k) \Delta t + g(t_k, \tilde{X}_k) \Delta W_{t_k} + \frac{1}{2} \frac{\partial}{\partial x} g(t_k, \tilde{X}_k) g(t_k, \tilde{X}_k) (\Delta W_{t_k}^2 - \Delta t), \tag{47}
\end{aligned}$$

where $\Delta W_{t_k} \sim \mathcal{N}_{0, \Delta t}$ is implemented as $\sqrt{\Delta t} \eta_{t_k}$ with $\eta_{t_k} \sim \mathcal{N}_{0,1}$. This numerical integration scheme converges with strong and weak order $\beta = \gamma = 1$ ([Burrage et al., 2004](#); [Higham, 2001](#); [Kloeden, 2011](#); [Kloeden & Platen, 1993](#)). It has no deterministic analogue. Note that in the case of additive noise, i.e., $\frac{\partial}{\partial x} g(t, x) \equiv 0$, the last summand

disappears, and the Milstein method coincides with the EM method (Eq. (40)), which then also fulfills $\gamma = 1$ (strong) for such types of SDEs.

An alternative is given by the stochastic generalization of the *Heun method* ([Rümelin, 1982](#)). It does not contain any derivatives of the coefficients f and g :

$$\begin{aligned} \tilde{X}_{k+1} = \tilde{X}_k &+ \frac{\Delta t}{2} \left[f(t_k, \tilde{X}_k) + f(t_k + \Delta t, \tilde{X}_k + f(t_k, \tilde{X}_k) \Delta t + g(t_k, \tilde{X}_k) \Delta W_{t_k}) \right] \\ &+ \frac{\Delta W_{t_k}}{2} \left[g(t_k, \tilde{X}_k) + g(t_k + \Delta t, \tilde{X}_k + f(t_k, \tilde{X}_k) \Delta t + g(t_k, \tilde{X}_k) \Delta W_{t_k}) \right]. \end{aligned} \quad (48)$$

As in the methods above, $\Delta W_{t_k} \sim \mathcal{N}_{0, \Delta t}$ is usually implemented as $\sqrt{\Delta t} \eta_{t_k}$ with $\eta_{t_k} \sim \mathcal{N}_{0,1}$. The convergence order is $\beta = \gamma = 1$ ([Kloeden, 2011](#); [Mannella, 2025](#); [McShane, 1974](#)), which is lower than the order 2 reached for ODEs in deterministic problems. One way to construct methods of higher order is to consider more terms of the Taylor-like expansion seen for the Milstein method, for example. Such a strategy may however be accompanied by some technical challenges impeding its applicability. That is why we return to numerical approximations of higher order in subchapter 8.2, where we thoroughly discuss the selection of appropriate solvers.

In summary, we have seen that SDEs differ substantially from ODEs in terms of their behavior and solvability. The potential unboundedness of the noise increments in the processes modeled via SDEs prevents a straightforward application of Riemannian calculus and requires the definition of stochastic integrals like in the sense of Itô or Stratonovich. While both concepts equal for additive noise, attention has to be paid in the more general case of multiplicative noise. Transformations of the drift term in the SDE may be necessary then to ensure consistency in the solutions. Numerical methods to solve SDEs can be derived from both perspectives by applying the respective stochastic chain rule in combination with a Taylor-like expansion. The quality of numerical approximations can be assessed via expected values in the notion of weak and strong convergence, which reflects yet another departure from the deterministic setting. Suited stochastic adaptations of common deterministic methods tend to have a lower convergence order for SDEs than their noise-free variants do have for ODEs.

Having glanced at the underlying principles of SDEs, we can now proceed to some concrete dynamical models and their optimization.

3 Dynamical models of brain activity

There exists a plenitude of dynamical models of brain activity in the literature. These simulation models vary in their attentional focus from microscopic cells to entire (networks of) brain regions, the number of considered state variables as well as the methodological concept regarding how and which properties of brain activity are simulated. As indicated earlier, we work with dynamical whole-brain models which mainly describe brain activity in terms of interactions between entire brain regions defined by a given brain atlas. Besides the measurement and modeling of region-wise BOLD signal fluctuations, there are also other concepts of whole-brain activity based on electrical impulses transmitted across brain regions, for instance. All such approaches have in common that they focus on collective dynamics and thereby complement studies on the level of individual neuronal cells. The presence of billions of neurons in the human brain let the usage of brain atlases emerge as a dimensionality reduction rendering whole-brain modeling tractable.

However, the field of mathematical neuroscience has its roots in cellular modeling, which attracted increased attention following the introduction of the biologically inspired *Hodgkin-Huxley (HH) model of neuronal spiking* in the early 1950s ([Hodgkin & Huxley, 1952](#)). Given the significant impact of this model, we will briefly describe this approach with a minimum of biological detail before shifting our attention to a few of the most prominent whole-brain models.

3.1 Cellular modeling / Hodgkin-Huxley (HH) model

The HH model has originally been designed for the squid brain and describes the generation of *action potentials*. These are brief electrical impulses of large amplitude that are considered a means to communicate signals between neurons ([Karbowski, 2014](#)). In accordance with that, the HH model describes the temporal change of voltage across a neuron's membrane. The relevant state variable representing the *membrane voltage* or *potential* (in millivolts, mV) is denoted by $V = V(t) \in \mathbb{R}$, where $t \geq 0$. Its value is influenced by the charge of ions inside and outside the neuronal cell. The presence of ions on either side depends on proteins that act as channels or pores in the membrane and regulate the in-/outflow of ions. For the HH model, the most relevant channels are those conducting sodium (Na^+) and potassium (K^+) ions. Apart from those ion fluxes, a neuron can also receive an external input from another neuron via a *synapse*. Synapses are located at the end of axons (*axon terminals*) and reflect the junctions between neurons for signal transmission ([Laughlin & Sejnowski, 2003](#)). When the *synaptic* input I_{ext} (in nanoamperes, nA) is zero, all ion channels are practically closed and the majority of ions inside the cell has a lower charge relative to those outside. The membrane voltage then tends to remain constant at a resting potential $V(t) = V_{\text{rest}} < 0$. However, when a neuron receives a synaptic input, its membrane voltage V begins to increase. As soon as it reaches a so-called *spiking threshold*, the sodium channels open as a biological consequence and allow for a rapid influx of positively charged Na^+ ions into the neuron's interior ([Karbowski, 2014](#)). The resulting sharp increase of V constitutes the generation of an action potential, which eventually propagates along an axon and then spreads to other neurons through synapses – neural communication via electrical signals. With some delay, on the one hand, the sodium channels switch to an inactive state, while, on the other hand, the potassium channels open. The latter initiate a flow of positively charged K^+ ions out of the neuron's interior. It opposes the positive Na^+ current into the cell and thereby slows down the increase of V and eventually leads to its decay to V_{rest} . It takes around 2 to 3 milliseconds (ms) for V , starting at V_{rest} , to generate an action potential and return to

V_{rest} (Karbowski, 2014). Hodgkin and Huxley suggested to model the described process in the following way (Hodgkin & Huxley, 1952):

On the one hand, the total membrane current I_{total} is given as a scalar multiple of the temporal derivative of the membrane voltage V , i.e.,

$$I_{\text{total}}(t) = \mathcal{C} \frac{d}{dt} V(t). \quad (49)$$

$\mathcal{C}$ is a biological constant denoting the membrane's *electric capacitance*, i.e., its ability to store electric charge. It is measured in nanoampere milliseconds per millivolt ($\frac{\text{nA ms}}{\text{mV}}$). On the other hand, I_{total} can be expressed as

$$I_{\text{total}}(t) = I_{\text{Na}}(t) + I_{\text{K}}(t) + I_{\text{L}}(t) + I_{\text{ext}}(t), \quad (50)$$

which is the sum of the sodium, potassium, *leaky* (see below) and external currents, respectively. Equating Eq. (49) and (50) yields

$$\frac{d}{dt} V(t) = \frac{1}{\mathcal{C}} (I_{\text{Na}}(t) + I_{\text{K}}(t) + I_{\text{L}}(t) + I_{\text{ext}}(t)). \quad (51)$$

Splitting the currents into biological components allows for a reformulation of Eq. (51) as a set of non-linear ODEs:

$$\begin{aligned} \frac{d}{dt} V(t) &= \frac{1}{\mathcal{C}} \left(\underbrace{-g_{\text{Na}}(t) (V(t) - V_{\text{Na}})}_{=I_{\text{Na}}(t)} - \underbrace{g_{\text{K}}(t) (V(t) - V_{\text{K}})}_{=I_{\text{K}}(t)} - \underbrace{g_{\text{L}} (V(t) - V_{\text{L}})}_{=I_{\text{L}}(t)} + I_{\text{ext}}(t) \right) \\ &= \frac{1}{\mathcal{C}} \left(\underbrace{-\overline{g_{\text{Na}}} m(t)^3 h(t) (V(t) - V_{\text{Na}})}_{=I_{\text{Na}}(t)} - \underbrace{\overline{g_{\text{K}}} n(t)^4 (V(t) - V_{\text{K}})}_{=I_{\text{K}}(t)} - \underbrace{\overline{g_{\text{L}}} (V(t) - V_{\text{L}})}_{=I_{\text{L}}(t)} + I_{\text{ext}}(t) \right) \end{aligned} \quad (52)$$

$$\frac{d}{dt} v(t) = \alpha_v(V(t)) (1 - v(t)) - \beta_v(V(t)) v(t), \quad (53)$$

where $v \in \{m, h, n\}$ and $m, h, n: \mathbb{R} \rightarrow \mathbb{R}$ denote time-dependent *gating variables* (see below). Due to a lack of stochastic terms, we omit a reformulation in integral form. Equation (52) describes the temporal evolution of the membrane voltage V . Here, $g_{\text{Na}}, g_{\text{K}}: \mathbb{R} \rightarrow \mathbb{R}$ and $\overline{g_{\text{L}}} = g_{\text{L}} \in \mathbb{R}$ denote the sodium, potassium and so-called *leak* conductance through the cell membrane, respectively (Karbowski, 2014). The latter is constant and summarizes other ions' minor contributions, e.g., Ca^{2+} . It reflects a leaky, permanently open channel. The values of g_{Na} and g_{K} in turn depend on the maximal conductance constants $\overline{g_{\text{Na}}}, \overline{g_{\text{K}}} \in \mathbb{R}$ as well as on the gating variables m, h, n . Similarly, $V_{\text{Na}}, V_{\text{K}}, V_{\text{L}} \in \mathbb{R}$ are ion-specific voltage constants, so-called *Nernst potentials*, while $I_{\text{ext}} \in \mathbb{R}$ denotes the synaptic input current. For brevity, we largely avoid the physical units of the mentioned quantities here. The gating variables regulate the transport of ions from and into the cell. They are defined to approach zero if $V(t) \approx V_{\text{rest}} (\approx V_{\text{L}})$, so that a value

of $I_{\text{ext}} = 0$ in this case leads to $\frac{d}{dt}V(t) \approx 0$ as explained above. Their precise behavior is summarized in Eq. (53). They share a common structure except for the specific values α_v, β_v for $v \in \{m, h, n\}$ that all depend on V in a different non-linear manner, for instance,

$$\alpha_h(V(t)) = 0.07 \exp\left(\frac{V(t)}{20}\right) \text{ and } \beta_h(V(t)) = \left(\exp\left(\frac{V(t) + 30}{10}\right) + 1\right)^{-1},$$

see ([Hodgkin & Huxley, 1952](#); [Karbowksi, 2014](#)). There exist different definitions in the literature, because Hodgkin and Huxley originally defined V as the displacement of the membrane voltage from its resting value V_{rest} , while other researchers treat it as the voltage as such. Slight adaptations are necessary then.

Note that in the model, there are two gating variables (m, h) for the sodium channels and only one for the potassium channels (n). The reason is that the sodium channels are not merely open or closed like potassium channels are but also switch between an active and inactive state. The interested reader is referred to related works for deeper explanations of the biological details including the selection, values and units of specific constants in the model ([Dayan & Abbott, 2001](#); [Hodgkin & Huxley, 1952](#); [Kandel et al., 2000](#); [Karbowksi, 2014](#)).

We summarize that four ODEs describe the voltage dynamics of neurons influenced by the kinetics of primarily sodium and potassium channels located on the neuron's membrane. The consideration of conductance-based biophysical models of the HH type is firmly established in mathematical neuroscience ([Breakspear et al., 2003](#); [Honey et al., 2007](#); [Popovych & Tass, 2018](#)). Such adaptations of the HH model sometimes incorporate more types of ion channels rendering the model more realistic from one side, but also computationally expensive from another side ([De Schutter & Bower, 1994](#); [Koch & Segev, 1989](#)). Conversely, there also exist numerous simplifications of the HH model that reduce the number of considered state variables ([Izhikevich, 2003](#); [Morris & Lecar, 1981](#)) and/or neglect biological realism for the sake of a more phenomenological approach as in the *FitzHugh-Nagumo spiking model*, for instance ([Ghosh et al., 2008](#); [Kuske, 2000](#)). Very popular are so-called *Integrate-and-Fire models* ([Abbott, 1999](#); [Brunel & Latham, 2003](#)). In the latter, linear ODEs are considered, and an action potential is said to be generated when the membrane voltage V reaches a given threshold. Afterwards, it is manually reset to $V \leq V_{\text{rest}}$ without accounting for other biological factors like synaptic input currents or the deactivation of ion channels ([Karbowksi, 2014](#)). Such models can often be solved analytically and do not require numerical solution strategies. It is a matter of problem-dependent user preference whether computationally expensive, biologically realistic models or simpler phenomenological approaches are applied. All in all, the HH model is nowadays described as the first example that the theory of differential equations can be useful in neuroscience, where it ushered in the era of *computational neuroscience*. At the same time, it is praised as one of the most impactful models in the entire research field ([Kandel et al., 2000](#); [Karbowksi, 2014](#)).

3.2 Neural population models

The human brain contains approximately 10^{10} neurons and far more synapses. Each neuron is connected to around 10^4 other neurons ([Karbowksi, 2014](#); [Laughlin & Sejnowski, 2003](#)). That is why in a whole-brain modeling endeavor, the sheer number of cells involved is simply too vast for any approach starting at the single-cell level to be tractable ([Wilson & Cowan, 1972](#)). Therefore, more attention has been paid to the concept

of brain regions and atlases. The activity simulated by whole-brain models, interpreted as a proxy for collective neuronal firing, can be studied and compared across brain regions and multiple subjects. As indicated in the beginning of chapter 3, the notion of brain activity as such may thereby have several interpretations and is not limited to the concept of BOLD signal fluctuations. In fact, the slow BOLD changes are considered a response to much faster neural dynamics such as the firing of action potentials or synaptic gating activities regulating the flux of ions (see *neurovascular coupling* in section 1.1.4). To simulate such properties, *neural mass* or *neural population models* can be very useful ([Freeman, 1975](#)). A central term in this setting is *neural synchronization* since a coherent electrical activity like, for example, a synchronized generation of action potentials by at least 10^6 neurons at once, can generate measurable potentials and magnetic fields outside the brain ([Pikovsky et al., 2001](#); [Singer, 1999](#)). *Electroencephalography* (EEG) and *magnetoencephalography* (MEG) provide the technical, clinical means to measure these types of brain activity via placing electrodes directly on the scalp and using magnetic field sensor helmets, respectively. When neurons are desynchronized in their activity, only random noise will be measured. This implies that the presence of distinct, measurable signals coincides with neural synchronization. The presence of a strong coherence in turn led researchers to the assumption that the ensemble activity is sufficiently close to the mean, so that the inherent variance can be discarded ([Breakspear, 2017](#)). Neural mass models are indeed based on this reasoning and therefore approximate the mean activity of entire brain regions, unlike cellular models. This dramatically reduces the number of considered variables and allows, for example, multiple interacting local neural populations to be modeled by a relatively small number of equations, each describing the mean activity of a neural population ([Breakspear, 2017](#); [Lopes da Silva et al., 1974](#)).

3.2.1 Wilson-Cowan (WC) model

One of the simplest population models with two neural masses is the *Wilson-Cowan (WC) model of spatially localized neural populations* ([Solodkin et al., 2018](#); [Wilson & Cowan, 1972](#)). Initially introduced in the 1970s, it gained increasing popularity, and its adaptations are frequently applied in modern works related to brain modeling ([Deco et al., 2009](#); [Domhof et al., 2022](#)). The model separately considers the activities of the *excitatory* and *inhibitory* subpopulation (E and I , respectively) within a large ensemble of neurons consisting of these two major classes, which are determined by the type of synapses they form with other neurons ([Karbowski, 2014](#)). Excitatory synapses transmit action potentials from a presynaptic neuron to elevate the membrane voltage of the postsynaptic cell, which can be another neuron or a muscle cell, for instance. Such an output fosters the generation of an action potential or another activity in the postsynaptic cell, cf. the mechanism described in the HH model. Due to synaptic failures, however, the actual input arriving at the target cell can be likely lower, which is why the term *excitatory postsynaptic potential* (EPSP) is used to distinguish it from the presynaptic action potentials originating from neural firing ([Laughlin & Sejnowski, 2003](#); [Purves et al., 2018](#)). Inhibitory synapses in turn have the opposite function and make action potential generations in the receiving cell less likely. Here, the analogous expression *inhibitory postsynaptic potential* (IPSP) describes the arriving input. In general, a postsynaptic cell receives input from various excitatory and inhibitory sources. Imbalances in favor of the EPSP prompt the generation of action potentials as soon as the membrane voltage exceeds a given threshold ([Purves et al., 2018](#)).

As indicated in section 1.1.4, the generation of action potentials is also known as neural firing. In line with that, *firing rates* describe the proportion of cells firing within a given unit of time. The WC model is based on this phenomenon and describes the average firing rates of the excitatory and inhibitory neurons within a brain region as the temporal derivatives of their (dimensionless) activities E and I . An underlying notion of this modeling approach is that in isolation, the activity of an ensemble of (excitatory) neurons decays exponentially and can be approximated by the following ODE:

$$\frac{d}{dt}E(t) = \frac{1}{\mu}(-E(t) + \Phi(E(t))), \quad t \geq 0,$$

where $\mu > 0$ is a biological constant related to the decay time (in milliseconds, ms) and $\Phi: \mathbb{R} \rightarrow \mathbb{R}$ is a response function, typically in sigmoid shape. Further discussions about the origins of the sigmoid shape and its purpose in such applications can be found in related works ([Deco et al., 2009](#); [Moran et al., 2013](#); [Wilson & Cowan, 1973](#)). Based on that, the WC model considers two neural populations, whose activities can be described as follows:

$$\frac{d}{dt}E(t) = \frac{1}{\mu_E}(-E(t) + \Phi(w_{EE} E(t) - w_{EI} I(t) + J)), \quad (54)$$

$$\frac{d}{dt}I(t) = \frac{1}{\mu_I}(-I(t) + \Phi(w_{IE} E(t))). \quad (55)$$

The excitatory population excites itself and the inhibitory one with the weights $w_{EE} > 0$ and $w_{IE} > 0$, respectively, while the inhibitory population only inhibits the excitatory one with the weight $w_{EI} > 0$. In the original approach, the weights were said to be related to the average number of excitatory and inhibitory synapses per cell, and $\mu_E, \mu_I > 0$ are biological constants ([Wilson & Cowan, 1972](#)). Further, only the excitatory neurons receive a diffuse, constant (dimensionless) background input $J \in \mathbb{R}$ ([Deco et al., 2009](#)).

This way researchers can model the interaction between the excitatory and inhibitory neuron ensembles within a brain region. The coupled ODEs in Eq. (54) and (55) allow for a mathematical description of the populations' mean firing rates (in 1/ms), i.e., the proportion of cells firing within a unit of time. However, this does not reflect a whole-brain modeling approach yet as it only describes the dynamics within one brain region. To design a proper network model in the sense of a graph $\mathcal{G} = (\mathcal{V}, \mathcal{E})$ (Eq. (1)), the vertices $\mathcal{V} = \{1, \dots, N\}$ must be connected via edges $w_{ij} \in \mathcal{E}$ based on the connectivities (SC and FC) in the brain.

For a network consisting of $N \in \mathbb{N}$ ROIs and vertices $i, j \in \mathcal{V}$, a WC-inspired whole-brain model contains the following symbolic system of coupled SDEs:

$$\begin{aligned} \frac{d}{dt}E_i(t) &= \frac{1}{\mu_E} \left(-E_i(t) + \Phi \left(\sum_{j=1}^N [(k_{ij} + \delta_{ij} w_{EE}) E_j(t - \tau_{ij})] - w_{EI} I_i(t) + J \right) \right) + \sigma \eta_{i,t}, \end{aligned} \quad (56)$$

$$\frac{d}{dt}I_i(t) = \frac{1}{\mu_I} (-I_i(t) + \Phi(w_{IE} E_i(t))) + \sigma \eta_{i,t}, \quad (57)$$

where

$$k_{ij} = \frac{SC_{ij} C}{\langle SC \rangle N} \quad \text{and} \quad \tau_{ij} = \frac{PL_{ij}}{\langle PL \rangle} \tau \quad (58)$$

are derived from the structural connectivity matrices SC and PL . The quantities in Eq. (58) are explained below. While the number of streamlines taken from the SC matrix shapes the intensity k_{ij} of couplings within the network of brain regions, the mean path lengths taken from the PL matrix influence the delay τ_{ij} in signal propagation between regions (Domhof et al., 2021). k_{ij} and τ_{ij} can thus be seen as two variants of the weighted network edges w_{ij} in Eq. (1). It is possible to consider either grand-averaged or subject-specific matrices reflecting the brain characteristics on the level of entire subject cohorts or single individuals, respectively. The operator $\langle . \rangle$ denotes the mean over all matrix elements without the diagonals. $C \geq 0$ and $\tau \geq 0$ are free model parameters referred to as the *global coupling strength* and *global delay*, respectively. They play the role of global weighting variables. The sum inside the response function Φ in Eq. (56) ensures that the delayed influences of all other excitatory populations are considered for the activity update of the population in brain region i . δ_{ij} is the Kronecker delta. Finally, $\eta_{i,t} := \eta_i(t)$ is a random noise term (here in 1/ms) with constant amplitude or *intensity*

$$g(t, E_i(t)) = g(t, I_i(t)) = \sigma \geq 0 \quad \forall i \in \{1, \dots, N\} \quad (59)$$

in Eq. (8), (10) and (11). It accounts for unpredictable perturbations of the system and increases its degree of realism. While C and σ are treated as dimensionless model parameters, τ is measured in the considered time unit. We omit the reformulation of the system equations in the proper integral form for brevity here.

In case of coupled brain regions, i.e., for $C > 0$, the numerical approximations of activity $\tilde{E}_i$ and $\tilde{I}_i$ exhibit an oscillatory behavior in the range of 8-12 Hz (α -frequency band) (Domhof et al., 2021). This is desirable in the setting of brain function modeling since α -oscillations dominate in EEG measurements of human resting-state brain activity and seem to interact with BOLD responses (Fraga González et al., 2018; Mayhew et al., 2013). We stress that this model generates comparably fast signals reflected by firing rates in the first place. These are still to be converted to BOLD signals to ensure comparability with fMRI data. Typically, this is done by the application of an *observation model* such as the *Balloon-Windkessel (BW) model* (Friston et al., 2003). It offers a way to convert electrical activity into perfusion changes, here variations in BOLD signal intensities. Simply speaking, it convolutes the time series of neural activity with a filtering function representing the blood flow- and vessel volume-related response, which allows for an estimation of BOLD signals. Details can be found in the associated literature (Buxton et al., 1998; Deco et al., 2009; Friston et al., 2003; Mandeville et al., 1999). The BW model is usually applied to the activity of the excitatory pool. Excitatory neurons make up to 80% of neurons present on the human cortex (Harris et al., 2015). That is how electrical activities of the WC model (≈ 10 Hz) can be converted to BOLD-like responses (≤ 0.1 Hz). These, in turn, are usable for the calculation of *simulated*, i.e., model-based FC (sFC) with help of the Pearson correlation coefficient in Eq. (2) and (3). The resulting coefficients sFC_{ij} reflect functional network edges w_{ij} in Eq. (1). Comparing sFC with its empirical counterpart obtained from fMRI measurements, i.e., empirical FC (eFC), is one of the most decisive steps of the considered whole-brain modeling approach. The studies presented in this thesis include such comparisons and focus on the maximization of the similarity

between sFC and eFC. We elaborate on the general procedure of model fitting in subchapter 3.4.

3.2.2 Jansen-Rit (JR) model

Another representative of neural mass models that includes the firing rates of excitatory and inhibitory populations is given by the *Jansen-Rit (JR) model* ([Jansen & Rit, 1995](#)). It is inspired by the *local neuron population model* created by Zetterberg and colleagues, which itself was based on the WC model ([Zetterberg et al., 1978](#)). The JR model aims for more biological realism and considers three neuronal populations per brain region: Two excitatory ones with different biological attributes and one inhibitory one. In addition, it does not consider any abstract, dimensionless quantities of activity as in the WC model. Instead, it works with excitatory and inhibitory postsynaptic currents (in millivolts per second, mV/s) that are interpreted as instantaneous rates of change of EPSPs and IPSPs (in mV). The model contains a set of second order differential equations. We will glimpse only at a reduced variant that keeps considering firing rates and currents as substrates for PSPs but simplifies the modeling to two pools of neurons (excitatory and inhibitory) again ([Jung et al., 2023](#)). This reduction was inspired by another two-population model of brain activity ([Lopes da Silva et al., 1974](#)).

The final model equations share properties with those of a deterministic, damped oscillator

$$y: \mathbb{R} \rightarrow \mathbb{R}, \quad y \in \mathcal{C}^2(\mathbb{R}),$$

where the acceleration

$$\frac{d^2}{dt^2} y(t) = y''(t)$$

depends on the location $y(t)$ and speed

$$\frac{d}{dt} y(t) = y'(t)$$

at time $t \geq 0$. For the EPSP $y_{i,E}$ and IPSP $y_{i,I}$ (in mV) of each brain region $i \in \{1, \dots, N\}$, we have

$$\begin{aligned} y''_{i,E}(t) &= \underbrace{AaR_i^2 \Phi_E \left(\sum_{j=1}^N [k_{ij} y_{j,E}(t - \tau_{ij})] - w_{EI} y_{i,I}(t) \right)}_{=: P_{i,E}(t)} - 2aR_i y'_{i,E}(t) - a^2 R_i^2 y_{i,E}(t) + \sigma \eta_{i,t}^E, \end{aligned} \quad (60)$$

$$\begin{aligned} y''_{i,I}(t) &= \underbrace{BbR_i^2 \Phi_I (w_{IE} y_{i,E}(t))}_{=: P_{i,I}(t)} - 2bR_i y'_{i,I}(t) - b^2 R_i^2 y_{i,I}(t) + \sigma \eta_{i,t}^I. \end{aligned} \quad (61)$$

Formally using $y'_{i,E} =: z_{i,E}$ and $y'_{i,I} =: z_{i,I}$ to denote the excitatory and inhibitory postsynaptic current (in mV/s), respectively ([Jansen & Rit, 1995](#)), the second order differential equations can be rewritten as

$$z'_{i,E}(t) = P_{i,E}(t) - 2aR_i z_{i,E}(t) - a^2 R_i^2 y_{i,E}(t) + \sigma \eta_{i,t}^E,$$

$$z'_{i,I}(t) = P_{i,I}(t) - 2bR_i z_{i,I}(t) - b^2 R_i^2 y_{i,I}(t) + \sigma \eta_{i,t}^I.$$

Note that we used the symbolic ODE notation for the SDEs and avoided the reformulation in the proper integral form. The constants $A, B > 0$ denote the maximum amplitude of the PSPs (in mV), while $a, b > 0$ are the reciprocals of cell-specific time constants (in 1/s), similar to μ_E, μ_I in the WC model. In addition, the $R_i > 0$ are dimensionless scaling factors for the response function $\Phi: \mathbb{R} \rightarrow \mathbb{R}$,

$$\Phi(x) := \frac{1}{1 + \exp(\varrho(v_0 - x))}. \quad (62)$$

It is commonly expressed as $\Phi_E := F_E \Phi$ or $\Phi_I := F_I \Phi$ to incorporate the maximal firing rates $F_E, F_I > 0$ (in 1/s) of the neural populations. The remaining constants $\varrho > 0$ (in 1/mV) and $v_0 \in \mathbb{R}$ (in mV) are related to the slope of Φ and the maximal neural activity, respectively. All of them are derived from biological cell properties ([Jansen & Rit, 1995](#)). The rest resembles the construction of the WC model, meaning that k_{ij} and τ_{ij} (Eq. (58)) are derived from empirical data representing the SC, and $C, \tau, \sigma \geq 0$ are free parameters. Likewise, the sum inside the response function Φ takes into account the delayed influences of all other regions' EPSPs $y_{j,E}$ as well as the same region's weighted IPSP $y_{i,I}$ when updating the excitatory activity of region i . For the inhibitory update, only the weighted EPSP $y_{i,E}$ is used, in analogy to the WC model (Eq. (54)-(58)). The addition of a random noise term, cf. Eq. (59), is supposed to cover random influences (here in mV/s²). We adapted the distinction between excitatory and inhibitory noise input ([Jung et al., 2023](#)), but for simplicity, we may also work with $\eta_{i,t}^E = \eta_{i,t}^I$ for all $i \in \{1, \dots, N\}, t \geq 0$ as in the WC model.

In summary, the JR model consists of N coupled nodes, each of which represents the mean electrical activity of a brain region. Within the regions, there are two neuronal populations (three in the non-reduced model) that interact via PSPs ([Lopes da Silva et al., 1974](#)). The couplings between regions are modeled by the terms $P_{i,E}$ and $P_{i,I}$ influencing the PSP oscillations based on excitatory signals from other regions as well as inhibitory signals from the same region. The arguments of Φ_E and Φ_I can be regarded as the total PSP inflow to the excitatory and inhibitory population, respectively, while the output is treated as the firing rates (in 1/s) ([Jansen & Rit, 1995](#)). We briefly verify for the excitatory population that there is no mismatch in the physical units in the model and that $y''_{i,E}$ in Eq. (60), i.e., the second derivative of the EPSP $y_{i,E}$ measured in mV, is given in mV/s²:

The argument of Φ_E contains only PSPs in mV and dimensionless weights, so that its unit is mV. Within the exponential function in the denominator of Φ_E in Eq. (62), v_0 in mV is added to the negative of the argument of Φ_E and then the sum is multiplied by ϱ in 1/mV, so that the entire denominator becomes dimensionless. Due to the subsequent multiplication with the maximal firing rate F_E in 1/s in the numerator, the output of Φ_E is given as a firing rate in 1/s as well. The right-hand side of Eq. (60) expressed in units only then reads

$$\text{mV} \cdot \frac{1}{s} \cdot 1^2 \cdot \frac{1}{s} - 1 \cdot \frac{1}{s} \cdot 1 \cdot \frac{\text{mV}}{s} - \frac{1}{s^2} \cdot 1^2 \cdot \text{mV} + 1 \cdot \frac{\text{mV}}{s^2},$$

which indeed describes a quantity measured in mV/s².

The approximated time series of EPSPs $y_{i,E}$ are treated as the final output of the JR model which can be used for further calculations of, e.g., sFC. Since these signals represent electrical activity, they are commonly inserted into the BW model to obtain BOLD-like responses. While the JR model is related to the WC model, from which it originates, it implicates more complexity. This is reflected by a set of second order SDEs that account for electric potentials and currents. Recently, the fitted JR model has proven beneficial for Parkinsonian patient classification based on human fMRI data ([Jung et al., 2023](#)).

3.2.3 Wong-Wang (WW) model

A converse approach to simulate region-wise brain activity is to focus on the sum of synaptic inputs into a given ROI. This is opposed to the firing of action potentials which reflect the output from the area. Although population firing rates and input currents into a given population are closely linked and both included, the *Wong-Wang (WW) model* distinguishes itself from the previous models (WC, JR). It primarily studies the temporal evolution of synaptic gating variables, i.e., the average fractions of open ion channels for neurons ([Deco et al., 2014](#); [Wong & Wang, 2006](#)). These dimensionless variables are denoted by S_i^E and S_i^I for the excitatory and inhibitory neural population of every brain region $i \in \{1, \dots, N\}$, respectively. They depend on the time $t \geq 0$, and the corresponding symbolic SDEs read:

$$\frac{d}{dt}S_i^E(t) = -\frac{1}{\mu_E}S_i^E(t) + \left(1 - S_i^E(t)\right) \Phi_E\left(\mathcal{I}_i^E(t)\right) + \sigma \eta_{i,t}, \quad (63)$$

$$\frac{d}{dt}S_i^I(t) = -\frac{1}{\mu_I}S_i^I(t) + \Phi_I\left(\mathcal{I}_i^I(t)\right) + \sigma \eta_{i,t}. \quad (64)$$

The general shape of Eq. (63) and (64) resembles that of Eq. (56) and (57) in the WC model. Indeed, as in the models presented so far, $\mu_E, \mu_I > 0$ (in s) describe biologically motivated time constants, while $\sigma \geq 0$ is the amplitude of an additive noise term $\eta_{i,t}$ (here in 1/s). Likewise, the WW model treats each cortical area as an ensemble of interacting excitatory and inhibitory neurons coupled through different types of synapses ([Deco et al., 2014](#)). The inter-area connections are constrained by the SC representing the anatomical connections between two brain regions. Here, this information is incorporated into the total input currents $\mathcal{I}_i^E, \mathcal{I}_i^I$ (in nanoamperes, nA) received by each neuronal pool. Their computation however considers the network properties of the brain as well as conductance values of certain biological receptors. $\Phi_E, \Phi_I: \mathbb{R} \rightarrow \mathbb{R}$ represent neural response functions in sigmoid shape that process this input, estimate firing rates and regulate the influence on the instantaneous rates of change of the synaptic gating variables S_i^E and S_i^I . Commonly, the S_i^E time series are fed to the WW model if BOLD responses are desired.

The original WW model has been introduced in 2006 ([Wong & Wang, 2006](#)), followed by modifications simplifying the interaction terms or reducing the number of neuronal pools from two to one, for example ([Deco et al., 2014](#); [Deco et al., 2013](#)). For more biological details including the utilized equations for the currents and neural responses, the interested reader is referred to the cited pieces of literature. We also recommend our joint work, where mathematical optimization was applied to fit the WW model for studying neuroscientific aspects of brain maturation in human adolescents ([Saber, Wischnewski, et al., 2025](#)). Besides a global coupling strength $C \geq 0$, the considered model contained 14 additional free parameters influencing the interactions between excitatory and inhibitory neural populations.

3.3 Phenomenological whole-brain models

Whole-brain models generally assume that functional connections between distant ROIs emerge from the embedding of biologically plausible local dynamics into the underlying anatomical connectivity structure ([Deco et al., 2014](#); [Ghosh et al., 2008](#); [Honey et al., 2009](#)). Due to reasons of computational feasibility, an average ensemble behavior is studied instead of detailed interactions between individual neurons. Such a neural mass approach constitutes a considerable simplification as compared to cellular models like the HH model. An even more wide-reaching facilitation is to abandon parts of the biological motivation and treat brain activity as a rather abstract, dimensionless quantity without immediate transferability to action potentials, firing rates, etc. This idea is pursued by phenomenological whole-brain models, where the model parameters are adjusted to match observed phenomena from the perspective of their global effects. These approaches aim to mimic brain dynamics via concepts of collective dynamic behavior such as the synchronization of activity-representative states, for instance ([Yeung & Strogatz, 1999](#)).

Besides their relative simplicity, an advantage of phenomenological models is that they are less restrictive in terms of biological plausibility. This can mean, for example, that they may just assume the presence of certain oscillations in the brain, but can neglect the driving mechanisms behind them. Further, internal model parameters like oscillation frequencies may be chosen in a range ensuring that the model output directly resembles ultra-slow (≤ 0.1 Hz) BOLD signal fluctuations. This annuls the need for further application of the BW model. Despite a potential lack of mechanistic explanations about the causes of empirical observations, phenomenological models can thus deliver useful predictive outcomes at comparably lower computational costs ([Bansal et al., 2018](#)). The studies presented in this thesis focus on one prominent representative of such approaches, namely the *Kuramoto model of coupled phase oscillators* ([Acebrón et al., 2005](#); [Kuramoto, 1984](#)). It can be regarded as the first paradigmatic model in which the phenomenon of synchronization of coupled oscillators has been described mathematically. In the field of neuroscience, it is considered one of the simplest models of whole-brain activity ([Bansal et al., 2018](#); [Cabral et al., 2014](#)). The model bases on the postulate that oscillations of neural activity are omnipresent in the brain. Originally, it featured a fully connected network of heterogeneous oscillators ([Breakspear et al., 2010](#); [Kuramoto, 1984](#)). Its more recent adaptations in neuroscience keep essential aspects of data-driven approaches and therefore constrain the interactions between individual oscillators by the SC data obtained from MRI scans of human subjects ([Cabral et al., 2011](#); [Cocchi et al., 2016](#); [Schmidt et al., 2015](#)). This renders it a plausible approach for simulating brain activity with a huge potential for mathematical analyses. We will describe the individual components of the model equations step by step.

3.3.1 Kuramoto model

The variables of interest in the Kuramoto model are the time-dependent *phases*

$$\theta_i(t) \geq 0, \quad t \geq 0$$

assigned to all brain regions $i \in \{1, \dots, N\}$. They are deemed to reflect the phases of the oscillating BOLD signals for every ROI and have to be computed numerically. The model assumes that in isolation, i.e., without any connection to other ROIs, the BOLD fluctuations of a brain region i can be interpreted as self-sustained periodic oscillations.

In general, periodic oscillations of a time-dependent variable $x(t) \in \mathbb{R}$ can be represented as a rotation of a point along a limit-cycle with the coordinates $(x(t), y(t)) \in \mathbb{R}^2$, where the second component may not be known immediately, see below. The phase θ is then a quantity that grows by 2π during one complete rotation on the limit-cycle, i.e., within one full oscillation of x . In the simplest scenario of a rotation along the unit circle in $\mathbb{R}^2$, specified by the coordinates $(\cos(\theta(t)), \sin(\theta(t)))$, the phase could be obtained via

$$\theta(t) = \arctan\left(\frac{\sin(\theta(t))}{\cos(\theta(t))}\right).$$

This corresponds to the angular variable $\varphi \in [0, 2\pi]$ when writing a complex number as $z = Re^{i\varphi} \in \mathbb{C}$ in polar coordinates (with amplitude $R > 0$). In the case of a constant amplitude R , any point on the limit-cycle can be uniquely identified with help of a line through the origin with inclination angle φ [Figure 5A]. Many natural phenomena however show rather complicated dynamics, meaning that oscillations may be somewhat irregular and of variable amplitude, so that the limit-cycle does not have the shape of a circle. (Here we mean sophisticated, periodic oscillations but allude to general, non-periodic cases later below.) Such a variable amplitude R prevents an unambiguous identification of points on the limit-cycle via the inclination angle φ due to several intersections with the line through the origin [Figure 5B]. In such situations, the phase still grows by 2π within one oscillation, but it cannot be thought of as a mere angle ([Pikovsky et al., 2001](#)).

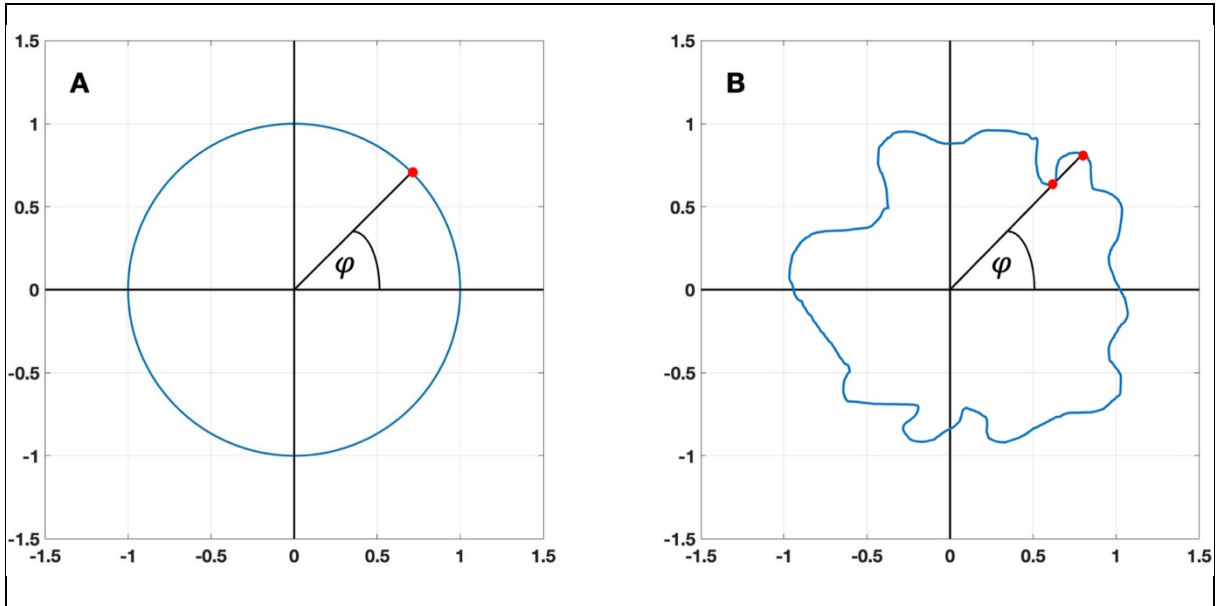


Figure 5: Illustration of two simple limit-cycles with (A) constant and (B) variable amplitude R . The intersections between a line through the origin and the respective limit-cycle are indicated in red color.

If the perimeter $L > 0$ of the limit-cycle is known, then the phase of a point having traveled the distance $l = l(t) \in [0, L]$ from a given starting time ($t = 0$) can be expressed as

$$\theta(t) = 2\pi \frac{l(t)}{L}.$$

Given an arbitrary (non-periodic) signal $s(t) \in \mathbb{R}, t \geq 0$, without further information whatsoever, one way to obtain the instantaneous phase $\theta(t)$ of the signal is to compute its *Hilbert transform* $s_H(t)$ and rewrite a new signal in complex coordinates as

$$\zeta(t) = s(t) + i s_H(t).$$

This enables the visualization of a corresponding limit-cycle in $\mathbb{R}^2$. A subsequent reformulation in polar coordinates, i.e.,

$$\zeta(t) = \underbrace{A(t)}_{>0} e^{i\varphi(t)},$$

may then lead to the desired phase at time t ([Gabor, 1946](#); [Pikovsky et al., 2001](#)). To ensure its uniqueness, however, the selection of the origin in the (s, s_H) -plane as well as the determination of the start and end of an oscillation play important roles. A broader discussion of the concept of phases, which goes beyond the scope of this thesis, can be found in the associated literature ([Pikovsky et al., 2001](#)).

For our purpose of simulating human resting-state BOLD signals through the Kuramoto model, we can stick only to the main property of θ , namely that it grows by 2π within one oscillation. This is possible, because the model comprises a *forward problem* to approximate BOLD signals from phases: The generated values of θ_i are used to compute BOLD signals for all brain regions $i \in \{1, \dots, N\}$, but no phases have to be inferred from estimated signals. Therefore, when constructing the model, we can resort to the following linear approximation of the phase for periodic oscillations ([Pikovsky et al., 2001](#)):

Given a period length $T_{\text{period}} > 0$ (for BOLD oscillations usually between 10s and 100s), we identify an *intrinsic* or *natural frequency*

$$\mathfrak{f} := \frac{1}{T_{\text{period}}} \tag{65}$$

and, relatedly, the *angular frequency*

$$\omega_0 := \frac{2\pi}{T_{\text{period}}} \stackrel{(65)}{=} 2\pi\mathfrak{f}. \tag{66}$$

Following that, we define the phase θ at time t as

$$\theta(t) := \Phi_0 + 2\pi \frac{t - t_0}{T_{\text{period}}} \tag{67}$$

for some initial values $\Phi_0, t_0 > 0$. Note that

$$\theta(t_0) = \Phi_0 \quad \text{and} \quad \theta(t_0 + T_{\text{period}}) = \Phi_0 + 2\pi.$$

Equation (67) can then be rewritten as

$$\theta(t) \stackrel{(66)}{=} \Phi_0 + \omega_0(t - t_0) = \underbrace{\Phi_0 - \omega_0 t_0}_{=: \theta_0} + \omega_0 t \stackrel{(66)}{=} \theta_0 + 2\pi f t.$$

The Kuramoto model draws on this setting and provides a suggestion for the temporal derivative of θ . We repeat the model assumption that in isolation, i.e., without any connection to other ROIs, the BOLD fluctuations of a brain region i can be interpreted as self-sustained periodic oscillations. We thus have

$$\frac{d}{dt} \theta_i(t) = 2\pi f_i \quad \forall i \in \{1, \dots, N\}, \quad (68)$$

where $f_i > 0$ denotes the intrinsic oscillation frequency of region i . A practical estimate in the relevant range between 0.01 and 0.1 Hz can be derived from empirical BOLD signal time series ([Domhof et al., 2021](#)). Conversely, a deliberate manipulation of the frequency parameters has been linked to the effects of external brain stimulation ([Gollob et al., 2017](#); [Schmidt et al., 2015](#)).

Incorporating the (delayed) couplings to other brain areas into the equation yields

$$\frac{d}{dt} \theta_i(t) = 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(\theta_j(t - \tau_{ij}) - \theta_i(t)) \quad \forall i \in \{1, \dots, N\}, \quad (69)$$

where k_{ij} and τ_{ij} are motivated by the underlying *SC* and *PL* matrices, respectively, as in Eq. (58). The application of the sine function on the phase differences is intended to reflect the oscillators' tendency to synchronize their behavior. It originates from a truncated Fourier series expansion of a 2π -periodic *phase interaction function* ([Breakspear et al., 2010](#)). The periodicity allows us to interpret the phase as restricted to

$$\theta_i(t) \in [0, 2\pi] \quad \forall i \in \{1, \dots, N\}, \quad t \geq 0.$$

Finally, an independent noise term is added to the derivative yielding

$$\frac{d}{dt} \theta_i(t) = 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(\theta_j(t - \tau_{ij}) - \theta_i(t)) + \sigma \eta_{i,t} \quad \forall i \in \{1, \dots, N\} \quad (70)$$

as the final, region-wise SDEs in symbolic sense. Numerical integration of these equations via, e.g., the stochastic Heun method (Eq. (48)), leads to approximated time series, or paths, of $\tilde{\theta}_i$ from which simulated BOLD signal intensities can be defined as $\sin(\tilde{\theta}_i)$. In cases when the intrinsic frequencies f_i in the model are based on faster neuronal dynamics, an additional application of the BW model may be necessary to estimate BOLD responses ([Cabral et al., 2011](#); [Fukushima & Sporns, 2018](#); [Pope et al., 2023](#)). The final step consists of correlating the simulated signals in order to derive the *sFC* matrix (Eq. (3)), see also subchapter 3.4.

In principle, the Kuramoto model has the same free parameters as the WC model, i.e., the global coupling strength $C \geq 0$, the global delay $\tau \geq 0$ and also the noise amplitude $\sigma \geq 0$. Study 1 is dedicated to parameter optimizations in such two-dimensional (C, τ) as well as three-dimensional (C, τ, σ) search spaces. It aims to test and identify the most favorable methods for a maximization of the subject-specific correlation between *sFC* and *eFC*.

Additional freedom is given by a potential adjustment of the region-specific frequency parameters f_i , which remained constant as derived from empirical MRI data in study 1, but were treated as free parameters in study 2. The need for investigating and documenting the benefits and challenges of a transition to such high-dimensional model parameter spaces constituted the motivation for study 2 as well as the subsequent application in study 3, see chapter 4.

We summarize that the Kuramoto model is principal for BOLD signal and FC data generation in all three publications presented in this thesis. That is why we included the following section to elaborate on the equations' theoretical solvability.

3.3.2 Solvability of the Kuramoto SDEs

In alignment with the conditions listed in subchapter 2.1, this section is dedicated to the existence of unique solutions to the equations defining the Kuramoto model. The model plays a leading role in the publications presented in this thesis. To show the solvability, we must take into account that the model is given as a set of $N \in \mathbb{N}$ coupled SDEs, where the couplings additionally include delays. The conditions given by Eq. (12)-(14) therefore need to be adapted accordingly ([Janković et al., 2010](#); [Mao, 2011](#); [Mizel & Trutzer, 1984](#); [Yin & Gan, 2015](#)). We start by identifying the functions f and g (cf. Eq. (8)) for the drift and noise amplitude, respectively, in a model variant with instantaneous couplings and generalize to the delay case afterwards.

In a delay-free setting, the complete, symbolic problem formulation reads

$$\begin{aligned} \frac{d}{dt}\theta_i(t) &= 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(\theta_j(t) - \theta_i(t)) + \sigma \eta_{i,t}, \quad t \in [0, T], \\ \theta_i(0) &= \theta_i^0 \in [0, 2\pi] \quad \forall i \in \{1, \dots, N\}, \end{aligned}$$

with its proper integral form, cf. Eq. (11), given by

$$\theta_i(t) = \theta_i^0 + \int_0^t \left(2\pi f_i + \sum_{j=1}^N k_{ij} \sin(\theta_j(s) - \theta_i(s)) \right) ds + \int_0^t \sigma dW_s.$$

Unlike in Eq. (8), where an isolated SDE with $\mathbb{R}$ -valued solution was considered, we now have $f, g: [0, T] \times \mathbb{R}^N \rightarrow \mathbb{R}$ given as functions with an $\mathbb{R}^N$ -valued second argument (reflecting N coupled phase oscillators). We deduce

$$f(t, x) = 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(x_j - x_i)$$

and

$$g(t, x) \equiv \sigma \in \mathbb{R}$$

for $t \in [0, T]$ and $x = (x_1, \dots, x_N)^T \in \mathbb{R}^N$. It follows that the noise is additive since g is constant with respect to x (cf. Eq. (32)), so that the integral concepts by Itô and Stratonovich coincide.

For completeness, we mention that such functions f and g are given for every $i \in \{1, \dots, N\}$ in the system of SDEs. We however omit an additional indexing here to avoid confusion with the frequency parameters denoted by f_i .

Proceeding to the delay case as given by Eq. (70), i.e.,

$$\frac{d}{dt}\theta_i(t) = 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(\theta_j(t - \tau_{ij}) - \theta_i(t)) + \sigma \eta_{i,t}, \quad t \in [0, T],$$

we emphasize that the initial condition is now given as a family of time-dependent random variables

$$\theta_i^0 = \{\psi_i(t) \mid t \in [-\tau_{\max}, 0]\} \quad \text{with} \quad \psi_i(t) \sim \mathcal{U}([0, 2\pi]) \quad \forall t \in [-\tau_{\max}, 0],$$

where $\tau_{\max} > 0$ denotes the longest delay, and importantly,

$$\theta_i(t) = \psi_i(t) \quad \forall t \in [-\tau_{\max}, 0],$$

in particular

$$\theta_i(0) = \psi_i(0) \quad \forall i \in \{1, \dots, N\}.$$

This constitutes the typical adaptation of initial value problems with delay ODEs, where an initial function specifies the system behavior prior to the considered starting time ([Myshkis, 1955](#)), to the considered SDE cases with delays ([Janković et al., 2010](#); [Mao, 2011](#); [Yin & Gan, 2015](#)).

For the drift and noise amplitude, the incorporation of delay terms leads to an additional argument, so that we have $f, g: [0, T] \times \mathbb{R}^N \times \mathbb{R}^N \rightarrow \mathbb{R}$ given as

$$f(t, x, x^\tau) = 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(x_j^\tau - x_i)$$

and

$$g(t, x, x^\tau) \equiv \sigma \in \mathbb{R},$$

where $x^\tau = (x_1^\tau, \dots, x_N^\tau)^T \in \mathbb{R}^N$ accounts for the phases with delayed argument (here we avoid a pronounced double-indexing as in τ_{ij} for simplicity).

Having extracted the relevant terms, we must show that the delay-adapted versions of the Lipschitz, linear growth and initial value condition (Eq. (12)-(14)) are fulfilled. The inequality in the Lipschitz condition (Eq. (12)) generalizes to

$$|f(t, x, x^\tau) - f(t, y, y^\tau)| + |g(t, x, x^\tau) - g(t, y, y^\tau)| \leq L (\|x - y\|_1 + \|x^\tau - y^\tau\|_1)$$

in our setting, as inferred from the related literature ([Mao, 2007](#); [Mizel & Trutzer, 1984](#); [Yin & Gan, 2015](#)).

Since

$$|g(t, x, x^\tau) - g(t, y, y^\tau)| = |\sigma - \sigma| = 0$$

for all $(t, x, x^\tau), (t, y, y^\tau) \in [0, T] \times \mathbb{R}^N \times \mathbb{R}^N$, it suffices to show that there exists $L > 0$, such that

$$|f(t, x, x^\tau) - f(t, y, y^\tau)| \leq L (\|x - y\|_1 + \|x^\tau - y^\tau\|_1).$$

For any $(t, x, x^\tau), (t, y, y^\tau) \in [0, T] \times \mathbb{R}^N \times \mathbb{R}^N$, we thus consider

$$\begin{aligned} & |f(t, x, x^\tau) - f(t, y, y^\tau)| \\ &= \left| 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(x_j^\tau - x_i) - 2\pi f_i - \sum_{j=1}^N k_{ij} \sin(y_j^\tau - y_i) \right| \\ &= \left| \sum_{j=1}^N k_{ij} [\sin(x_j^\tau - x_i) - \sin(y_j^\tau - y_i)] \right| \\ &\leq \sum_{j=1}^N |k_{ij} [\sin(x_j^\tau - x_i) - \sin(y_j^\tau - y_i)]| \\ &= \sum_{j=1}^N |k_{ij}| |\sin(x_j^\tau - x_i) - \sin(y_j^\tau - y_i)| \\ &\leq \max_{i,j \in \{1, \dots, N\}} \{|k_{ij}|\} \sum_{j=1}^N \left| \sin(\underbrace{x_j^\tau - x_i}_{=:a}) - \sin(\underbrace{y_j^\tau - y_i}_{=:b}) \right|. \end{aligned} \tag{71}$$

To find an upper bound for the terms in the sum, we may assume $a \leq b$ without loss of generality and resort to the mean value theorem:

$$\begin{aligned} & \exists \lambda \in]a, b[, \text{ such that } \underbrace{\sin'(\lambda)}_{=\cos(\lambda)} = \frac{\sin(b) - \sin(a)}{b - a} \\ & \Rightarrow |\cos(\lambda)| = \frac{|\sin(a) - \sin(b)|}{|a - b|} \\ & \Rightarrow |\sin(a) - \sin(b)| = \underbrace{|\cos(\lambda)|}_{\leq 1} |a - b| \leq |a - b|. \end{aligned} \tag{72}$$

Using the last inequality, we obtain

$$\begin{aligned} & |f(t, x, x^\tau) - f(t, y, y^\tau)| \\ & \stackrel{(71)}{\leq} \underbrace{\max_{i,j \in \{1, \dots, N\}} \{|k_{ij}|\}}_{=: \tilde{k}} \sum_{j=1}^N |\sin(a) - \sin(b)| \stackrel{(72)}{\leq} \tilde{k} \sum_{j=1}^N |a - b| \\ & = \tilde{k} \sum_{j=1}^N |x_j^\tau - x_i - y_j^\tau + y_i| = \tilde{k} \sum_{j=1}^N |(x_j^\tau - y_j^\tau) - (x_i - y_i)| \end{aligned}$$

$$\begin{aligned}
&\leq \tilde{k} \sum_{j=1}^N (|x_j^\tau - y_j^\tau| + |x_i - y_i|) = \tilde{k} \left(\sum_{j=1}^N |x_j^\tau - y_j^\tau| + \underbrace{\sum_{j=1}^N |x_i - y_i|}_{=N|x_i - y_i|} \right) \\
&\leq \tilde{k} \left(N \sum_{j=1}^N |x_j^\tau - y_j^\tau| + N \sum_{i=1}^N |x_i - y_i| \right) = \tilde{k} N \left(\sum_{i=1}^N |x_i - y_i| + \sum_{j=1}^N |x_j^\tau - y_j^\tau| \right) \\
&= \tilde{k} N (\|x - y\|_1 + \|x^\tau - y^\tau\|_1),
\end{aligned}$$

so that

$$\begin{aligned}
&|f(t, x, x^\tau) - f(t, y, y^\tau)| + |g(t, x, x^\tau) - g(t, y, y^\tau)| \\
&\leq \tilde{k} N (\|x - y\|_1 + \|x^\tau - y^\tau\|_1) =: \tilde{L} (\|x - y\|_1 + \|x^\tau - y^\tau\|_1).
\end{aligned} \tag{73}$$

Recall that N is the fixed number of brain regions and not a number of subdivisions in a discretization.

Now we show that the linear growth condition (Eq. (13)), adapted to

$$|f(t, x, x^\tau)|^2 + |g(t, x, x^\tau)|^2 \leq L^2 (1 + \|x\|_1^2 + \|x^\tau\|_1^2)$$

based on the literature ([Mao, 2007](#); [Mizel & Trutzer, 1984](#); [Yin & Gan, 2015](#)), is fulfilled.

For any $(t, x, x^\tau) \in [0, T] \times \mathbb{R}^N \times \mathbb{R}^N$, we have

$$\begin{aligned}
|f(t, x, x^\tau)| &= \left| 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(x_j^\tau - x_i) \right| \\
&\leq 2\pi f_i + \tilde{k} \sum_{j=1}^N \underbrace{|\sin(x_j^\tau - x_i)|}_{\leq 1} \\
&\leq 2\pi f_i + \tilde{k} N =: \tilde{K} \\
&\Rightarrow |f(t, x, x^\tau)|^2 \leq \tilde{K}^2.
\end{aligned} \tag{74}$$

Since $1 + \|x\|_1^2 + \|x^\tau\|_1^2 \geq 1$, we obtain in particular

$$|f(t, x, x^\tau)|^2 \leq \tilde{K}^2 (1 + \|x\|_1^2 + \|x^\tau\|_1^2). \tag{75}$$

For the amplitude of stochastic fluctuations, we have

$$|g(t, x, x^\tau)|^2 = \sigma^2 \leq \max\{\sigma^2, \tilde{K}^2\} (1 + \|x\|_1^2 + \|x^\tau\|_1^2). \tag{76}$$

Following these estimates, we define

$$\frac{L^2}{2} := \max\{\sigma^2, \tilde{K}^2\} \Rightarrow L = \sqrt{2 \max\{\sigma^2, \tilde{K}^2\}}.$$

This constant satisfies $L \geq \tilde{L} > 0$, so that we ultimately obtain

$$\begin{aligned} & |f(t, x, x^\tau) - f(t, y, y^\tau)| + |g(t, x, x^\tau) - g(t, y, y^\tau)| \\ & \stackrel{(73)}{\leq} \tilde{L} \|x - y\|_1 + \|x^\tau - y^\tau\|_1 \leq L \|x - y\|_1 + \|x^\tau - y^\tau\|_1 \end{aligned}$$

and

$$\begin{aligned} |f(t, x, x^\tau)|^2 + |g(t, x, x^\tau)|^2 & \stackrel{(75)-(76)}{\leq} \frac{L^2}{2} (1 + \|x\|_1^2 + \|x^\tau\|_1^2) + \frac{L^2}{2} (1 + \|x\|_1^2 + \|x^\tau\|_1^2) \\ & = L^2 (1 + \|x\|_1^2 + \|x^\tau\|_1^2), \end{aligned}$$

showing that the adapted versions of both the Lipschitz (Eq. (12)) and linear growth condition (Eq. (13)) are fulfilled. The generalized initial value condition ([Janković et al., 2010](#); [Yin & Gan, 2015](#)) as presented below (cf. Eq. (14)) is also satisfied, because the values of the phase up to the initial time $t = 0$ are sampled from a family of random variables

$$\theta_i^0 = \{\psi_i(t) \mid t \in [-\tau_{\max}, 0]\}$$

uniformly distributed over a finite interval, i.e.,

$$\theta_i(t) = \psi_i(t) \quad \text{with} \quad \psi_i(t) \sim \mathcal{U}([0, 2\pi]) \quad \forall t \in [-\tau_{\max}, 0]$$

$$\Rightarrow \mathbb{E} [\|\theta_i^0\|^2] = \mathbb{E} \left[\left(\sup_{t \in [-\tau_{\max}, 0]} |\psi_i(t)| \right)^2 \right] < \infty,$$

and, by construction, θ_i^0 is independent of the increments ΔW_t of the considered Wiener process.

All in all, we demonstrated that the simulation of BOLD signals via the Kuramoto model of coupled phase oscillators is a well-posed initial value problem. Its numerical solution and the subsequent use of optimization methods to fit the model to empirical data constitute the methodological essence of this thesis.

3.3.3 Hopf / Limit-cycle model

To conclude the chapter about human brain modeling, we summarize one more representative from the class of phenomenological models, namely a model consisting of a system of coupled Stuart-Landau limit-cycle oscillators ([Panteley et al., 2015](#)). It represents the normal form of a so-called *Andronov-Hopf bifurcation* ([Kuznetsov, 1998](#)), and may also be known as *Hopf model* ([Deco et al., 2017](#)) or *Limit-cycle model* ([Popovych et al., 2021](#)). Unlike in the Kuramoto model, an additional control parameter accounts for the oscillation amplitude of the simulated time series of brain activity. This may increase the realism and model personalization as simulated signals are not restricted to the range $[-1, 1]$. Still, caution should be exercised regarding an immediate neurobiological interpretation of the underlying principles. The model merely tries to phenomenologically replicate human BOLD signals with help of an abstract, time-dependent variable

$$z(t) = x(t) + i y(t) \in \mathbb{C}, \quad t \geq 0,$$

whose real part, $x(t)$, is deemed to reflect the simulated signals ([Deco et al., 2019](#)). Considering N brain areas, the core of the model is the following set of complex ODEs:

$$\frac{d}{dt} z_j(t) = \left(2\pi f_j \mathbf{i} + a_j - |z_j(t)|^2 \right) z_j(t) \quad \forall j \in \{1, \dots, N\}, \quad (77)$$

where $f_j > 0$ and $a_j > 0$ denote the region-wise frequency (cf. Eq. (65)) and amplitude of the oscillating variable $z_j \in \mathbb{C}$, respectively. We quickly demonstrate that for $t \rightarrow \infty$ and without any connections to other brain regions, all oscillators of the ensemble will independently rotate with angular frequency $2\pi f_j$ along a limit-cycle (in $\mathbb{C}$) with radius $\sqrt{a_j}$. Omitting the index j for brevity, we first rewrite

$$z(t) = R(t) e^{i\varphi(t)} \quad (78)$$

in polar coordinates with radial amplitude $R > 0$ and angular variable $\varphi \in [0, 2\pi]$. Then the derivative of z can be expressed as

$$\frac{d}{dt} z(t) = R'(t) e^{i\varphi(t)} + \mathbf{i} \varphi'(t) R(t) e^{i\varphi(t)}. \quad (79)$$

Equating Eq. (77) and (79) in view of Eq. (78) yields

$$\begin{aligned} \left(2\pi \mathbf{i} + a - \underbrace{R(t)^2}_{=|z(t)|^2} \right) R(t) e^{i\varphi(t)} &= R'(t) e^{i\varphi(t)} + \mathbf{i} \varphi'(t) R(t) e^{i\varphi(t)} \\ \Rightarrow (2\pi \mathbf{i} + a - R(t)^2) R(t) &= R'(t) + \mathbf{i} \varphi'(t) R(t). \end{aligned}$$

Separating real and imaginary parts gives us

$$R'(t) = (a - R(t)^2) R(t), \quad (80)$$

$$\varphi'(t) = 2\pi. \quad (81)$$

While it is obvious now that φ grows linearly in time (cf. Eq. (68), i.e., the phase in the Kuramoto model without couplings), some more steps are required to reveal $R(t) \xrightarrow[t \rightarrow \infty]{} \sqrt{a}$.

We rewrite Eq. (80) as

$$R'(t) - a R(t) + R(t)^3 = 0 \quad (82)$$

and see that this is a *Bernoulli differential equation* of general shape

$$y'(t) + P(t) y(t) + Q(t) y^\alpha(t)$$

with $P(t) \equiv -a$, $Q(t) \equiv 1$ and $\alpha = 3$. It can be solved via the following transformation to a linear differential equation:

Let

$$\begin{aligned}\psi(t) &:= R(t)^{1-\alpha} = \frac{1}{R(t)^2} \geq 0 \\ \Rightarrow R(t) &= \psi(t)^{\frac{1}{1-\alpha}} = \pm \frac{1}{\sqrt{\psi(t)}}\end{aligned}\tag{83}$$

$$\Rightarrow R'(t) = \frac{1}{1-\alpha} \psi'(t) \psi(t)^{\frac{1}{1-\alpha}-1} = \frac{1}{1-\alpha} \psi'(t) \psi(t)^{\frac{\alpha}{1-\alpha}}.\tag{84}$$

Inserting Eq. (83) and (84) into Eq. (82), we obtain

$$\frac{1}{1-\alpha} \psi'(t) \psi(t)^{\frac{\alpha}{1-\alpha}} - a \psi(t)^{\frac{1}{1-\alpha}} + \psi(t)^{\frac{\alpha}{1-\alpha}} = 0,$$

which we multiply by $(1-\alpha) \psi(t)^{\frac{-\alpha}{1-\alpha}}$ to have

$$\begin{aligned}\psi'(t) - (1-\alpha) a \psi(t) + (1-\alpha) &= 0 \\ \xRightarrow{\alpha=3} \psi'(t) + 2a \psi(t) - 2 &= 0.\end{aligned}\tag{85}$$

This is an inhomogeneous linear differential equation. Its homogeneous component,

$$\psi'_h(t) + 2a \psi_h(t) = 0,$$

has the solution

$$\psi_h(t) = c e^{-2at}, \quad c \in \mathbb{R}.$$

For the inhomogeneous solution, we apply the *variation of constants* and set

$$\psi_{\text{inh}}(t) = c(t) e^{-2at} \quad \text{for } c: \mathbb{R} \rightarrow \mathbb{R}.$$

Then we have

$$\psi'_{\text{inh}}(t) = c'(t) e^{-2at} - 2a c(t) e^{-2at},$$

which we insert into Eq. (85) to obtain

$$c'(t) e^{-2at} - 2a c(t) e^{-2at} + 2a c(t) e^{-2at} - 2 = 0 \Leftrightarrow c'(t) = 2e^{2at}.$$

Finally, we integrate c' to compute c :

$$c(t) = \int c'(t) dt = \int 2e^{2at} dt = \frac{1}{a} e^{2at} + \tilde{c}, \quad \tilde{c} \in \mathbb{R}.$$

So, the solution of Eq. (85) is

$$\psi(t) = c(t) e^{-2at} = \left(\frac{1}{a} e^{2at} + \tilde{c} \right) e^{-2at} = \tilde{c} e^{-2at} + \frac{1}{a},$$

which we can transfer back to R via Eq. (83)

$$R(t) = \pm \frac{1}{\sqrt{\tilde{c}e^{-2at} + \frac{1}{a}}}.$$

Since $R > 0$ is considered an amplitude in the Hopf model, we can neglect the negative solution and focus on

$$R(t) = \frac{1}{\sqrt{\tilde{c}e^{-2at} + \frac{1}{a}}} \quad \text{with} \quad \tilde{c} > \frac{-e^{2at}}{a} \quad \forall t \geq 0.$$

Now we easily see that

$$\lim_{t \rightarrow \infty} R(t) = \frac{1}{\sqrt{0 + \frac{1}{a}}} = \sqrt{a}.$$

Together with the linearly increasing angular variable φ , this indicates asymptotic oscillations of z (Eq. (78)), the main model variable, with a constant amplitude $\sqrt{a}$. Of note, an amplitude parameter $a < 0$ would cause

$$\lim_{t \rightarrow \infty} R(t) = 0 \Rightarrow \lim_{t \rightarrow \infty} z(t) = 0,$$

i.e., no oscillations in the coupling-free model (Eq. (77)). In the setting of dynamical systems, the parameter a is also referred to as *bifurcation parameter*, because its manipulation may cause an abrupt qualitative change of the system behavior, like here the onset and offset of periodic oscillations ([Kuznetsov, 1998](#)). Neuroscientific studies simulate external stimulations of selected brain areas via a deliberate alteration of a ([Deco et al., 2019](#); [Irvani et al., 2021](#)).

Having clarified the basic model behavior for isolated brain regions, we can proceed to the complete model formulation containing (delayed) couplings to other ROIs as well as additive complex noise. For every brain region $j \in \{1, \dots, N\}$, we have the symbolic representation

$$\frac{d}{dt} z_j(t) = \left(2\pi f_j i + a_j - |z_j(t)|^2 \right) z_j(t) + \sum_{l=1}^N k_{jl} \left(z_l(t - \tau_{jl}) - z_j(t) \right) + \sigma \underbrace{\eta_{j,t}}_{\in \mathbb{C}}. \quad (86)$$

This can be subdivided into real and imaginary parts to obtain two first order, non-linear SDEs in $\mathbb{R}$:

$$\begin{aligned} \frac{d}{dt} x_j(t) &= (a_j - x_j(t)^2 - y_j(t)^2) x_j(t) - 2\pi f_j y_j(t) + \sum_{l=1}^N k_{jl} \left(x_l(t - \tau_{jl}) - x_j(t) \right) + \sigma \operatorname{Re}(\eta_{j,t}), \quad (87) \end{aligned}$$

$$\frac{d}{dt}y_j(t) = (a_j - x_j(t)^2 - y_j(t)^2)y_j(t) + 2\pi f_j x_j(t) + \sum_{l=1}^N k_{jl} (y_l(t - \tau_{jl}) - y_j(t)) + \sigma \text{Im}(\eta_{j,t}). \quad (88)$$

The model parameters k_{jl} and τ_{jl} are derived from empirical data (*SC* and *PL*) as in Eq. (58), incorporating the free global parameters $C, \tau \geq 0$. The additive noise, originally complex-valued, can be separated into its real and imaginary part with tunable amplitude $\sigma \geq 0$. If not treated as free, the parameters $f_j > 0$ and $a_j > 0$ may also be estimated from MRI data by considering the maximal spectral peaks and the standard deviation of empirical BOLD signals, respectively ([Domhof et al., 2021](#); [Popovych et al., 2021](#)). An extension of the Hopf model with time-varying frequencies f_j has been applied to study elements of attention deficit hyperactivity disorder and potentially reveal new subtypes of the disease ([Iravani et al., 2021](#)).

In summary, we have discussed several approaches attempting to simulate human brain activity. The attention can vary from the cellular level of individual neurons to entire networks of spatially distinct brain regions. Moreover, the presented models allow for a mathematical description of brain activity in terms of variables reflecting either some biological characteristics such as synaptic activities and the firing of action potentials, or more abstract and purely phenomenological properties like the general temporal patterns of neural oscillations and resulting BOLD fluctuations. At the core of the presented whole-brain models, there is typically a first or second order ODE for every brain region. Its solution often shows properties of regular, self-sustained oscillations if uncoupled to other oscillating units, as suspected to occur in the brain ([Baria et al., 2011](#); [Stiefel & Ermentrout, 2016](#)). Then these ODEs are equipped with an additive coupling term to incorporate the (delayed) interactions with other brain regions. These are perturbed by noise to account for random, unpredictable influences. The resulting SDEs constitute an important factor of mathematical modeling in neuroscience.

We described several representatives of the different modeling approaches, but do not claim that our list is conclusive, see the related literature for more examples of dynamical whole-brain models ([Cabral et al., 2014](#); [Messe et al., 2014](#); [Moran et al., 2013](#)). One class of models that we did not include is given by the so-called *neural field models* which use partial differential equations to describe brain activity as a process continuous both in time and space ([Atasoy et al., 2016](#); [Breakspear, 2017](#); [Gollo et al., 2017](#); [Moran et al., 2013](#)). Here, other metrics must be applied to assess the value of mathematical simulations. The concept of atlases with spatially discrete brain regions having structural and functional interconnections is not directly applicable. However, all models have in common that their generated output depends on a set of free, user-defined model parameters. Their efficient optimization is the main ambition underlying this thesis. We want to know how the use of optimization algorithms can assist in boosting the utility of simulations. The framework is given by whole-brain models that treat brain activity as the result of collective neuronal dynamics across atlas-defined brain regions. In the following section, we proceed to the mathematical formulation of the considered problems.

3.4 Applicability of derivative-free optimization methods

The modeling and optimization workflow pursued in the presented publications can be summarized as follows. We consider the Kuramoto model of coupled phase oscillators (Eq. (70)) to simulate personalized brain activity in the resting-state. The theoretical solvability of the associated initial value problem has been demonstrated in section 3.3.2 of this thesis. The model's dynamical variable is θ_i , which is deemed to represent the time-dependent and region-specific phase of the BOLD signal in region $i \in \{1, \dots, N\}$. Information about the anatomical network structure of every subject's individual brain is incorporated into the instantaneous rate of change of θ_i via k_{ij} and τ_{ij} , $i, j \in \{1, \dots, N\}$, cf. Eq. (58). These quantities are derived from the structural connectivity matrices SC and PL , respectively. This way, the model uses the brain structure of individual subjects to guide the functional interactions between brain regions. As indicated above, the ROIs are treated as oscillators with instantaneous phase θ_i . Their intrinsic frequencies f_i can either remain constant as derived from empirical data or can be added to the list of free model parameters containing the global coupling strength C , the global delay τ and the noise amplitude σ . We solve the resulting set of coupled SDEs numerically via the stochastic adaptation of the Heun method (Eq. (48)) with a discrete time step Δt . Hence, we obtain an approximation

$$\mathcal{B}_i := \{\tilde{\theta}_i(t_k) \mid t_k = t_0 + k \Delta t, k \in \{0, \dots, n\}\}$$

of one phase time series for every brain region i . Depending on the discretization $0 \leq t_0 \leq t_1 \leq \dots \leq t_n = T, n \in \mathbb{N}$, of $[t_0, T]$, we interpret it as $\mathcal{B}_i \in \mathbb{R}^{n+1}$. A subsequent application of the sine function (see section 3.3.1) yields the simulated BOLD signals

$$\text{sBOLD}_i := \sin(\mathcal{B}_i) \in \mathbb{R}^{n+1}.$$

Afterwards, we compute the Pearson correlation coefficient $r \in [-1, 1]$ (Eq. (2)) of the signals across all pairs of brain regions $i, j \in \{1, \dots, N\}$ to identify the matrix of simulated functional connectivity, $sFC \in \mathbb{R}^{N \times N}$, where in accordance with Eq. (3),

$$sFC_{ij} = r(\text{sBOLD}_i, \text{sBOLD}_j). \quad (89)$$

We stress that $sFC = sFC^T$ and $\text{diag}(sFC) = 0 \in \mathbb{R}^N$ as explained in section 1.1.5. Subsequently, we compare this model-generated output with an empirical observation of human brain activity obtained from fMRI measurements. It is given by the matrix of empirical functional connectivity, $eFC \in \mathbb{R}^{N \times N}$ (Eq. (3)). By computing the Pearson correlation coefficient (Eq. (2)) between (the vectorized upper triangular parts of) the matrices sFC and eFC , we obtain a quality measure of the model fit to empirical data. A value of $r = 1$ would correspond to an ideal positive, linear relationship, which is why higher values are favored.

Here we highlight that the model fit critically depends on the selected model parameter values. The input vector of parameters

$$\hat{\mathcal{P}} := (C, \tau, \sigma, f_1, \dots, f_N) \in \mathbb{R}^{N+3}$$

shapes the time series of simulated phases $\tilde{\theta}_i$, resulting BOLD signals and thereby the matrix $sFC = sFC(\hat{\mathcal{P}})$. The latter is ultimately compared to eFC to evaluate the quality of the simulations. We refer to the highest observed similarity between the model output

and empirical measurements as the model's *goodness-of-fit* (GoF). This property is influenced by the number of parameters treated as *free* [Figure 6]. Since we do not always optimize all $N + 3$ components of $\hat{\mathcal{P}}$, we introduce $\text{Dim} \leq N + 3$ to describe the effective dimension of the search space, i.e., the number of free parameters in the considered model. Accordingly, we may write the vector of considered parameters as $\mathcal{P} \in \mathbb{R}^{\text{Dim}}$.

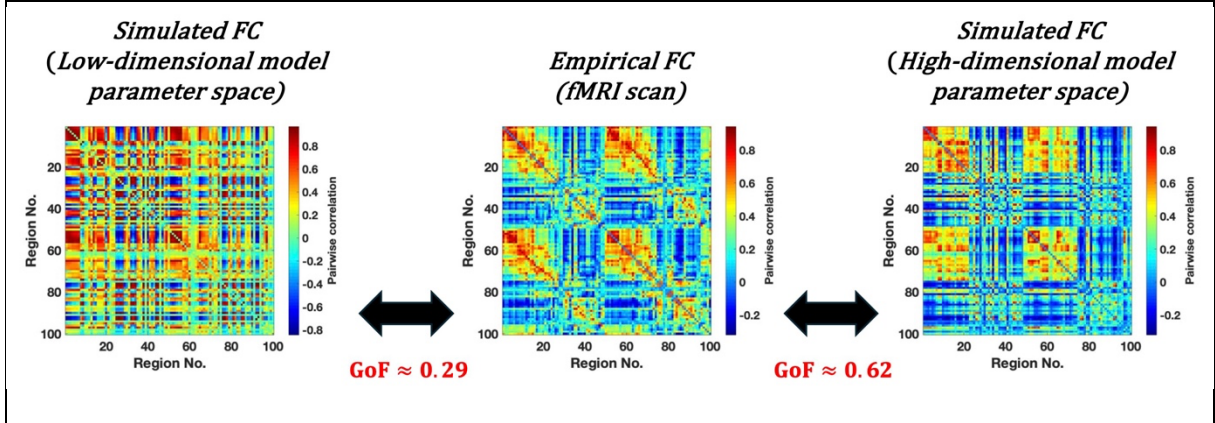


Figure 6: Functional connectivity comparison between simulated model output and empirical measurement. The leftmost matrix shows the functional connectivity as obtained from model simulations (*simulated FC*) with a model parameter optimization performed in a two-dimensional search space. It is compared to the matrix of empirical functional connectivity (*empirical FC*, center) derived from functional magnetic resonance imaging (fMRI). The rightmost matrix represents the functional connectivity deduced from model simulations with a parameter optimization performed in a 103-dimensional search space. It is also compared to the *empirical FC* matrix in the center. The highest observed correlation between the empirical and the respective simulated matrices, i.e., the goodness-of-fit (GoF) of the considered model is indicated in red color.

From a mathematical perspective, the search for the model parameter values that maximize the model fit corresponds to a (constrained) optimization problem of an objective function

$$F: X \rightarrow [-1, 1]$$

$$\mathcal{P} \mapsto r(sFC(\mathcal{P}), eFC)$$

defined on some domain $X \subseteq \mathbb{R}^{\text{Dim}}$ denoting the search space. Here, $r(sFC(\mathcal{P}), eFC)$ is defined as in Eq. (89) after vectorizing the upper triangular parts of the matrices $sFC(\mathcal{P})$ and eFC . The input argument of F is the vector of free model parameters $\mathcal{P} \in X$ while its output is the Pearson correlation coefficient r (Eq. (2)) between simulated and empirical data, i.e., our quality measure. It is reasonable to assume that F is continuous: The phase θ_i depends continuously on the time t , the Kuramoto equations (Eq. (70)) for its temporal development include only continuous terms in the drift, and the computation of r from two vectors involves only the calculation of (co)variances and standard deviations. Due to the stochastic term in the model, however, our evaluations of the objective function are perturbed and lead to a somewhat noisy appearance of the shape of F . No further information about F can be provided. This is tantamount to the lack of a closed form, no knowledge about smoothness or convexity, and the unavailability of derivatives. In other words, function evaluations are the only means to learn some characteristics of F . This prevents the application of several efficient optimization methods from the field of gradient and quasi-Newton methods. Examples are the *Heavy Ball Method* (Polyak, 1964), *Nesterov's Accelerated Gradient Method* (Nesterov, 1983, 2014), the *Broyden-Fletcher-*

Goldfarb–Shanno (BFGS) Algorithm ([Powell, 1976](#)) and the *Symmetric Rank One (SR1) Method* ([Khalafan et al., 1993](#)). Here, convergence properties under given conditions such as convexity of the objective function have been studied and well documented ([Conn et al., 1991](#); [Dai, 2002](#); [Diakonikolas & Jordan, 2021](#)). In some cases it is possible to derive explicit estimates for the number of iterations needed to ensure any desired reduction of the Euclidean distance between the iterate and the optimal solution ([Hagedorn & Jarre, 2023](#)).

Given the scarcity of information about the objective function F , we resort to *direct*, i.e., derivative-free search methods that seek optima essentially by comparing objective function values for different samples. The heuristic nature of the utilized approaches renders the formulation of theoretically valid and practically useful convergence properties difficult, if not impossible. That is why empirical testing and repeated application on different problems is essential for analyzing the true value of such methods ([Hicken et al., 2012](#); [Pedersen, 2010](#)). In study 1, we therefore compare the optimization performance by considering the detected objective function values, the invested computational resources as well as the spread of solution candidates. All is put in relation to the alleged optima identified via a dense grid search (GS), where the objective function is systematically evaluated on a dense parameter grid in the considered search space. This method constitutes a brute force approach to approximate optima. To further quantify the computational requirements of finding a qualitatively high solution, we empirically establish a *success probability* to reach a certain objective function value after a given number of algorithm executions.

Precisely speaking, we apply four derivative-free optimization algorithms to maximize the Pearson correlation coefficient between the parameter-dependent matrix $sFC(\mathcal{P})$ derived from the Kuramoto model and the subject-specific matrix eFC obtained from fMRI measurements. The considered methods are the *Nelder-Mead Algorithm* (NMA) ([Nelder & Mead, 1965](#)), *Particle Swarm Optimization* (PSO) ([Kennedy & Eberhart, 1995](#)), the *Covariance Matrix Adaptation Evolution Strategy* (CMAES) ([Hansen, 2006](#); [Hansen & Ostermeier, 1996](#)) and *Bayesian Optimization* (BO) ([Frazier, 2018](#); [Jones et al., 1998](#)). None of these methods requires the objective function to be differentiable or convex. Even the criterion of continuity has been relaxed for some, see below. In addition, all methods have been described as suited to handle noisy evaluations of the objective function. We therefore only assume that F is not constant, so that a search for optima is not trivial and the applicability of the described methods is assured.

The following descriptions of the algorithms are kept short, because detailed explanations of all updating rules and their characteristics are provided in the supplementary materials of study 1, see chapter 5.

NMA is a deterministic, local search method. In every iteration step, $\text{Dim}+1$ candidate solutions are sampled and ordered according to their corresponding objective function values. The algorithm then replaces the worst point by a new sample obtained from a series of transformations around the centroid of the remaining, more favorable candidates. A continuous surface of F together with a unique optimum in the search space X had originally been described as important for NMA applicability ([Nelder & Mead, 1965](#)). Newer works relaxed the assumption of continuity, stressed the ranking-based comparison of function values and touted NMA’s ability to handle noisy F -evaluations ([Elster & Neumaier, 1997](#); [Hicken et al., 2012](#); [Žic & Pereverzyev, 2019](#)).

The PSO method belongs to the class of population-based, global search strategies. It is a stochastic optimization scheme, related to genetic algorithms, in which a swarm of $\Lambda \in \mathbb{N}$ candidate solutions in form of particles with individual velocities explores the search space X ([Eberhart & Shi, 2000](#)). During the update step, every particle adjusts its moving direction according to the distance to both its individual most favorable position in X and the incumbent best point of all swarm members. The motivation behind this method is to seize the advantage of information exchange among particles in each iteration step. PSO has been designed for continuous functions ([Kennedy & Eberhart, 1995](#)). However, it has also been described as robust for non-differentiable, multimodal functions with discontinuous surfaces ([Perez & Behdinan, 2007](#); [Shi & Eberhart, 1998](#)) and problems with noisy F -evaluations ([Banks et al., 2007](#); [Parsopoulos & Vrahatis, 2001](#); [Poli et al., 2007](#)).

Another representative of population-based approaches is CMAES. Here, every iteration contains a set of $\Lambda \in \mathbb{N}$ non-moving particles in X which are treated as a *generation*. After identifying the most favorable members in terms of their corresponding F -values, a weighted mean of their coordinates is computed. It defines the mean of a multivariate normal distribution from which the next generation of solution candidates is sampled. The covariance of the search distribution is determined by a matrix $\mathbf{C}$ whose updates take the location of the current best points into account. Empirical experiments suggest that $\mathbf{C}$ approximates the inverse Hessian matrix (up to a constant factor) in case of a twice differentiable objective function ([Hansen, 2006](#); [Hansen & Ostermeier, 2001](#)). The criteria for applying CMAES are rather weak, continuity of F is rarely formulated in studies ([Shala et al., 2020](#)). In fact, the inventor commended the method for its robustness in dealing with non-convex and rugged search landscapes comprising sharp bends, discontinuities, outliers, noise and local optima ([Hansen, 2016](#)). One advantage is that while CMAES is based on the ranking of objective function values, it is also *non-elitist*, meaning that solutions with erroneously good F -values survive only one generation and therefore do not bias the search ([Hansen et al., 2009](#)).

BO is dedicated to the optimization of objective functions that may not be known to the user and/or expensive to evaluate ([Brochu et al., 2010](#)). It is a strategy of sequential design that implements a probabilistic surrogate model to estimate the shape of F , similar as in the related field of *kriging* ([Kriging, 1951](#); [Matheron, 1971](#)). The surrogate can be updated after every new F -evaluation, while new solution candidates are found sequentially via the maximization of an *acquisition function*. Being comparably easy to optimize, the acquisition function indicates the area where the most favorable objective function values can be anticipated. This way, the algorithm incorporates information from sequential F -evaluations into the search for optima. BO is best suited for problems featuring less than 20 free parameters ([Frazier, 2018](#)), where it belongs to the most efficient approaches regarding the number of required function evaluations ([Brochu et al., 2010](#)). The algorithm assumes the objective function F to be continuous, but tolerates noise perturbations in its observations ([Brochu et al., 2010](#); [Frazier, 2018](#)).

At this point, we stress that we apply the methods to personal fMRI data of human subjects. Each person defines a new function to be optimized. In addition, the consideration of two, three or more free model parameters in the objective function leads to separate optimization problems. The same applies to the investigation of different atlases which shape the representation of the SC and FC. Our consideration of $S = 105$ subjects in study 1 for one atlas and two parameter spaces ($\text{Dim} \in \{2,3\}$) therefore

corresponds to $105 \times 1 \times 2 = 210$ optimization problems. These were tackled by the described four algorithms as well as a manual search on a dense parameter grid. Study 2 broadens the horizon and deals with $S = 272$ subjects, two atlases and an additional consideration of one high-dimensional parameter space for each atlas ($\text{Dim} \in \{2,3,99\}$, $\text{Dim} \in \{2,3,103\}$). This results in a total of $272 \times 2 \times 3 = 1632$ optimization problems which were investigated by two methods, CMAES and BO. Study 3 utilizes the data from the previous studies for predictive approaches focusing on character traits and phenotypical properties. In the following chapter, we elaborate on the aims of our work.

4 Aims of this thesis

In this thesis, we utilize concepts of mathematical optimization to contribute to an enhanced understanding of the functioning of the human brain. The goal is to seize more of the huge potential of dynamical whole-brain models, for which an efficient parameter fitting to empirical data is vital. We want to suggest alternatives to brute force parameter scans that have dominated the literature for years. Here we are not only interested in obtaining similar results as from a dense GS with considerably less computational efforts. We also want to know how mathematical optimization methods can help in exploring new model parameter spaces, where the number of considered variables is substantially higher and grid-based parameter scans are no longer an option. Finally, we want to find out how useful our presented workflow proves for predictive investigations of inter-individual variability. Any fitted model like the considered Kuramoto model provides novel information in terms of the simulated human brain activity as well as its associated model parameter values. This is an additional contribution compared to empirical data obtained from fMRI measurements alone. Combining the insights from both approaches appears reasonable and beneficial for the study of phenotypical and behavioral differences. We pursue our aims with the three publications explained below.

Study 1

Wischniewski, K. J., Eickhoff, S. B., Jirsa, V. K., & Popovych, O. V. (2022). Towards an efficient validation of dynamical whole-brain models. *Scientific Reports*, 12(1), 4331.

In study 1, we test and compare four direct optimization algorithms to maximize the correlation between sFC and eFC. We consider low-dimensional parameter spaces ($\text{Dim} \in \{2,3\}$). The results of a dense GS serve as a benchmark to assess the method performance on a total of 210 subject-specific optimization problems. We document the internal hyperparameter settings and study the observed convergence behavior. The quality and utility of the optimization algorithms are assessed by comparing the potential susceptibility to local optima as well as the invested computational resources. We want to know whether a dense GS can be reliably replaced by the considered optimization algorithms. Further, we aim to identify the most efficient approaches for further applications.

Study 2

Wischniewski, K. J., Jarre, F., Eickhoff, S. B., & Popovych, O. V. (2025). Exploring dynamical whole-brain models in high-dimensional parameter spaces. *PloS One*, 20(5), e0322983.

The focus of study 2 lies on the parameter optimization in high-dimensional search spaces ($\text{Dim} \in \{99,103\}$). We want to find out which advantages and challenges arise from a transition from low- to high-dimensional cases. Based on the systematic evaluation of the results from study 1, we apply the two algorithms that turned out most effective in terms of robustness and computational costs. Considering 1632 optimization problems altogether, we investigate the reliability of the results and suggest strategies to select one solution in the presence of multiple near-optimal candidates. We also deploy our data in a classification problem to estimate their benefit for studies on behavioral and phenotypical differences.

Study 3

Jung, K., Wischnewski, K. J., Eickhoff, S. B., & Popovych, O. V. (2025). Effective workflow from multimodal MRI data to model-based prediction. *Scientific Reports*, 15(1), 20126.

Study 3 was conceived with the goal of embedding dynamical whole-brain modeling into a workflow from raw MRI data acquisition to the prediction of behavioral traits and phenotypical characteristics. We extend the efforts from study 2 to a systematic evaluation of the performance of our simulation results in machine learning tasks. This includes demonstrations of sex classification as well as predictions of personality traits and general intelligence. The main objective is to illustrate a comprehensive prediction approach, where the optimized modeling outcome is leveraged for machine learning. It enables us to evaluate the practical utility of the simulated human brain activity for investigations of inter-individual variability.

5 Study 1: Towards an efficient validation of dynamical whole-brain models

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The scientific content of the main text is presented as in the online publication. In the supplementary materials, minor errors have been corrected, and complementary information has been added. The referencing style and figure labeling reflect the requirements of the publishing journal. Equations are enumerated with the appendix “S1” to distinguish them from the equations used in the other chapters of this thesis.



OPEN

Towards an efficient validation of dynamical whole-brain models

Kevin J. Wischniewski^{1,2}, Simon B. Eickhoff^{1,2}, Viktor K. Jirsa³ & Oleksandr V. Popovych^{1,2}✉

Simulating the resting-state brain dynamics via mathematical whole-brain models requires an optimal selection of parameters, which determine the model's capability to replicate empirical data. Since the parameter optimization via a grid search (GS) becomes unfeasible for high-dimensional models, we evaluate several alternative approaches to maximize the correspondence between simulated and empirical functional connectivity. A dense GS serves as a benchmark to assess the performance of four optimization schemes: Nelder-Mead Algorithm (NMA), Particle Swarm Optimization (PSO), Covariance Matrix Adaptation Evolution Strategy (CMAES) and Bayesian Optimization (BO). To compare them, we employ an ensemble of coupled phase oscillators built upon individual empirical structural connectivity of 105 healthy subjects. We determine optimal model parameters from two- and three-dimensional parameter spaces and show that the overall fitting quality of the tested methods can compete with the GS. There are, however, marked differences in the required computational resources and stability properties, which we also investigate before proposing CMAES and BO as efficient alternatives to a high-dimensional GS. For the three-dimensional case, these methods generated similar results as the GS, but within less than 6% of the computation time. Our results contribute to an efficient validation of models for personalized simulations of brain dynamics.

Following the ground-breaking work of Biswal et al.¹, neuroimaging research has experienced a shift in attention towards resting-state brain activity^{2,3}. The discovered similarity between the task-evoked functional networks and the corresponding connectivity patterns observed from human brain activity at rest strongly motivated the investigation of the latter^{1,4,5}. A multitude of study approaches and applications of the resting-state dynamics have been developed. They aimed at understanding the brain architecture and function on the one hand and at a differentiation between individuals in health and disease on the other hand^{6–12}. A promising avenue to achieve both of these goals is provided by numerical simulations of complex spatio-temporal brain activity patterns via dynamical whole-brain models^{13–19}.

The data-driven dynamical models allow for the incorporation of anatomical information about the human brain into the simulation of its dynamical properties. In other words, they enable researchers to investigate the relationship between brain structure and function with a particular focus on the question whether and how the latter emerges from the former and how they correlate^{13–19}. Additionally, models offer a quick in silico experimental way to study and compare different brain parcellations, network configurations and parameters of data-preprocessing, which again contributes to a deeper understanding of the interaction between the brain architecture and dynamics^{20–22}. Another advantage of the discussed modeling approach is that it allows for a meaningful description of complex natural phenomena by a set of interpretable parameters. The whole-brain models are designed to mimic human brain dynamics in a way that fairly reduces its intricacy and renders it accessible for deep and systematic analyses²³. Differentiation between individuals in health and disease can thus be facilitated on the basis of biologically motivated model parameters and model dynamics. Model simulations can also improve the overall interpretability by performing a certain denoising, meaning that only the relevant dynamics and phenomena are modeled, but not the unwanted effects of random noise. In particular, model simulations showed a potential to reveal previously unknown characteristics of neural activity, allowing, for example, to distinguish between disease subtypes which cannot be identified by considering empirical brain imaging data only²⁴.

Current understanding of the mechanisms underlying the observed complex patterns of collective neuronal dynamics and connectivity remains, however, highly fragmented, and deeper investigations are still required. In this effort, it is crucial to seize the full potential of the broad spectrum of available computational models^{25–31} developed in the course of brain research. Notably, with a rising number of neural activity models on several

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scales (single neurons, neuronal populations, brain regions) and their complexity, the challenge of their adequate validation against empirical data has become apparent. More precisely, model validation consists of adjusting the parameters, which have a well-founded relation to brain characteristics, e.g. global and local coupling, signal transmission delay or an excitation-inhibition balance^{14,15,19}, in a way that the best possible correspondence between simulated and empirical dynamics is obtained. It is of highest relevance for recent investigations of personalized brain modeling, where a search for subject-specific optimal parameters is conducted^{32–35}. Additionally, the application of individualized brain models in population-based approaches offers a promising way to examine between-subject effects and possible parametrizations of inter-individual differences^{24,36}.

An intuitive approach is to optimize model parameters by a systematic exploration along a dense discrete grid in the parameter space. This procedure, often termed *grid search*, has been applied in a variety of model-based studies^{16,35,37,38}. On first sight, such a brute force approach may appear to be the *safe* way to explore the parameter space, but it holds several conceptual and technical challenges. Foremost, the number of parameters used in a grid search is typically small (such as 2–5), where in the real system adjustments can be made for many more parameters. Arguments are evoked that these parameters can be estimated from data, which usually assumes independent measurements. As joint probabilities of parameters are not necessarily limited to second orders (see, for instance, the work of Marder and Goaillard³⁹), degeneracy will be a major contaminating factor for a proper interpretation of the simulation results. The second conceptual challenge is the extraction of data features used for the comparison between simulated and empirical data. The selective use of simplifying data features facilitates the analysis, but also imposes theory-driven filters in interpreting the results. The technical challenges are computational. Given that the grid is dense enough, the probability to miss important characteristics (such as the maximal similarity between simulated and empirical data) is low. Unfortunately, an exploration of the entire parameter space on a dense grid is computationally expensive and becomes unfeasible for complex models with many free parameters. If, for example, a machine equipped with $p = 48$ processors required only $t = 100$ s per subject to perform a one-dimensional grid search covering p parameter points, then the total time consumption of a grid search covering p^{Dim} ($= 110\,592$) parameter points for a model with $\text{Dim} = 3$ free parameters would roughly be given as $t p^{\text{Dim}-1} = 64$ h. For a cohort of $S = 100$ subjects, the demands rise to $S t p^{\text{Dim}-1}$, which corresponds to around 9 months of calculations. Another aspect, whose importance must not be neglected, is that the sheer mass of occurring parameter points renders the entire investigation intractable, too. That is why already a three-dimensional grid search with adequate granularity as, for example, in Schirner et al.³⁵, is rather exceptional than usual. Additionally, the strategy of a sequential tuning of certain parameters^{14,36}, where individual components are optimized separately from each other and afterwards fixed, may not always be applicable for multi-dimensional tasks that are not separable into low-dimensional subproblems. These aspects hamper high-dimensional model studies in their potential to infer parameter-dependent differences between subjects. Papers discussing individualized simulations of brain dynamics are therefore based on models that hardly ever exceed five free parameters, with a majority investigating up to three variables only. Studies bringing forward desirable enhancements to more than 100 region-specific model parameters, as described in Wang et al.⁴⁰, for example, currently lack feasible ways of implementation.

Previous works^{40–43} have already identified the so-called *inverse problem* of estimating optimal parameters from given empirical data and advocated for the use of alternatives to a thorough parameter space scan. We emphasize that optimal parameters usually comprise degenerate manifolds that ideally would be sampled systematically by Monte Carlo approaches^{32,33}, but the use of mathematical optimization algorithms is often the more practical solution^{44–46}. These methods enable the exploration of high-dimensional parameter spaces (under certain limiting assumptions), for which a grid search is impracticable. In good practice, when aware of the limitations and underlying hypothesis (such as the existence of a unimodal posterior distribution), these approaches can be very powerful. Currently, the literature lacks an evaluation of the particular advantages and limitations connected to their applicability in individualized whole-brain modeling. Studies based on larger subject cohorts could underpin their robustness in dealing with in vivo data that feature increased complexity compared to purely theoretical and noise-free mathematical problems, which constitute a common field of their application.

In this work, we focus on the technical computational challenges. We implemented and tested several such optimization schemes which were designed to extensively explore complex high-dimensional parameter spaces in an adequate amount of computation time. Searching for subject-specific optima, we investigated the applicability of these techniques for the validation of whole-brain models. We systematically compared their outcomes as well as computational costs with each other and the grid search approach. In particular, we considered a system of phase oscillators with delayed coupling^{47–49} to model the resting-state blood oxygen level-dependent (BOLD) dynamics, from which we extracted the simulated data feature of functional connectivity (FC). For a cohort of 105 subjects, the model was built upon the individual anatomical brain connectivity obtained from diffusion-weighted magnetic resonance imaging (dwMRI). It determined the coupling weights and time delays between individual network nodes. The individual model was then validated against the corresponding functional neuroimaging data (empirical FC) for each subject. Model parameters were optimized in order to maximize the model fit given by the correlation between simulated and empirical FCs. The highest possible similarity between these quantities was termed the model's *goodness-of-fit*.

We studied four derivative-free methods as given by the Nelder-Mead Algorithm⁵⁰, Particle Swarm Optimization⁵¹, Covariance Matrix Adaptation Evolution Strategy^{52,53} and Bayesian Optimization⁵⁴. These methods were directly applied to the simulation output obtained from the numerical integration of the model equations. Our investigations were made for two and three free parameters in the utilized model. To better assess the quality of the algorithm solutions, we also included a systematic parameter variation (grid search) for each subject in both dimensionalities of the parameter space. It served as a good approximation of a *ground truth* provided that the grid is dense enough in the considered range of parameters. The comparison criteria considered

the obtained goodness-of-fit, the required computation time and the location of optimized parameters, or, more precisely, the spread of the algorithm solutions combined with their distance to the grid search optima.

Our study aims at suggesting efficient and reliable algorithms for the optimization of the correspondence of functional connectivity within simulated and empirical data in whole-brain modeling. The intention is to point up the ways that have to be taken in higher dimensions, where the grid search approach becomes inapplicable due to insurmountable numbers of parameter constellations that would have to be evaluated. After analyzing the advantages and drawbacks of the tested methods, we eventually arrive at a recommendation for two particular algorithms that provide a favorable trade-off between the result robustness and invested computational resources.

Methods

Overview. In this study, we worked with neuroimaging data of $S=105$ healthy, unrelated subjects (age 28.5 ± 3.4 years, 51 males) from the Human Connectome Project (HCP) S1200 public dataset release⁵⁵. Approval for the study was given by the local ethics committee of the HCP WU-Minn and written, informed consent was obtained from all subjects. All methods were performed in accordance with the relevant guidelines and regulations. The given datasets had been utilized for the extraction of structural and resting-state functional connectivity (SC and FC, respectively) in related works^{20–22}. We used the obtained empirical connectomes for the model derivation and validation. More precisely, Schaefer's atlas⁵⁶ with $N=100$ cortical regions was employed as a brain parcellation for the calculation of an atlas-based SC. The latter served as a basis for the underlying network in the dynamical model and was used to determine the coupling weights and delays between individual network nodes (brain regions or parcels). The model then was deployed to simulate the resting-state brain dynamics and eventually generate simulated FC (simFC). This in turn was fitted to the empirical FC (empFC) by adjusting up to three model parameters simultaneously: global coupling and delay in a two-dimensional parameter space (see also Cabral et al.^{57,58}) and additionally the noise intensity when a three-dimensional scenario was considered (see also Deco et al.¹⁴).

Besides an extensive parameter sweep exploration on a dense grid, referred to as a grid search, we implemented four mathematical optimization algorithms in order to determine the optimal parameter values which maximize the similarity between simulated and empirical data. We measured this similarity with the Pearson correlation coefficient between simFC and empFC. To compare the algorithms' outcomes systematically with each other and the grid search, we focused on the following criteria: For every subject, we analyzed the goodness-of-fit values detected within a predefined number of algorithm executions with different initial conditions. The highest value as well as the standard deviation of all solutions were considered and compared across the methods. Then, the required computation time of the optimization algorithms was put in relation to the grid search's demands. In addition, we investigated the reliability of the results by examining the location of the obtained solutions in the parameter space. The spread of the supposed optima detected by a given algorithm for a particular subject was analyzed together with the averaged distance to the respective optimal parameters found by the grid search. We want to highlight that, despite the important aspect of a reduced computation time, we were also concerned with finding stable methods that detect the global optima most reliably (which may be manifested by a low spread of solutions in the parameter space, for example). Our main goal was to suggest alternative ways for model validation that promise a clearly lower computational burden than the grid search combined with a favorable robustness. We thus analyzed the obtained results based on the three mentioned criteria, which can be summarized as

- the goodness-of-fit,
- the necessary computation time and
- the location/spread of the optimized parameters.

Data preparation. The pipeline implemented for the extraction of SC comprised four major steps: pre-processing of raw magnetic resonance images (MRIs), calculation of a whole-brain tractography (WBT), transformation of the brain parcellation images to the native space and, finally, SC reconstruction based on the brain parcellation. In this procedure, software tools from ANTs⁵⁹, FreeSurfer⁶⁰, FSL⁶¹ and MRtrix3⁶² were applied, see Jung et al.²¹ and Popovych et al.²² for the details.

In the first step, the T1-weighted images and the diffusion-weighted MRIs (dwMRIs) were preprocessed (intensity normalization, denoising, motion correction, tissue segmentation, etc.) with functions from FreeSurfer and MRtrix3. Subsequently, a co-registration via FSL was performed. In the second step, functions from MRtrix3 were used to compute a WBT. A set of 10 M streamlines in total was extracted by the help of a probabilistic algorithm⁶³. Afterwards, linear and non-linear transformations were applied to the image of Schaefer's atlas in order to transfer it from the Montreal Neurological Institute (MNI) standard space, in which it was sampled, to the native diffusion space. The workflow in this step involved functions from FSL. Finally, the MRtrix3 function *tk2connectome* was used to reconstruct the parcellation-based SC that comprised two matrices: one with the number of streamlines between individual regions, i.e. the streamline count, henceforth referred to as SC, and another one containing the average length of the streamlines between regions, termed path lengths (PL).

For the calculation of empFC in turn, the ICA-FIX⁶⁴ preprocessed resting-state functional MRI (fMRI) data provided by the HCP repository were considered. Time series of the BOLD signals were extracted as mean signals averaged over all voxels of individual brain regions. Then, calculating the Pearson correlation for each pair of linearly detrended and z-scored BOLD time series from the respective cortical areas eventually yielded the corresponding FC matrix.

In this setting, four fMRI sessions of 1200 volumes sampled with a repetition time of $TR=0.72$ s each were available for every subject (scans were performed twice using different phase-encoding directions on two days). Additionally, a concatenated BOLD signal was generated by combining the z-scored BOLD time series from the

mentioned sessions. We focused on the empFC matrix derived from the concatenated session for the optimization of model parameters in terms of the best fit between simulated and empirical data.

Model simulations. To obtain simFC, we implemented the Kuramoto model of coupled phase oscillators^{48,49,57}, which is one of the simplest models used for simulating features of resting-state brain activity (here the phase dynamics)³⁷. Its reduced complexity compared to other whole-brain models makes it suitable to investigate the immediate impact of the model parameters on the simulated dynamics. We do not suspect, however, that our insights and qualitative results depend on the selected modeling approach. We therefore worked with this basic model, in which each of N oscillators represented one brain region defined by the underlying parcellation ($N=100$ for the considered atlas). Their temporal dynamics served as a basis to compute simulated BOLD signals that were eventually cross-correlated in order to derive the simFC matrix. More precisely, the model assumes that the phase dynamics of the mean BOLD signal of a brain region $i \in \{1, \dots, N\}$ can be described by the following differential equation:

$$\dot{\theta}_i(t) = 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(\theta_j(t - \tau_{ij}) - \theta_i(t)) + \sigma \eta_i(t). \quad (1)$$

For a given time t , $\theta_i(t) \in [0, 2\pi]$ denotes the value of the phase that oscillates with a natural frequency f_i if left uncoupled ($k_{ij}=0$) from the other oscillators. The frequencies f_i were estimated from the maximal spectral peaks (restricted to the frequency range from 0.01 Hz to 0.1 Hz) of the empirical BOLD time series.

Apart from intrinsic oscillations, the phase dynamics is governed by delayed interactions with the other oscillators. The individual coupling strengths k_{ij} and delay values τ_{ij} were determined on the basis of the empirical matrices $SC = (SC)_{1 \leq i, j \leq N}$ and $PL = (PL)_{1 \leq i, j \leq N}$, respectively:

$$k_{ij} = \frac{SC_{ij}}{\langle SC \rangle N} C, \quad \tau_{ij} = \frac{PL_{ij}}{\langle PL \rangle} \tau. \quad (2)$$

In this context, $\langle \cdot \rangle$ indicates the mean over all matrix elements, excluding the zero diagonals. C and τ are global weighting factors that influence the strength and delay of the interactions between individual oscillators, respectively. These quantities can be interpreted as free parameters in the dynamical system. Additionally, it is possible to adjust the intensity σ of the independent noise $\eta_i(t)$ which is sampled from a uniform distribution over $[-1, 1]$ and perturbs the individual oscillators. While C and σ can be regarded as dimensionless quantities, τ is measured in seconds.

We solved Eq. (1) numerically using Heun's method for stochastic differential equations⁶⁵ with a discrete time step of $\Delta t = 0.06$ s. The calculated phases were downsampled to 0.72 s in order to match the repetition time of the fMRI data provided by the HCP. With the model at hand, we generated simulated BOLD time series by computing $\sin(\theta_i(t))$ for all $i \in \{1, \dots, N\}$ corresponding to the regions in the considered brain parcellation. As mentioned above, the matrix simFC was then derived from the Pearson correlation coefficients across all pairs of simulated time series. These featured a length of 3500 s after excluding an initial transient of 500 s. We assessed the similarity between simulated and empirical data by correlating the matrices of $\text{simFC} = \text{simFC}(C, \tau, \sigma)$ and empFC.

Parameter optimization. Mathematically, the search for the parameters that maximize the correspondence between simFC and empFC (the model fit) can be interpreted as an optimization problem of a goal function $F = F(C, \tau, \sigma)$ that returns the Pearson correlation coefficient between the model output and the corresponding empirical measurement. Our knowledge about F is limited to a numerical calculation of its values (numerical integration of Eq. (1) and correlation between simFC and empFC) depending on the relevant model parameters (e.g. global coupling C , global delay τ and noise intensity σ) and the assumption of continuity. We thus supposed that the function F is not available in a closed form, and no claim was made about the existence of derivatives. In other words, we were to a great extent dealing with a black-box optimization problem. We optimized the model parameters by a systematic variation on a dense grid, before testing the performance of derivative-free optimization algorithms on the same problem.

All model fitting simulations for this study were performed on the CPU partition of the high-performance supercomputing cluster JURECA⁶⁶ at Forschungszentrum Jülich. Each computation node featured two Intel Xeon E5-2680 v3 12-core Haswell CPUs, and each core supported two hardware threads, so that one computation node (consisting of two 12-core CPUs) ultimately offered $2 \times 2 \times 12 = 48$ threads for simultaneous computations. The base frequency of the CPUs was 2.5 GHz and the maximum memory bandwidth of one node was 136 GB/s. We refer to the work of Krause and Thörnig⁶⁶ for further details about the configuration of JURECA.

Grid search. At first, we considered a two-dimensional (2Dim) parameter space in which the noise intensity was fixed at $\sigma = 0.3$. The global weights for coupling $C \in [0, 0.945]$ and delay $\tau \in [0, 94]$ were tuned along a set of $64 \times 48 = 3072$ discrete, equidistant points. The selected parameter range for the considered model was suspected to include the optimal model parameters of the best correspondence between simulated and empirical data, which was confirmed by post-simulation analyses²². Furthermore, the considered grid granularity was selected as a trade-off between the computational costs and a favorable density that allowed for a close approximation of the goodness-of-fit values as confirmed in this study by comparing the fitting results with those of other optimization methods. For each tuple (C, τ) , we generated simFC which we compared to the empirical data, resulting in a total of 322 560 ($64 \times 48 \times 105$) model simulations for the considered cohort of 105 subjects. One subject required approximately 100 min (≈ 1.67 h) of calculation time on a CPU node with 48 threads for paral-

lel computations ($24 \text{ cores} \times 1.67 \text{ h} \approx 40 \text{ core-hours}$). Subsequently, we performed another thorough parameter scan in which we also varied the noise intensity σ . This three-dimensional (3Dim) grid search was executed for $48 \times 22 \times 81 = 85536$ tuples (C, τ, σ) and required approximately 1200 core-hours per subject. While the individual values for $C \in [0, 0.94]$ and $\sigma \in [0, 2]$ were equidistant, $\tau \in [0, 48]$ was distributed more densely for smaller values. For a broad exploratory investigation of the noise impact, its intensity was varied between 0 (noise-free scenario) and a maximal amplitude of 2, which was inspired by Deco et al.¹⁴ and indicates a very strong perturbation of the system dynamics. In view of the rising computational requirements, the highest value of delay τ was reduced to 48, which however did not distort the results, because the parameters maximizing the model fit did not suggest very large delays²². The search in 3Dim comprised about 9 M model simulations for 105 subjects included in the study.

A few examples of the goal function $F = F(C, \tau)$ depending on the global coupling C and delay τ are shown in Supplementary Fig. S1, where the noise intensity is set to $\sigma = 0.3$ (in accordance with our definition of the 2Dim parameter space). F exhibits a different shape for every single subject, and thus, also the value and location of the maxima are different (dark red color). Finding the subject-specific maximum of F constitutes the model validation against empirical data.

In the following, we outline the investigated mathematical optimization schemes that we applied in addition to the grid search. The goal was, again, to maximize the goal function F for each subject in the respective (2Dim or 3Dim) parameter space. Since most methods are traditionally formulated as function minimizers, we internally worked with $-F$: a maximization of F is equivalent to a minimization of $-F$.

Nelder-Mead Algorithm. The first method tested was the Nelder-Mead Algorithm (NMA), introduced more than 50 years ago by Nelder and Mead⁵⁰. It is also known as the Downhill Simplex Method and belongs to the class of direct local search methods. Its derivative-free optimization procedure is purely deterministic, updating in each iteration the worst of the given trial solutions based on the ordering of the respective function values. More precisely, the algorithm starts with an initial set of $\Lambda = \text{Dim} + 1$ points that define the vertices of a simplex in the parameter space. In the most vivid case, $\text{Dim} = 2$, this corresponds to a simple triangle. After evaluating the objective function at all vertices, the algorithm replaces the vertex with the highest function value by a new point found through a series of transformations around the centroid of the remaining ones. These operations include, among others, expansions and contractions of the current simplex. Ideally, this procedure will create a sequence of simplices of decreasing size which accumulate around the desired optimum of F . More details on the strategy can be found in Lagarias et al.⁶⁷ and Hicken et al.⁶⁸ as well as in the Supplementary Materials. We also define the utilized stopping criterion (sufficiently short simplex edges), which effectively terminated the optimization before reaching the maximum of 80 iterations in more than 99% of the performed algorithm executions. A few examples of the best goal function values depending on the number of executed iterations are shown in Supplementary Fig. S2.

Particle swarm optimization. The algorithm of Particle Swarm Optimization (PSO) was the second method in our considerations. It is a population-based variant of global stochastic search strategies and has originally been introduced by Kennedy and Eberhart^{51,69}. Derived from the simulation of natural phenomena such as bird flocking or fish schooling, it features a swarm of $\Lambda \in \mathbb{N}$ particles (we selected $\Lambda = 60$ after an internal hyperparameter optimization) exploring the parameter space collaboratively and exchanging information about the discovered function values in each step. The individual particles are given by their coordinates in the parameter space and can be regarded as trial solutions in the iterative optimization of the goal function. They are equipped with particular velocities that are repeatedly updated and therefore enable an exploratory roaming along distinct trajectories. Throughout the iterations, every particle remembers its individual best position, i.e. the location in the parameter space where an evaluation of the objective function yielded the lowest value on the particle's way so far. This information is shared with the entire swarm, so that the current global best position of all individuals can be determined and communicated across particles based on the respective function values. In the velocity update, each particle then adjusts its moving direction according to the distance to both its individual most satisfactory position and the global best point. The aim of this strategy is to seize the advantages of social sharing of information during a collaborative search. Individual best points lying close to the global one, eventually lead to a dense swarm with particles gathered around the suspected global optimum of F . More detailed outlines of the algorithm can be found in related mathematical works^{70–72} and in the Supplementary Materials. In roughly 11% of the executions we performed, the optimization was terminated prematurely due to a saturation and lack of improvement during 50 (out of 80) consecutive iterations. A few examples of the convergence and the optimal F -values depending on the iteration steps are illustrated in Supplementary Fig. S2.

Covariance matrix adaptation evolution strategy. The third algorithm under our investigation was the Covariance Matrix Adaptation Evolution Strategy (CMAES). Since its introduction⁵² and subsequent concretization⁵³, it has proven robust and successful in many black-box optimization problems^{73–75}. CMAES shares PSO's feature of being a population-based optimization approach. In the evolution strategy, however, the underlying concept is different, and particles do not roam the parameter space on individual trajectories. Instead, the points from every iteration are regarded as a *generation* from which only the best members are selected to form the population for the next step. The optimization procedure starts with a particle generation of moderate size (default $\Lambda = 4 + \lfloor 3 \ln(\text{Dim}) \rfloor$)⁷⁶, which may be increased. We selected $\Lambda = 24$ after an extensive algorithm testing. Then, it works with a weighted mean of $\lfloor \Lambda/2 \rfloor$ solutions which yield the lowest values of the goal function. Afterwards, a new generation of search points is obtained by taking Λ samples from a multivariate normal distribution centered around the weighted mean of these most promising points. The (co)variance

is determined by a matrix whose update formulas take the location of the current best points into account. In this way, the search distribution is adapted iteratively towards a concentration around the optimal solutions, see Hansen et al.^{76,77} and the Supplementary Materials for further details. An early termination due to saturation and lack of improvement of the goal function during 50 (out of 80) consecutive iterations was observed in approximately 24% of the executions we performed. A few examples of the convergence and optimal F -values generated by the algorithm after every iteration step are presented in Supplementary Fig. S2 for a few subjects.

Bayesian optimization. Lastly, we also considered the strategy of Bayesian Optimization (BO). Some of its conceptual principles can already be found in early works^{78,79}. However, the current form of BO as a sequential design strategy for global optimizations of black-box functions has been discussed in more recent papers^{34,80}. Starting with a random sample of a small to moderate number of candidate solutions ($\Lambda \leq 10$ Dim, we used $\Lambda = 5$ to 10) in the parameter space, BO works with a probabilistic surrogate model for the goal function. Typically, *Gaussian Process Regression*⁸¹ is applied. The model is adjusted based on every new function evaluation, and further sampling points are found iteratively by an *acquisition function*. It indicates the area where the highest gain can be expected. One advantage of this algorithm is that it incorporates the information from all previous evaluations in order to estimate the shape of F . Additionally, the internal procedures can be adjusted especially for the case of function values perturbed by noise. Detailed descriptions of the individual steps can be found in algorithm-related works^{82,83} and in the Supplementary Materials. In our simulations, we used the C++ software package *BayesOpt*⁸⁴. It allowed for the utilization of the stopping criterion in the form of a maximal number of iterations, which we set to 80. A few examples of the method convergence and the optimal values of the goal function depending on the number of executed iterations are shown in Supplementary Fig. S2.

Algorithm executions and success probability. For all tested subjects, we first executed each method for $R_{\max} = 15$ times with different random initial data in the respective parameter spaces. From the individual runs, we extracted the highest model fitting value and the corresponding parameter constellation. The values for optimization were bounded to $(C, \tau) \in [0, 1] \times [0, 100]$ in the 2Dim scenario and to $(C, \tau, \sigma) \in [0, 1] \times [0, 100] \times [0, 2]$ in the 3Dim case.

Then, we also investigated how the number of algorithm executions with different initial data can influence the model validation results. We therefore evaluated how many runs of a given optimization method are on average necessary to obtain a goodness-of-fit of at least 95% of that from the grid search. In cases where the quality of the model validation of the grid search was not reached by a given algorithm after the default number of $R_{\max} = 15$ runs, we performed some additional simulations to test whether a larger number of algorithm executions can improve the model fitting. This resulted in a total of $R_{\max} = 24$ executions for NMA and BO, see “Results”.

To calculate a probability of reaching 95% of the goodness-of-fit of the grid search for a given number of runs, we started with randomly selecting $R = 1, 2, \dots, R_{\max}$ goodness-of-fit values out of the available solutions of a given algorithm. After comparing the selected values to the threshold, we assigned either 0 (for failure, i.e. the grid search result was not reached by any of the selected values) or 1 (for success, i.e. grid search result was reached by at least one of the selected values) to the current set of R goodness-of-fit values. This procedure was repeated 500 times for every choice of R , subject and optimization algorithm. For every method, we then computed the mean success rate (from all 500 trials) for each subject and then averaged it over all subjects for every value of R . This gave us a subject-independent estimate of the probability to reach the threshold with R algorithm runs. We henceforth refer to this quantity as a *success probability*. In such a way we evaluated the expected number of optimization runs needed by every considered method to reach a certain success probability of the model fitting quality comparable with the grid search results. This number of runs played a crucial role in comparing the actual time requirements of the individual algorithms, where the computational resources were calculated for the number of runs needed to reach the same success probability.

Cost function Ψ_{cost} . For a systematic evaluation and comparison of the tested optimization algorithms, we defined a cost function Ψ_{cost} that combines several individual properties of the algorithms including the goodness-of-fit, the computation time and the location of the optimized parameters that can be used to assess the quality of the optimization. The components of the cost function represent the features along which we estimated every method's advantages and limitations. In this procedure, we assigned each algorithm a certain cost value for every subject and interpreted lower costs as better results.

To construct Ψ_{cost} , we specify the notation that we will use in the following. For each subject and algorithm,

we calculated a vector $\text{Fit} = \begin{pmatrix} \text{Fit}_1 \\ \vdots \\ \text{Fit}_{15} \end{pmatrix} \in \mathbb{R}^{15}$ collecting the goodness-of-fit values from all 15 executions, a matrix

$$\text{Points} = \begin{pmatrix} P_1 \\ \vdots \\ P_{15} \end{pmatrix} = \begin{pmatrix} C_1 & \tau_1 & \sigma_1 \\ \vdots & \vdots & \vdots \\ C_{15} & \tau_{15} & \sigma_{15} \end{pmatrix} \in \mathbb{R}^{15 \times \text{Dim}} \quad (3)$$

of dimension $15 \times \text{Dim}$ containing the optimal values of the respective model parameters (C, τ, σ) , and a scalar $\text{Time} \in \mathbb{R}$ representing the cumulated computation time required for executing the number of algorithm runs needed to obtain a success probability of 80% (see previous section). In the 2Dim case, the third column with the noise intensity σ disappears in the matrix Points .

For the grid search in turn, we extracted a matrix

$$\text{GridPoints} = \begin{pmatrix} G_1 \\ \vdots \\ G_5 \end{pmatrix} = \begin{pmatrix} C_1^{GS} & \tau_1^{GS} & \sigma_1^{GS} \\ \vdots & \vdots & \vdots \\ C_5^{GS} & \tau_5^{GS} & \sigma_5^{GS} \end{pmatrix} \in \mathbb{R}^{5 \times \text{Dim}} \quad (4)$$

of dimension $5 \times \text{Dim}$ that contains the parameter values corresponding to the five highest correlations between simFC and empFC discovered in the exhaustive parameter space scan. Again, the last column listing the noise intensities was removed in the 2Dim case. The cost function Ψ_{cost} can then be constructed from its individual components as explained below.

1. The first factor considers the highest goodness-of-fit value that a particular algorithm discovered based on its 15 executions. Since the model fit is measured by the Pearson correlation coefficient between empFC and simFC, this quantity is limited to the range $[-1, 1]$. Then the simple difference $1 - \max\{\text{Fit}_i\}$, $1 \leq i \leq 15$, reflects higher Fit values as lower costs.
2. For the second factor, we took the spread of the objective function values (i.e. the detected goodness-of-fit values) into account. We therefore computed the standard deviation (SD) of the 15 model fits for every algorithm and subject. This quantity assigns higher costs to methods that tend to converge to local maxima besides the global ones, reflected by a higher variance in the respective goodness-of-fit values.
3. The third component incorporates the computation time required for the number of algorithm executions necessary to reach a success probability of 80% (see previous section).
4. As the next important ingredient of Ψ_{cost} , we considered the spread of the optimized parameters across replications. We therefore computed the mean Euclidean distance between the 15 solutions of a given algorithm in the parameter space (normalized to $[0, 1]^{\text{Dim}}$). In this setting, a lower spread indicates a higher stability of the respective method, while larger values hint at a convergence to more than one (local) optimum.
5. Finally, the distance of the algorithm solutions to the optima found by the grid search plays a role in the cost function. For the latter method, we extracted five parameter points per subject (GridPoints) that provided the highest goodness-of-fit values and which approximated the global optimum, as mentioned above. We then computed the average pairwise Euclidean distances between the 15 algorithm solutions on one side and the five grid search solutions on the other side. This term was included in the cost function in order to evaluate how much the calculated algorithm solutions deviate from the approximate ground truth given by the results of the grid search. Additionally, we aimed at making more precise differentiations in cases where the algorithms converge to more than one solution.

For better interpretability, the calculated values were normalized to the interval $[0, 1]$ by dividing by the corresponding maxima (calculated over all algorithms for a given component in the respective parameter space).

We multiplied the mentioned components in order to obtain the final values of Ψ_{cost} for each algorithm and subject. In summary, we obtained a 105×4 matrix (subjects $\times$ algorithms) containing all values. The complete form of the cost function is the following:

$$\begin{aligned} \Psi_{\text{cost}} = & \left(1 - \max_i \{\text{Fit}_i\}\right) \cdot \left(\sqrt{\frac{1}{15} \sum_i \left(\text{Fit}_i - \frac{1}{15} \sum_i \text{Fit}_i\right)^2}\right) \\ & \cdot \text{Time} \cdot \left(\frac{1}{105} \sum_{i>j} \|P_i - P_j\|_2\right) \\ & \cdot \left(\frac{1}{15} \sum_i \min_k \|P_i - G_k\|_2\right). \end{aligned} \quad (5)$$

In addition to the mere distribution of costs, we also evaluated for how many subjects a given method performed better than the others. To compute this quantity, we compared the costs of all algorithms for every subject individually. In other words, we sorted the cost function values assigned to the four methods (NMA, PSO, CMAES and BO) in ascending order and selected the algorithm featuring the minimal value as the favorable method for the particular subject. Repeating this procedure for the entire cohort yielded a vector of 105 subject-specific algorithm recommendations. The method gathering most of the recommendations (subjects) can be regarded as the *winner of the competition*.

Results

To explain and analyze the characteristics of the investigated optimization methods, we will pursue the following presentation flow. We start with an illustration of their performance for one subject, where we briefly address the three evaluation criteria (see Sect. “Overview” in “Methods”) along which the individual methods may differ from each other.

Then, we turn to analyzing the algorithms more systematically based on their results across all subjects. These investigations will be guided by the three criteria from above, too. With the help of the cost function Ψ_{cost} , we ultimately take all methods’ particular advantages and limitations into account and identify the most favorable approaches.

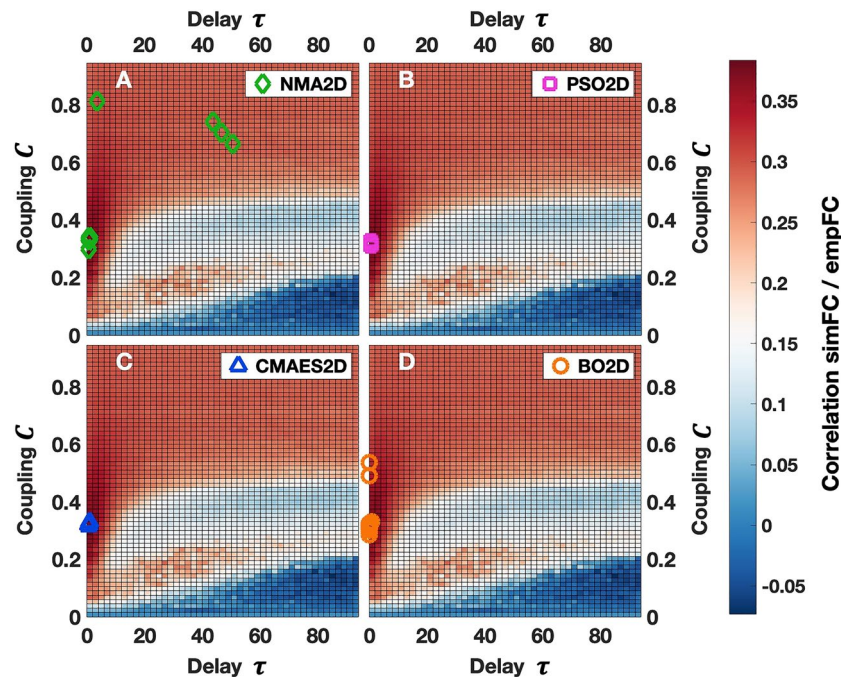


Figure 1. Examples of the algorithms' solutions in the 2Dim parameter space. All plots illustrate the outcome for the same subject. As indicated in the legends, the results of the 2Dim parameter optimizations via NMA (NMA2D), PSO (PSO2D), CMAES (CMAES2D) and BO (BO2D) are visualized by colored symbols (diamonds, squares, triangles and circles, respectively). For each method, 15 optimal parameter points obtained from 15 algorithm executions with random initial conditions are indicated. The background fill of the plots illustrates the shape of the parameter space as discovered by the grid search, see also Fig. S1. It shows the similarity (Pearson correlation) between simulated and empirical FC on a color scale reaching from dark blue (low similarity) to dark red (high similarity). The figure was created with MATLAB R2018a (www.mathworks.com).

	Optimal coupling C	Optimal delay τ	Goodness-of-fit	Invested core-h
GS2D	0.2850	0.0000	0.3779	0040.0
NMA2D	0.3323	0.8381	0.3789	0017.5
PSO2D	0.3134	0.8941	0.3814	1378.8
CMAES2D	0.3283	0.9082	0.3753	0395.9
BO2D	0.3072	0.0070	0.3873	0015.1

Table 1. Optimal parameter points, goodness-of-fit and the used computation time for the examples presented in Fig. 1. The indicated parameter values (coupling and delay) and the goodness-of-fit pertain to the best solution (highest goodness-of-fit) found across all 15 algorithm runs for the four optimization methods (NMA2D, PSO2D, CMAES2D, BO2D). For the grid search in 2Dim (GS2D), the best parameter constellation obtained from a single parameter space scan is shown. The invested core-hours (core-h) for GS2D and the optimization methods represent the required resources for one thorough scan and all 15 runs in total, respectively.

Examples of the model validation for one subject. In the illustrative example in Fig. 1, we observe that all methods are able to find the area of the highest similarity (global optimum) between simulated and empirical FC, which can be verified by the results of the grid search (dark red color). The highest values (out of 15 runs) of the detected goodness-of-fit and the corresponding optimal parameters may, however, vary to small extent across the considered methods (Table 1). A possible cause of this effect may be the stochastic impact of the noise included in the model that influences the results. Most methods in the considered example outperform the grid search slightly (between 0.3% and 2.5%) with respect to the goodness-of-fit values, except for CMAES (−0.7%). However, this does not necessarily imply that the global optimum in the parameter space has been missed here; the solutions are rather perturbed by noise. Therefore, the values may be somewhat below the goodness-of-fit obtained by the grid search, despite the fact that the optimal parameters have correctly been identified within the dark red region.

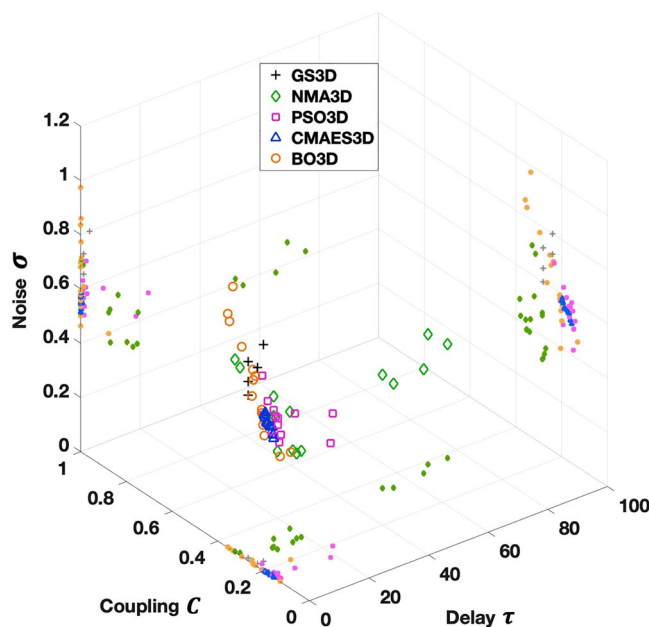


Figure 2. Exemplary parameter optimization in the 3Dim case. The outcomes (optimal parameter points) for all tested methods are combined in one plot. Besides the solutions in the 3Dim parameter space (larger markers), projections to 2Dim plains are presented (smaller markers). For the grid search in 3Dim (GS3D), five parameter points are considered (black crosses). In terms of the model similarity to empirical data, these points represent the five best solutions out of all values calculated on the parameter grid. As indicated in the legend, the results of the 3Dim parameter optimizations via NMA (NMA3D), PSO (PSO3D), CMAES (CMAES3D) and BO (BO3D) are visualized by colored diamonds, squares, triangles and circles, respectively. For each algorithm, 15 markers are shown (plus projections) which indicate the solutions of 15 runs executed at random initial conditions. The figure was created with MATLAB R2018a (www.mathworks.com).

	Optimal coupling C	Optimal delay τ	Optimal noise σ	Goodness-of-fit	Invested core-h
GS3D	0.2400	3.0000	0.8000	0.3310	1200.0
NMA3D	0.3287	0.2883	0.7079	0.3173	0020.2
PSO3D	0.1603	7.5195	0.5717	0.3489	1382.5
CMAES3D	0.1603	0.1554	0.5230	0.3479	0303.3
BO3D	0.2358	0.0042	0.6991	0.3298	0016.4

Table 2. Optimal parameter points, goodness-of-fit and the used computation time for the results presented in Fig. 2. The indicated parameter values (coupling, delay and noise) and the goodness-of-fit pertain to the best solution (highest goodness-of-fit) found across all 15 algorithm runs for the four optimization methods (NMA3D, PSO3D, CMAES3D, BO3D). For the grid search in 3Dim (GS3D), the best parameter constellation obtained from a single parameter space scan is shown. The invested core-hours (core-h) for GS3D and the optimization methods represent the required resources for one thorough scan and all 15 runs in total, respectively.

For the 3Dim case, we refrained from showing the complete outcome of the grid search for illustrative purposes, but rather included only the five best points that yielded the highest fitting according to the exhaustive parameter space scan (Fig. 2). For the other optimization algorithms, the highest detected goodness-of-fit values again fluctuate around the result of the grid search (Table 2). In this example, PSO and CMAES outperform the exhaustive scan (up to 5.4%), whereas NMA and BO generate slightly lower values (between – 0.4% and – 4.1%). Importantly, the invested computational resources vary greatly across the algorithms in the presented examples (Tables 1, 2). While 15 executions of either PSO (3447.0%) or CMAES (989.8%) surpass the requirements of a two-dimensional grid search clearly, NMA (43.8%) and BO (37.8%) already demonstrate speedup factors higher than 2. In the 3Dim case, the gains seem to be even more pronounced. All methods except for PSO require less resources for 15 independent optimization runs than one thorough grid search. CMAES (25.3%) appears to be nearly 4 times faster, whereas NMA (1.7%) and BO (1.4%) reach speedups close to 60 and 73, respectively. Another crucial aspect of the method performance is the algorithm’s susceptibility with respect to local optima and the spread of solutions. We tested this by restarting the optimization for $R_{\max} = 15$ random initial conditions as mentioned above and highlighted the spread of the obtained solutions by 15 corresponding markers in the

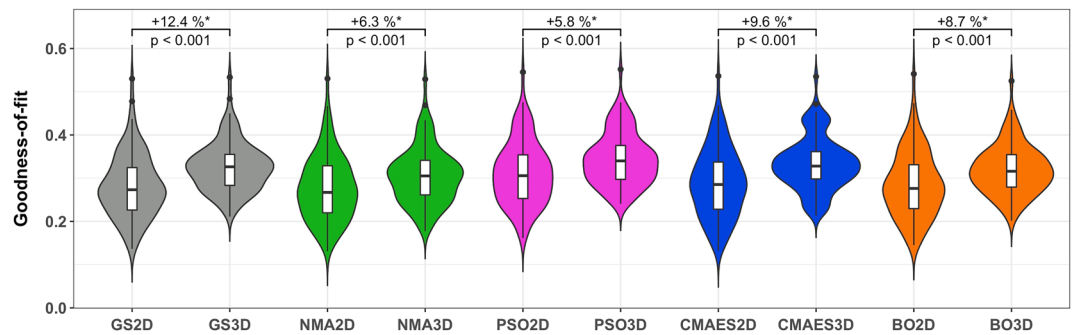


Figure 3. Distributions of the goodness-of-fit values for all tested approaches and dimensionalities. The considered methods and the respective parameter space's dimension are indicated on the horizontal axis (GS2D, NMA2D, PSO2D, CMAES2D, BO2D in 2Dim and GS3D, NMA3D, PSO3D, CMAES3D, BO3D in 3Dim) along with the detected goodness-of-fit values on the vertical axis. Violins show the distributions of the highest model fit detected for all subjects. The medians (across subjects) of the relative increase between the results in 2Dim and 3Dim are indicated in the plots together with p -values of the Wilcoxon signed-rank test. Statistically significant differences are marked with an asterisk (the significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons).

parameter spaces in Figs. 1 and 2 for 2Dim and 3Dim, respectively. In the considered examples, the solutions do not always aggregate in a relatively small, distinct area, which especially becomes obvious in the 3Dim case (Fig. 2; Table 2). Instead, they may be distributed across a broader region within the parameter space. NMA, as a local search method, demonstrates a large susceptibility to local optima, to give an example. For CMAES, by contrast, the solutions converged to a specific area of the parameter space, where they form a dense cluster. We discuss the stability of the considered optimization methods as well as the other comparison criteria in more detail later below.

Group-level analysis. Goodness-of-fit. To evaluate the performance of the investigated optimization methods in more detail, we compared the detected goodness-of-fit values across all subjects. Here, we observed that the fitting quality is higher in 3Dim than in 2Dim, regardless of the applied algorithm (Fig. 3). The averaged improvement is around 8.6%. Moreover, the goodness-of-fit values obtained by the optimization methods for individual subjects can compete with those calculated by the extensive parameter optimization on a dense grid (Fig. 4). The medians of the individual relative differences to the grid search solutions evaluated across subjects range from -0.3% to $+11.3\%$ for optimizations in the 2Dim parameter space and from -5.1% to $+3.8\%$ in the 3Dim case (Fig. 4). Among the methods, the order $NMA < BO < CMAES < PSO$ can be observed (Fig. 5).

From the first component (goodness-of-fit) of the cost function Ψ_{cost} , we see that the differences between the algorithms are not very pronounced in terms of the distribution of costs (Figs. 6A, 7A and, for the exact values, Supplementary Table S1). Nevertheless, PSO appears to produce the best results across all 105 subjects under investigation (Figs. 6F, 7F and Supplementary Table S1). Regarding the recommendations, it clearly dominates with 80% in the 2Dim case and the other methods cannot keep up with PSO here. In the 3Dim case, CMAES attracts slightly more than 30% of the subjects, but it still does not reach the performance of PSO (62%). It is remarkable that NMA does not even receive a single recommendation, meaning that it is always outperformed by at least one other method with respect to the detected goodness-of-fit values.

When analyzing the spread (standard deviation, SD) of the 15 model fits obtained for each subject and method, i.e. the second component of the cost function Ψ_{cost} , we found that CMAES appears to demonstrate the best results, followed by PSO in 2Dim and by BO in 3Dim (Figs. 6B, G, 7B, G; Supplementary Table S1). NMA again reveals the poorest performance in both considered parameter spaces.

So, when compared to the other methods, PSO demonstrated an advantage in detecting the highest individual goodness-of-fit value within 15 executions. However, the solutions generated by CMAES have the lowest variation across 15 replications, indicating a stronger robustness against outliers and a higher stability of the fitting results.

Optimizing the number of algorithm executions. We observed above that the quality of the model validation (goodness-of-fit) of the grid search may on average not be reached for some of the considered optimization algorithms even after $R_{\text{max}} = 15$ executions. This is the case for NMA in both considered dimensionalities and for BO in 3Dim (see Fig. 4). To test whether a larger number of algorithm runs can improve the model fitting, we thus performed some additional simulations for NMA and BO, leading to a total of $R_{\text{max}} = 24$ executions, which we took into account when analyzing the behavior of the success probability (see “Methods”).

Performing the discussed calculations, we found the following (Fig. 8): The success probability is a monotonically increasing function of the number of executed runs. The growth rate (slope of the curves), however, decays with a rising number of algorithm executions. NMA needs 4 initializations in 2Dim to reach a success probability above 50% and 16 runs to surpass 80%. PSO in turn manages to reach 80% (and 50%, of course) with only 1 initialization. For CMAES, a success probability of 50% is achieved within 1 run, compared to 10 runs for 80%. BO requires 2 executions to reach 50% and 9 to surpass a success probability of 80%. In the 3Dim

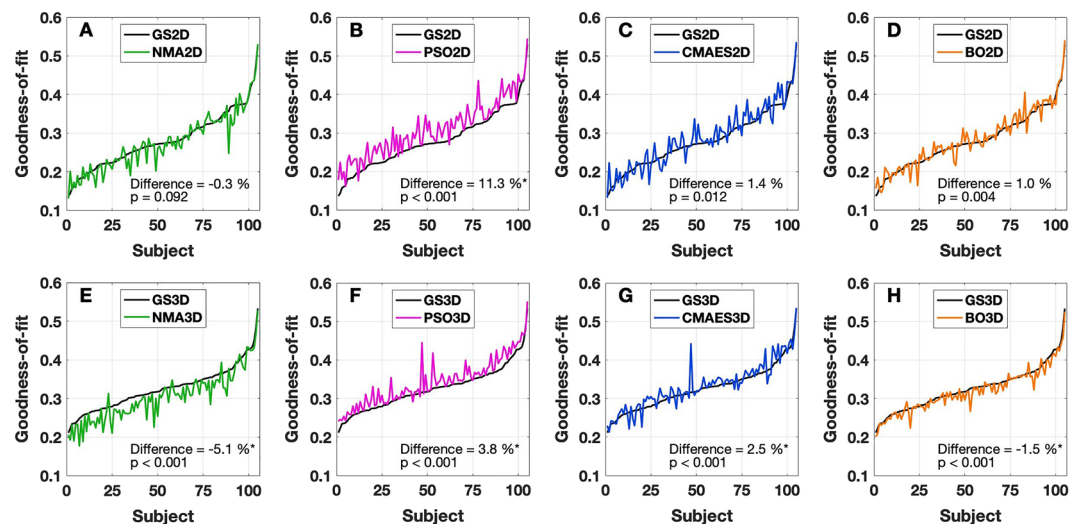


Figure 4. Goodness-of-fit values for individual subjects and optimization approaches. As indicated in the legends, colored curves illustrate the outcome (subject-dependent goodness-of-fit) for each method in the (A–D) 2Dim (NMA2D, PSO2D, CMAES2D, BO2D) and (E–H) 3Dim (NMA3D, PSO3D, CMAES3D, BO3D) cases. The subjects are sorted in ascending order, based on the maximal fitting values detected by the grid search (black curves) in 2Dim and 3Dim (GS2D and GS3D, respectively). The medians (across subjects) of the relative differences between the results of the optimization algorithms and the grid search are indicated in the plots together with p -values of the Wilcoxon signed-rank test. Statistically significant differences are marked with an asterisk (the significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons). The figure was created with MATLAB R2018a (www.mathworks.com).

	GS2D	NMA2D	PSO2D	CMAES2D	BO2D	GS3D	NMA3D	PSO3D	CMAES3D	BO3D	
GS2D	0.0	-0.3	11.3*	1.4	1.0	12.4*	6.1*	21.7*	16.4*	10.6*	20
NMA2D	0.3	0.0	9.9*	2.7*	1.4*	15.5*	6.3*	21.3*	16.0*	10.9*	15
PSO2D	-10.1*	-9.0*	0.0	-2.8*	-7.6*	1.0	-2.1	5.8*	2.4*	0.1	10
CMAES2D	-1.4	-2.6*	2.9*	0.0	-0.7	8.2*	3.4*	16.9*	9.6*	10.4*	5
BO2D	-1.0	-1.4*	8.2*	0.8	0.0	11.0*	4.2*	20.0*	14.0*	8.7*	0
GS3D	-11.1*	-13.4*	-1.0	-7.6*	-9.9*	0.0	-5.1*	3.8*	2.5*	-1.5*	-5
NMA3D	-5.8*	-5.9*	2.1	-3.3*	-4.1*	5.3*	0.0	11.4*	7.9*	3.9*	-10
PSO3D	-17.8*	-17.5*	-5.5*	-14.5*	-16.6*	-3.6*	-10.3*	0.0	-0.8*	-5.3*	-15
CMAES3D	-14.1*	-13.8*	-2.3*	-8.8*	-12.2*	-2.4*	-7.3*	0.8*	0.0	-4.1*	-20
BO3D	-9.6*	-9.8*	-0.1	-9.4*	-8.0*	1.5*	-3.7*	5.6*	4.2*	0.0	

Figure 5. Comparison of the considered methods with regard to the detected goodness-of-fit values across all subjects. For every optimization technique and subject, the highest goodness-of-fit value is considered. The medians of the relative differences between any two methods are indicated in the cells which are highlighted in color. To this end, the goodness-of-fit values of the approaches listed on the vertical axis (lines) are subtracted from those of the methods indicated on the horizontal axis (columns). Results that proved statistically significant in the Wilcoxon signed-rank test are marked with an asterisk (the significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons). The figure was created with MATLAB R2018a (www.mathworks.com).

case, by contrast, NMA needs at least 16 executions for 50%, but it cannot guarantee a success probability of 80% within the maximal number of $R_{\max} = 24$ performed runs. PSO's required number of runs is 1 for 50% and 2 for 80%. Interestingly, CMAES seems to perform better in 3Dim than in 2Dim. While a success probability of 50% is achieved within 1 run in either dimensionality, 3 runs already seem to suffice for 80% in 3Dim, which is much less than in 2Dim. Lastly, BO requires 2 executions to reach 50%, while 17 runs are needed to surpass a success probability of 80%.

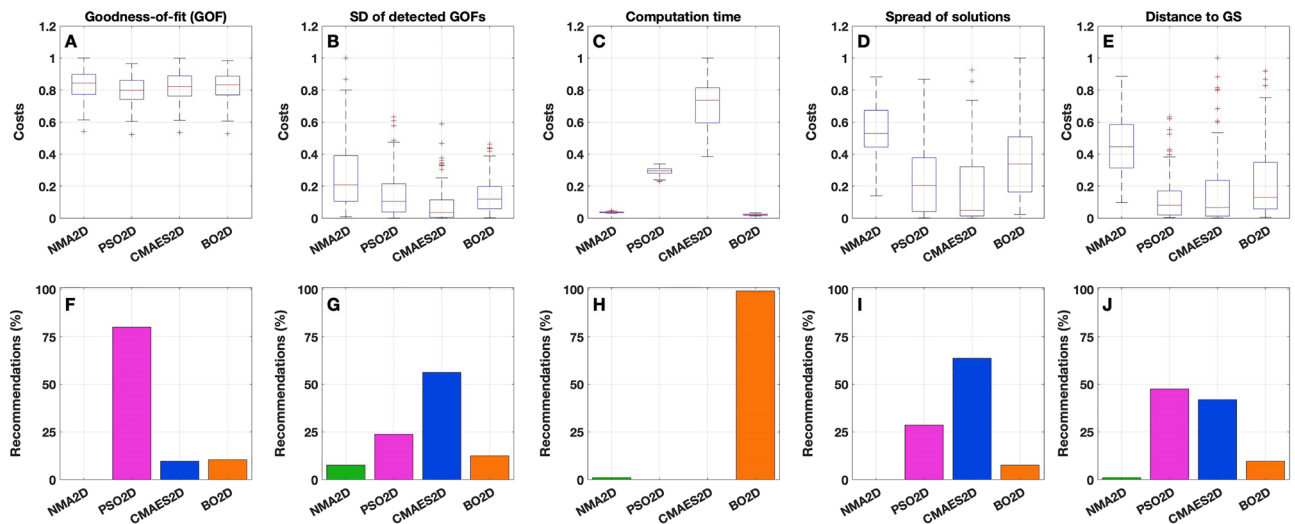


Figure 6. Components of the cost function Ψ_{cost} for the 2Dim case. (A–E) Boxplots illustrate the distributions of the values of the components indicated in the titles (see text for details). All values were normalized by the respective maxima (given as one quantity over all algorithms for a given component). The individual cost values are shown on the vertical axes while the corresponding algorithms (NMA2D, PSO2D, CMAES2D and BO2D) are indicated on the horizontal axes. (F–J) For each cost component, histograms show the relative number of recommendations obtained by a given optimization algorithm across all subjects. This quantity was calculated by counting the number of subjects for which the respective algorithm is considered *recommendable*, i.e. where it provides the lowest costs among all four investigated methods. The absolute value was then divided by the total cohort size of 105 subjects. As before, the methods are listed on the horizontal axes. On the vertical axes, it is indicated for which fraction of subjects a particular method is recommended. The figure was created with MATLAB R2018a (www.mathworks.com).

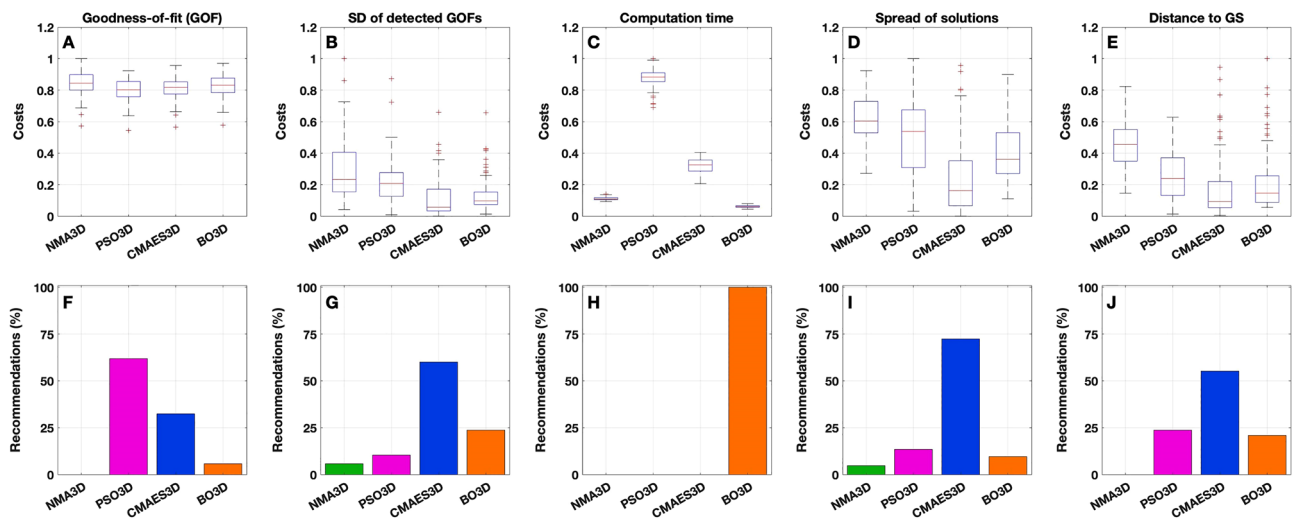


Figure 7. Components of the cost function Ψ_{cost} for the 3Dim case. As in Fig. 6, (A–E) boxplots illustrate the distributions of the values (normalized by the respective maxima) of the components indicated in the titles, and (F–J) histograms show the relative number of recommendations obtained by a given optimization algorithm (NMA3D, PSO3D, CMAES3D and BO3D) for each cost component. The figure was created with MATLAB R2018a (www.mathworks.com).

From the success probability's level of saturation (Fig. 8) we found that the observed success probability improvements were only marginal between 15 and 24 runs for NMA and BO. We can thus conclude that a larger number ($R_{\text{max}} = 24$) of executions did not improve the performance of these techniques considerably. In particular, we did not consider performing additional executions for PSO and CMAES and continued to focus on the standard 15 runs for all tested mathematical optimization algorithms unless otherwise indicated (needed computation time, see next paragraph).

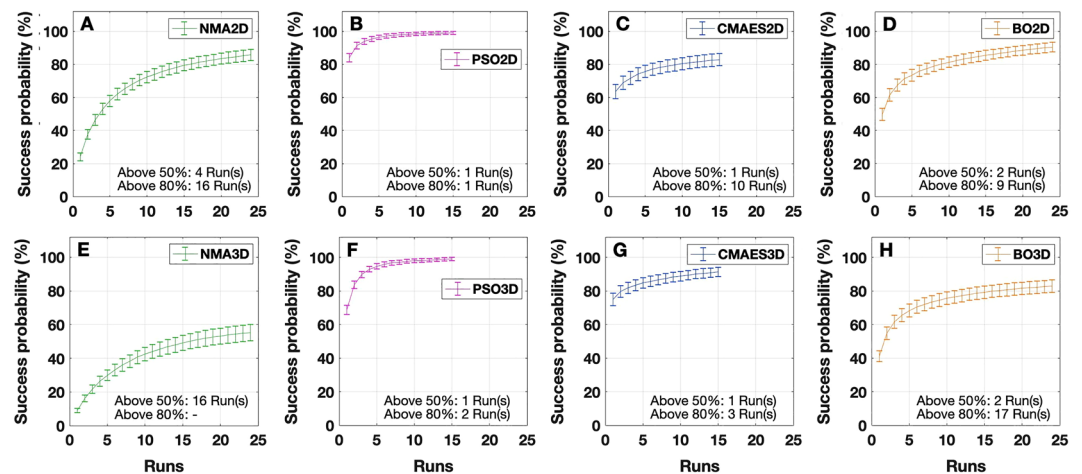


Figure 8. Numbers of algorithm executions and corresponding probabilities to obtain a goodness-of-fit not smaller than 95% of that from the grid search in the 2Dim (A–D) and 3Dim (E–H) cases. The probabilities were evaluated by randomly selecting $R \in \{1, \dots, R_{\max}\}$ goodness-of-fit values from the $R_{\max}$ algorithm executions available for every subject ($R_{\max} = 15$ for PSO and CMAES, $R_{\max} = 24$ for NMA and BO). A success was noted when at least one of the selected values was above or equal to the threshold. For every choice of R (i.e. the number of performed runs indicated on the horizontal axes), this procedure was repeated 500 times. The results were then averaged across all subjects in order to obtain the mean success probabilities indicated on the vertical axes. For the optimization methods presented in the legends (same notations as before), the plots illustrate the mentioned success probabilities together with the respective standard error (error bars). Additionally, it is indicated after how many runs success probabilities of 50% and 80% could be surpassed. The figure was created with MATLAB R2018a (www.mathworks.com).

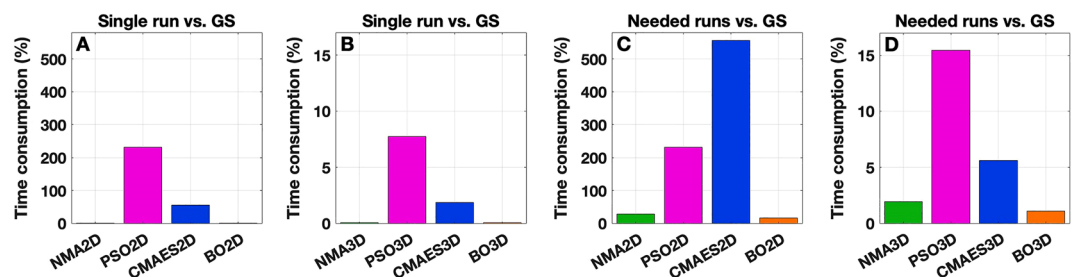


Figure 9. Computation time necessary for the execution of the optimization algorithms in relation to that used for the grid search (GS). (A, B) Ratios between the computation time of a single run of the optimization algorithms and the grid search averaged over all algorithm executions and subjects. The individual ratios are (A) 2Dim case: NMA2D 1.8%, PSO2D 231.0%, CMAES2D 55.6% and BO2D 1.9%; (B) 3Dim case: NMA3D 0.1%, PSO3D 7.7%, CMAES3D 1.9% and BO3D 0.1%. (C, D) Relative computation time necessary for reaching 80% of the success probability (see Fig. 8) compared to the time invested for the grid search. The values are obtained by multiplying those from the plots A and B by the respective numbers of needed runs provided in Fig. 8. For NMA3D, where a success probability of 80% could not be reached, 24 runs are considered necessary. The algorithms are indicated on the horizontal axes along with the percental values of time consumption on the vertical axes for the 2Dim (A, C) and 3Dim (B, D) cases. The figure was created with MATLAB R2018a (www.mathworks.com).

Computation time. The computation time that needs to be invested in order to identify the optimal model parameters constitutes a major difference between the individual approaches (Fig. 9). Under the simulation conditions used for the grid search in 2Dim, one subject required approximately 40 core-hours of computation time to exhaustively scan the parameter space, see “Methods”. We regarded this quantity as 100% and compared the algorithms’ mean time consumption (across all executions and subjects) in 2Dim relative to it. In this respect, we observed that NMA (1.8%) and BO (1.9%) require little computation time for a single run, while CMAES (55.6%) and especially PSO (231.0%), featuring clearly more F -evaluations, are computationally more expensive (Fig. 9A). Therefore, the execution of 15 optimization runs for each of the latter two methods requires much more computational resources than a parameter sweep on a dense grid. A different situation was observed for the 3Dim case, where three parameters (coupling C , delay τ , noise σ) were optimized simultaneously. The amount of computation time necessary for the grid search drastically increases (1200 core-hours per subject,

see “Methods”), whereas only a moderate change can be detected for one execution of the other investigated optimization methods. Consequently, a single run of NMA (0.1%), PSO (7.7%), CMAES (1.9%) and BO (0.1%) proves computationally inexpensive when compared to the extensive parameter space exploration. All methods except for PSO remain lucrative even if all 15 runs were necessary (Fig. 9B).

Furthermore, we investigated the algorithms’ time consumption for the number of executions that were necessary, for example, to reach a success probability of 80% (Fig. 8). We thus multiplied the number of the needed runs with the computational costs of a single run (Fig. 9). In this setting, CMAES turned out to be the most expensive method in the 2Dim parameter space, requiring more than five times (556.1%) the computational resources of the grid search (on average per subject). PSO (231.0%) is more lucrative than CMAES, but stays clearly above 100%, too. By contrast, NMA and BO require less computation time than the grid search (28.8% and 16.9%, respectively) and therefore seem favorable in this respect (Fig. 9C). They are between 3.5 (NMA) and 6 (BO) times faster than the considered grid search. In the 3Dim case, all methods manifest themselves as resource-saving alternatives to a thorough parameter space scan on a dense grid (Fig. 9D). PSO (15.5%) appears to be the method with the highest demands, followed by CMAES (5.6%), NMA (2.0%) and BO (1.1%). Equivalently, their speedup factors are close to 6, 18, 50 and 91, respectively. Note that we considered the maximum of $R_{\max}=24$ runs to be necessary for NMA, although a success probability of 80% could not be reached within 24 executions of this method. The actual amount of required computational resources for this approach may therefore be higher than indicated.

The results are further enhanced when looking at the respective component of the cost function in Figs. 6C, 7C and Supplementary Table S1, where NMA and BO clearly outperform the population-based approaches PSO and CMAES. Regarding the quantity of recommendations, BO appears to be the most favorable method in either dimensionality (Figs. 6H, 7H and Supplementary Table S1).

We summarize and conclude that BO is the preferable algorithm for a computational speedup.

Location of optimized parameters. In the initial examples (Figs. 1, 2), we have seen that the algorithms can vary greatly regarding the spread of the detected optimal parameter points in the model parameter space. The fourth component of the cost function is dedicated to this property and therefore describes the algorithms’ stability/robustness against local optima. In our analysis, CMAES turned out to have the highest stability in detecting global solutions in either dimensionality (Figs. 6D, 7D; Supplementary Table S1) and also appeared to be the recommended method for the majority of subjects (Figs. 6I, 7I; Supplementary Table S1). This property is crucial for the reliable validation of the models against empirical data. PSO features the second lowest median of costs and the second highest proportion of recommendations in the 2Dim case. It beats NMA and BO. After the transition to the 3Dim scenario, however, the PSO algorithm does not produce as stable results as in 2Dim. BO shows a clearly lower median of costs than PSO in 3Dim (i.e. a higher stability against local optima) and comes closer to PSO’s proportion of recommendations. NMA in turn demonstrates a weakness to avoid local optima, which is reflected by the highest costs and fewest recommendations in both considered dimensionalities of the parameter space.

Investigating the distributions of the obtained optimal model parameters across all subjects, we found similarities between the considered optimization algorithms and the grid search (Fig. 10). The results presented here pertain to the approach of selecting the five best solutions featuring the highest goodness-of-fit values to estimate the parameter distributions. No qualitative changes can be noted when only one best point is considered per subject and method (see Supplementary Fig. S3). In Fig. 10, we observe that most of the methods identify the highest concentration of optimal coupling values C in the interval $[0, 0.4]$ for the 2Dim case. NMA constitutes an exception, because the optimal coupling can spread to larger values for this approach (Fig. 10A, C2). A transition of the coupling strength towards an aggregation in the interval $[0.8, 1]$ can then be observed for optimizations in the 3Dim parameter space (Fig. 10D), where also the noise intensity σ was varied as a free parameter. This effect is most pronounced for CMAES and BO, where skewed and nearly unimodal distributions at high coupling values can be noted. For other methods including the grid search, a broad and practically bimodal shape of the distribution of the optimal global coupling C emerges. In addition, all methods detect the clear majority of optimal parameters close to small (zero) delay values τ , regardless of whether a 2Dim or 3Dim parameter space is considered (Fig. 10B, C, E). Finally, we found that the arrangement of optimal noise intensities σ in 3Dim shows a bimodal pattern, mostly visible for the grid search, CMAES and BO (Fig. 10F). The peaks are located within the intervals $[0.2, 0.6]$ (small noise) and $[1.5, 1.9]$ (large noise).

Analyzing the discussed parameter distributions with the help of the cost function’s respective component, we found that the performance of both PSO and CMAES remains comparable in the 2Dim case, where the former gains more recommendations (Fig. 6J; Supplementary Table S1), and the latter demonstrates a lower median in the cost distributions (Fig. 6E; Supplementary Table S1). In the 3Dim case, the CMAES technique clearly outperforms the other algorithms (Fig. 7E, J; Supplementary Table S1). PSO and BO strive to be the next best method while NMA is left behind.

From the findings in this section we infer that CMAES is the most reliable method in terms of stability of the optimal parameters.

Relationships between the cost function components. Before continuing, it is important to evaluate whether the considered components of the cost function may demonstrate a mutual interdependence. The robustness of the algorithms, for example, which is reflected by the spread of the solutions and their distance to the optima indicated by the grid search (components 4 and 5), but also the variation of the detected goodness-of-fit values (component 2) for a given subject, does not depend on the simulation time (Supplementary Fig. S4). Additionally, we did not find any strong linear relationships between the robustness of a method and its preci-

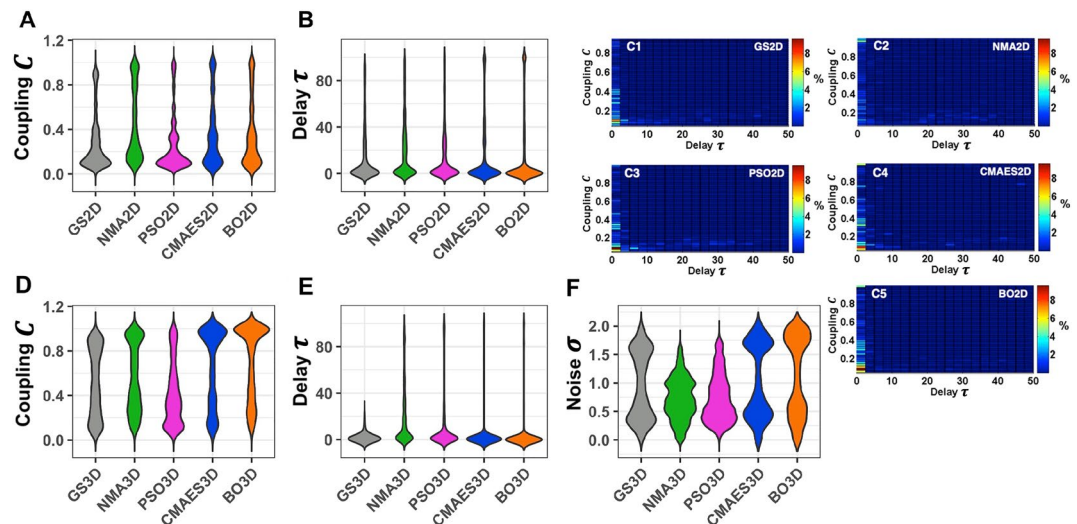


Figure 10. Distributions of the optimal model parameters detected by the considered techniques across all subjects. For each approach and subject, the five best solutions featuring the highest goodness-of-fit values are considered to estimate the distribution. They were selected from all similarity values computed on the 2Dim or 3Dim parameter grids (for the grid search GS2D or GS3D) and from all goodness-of-fit values obtained by 15 independent runs of the optimization algorithms (NMA2D, PSO2D, CMAES2D, BO2D in 2Dim and NMA3D, PSO3D, CMAES3D, BO3D in 3Dim). In the violin plots of one-parameter distributions for the 2Dim (A, B) and 3Dim (D–F) cases, the methods are indicated on the horizontal axes along with the optimized parameter values on the vertical axes. The plots (C1–C5) show the distributions of the optimal model parameters in the 2Dim space, where the relative frequency of the optimal parameter values is depicted by color and the respective methods are indicated in the plots. The figure was created with MATLAB R2018a (www.mathworks.com).

sion, i.e. the obtained goodness-of-fit (Supplementary Fig. S5). These results underline the necessity to analyze the tested algorithms from different perspectives, such as the three utilized evaluation criteria (see Sect. “Overview” in “Methods”) and the corresponding components of the cost function, before recommending a particular method. Researchers may nevertheless base their choice of algorithm on the properties best suited to a given application. One may intend, for example, to pick the method which most reliably detects the correct parameter region as the one featuring the highest model fit, irrespective of any other algorithm properties. This might then require assigning larger weights to the cost function components 4 and 5, for instance.

Overall costs and final argumentation. In this paragraph, we investigate the overall costs of the algorithms and therefore consider the complete cost function Ψ_{cost} which was generated by multiplying the individual components that we discussed above. The distributions of the cost function values for the tested algorithms in the considered parameter spaces are illustrated in Fig. 11. Additionally, the figure shows which methods most frequently perform better for individual subjects and can therefore be recommended for optimizations of the similarity between empirical and simulated data. The exact values are provided in Supplementary Table S1. In the 2Dim case, the algorithms show a similar distribution of low costs (Fig. 11A; Supplementary Table S1), and a precise differentiation therefore seems difficult. Based on the median cost values only, NMA appears least favorable. This is also confirmed by the proportion of recommendations calculated as explained in “Methods”, which is highest for CMAES (37%), followed by BO (32%) (Fig. 11B; Supplementary Table S1). It is remarkable that CMAES outperforms the other methods despite the fact that it features the highest computation time and corresponding costs (Figs. 6C, 9C; Supplementary Table S1). This effect may be caused by CMAES’ advantageous results for the other components of Ψ_{cost} (Fig. 6A, B, D, E; Supplementary Table S1). In the 3Dim case, PSO demonstrates comparably high costs, i.e. a lower efficacy (Fig. 11C; Supplementary Table S1). Unlike CMAES, the optimization quality as reflected by the components 1, 2, 4 and 5 of Ψ_{cost} (Fig. 7A, B, D, E; Supplementary Table S1) does not seem to be high enough for PSO to compensate for the computational resources invested for this method. PSO thus obtained fewer recommendations in the 3Dim parameter space (Fig. 11D; Supplementary Table S1). The same is true for NMA which may have the advantage of a low computation time, but does not produce as stable results as the BO algorithm, for example (Figs. 6A–E, 7A–E; Supplementary Table S1). Regarding the proportion of received recommendations in 3Dim, BO gains the most attractiveness (47%) and slightly surpasses CMAES (46%).

In summary, the mere distribution of the cost function values implies that NMA and PSO are the least favorable of the considered mathematical optimization algorithms in both the 2Dim and 3Dim parameter spaces. Further differentiations covering specific characteristics of the methods can be made either by analyzing the individual components of Ψ_{cost} (Figs. 6, 7; Supplementary Table S1) or by investigating the proportion of recommendations for a particular method. In the latter option, two algorithms prevalently outperform the others with their results. More precisely, for the clear majority of considered subjects, the best parameter optimization can

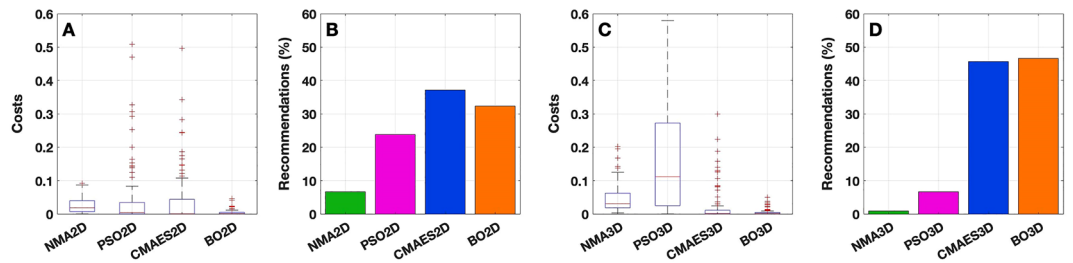


Figure 11. Cost function values and recommendations pertaining to the optimization algorithms for the 2Dim (A, B) and 3Dim (C, D) cases. (A, C) Boxplots illustrate the distribution of costs (normalized by the respective maxima, i.e. one value over all algorithms in the given parameter space). The considered methods are depicted on the horizontal axes together with the values of Ψ_{cost} on the vertical axes. A few outliers for PSO (>0.6 in 3Dim) and CMAES (>0.6 in 2Dim) are not included in the plots. (B, D) Histograms show the relative number of recommendations obtained by a given optimization algorithm (calculated as in Fig. 6). The methods are listed on the horizontal axes. On the vertical axes, it is indicated for which fraction of subjects a particular method is recommended. The figure was created with MATLAB R2018a (www.mathworks.com).

be observed for either CMAES or BO (Fig. 11; Supplementary Table S1). This applies to both tested parameter spaces. The particular constellations of recommendations for CMAES and BO, respectively, read as follows: $37\% + 32\% = 69\%$ (2Dim) and $46\% + 47\% = 93\%$ (3Dim).

From the presented results we conclude that CMAES and BO are the most promising methods. CMAES turned out as the preferable approach in terms of stability, which is reflected by the low cost medians and high proportions of recommendations at the components 2, 4 and 5 of the cost function Ψ_{cost} . Importantly, also the consideration of the computational demands, which are clearly higher for the population-based approaches PSO and CMAES (see Fig. 9), does not prevent CMAES from outperforming the other algorithms regarding the overall costs and recommendations (see Fig. 11; Supplementary Table S1). BO in turn convinces with its efficient use of resources. Its results may not be as stable as those obtained by CMAES (see the results for the components 2, 4 and 5 of Ψ_{cost}), however, especially in the 3Dim case, they rival those of PSO. Since one execution of BO in 3Dim is performed more than 75 times faster than one of PSO, we regard BO as a more efficient method. CMAES and BO thus stand out, and we recommend to use either one or both of these mathematical schemes instead of a grid search, especially in higher dimensions ($\text{Dim} \geq 3$). A thorough parameter scan on a dense grid becomes computationally unfeasible for complex models with increasingly many parameters that have to be tuned simultaneously during the process of model validation. We have demonstrated that across subjects, it is possible to obtain robust results thanks to resource-saving alternatives, i.e. mathematical optimization algorithms. Compared to a thorough parameter space scan with three free parameters, CMAES and BO provided a speedup factor close to 18 and 91, respectively. Further, the saved resources may be invested to study additional subjects in larger cohorts.

Discussion

Synopsis. Model-based studies should not be limited by inefficient ways to optimize model parameters. Exponentially increasing requirements in computation time, which are intrinsic to a dense grid search, triggered and motivated the search for alternatives. The intention of this study was thus to investigate the performance of several mathematical optimization algorithms in the validation of data-driven dynamical whole-brain models. We considered four well-known derivative-free methods that covered a broad spectrum of optimization techniques ranging from local deterministic (NMA) to global probabilistic (BO) and population-based (PSO, CMAES) approaches. Our results show that optimization algorithms are indeed applicable and recommendable to perform a parameter-dependent maximization of the similarity between simulated and empirical neuroimaging data. We verified this by comparing the output of the methods to the results of systematic parameter variations on a two- and three-dimensional grid. Our comparison criteria considered the obtained goodness-of-fit, the necessary computation time and the location of the optimized parameters. For the best two approaches, CMAES and BO, we obtained goodness-of-fit values being very close to the grid search solutions: The medians of relative differences across all 105 subjects ranged from -1.5 to $+2.5\%$ in the considered parameter spaces. At the same time, we were able to save a great extent of computational resources when optimizing three model parameters simultaneously: While CMAES already provided a speedup close to 18, BO turned out to be almost two orders of magnitude faster than a corresponding grid search. In that respect, BO demonstrated the most efficient use of resources across all tested methods. CMAES in turn produced the most stable results, which was reflected by the lowest spread of the detected parameter points and the corresponding goodness-of-fit values over 15 replications as well as by its solutions' small distance to the optima detected by the grid search. In view of these results, further applications of the considered methods hold a lot of promise regarding the desire to facilitate the validation of higher-dimensional models.

Contextual classification. Our efforts were in line with previous studies that analyzed and compared the performance of several mathematical methods for theoretical as well as experimental scenarios^{44–46,85,86}. Similar to our strategy of incorporating the grid search to determine ground truth values, other researchers evaluated the tested algorithms' performance on the basis of pseudo-experimental data for which the underlying param-

eters were known^{44,46,85,86}. To our knowledge, however, no systematic comparison between the performance of mathematical optimization techniques and a grid search has been made for purely experimental data of resting-state brain dynamics measured by fMRI as in this study.

Working with electroencephalography (EEG) measurements, Hartoyo et al.⁴⁴ and Hashemi et al.⁴⁵ used mathematical approaches to minimize a least squares goal function that described the error between estimated and empirical power spectra. The estimated data were computed analytically and did not require the numerical solution of differential equations, therefore saving a great extent of computation time. This way of model fitting has been termed *spectral validation* by Cabral et al.⁸⁷. The authors highlighted that this approach is less suited for obtaining an optimal quantitative fit, but should rather be used to determine a certain range of input parameters for which a model can explain the empirical data in phenomenological terms.

Our aim to maximize the correlation between simulated and empirical resting-state FC, by contrast, belongs to the so-called *spatial validation* and aligns with many previous studies^{17,18,57,88,89}. Outstandingly, Wang et al.⁴⁰ proposed an alternative to a grid search when working with resting-state fMRI data. To optimize the goodness-of-fit of a data-driven model that generated FC, the authors implemented a method derived from the expectation–maximization algorithm commonly used in dynamic causal modeling^{90,91}. However, they worked with group-averaged matrices for SC as well as FC and did not perform a parameter optimization for individual subjects. A validation of the detected parameters in terms of estimating the distance to the optimal ones found in a grid search was not included, either.

A Bayesian approach closely related to the BO method which we investigated was tested for the validation of a noise-free whole-brain model that generated simulated magnetoencephalography (MEG) data⁴². The distributions of the optimized parameters from a two- and five-dimensional parameter space were thoroughly investigated, albeit without a systematic comparison to ground truth values. Further following the suggested Bayesian framework, Hashemi et al.³³ used it to infer hidden characteristics of brain dynamics from optimized parameters in a personalized model of epilepsy spread.

Our study contributes to the existing literature by applying several mathematical optimization methods to combine a spatial validation based on simulated resting-state FC data with efforts of subject-specific whole-brain modeling. In addition, the robustness of the advocated techniques was highlighted by explicitly comparing the obtained results with the approximated ground truth given by the outcome of an exhaustive grid search. Given the topical efforts to simulate non-stationary data features such as dynamical FC, our described acceleration of computational operations appears even more welcome and relevant for the current brain research. As already envisioned by Hansen and colleagues⁹², models may be fine-tuned to not only fit static brain features, but also to account for dynamical changes in form of discrete onsets of novel behaviors, which bear an intrinsic difficulty of computing time-dependent quantities. This can be reflected by continuously changing optimal model parameters^{38,93} that need to be detected (and repeatedly updated) via efficient mathematical optimization.

Limitations. At this point, we note that there are limitations associated with the application of the tested optimization schemes. The choice of a proper number of maximal iterations along with another adequate stopping criterion may constitute a challenge since these decisions need to be made problem-dependent. On the one hand, a low number of iterations can save precious computation time, but may not be large enough to capture an algorithm's final point of convergence. On the other hand, a very high number of performed iterations may lead to a waste of computational resources when the algorithm is trapped in a local extremum, but may also enable a more global exploration of the parameter space. In our simulations, we chose, after an initial optimization of the methods' internal parameters, to terminate the population-based approaches (PSO and CMAES) either after 80 iterations or if their results would not improve for 50 consecutive iterations. Stopping earlier might have been acceptable for some subjects, but not in all cases, since sudden improvements may also occur after longer periods of no gain (see Supplementary Fig. S2). Therefore, additional iterations may give the algorithms a certain amount of time to underline their potential, converge to optimal solutions and outperform the grid search. In general, we recommend to perform a series of test runs with a higher number of iterations in order to explore the characteristics and potential asymptotic behavior of a given method for a given optimization problem. Afterwards, the stopping criteria can be intensified whenever reasonable and the saved resources may be invested in additional algorithm runs with different initial data. Several executions are crucial, since the algorithms may demonstrate some sensitivity to initial data and/or do not converge to identically the same solution for different starting points. This particular issue is most pronounced for local search methods, but also applies to global approaches. In such cases, the algorithms show a high spread of solutions and fail to provide a clear tendency about the location of the global best point. A deterioration in convergence properties due to noisy measurements was reported when comparing several algorithms including PSO to each other⁸⁶. Even global probabilistic methods turned out to be trapped in local optima mainly induced by noise fluctuations. That implies that optimization schemes can detect solutions of minor quality which deviate from the grid search result. More clearly, none of the tested algorithms provides a guarantee to find the desired optimum. Performing several runs with different initial conditions combined with an evaluation of the success probability might constitute an adequate solution to this limitation. Therefore, as presented in this study, a detailed comparison to the results of the exhaustive parameter sweep exploration is necessary to assess the methods' performance before their application to more complex problems.

Noise impact on the observed goodness-of-fit. As already indicated, we regard the grid search as an approximation of the ground truth (see “Methods”). However, parameter values between the grid nodes may yield slightly higher goodness-of-fit values than we observed. It is therefore not surprising that the optimization methods outperform the grid search for some subjects. The algorithms enjoy the advantage of a continuous

search and do not depend on a selected grid granularity to detect optimal solutions. In addition, the methods outperforming the grid search most obviously (PSO and CMAES, see “Results”) are the population-based approaches. Here, many parameter combinations are evaluated in each execution, and only the best solutions of them were selected to determine the final goodness-of-fit values depicted in Fig. 4, for example. Repeating this procedure in presence of a random noise that ‘kicks’ the similarity between simulated and empirical data to higher values from time to time may induce a cumulative effect which leads to a somewhat higher goodness-of-fit in the end. Nevertheless, the considered parameter grid still delivers a reasonably good approximation of the ground truth.

Outlook: personalized modeling. Given the algorithms, we see a huge potential for studies dealing with high-dimensional brain models. With the proper tools for model validation, it appears realistic to extract new and further insights about human brain dynamics from models that feature region-specific parameters or parameters associated with distinct neural populations^{40,44}. Assigning a particular optimal point in the parameter space to an individual subject may be one step on the road towards possible parametrizations of inter-individual differences and a starting point for sampling individual degenerate manifolds of optimal parameters. We suppose that, in biologically motivated models, the location of optimal parameters can serve as an individual subject’s personal profile. It becomes more distinguishable from others when the underlying model simulations allow for an increased variability in form of many tunable input parameters.

The application of search algorithms might therefore play a decisive role regarding personalized modeling of brain dynamics and its implications. Thanks to the efficiently optimized demand for computational resources, further studies featuring multi-dimensional parameter space explorations on large subject cohorts may be facilitated. In this effort, the optimization procedures allow for various ways of usage. We performed up to 24 runs of each considered method in a bounded relevant parameter space and analyzed the results considering quantities such as the spread of solutions (see “Results”). Alternatively, the algorithms may also be used as a first approach to shed light into a completely unknown parameter space. A moderate number of executions could be used to determine approximate ranges or intervals of optimal parameters. These insights in turn might serve as a basis for a more precise (grid) search on an essentially smaller parameter region. In this hierarchical approach, it would be crucial to choose a method with good global convergence properties and a high stability against local optima in the first step. Afterwards, a precise strategy for the local fine-tuning of the parameters in the predetermined target region would be essential. We assume that a combination of CMAES and NMA or BO might perform well in this scenario.

Summary and conclusions

We tested four mathematical optimization algorithms and aimed at an evaluation of the most appropriate one(s) for the fitting of dynamical whole-brain models derived from and validated against empirical neuroimaging data. To evaluate the quality of the algorithms’ output, we compared their performance on a phase oscillator model with one another as well as with a parameter space exploration on a dense grid. The results of the grid search served as an approximation of the ground truth with respect to the highest possible fit and the location of the corresponding optimal model parameters. We demonstrated that the tested methods vary greatly regarding their stability against local optima and the required computational resources. Two methods (CMAES, BO) turned out as favorable alternatives to a thorough grid search. While CMAES proved most robust in detecting global optima, BO compensated a slightly lower stability with the most efficient use of resources. We recommend CMAES and BO for optimizations starting with three free parameters, where they were around 18 and 91 times faster than a dense grid search, respectively. Our findings may contribute to a more efficient validation of complex models with high-dimensional parameter spaces and also facilitate precise and personalized modeling and analyses of human brain dynamics.

Data availability

Anonymized MRI data used for this study are available from ConnectomeDB (<https://db.humanconnectome.org/>). The C++ source codes of our implementations of the tested optimization algorithms are available from the corresponding author upon reasonable request.

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Supplementary Materials

for the manuscript

Towards an efficient validation of dynamical whole-brain models

by

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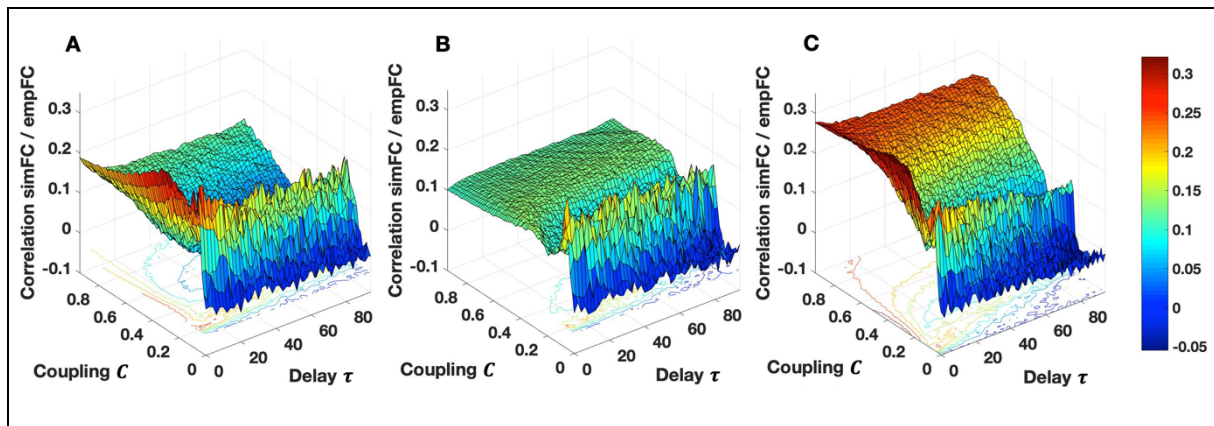


Figure S1: Examples of the objective function $F = F(C, \tau)$ for three selected subjects in the 2Dim case (with fixed noise intensity $\sigma = 0.3$). The correlation between simulated and empirical functional connectivity (simFC and empFC, respectively) is plotted versus the model parameters of global coupling C and delay τ . The values of F are also depicted by colors ranging from blue (small values) to red (large values), where the latter correspond to a better model fitting. The figure was created with MATLAB R2018a (www.mathworks.com).

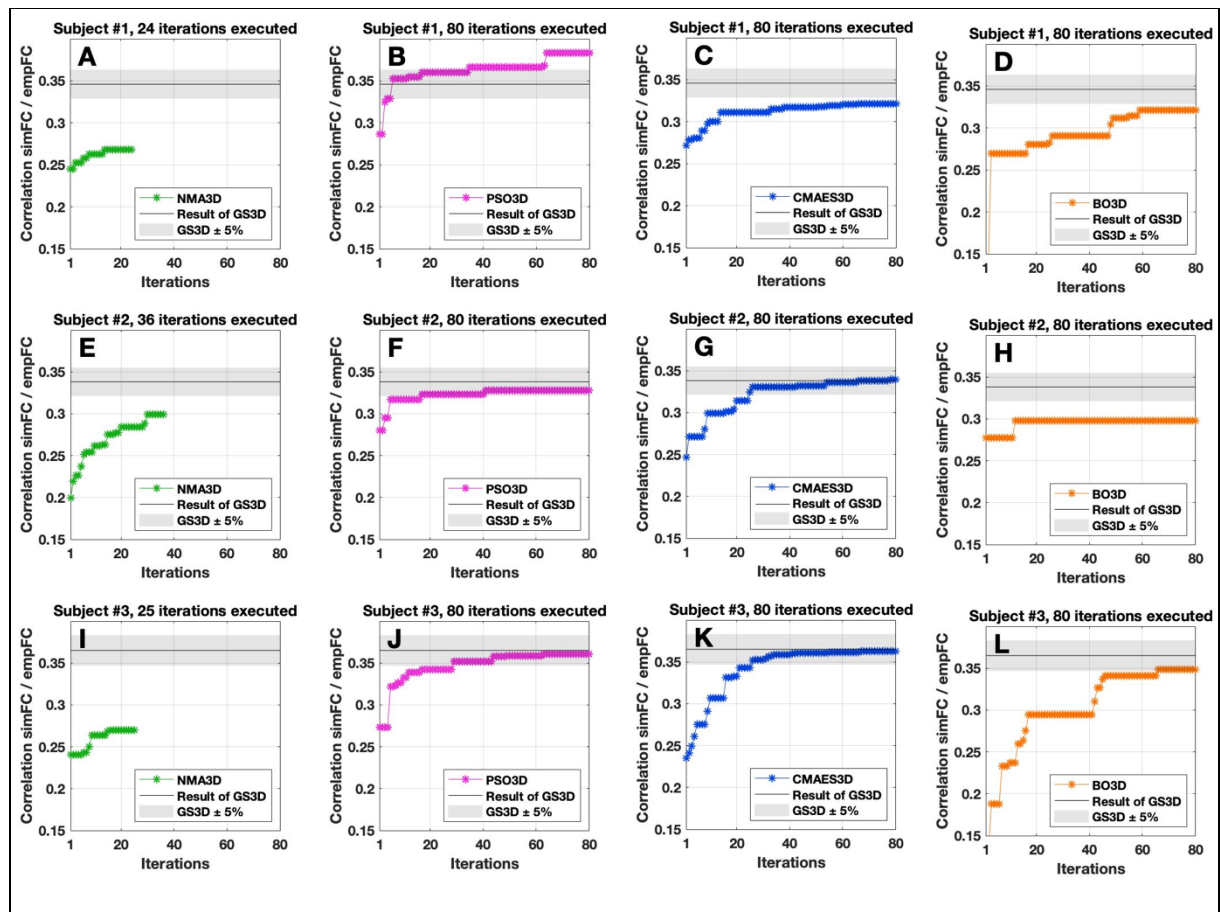


Figure S2: Examples of the algorithms' convergence as given by the values of the goodness-of-fit versus the iteration number. The plots show the gradual development of the obtained correlation $\text{corr}(\text{simFC} / \text{empFC})$ between simulated and empirical FC (colored lines) for one run of the methods indicated in the legends (NMA3D, PSO3D, CMAES3D and BO3D for NMA, PSO, CMAES and BO in the 3Dim parameter space, respectively). In addition to the algorithm results, the final outcome of the grid search is shown (GS3D, black line), where the shaded area represents the range from 95% to 105% of the grid search value ($\text{GS3D} \pm 5\%$). Each row represents the results for one randomly selected subject, which is mentioned in the titles along with the final number of executed iteration steps. The figure was created with MATLAB R2018a (www.math-works.com).

	Goodness-of-fit (GOF)		SD of detected GOFs		Computation time		Spread of solutions		Distance to GS		Overall Ψ_{cost}	
	MOC	REC	MOC	REC	MOC	REC	MOC	REC	MOC	REC	MOC	REC
NMA2D	0.84	0	0.21	8	0.04	1	0.53	0	0.45	1	0.0187	7
PSO2D	0.80	80	0.11	24	0.30	0	0.20	29	0.08	48	0.0041	24
CMAES2D	0.82	10	0.04	56	0.74	0	0.05	64	0.07	42	0.0005	37
BO2D	0.83	10	0.12	12	0.02	99	0.34	8	0.13	10	0.0012	32
NMA3D	0.84	0	0.23	6	0.11	0	0.60	5	0.45	0	0.0308	1
PSO3D	0.80	62	0.21	10	0.88	0	0.54	13	0.24	24	0.1116	7
CMAES3D	0.82	32	0.06	60	0.33	0	0.16	72	0.09	55	0.0012	46
BO3D	0.83	6	0.10	24	0.06	100	0.36	10	0.15	21	0.0014	47

Table S1: Medians of costs (MOC) across subjects and proportions of recommendations (REC, in %) for the tested optimization algorithms in both the 2Dim and 3Dim parameter space. The presented values pertain to the overall cost function Ψ_{cost} as well as to its individual components (see main text for details). Bold letters indicate the most favorable numbers (i.e. lowest costs, highest proportions of recommendations) for every cost factor and dimensionality of the parameter space. The values for REC were rounded to the nearest integer.

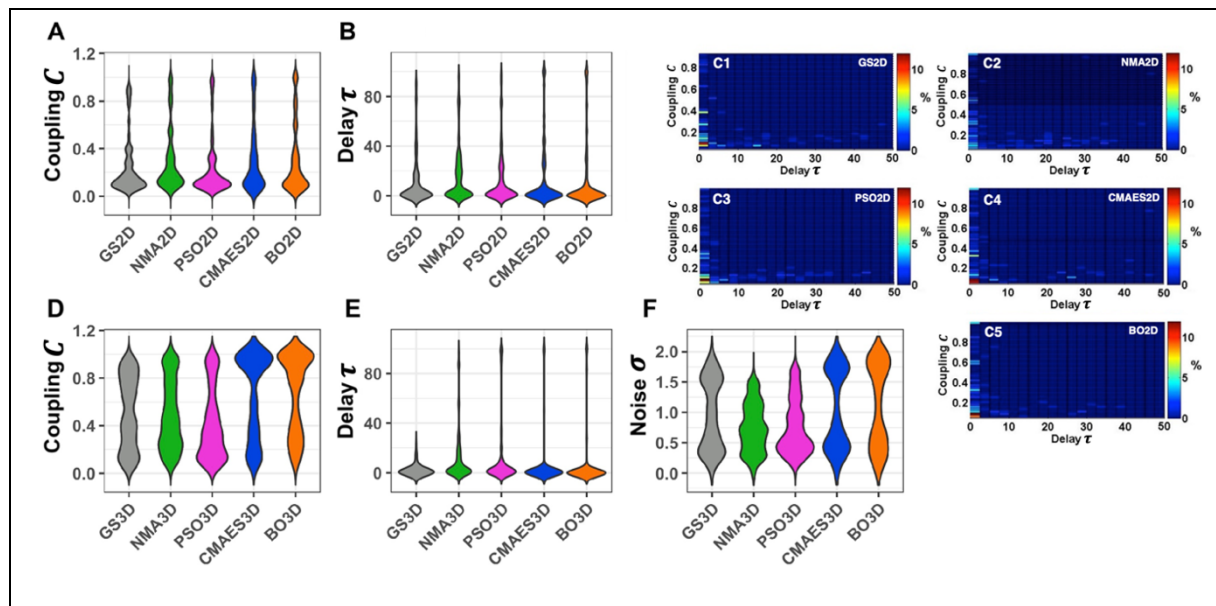
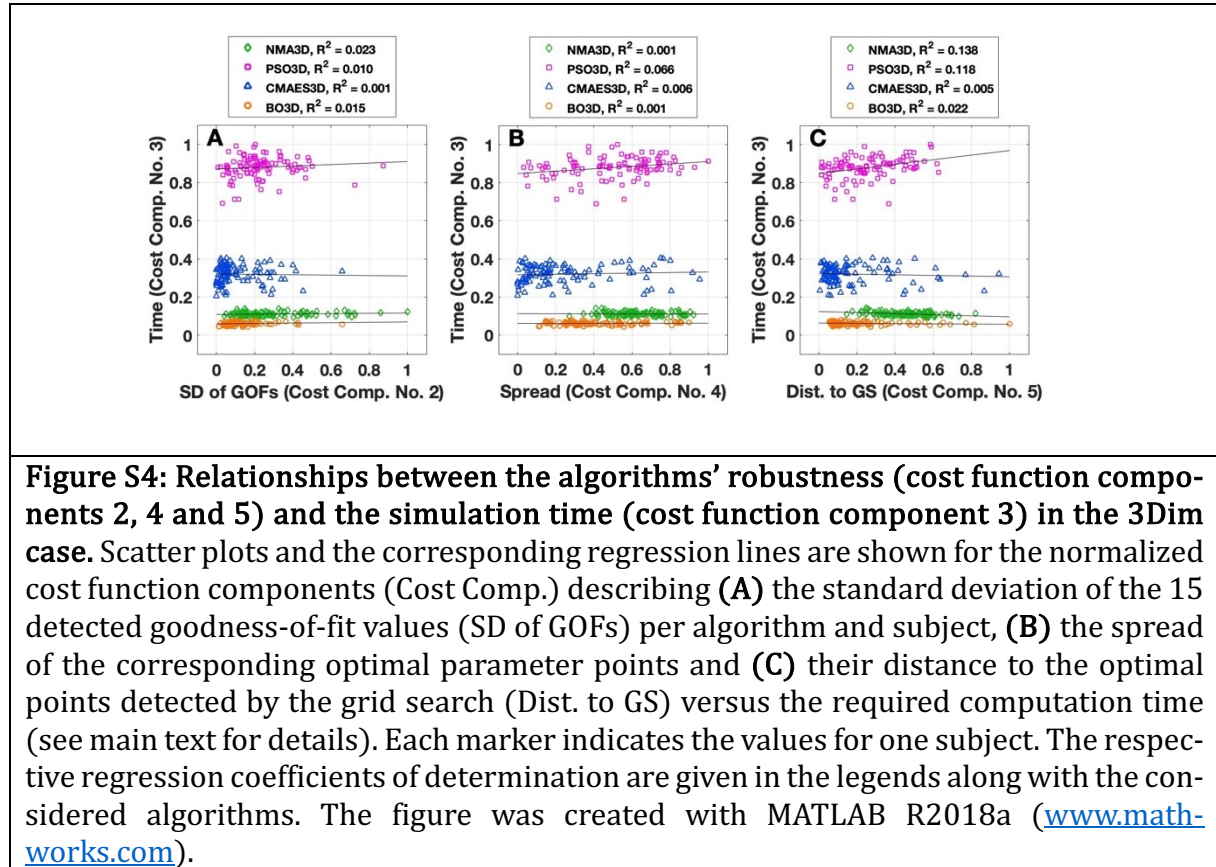


Figure S3: Distributions of the optimal model parameters detected by the considered techniques across all subjects. For each approach and subject, the best solution featuring the highest goodness-of-fit value is considered to estimate the distribution. It was selected from all similarity values computed on the 2Dim or 3Dim parameter grids (for the grid search GS2D or GS3D) and from all goodness-of-fit values obtained by 15 independent runs of the optimization algorithms (NMA2D, PSO2D, CMAES2D, BO2D in 2Dim and NMA3D, PSO3D, CMAES3D, BO3D in 3Dim). In the violin plots of one-parameter distributions for the 2Dim (A, B) and 3Dim (D-F) cases, the methods are indicated on the horizontal axes along with the optimized parameter values on the vertical axes. The plots (C1-C5) show the distributions of the optimal model parameters in the 2Dim space, where the relative frequency of the optimal parameter values is depicted by color and the respective methods are indicated in the plots. The figure was created with MATLAB R2018a (www.mathworks.com).



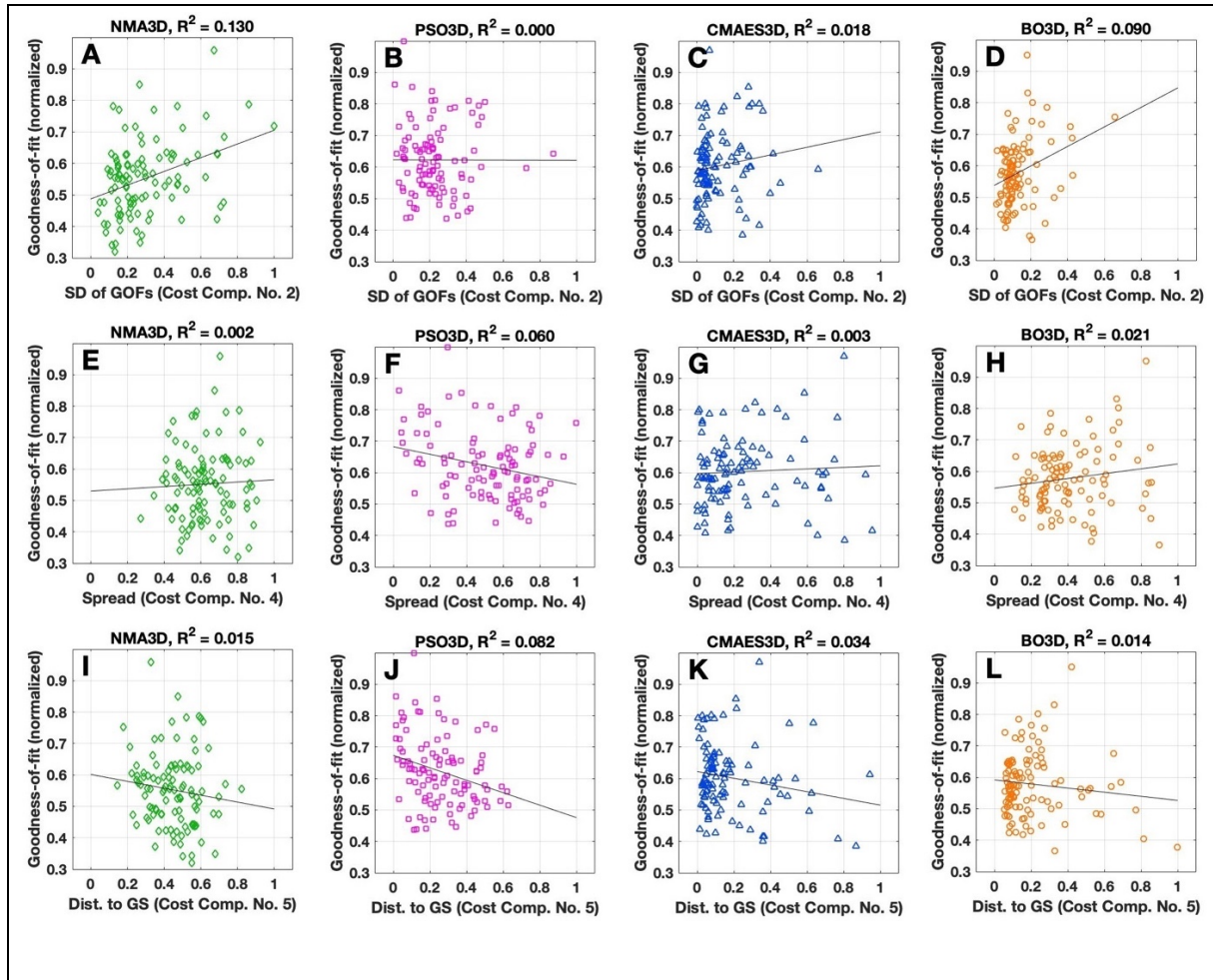


Figure S5: Relationships between the algorithms' robustness (cost function components 2, 4 and 5) and precision (goodness-of-fit derived from cost function component 1) in the 3Dim case. As in Fig. S4, scatter plots and the corresponding regression lines are shown for the cost function components indicated on the horizontal axes along with the normalized goodness-of-fit values on the vertical axes. Each marker indicates the values for one subject. The respective regression coefficients of determination are provided in the titles of the subplots together with the considered algorithms. The figure was created with MATLAB R2018a (www.mathworks.com).

In the following, we provide the details about the mathematical optimization schemes whose performance we discussed and compared in the presented article. The algorithms were applied to maximize the objective function F which returns the Pearson correlation coefficient between the matrices of simulated FC and empirical FC (after a vectorization of the upper triangular parts of the respective matrices).

As stated in the main text, our intended maximization of F can be formulated equivalently as a minimization of $-F$ in order to fit to the traditional manner of describing optimization problems as minimization problems. This adaptation allowed for the usage of mathematical algorithms aiming to minimize a real-valued function $F: X \rightarrow \mathbb{R}$ defined on a parameter space $X \subseteq \mathbb{R}^{\text{Dim}}$ with $\text{Dim} \in \mathbb{N}$.

Nelder-Mead Algorithm

Following Hicken et al.¹, the optimization starts with an initial set of $\Lambda = \text{Dim}+1$ points $x_1, \dots, x_{\text{Dim}+1} \in X$ not lying in the same plane and therefore defining the vertices of a *simplex*. In the most vivid case, $\text{Dim} = 2$, a simplex corresponds to a simple triangle. Tetrahedrons ($\text{Dim} = 3$) and more abstract structures appear in higher dimensions.

After computing the objective function values at all initial simplex points, those are re-ordered, so that $F(x_1) \leq \dots \leq F(x_{\text{Dim}}) \leq F(x_{\text{Dim}+1})$. We assume here that F is not constant and therefore a meaningful ordering is possible. Then, in each iteration, the algorithm replaces the worst vortex $x_{\text{Dim}+1}$ (i.e. the one with the highest function value) by a new point found through a series of transformations around the centroid of the remaining vertices $\bar{x} = \sum_{i=1}^{\text{Dim}} x_i$.

These operations are *reflection*, *expansion*, *inside contraction*, *outside contraction* and *shrinking*, whereas the last one is special in the sense that it does not just replace the worst point, but decreases the size of the entire simplex instead, keeping only the current best point and adding Dim new vertices. Which of the mentioned transformations will eventually determine the new simplex for the next iteration, depends on the value of the objective function F at the proposed points relative to the current ones.

Having computed $\bar{x}$, it is probable that the straight line crossing $x_{\text{Dim}+1}$ and $\bar{x}$ defines a descent direction. *Reflection* proposes a new point lying on this line, namely

$$x_r = \bar{x} + \rho(\bar{x} - x_{\text{Dim}+1}), \quad \rho > 0. \quad (\text{S1.1})$$

Visually, it is the mirrored equivalent of $x_{\text{Dim}+1}$ if the simplex was flipped around. We replace $x_{\text{Dim}+1}$ by x_r in case the condition $F(x_1) \leq F(x_r) < F(x_{\text{Dim}})$ is fulfilled, meaning that we obtained an amelioration compared to $F(x_{\text{Dim}})$ and $F(x_{\text{Dim}+1})$, but not yet to $F(x_1)$. If $F(x_r) < F(x_1)$, then this search direction seems to be particularly promising and we investigate the objective function value further on this line, at the *expanded* point

$$x_e = \bar{x} + \rho\chi(\bar{x} - x_{\text{Dim}+1}), \quad \chi > \rho. \quad (\text{S1.2})$$

If $F(x_e) < F(x_r)$, then $x_{\text{Dim}+1}$ is replaced by x_e , otherwise x_r becomes the new vertex of the simplex. In case the search direction from above leads to no immediate satisfactory improvement, i.e. $F(x_r) > F(x_{\text{Dim}})$, we check whether a better point can be found by *contractions*. If even $F(x_r) \geq F(x_{\text{Dim}+1})$, we look inside the current simplex, between $x_{\text{Dim}+1}$ and $\bar{x}$, and perform an *inside contraction*, leading to

$$x_{ic} = \bar{x} + \gamma(x_{\text{Dim}+1} - \bar{x}), \quad 0 < \gamma < 1, \quad (\text{S1.3})$$

which will be accepted if it is better than $x_{\text{Dim}+1}$, i.e. $F(x_{ic}) < F(x_{\text{Dim}+1})$. Should the condition for an *inside contraction* not be fulfilled, in other words $F(x_r) < F(x_{\text{Dim}+1})$, then an *outside contraction* with

$$x_{oc} = \bar{x} + \gamma(x_r - \bar{x}) \quad (\text{S1.4})$$

is tested. x_{oc} replaces $x_{\text{Dim}+1}$ if $F(x_{oc}) \leq F(x_r)$ is satisfied.

Following these steps, it may still happen that no replacement for the worst point $x_{\text{Dim}+1}$ has been found. In that case, the Nelder-Mead Algorithm *shrinks* its current simplex and

defines the vertices of the new one by x_1 and

$$y_i = x_i + \kappa(x_i - x_1), \quad 0 < \kappa < 1, \quad (\text{S1.5})$$

for $i \in \{2, \dots, \text{Dim} + 1\}$. Ideally, this procedure will create a sequence of simplices of decreasing size which accumulate around the searched-for minimum of F .

For this method, we did not perform an internal parameter tuning and chose the default values¹⁻³

$$\rho = 1, \chi = 2, \gamma = \frac{1}{2} \text{ and } \kappa = \frac{1}{2}.$$

The construction of the initial simplex was based on previously published ideas⁴⁻⁶. Starting with a point x_1 sampled from a uniform distribution over the parameter space, we defined a scaling value

$$c_s = \max\{1, \|x_1\|_2\}$$

together with two helper variables,

$$\beta_1 = \frac{c_s}{\sqrt{2}\text{Dim}} (\sqrt{\text{Dim} + 1} + \text{Dim} - 1) \text{ and } \beta_2 = \frac{c_s}{\sqrt{2}\text{Dim}} (\sqrt{\text{Dim} + 1} - 1),$$

in order to construct a regular simplex whose vertices are given by

$$x_i = (x_{i,1}, \dots, x_{i,\text{Dim}})^T \text{ with } x_{i,j} = x_{1,j} + \delta_{j,i-1}\beta_1 + (1 - \delta_{j,i-1})\beta_2, \quad (\text{S1.6})$$

where $\delta_{i,j}$ denotes the Kronecker delta and $i \in \{2, \dots, \text{Dim} + 1\}$. However, we modified the procedure slightly by working with $\tilde{x}_1 = 0.35 x_1$ as starting point and $\tilde{c}_s = 0.7 c_s$ as scaling value. The reason for this alteration was the fact that in the original setting, the majority of our initial simplexes contained only one or two feasible points within our relevant parameter space. Since we handled boundaries by assigning a high function value, $F(x_{\text{unfeas}}) = 1$, to unfeasible points, as suggested in the algorithm's introductory work³, this led to a somewhat predictable behavior of the algorithm, namely that its optimization always began with a shrinking step. We note that this way of boundary handling may be outperformed by other alternatives⁷, however, having obtained nearly degenerated simplexes when testing Box's method⁸ and in view of the results⁷ that even transformations of the input variables may not always be the ideal way, we held on to the comparably simple penalty approach for this algorithm.

For a stopping criterion, we focused on the length of the simplex edges. If

$$\frac{1}{\max\{1, \|x_1\|_2\}} \max_i \{\|x_i - x_1\|_2\} < 0.005,$$

then the simplex is considered small enough to stop the optimization. Additionally, we defined a maximal number of 80 iterations.

Particle Swarm Optimization

To begin the iterative minimization of F , it is necessary to define a swarm^{9,10} of $\Lambda \in \mathbb{N}$ particles $x_1^0, \dots, x_\Lambda^0 \in X$ equipped with initial velocities $v_1^0, \dots, v_\Lambda^0 \in X$. One way to initialize x_i^0 and v_i^0 for $i \in \{1, \dots, \Lambda\}$ is to choose them uniformly distributed within the bounded search space X ; alternatives are reviewed in other works^{11,12}. Subsequently, the objective function F is evaluated at each position in the swarm and L_i , $i \in \{1, \dots, \Lambda\}$, which will serve as every individual particle's current best location, is set to $L_i^0 = x_i^0$ for all $i \in \{1, \dots, \Lambda\}$, whereas the global best position of all particles is denoted by G and initialized to $G^0 = \operatorname{argmin}\{F(x_i^0)\}$. Then, in every iteration k , the quantities v_i and x_i are updated according to

$$v_i^{k+1} = wv_i^k + \phi_L r_1^k (L_i^k - x_i^k) + \phi_G r_2^k (G^k - x_i^k), \quad (\text{S1.7})$$

$$x_i^{k+1} = x_i^k + v_i^{k+1}, \quad (\text{S1.8})$$

where w denotes an inertia term¹³, ϕ_L, ϕ_G represent a fixed cognitive and social parameter, respectively, and r_1^k, r_2^k are chosen randomly from the interval $[0,1]$.

If a particle discovers a new location that is better than its current best, i.e., $F(x_i^{k+1}) < F(L_i^k)$, then an update is made and L_i^{k+1} is set to x_i^{k+1} , otherwise $L_i^{k+1} = L_i^k$.

Analogously, the best position of the swarm is updated if $F(L_i^{k+1}) < F(G^k)$ for some $i \in \{1, \dots, \Lambda\}$. In that case, the swarm has discovered a new global best point and $G^{k+1} = L_i^{k+1}$, otherwise $G^{k+1} = G^k$. This procedure is repeated until a stopping criterion is met.

According to Kennedy and Eberhart¹⁰, L_i corresponds conceptually to autobiographical memory, meaning that each particle remembers the most fortunate location of its own experience. The term $\phi_L r_1^k (L_i^k - x_i^k)$ in the velocity adjustment can hence be interpreted as nostalgia; an individual tends to return to the place that most satisfied it in the past. G , by contrast, is described as publicized knowledge in the sense of a group norm or social standard that individuals strive to attain, here by the part $\phi_G r_2^k (G^k - x_i^k)$ of the velocity adjustment.

Consequently, the ratio between ϕ_L and ϕ_G determines whether a particle adjusts its velocity rather based on personal or public experiences. Tuning the balance can give the algorithm a (desired) bias towards either side and therefore guides the amount of communication among particles. Additionally, the parameter w controls the velocity updates in a way that higher values for the inertia term enforce larger update steps leading to a more global exploration of the search space while lower values render the search more detailed on a smaller, local level. w is typically initialized close to 1 and may then be gradually decreased throughout the optimization¹².

In our implementation, we tested different alternatives¹² for w (constant, linear decrease, dynamical decrease) and, besides the common choice^{11,14}, $\phi_L = \phi_G \approx 1.496$, we also modified the ratio ϕ_L/ϕ_G by setting either value to 1 and varying the other between 1.1, 1.2 and 1.5. Additionally, we investigated 16 different swarm sizes with Λ between 8 and 144.

Based on the results for a set of random test subjects with respect to convergence speed, most favorable objective function values and the final spread of particles in the swarm (using criteria analogous to those considered for the cost function Ψ_{cost} in the main text), we finally arrived at $\Lambda = 60$ and $\phi_L = 1 < 1.5 = \phi_G$ as the internal algorithm parameters

best suited for our problems. For the inertia weight w , we adapted a procedure of dynamical decrease¹², in which we initially set $w = 0.95$ and multiplied it by 0.975 if G had not improved for 5 consecutive iterations. Similarly, we also used the adaptive penalty approach presented in the same article¹², allowing us to handle unfeasible points by adding penalties ‘based on the average of the objective function and the level of violation of each constraint during each iteration step’.

Even though a component-wise limitation of the particles’ velocities was no longer vital due to the introduction of the inertia weight^{14,15}, we still prevented too large position updates by incorporating a multiplier¹⁶ of 0.9 for velocities whose components exceeded 20% of the feasible interval length (e.g. delay $\tau \in [0, 100]$, update limited to 20) in the respective dimension of the search space X . The optimization procedure was stopped if G had not improved for 50 iterations or if a maximum of 80 iterations had been reached.

Covariance Matrix Adaptation Evolution Strategy

As a preparation for the optimization of F , a set of quantities has to be defined. Importantly, the number Λ of particles (candidate solutions to minimize F) that form a *generation* can be freely chosen, analogously to the swarm size in Particle Swarm Optimization. However, as Hansen¹⁷ states, ‘[s]mall population sizes usually lead to faster convergence, large population sizes help to avoid local optima’. A popular recommendation is therefore to set $\Lambda = 4 + \lfloor 3 \ln(\text{Dim}) \rfloor$ at least^{17,18}. Next, $\mu = \lfloor \Lambda / 2 \rfloor$ is defined. It quantifies the number of particles that will later serve as a basis to compute the generation of candidate solutions for the next iteration. More precisely, the members of the new generation $k + 1$ will be sampled from a multivariate normal distribution centered around a weighted mean m^k of the μ best individuals from the previous iteration k . The selection of the best individuals is based on their respective objective function values (lower = better) and the weights are given as

$$w_i = \frac{\ln(\mu + 1) - \ln(i)}{\sum_{l=1}^{\mu} (\ln(\mu + 1) - \ln(l))} \quad \text{for } i \in \{1, \dots, \mu\}.$$

With this definition, it is clear that the weights sum up to 1.

The (co)variance of the considered distribution depends on a matrix $\mathbf{C}^k \in \mathbb{R}^{\text{Dim} \times \text{Dim}}$ which is adapted in every iteration. For the update, the evolution path $p_{\Omega}^k \in \mathbb{R}^{\text{Dim}}$, the conjugate evolution path $p_c^k \in \mathbb{R}^{\text{Dim}}$ and the step size $\Omega^k > 0$ are computed, along with the following quantities:

$$\mu_{\text{eff}} = \frac{1}{\sum_{i=1}^{\mu} w_i^2}, \quad c_{\Omega} = \frac{\mu_{\text{eff}} + 2}{\text{Dim} + \mu_{\text{eff}} + 3} \quad \text{and} \quad d_{\Omega} = 1 + 2 \max \left\{ 0, \sqrt{\frac{\mu_{\text{eff}} - 1}{\text{Dim} + 1}} - 1 \right\} + c_{\Omega}.$$

The latter play a role in controlling the step size. Additionally, the adaptation of the covariance matrix $\mathbf{C}^k$ depends on

$$c_c = \frac{4}{\text{Dim} + 4}, \quad \mu_{\text{cov}} = \mu_{\text{eff}} \quad \text{and} \\ c_{\text{cov}} = \frac{1}{\mu_{\text{cov}}} \frac{2}{(\text{Dim} + \sqrt{2})^2} + \left(1 - \frac{1}{\mu_{\text{cov}}} \right) \min \left\{ 1, \frac{2\mu_{\text{eff}} - 1}{(\text{Dim} + 2)^2 + \mu_{\text{eff}}} \right\}.$$

Having defined the constants, we initialize the evolution paths to $p_\Omega^0 = p_c^0 = \mathbf{0} \in \mathbb{R}^{\text{Dim}}$ and select $\mathbf{C}^0 = \mathbf{I} \in \mathbb{R}^{\text{Dim} \times \text{Dim}}$ as the initial covariance matrix. Here, $\mathbf{I}$ denotes the identity matrix. The step size Ω^0 and the distribution mean m^0 have to be chosen problem-dependent.

If the algorithm is used to optimize a function within a normalized space $[0,1]^{\text{Dim}}$, then $\Omega^0 = 0.5$ and m^0 uniformly randomly within $[0,1]^{\text{Dim}}$ are the popular choices¹⁸ that we also adapted. We stress that the literature lacks a rigorous proof of the optimality of the presented quantities. In fact, they were all introduced, evaluated and modified based on heuristics in empirical experiments. An early work¹⁹ set the weights to $w_i = 1/\mu$ for all $i \in \{1, \dots, \mu\}$ and analyzed the effects of μ as a hyperparameter, for instance. In a newer version¹⁷, alternative definitions not only for the weights w_i , but also for the starting points and some other constants are presented. In our test runs of the algorithm, however, the described version¹⁸ (from 2006) yielded slightly better results, so that we held on to it and its default values.

After these preparations, the following steps are repeated for every iteration k until a stopping criterion is met. At first, a generation of candidate solutions

$$x_j^{k+1} \sim \mathcal{N}(m^k, (\Omega^k)^2 \mathbf{C}^k), \quad j \in \{1, \dots, \Lambda\}, \quad (\text{S1.9})$$

is computed according to

$$x_j^{k+1} = m^k + \Omega^k B^k D^k z_j^k \quad \text{with} \quad z_j^k \sim \mathcal{N}(\mathbf{0}, \mathbf{I}). \quad (\text{S1.10})$$

$\mathcal{N}$ denotes the (multivariate) normal distribution, all components of $z_j^k \in \mathbb{R}^{\text{Dim}}$ are independently $\mathcal{N}(0,1)$ -distributed. The matrices B^k and D^k are derived from an eigenvalue decomposition of $\mathbf{C}^k = B^k \tilde{D}^k (B^k)^T$, where B^k is an orthogonal matrix containing the normalized eigenvectors of $\mathbf{C}^k$, and $\tilde{D}^k$ is a diagonal matrix containing the corresponding eigenvalues. D^k is then obtained from $\tilde{D}^k$ by applying the square root for the entries on the diagonal, so that $\mathbf{C}^k = B^k D^k D^k (B^k)^T$. The definition of x_j^{k+1} makes use of the fact that $Az \sim \mathcal{N}(\mathbf{0}, AA^T)$ for any non-singular $A \in \mathbb{R}^{\text{Dim} \times \text{Dim}}$ if $z \sim \mathcal{N}(\mathbf{0}, \mathbf{I})$ ²⁰. Afterwards, the objective function F is evaluated at every x_j^{k+1} , $j \in \{1, \dots, \Lambda\}$, and the candidate solutions are indexed in a way that

$$F(x_{j_1}^{k+1}) \leq \dots \leq F(x_{j_\mu}^{k+1}) \leq F(x_{j_{\mu+1}}^{k+1}) \leq \dots \leq F(x_{j_\Lambda}^{k+1}).$$

As mentioned before, the μ best individuals are then selected for the new weighted mean m^{k+1} , which will shift the center of the particles' distribution towards the locations of the most favorable solutions:

$$\begin{aligned} m^{k+1} &= \sum_{i=1}^{\mu} w_i x_{j_i}^{k+1} \stackrel{(\text{S1.10})}{=} \sum_{i=1}^{\mu} w_i (m^k + \Omega^k B^k D^k z_{j_i}^k) \\ &= \underbrace{\sum_{i=1}^{\mu} w_i m^k}_{=1} + \sum_{i=1}^{\mu} w_i \Omega^k B^k D^k z_{j_i}^k \\ &= m^k + \Omega^k B^k D^k \sum_{i=1}^{\mu} w_i z_{j_i}^k. \end{aligned} \quad (\text{S1.11})$$

Subsequently, the evolution paths p_Ω^k , p_c^k and the step size Ω^k are updated:

$$p_\Omega^{k+1} = (1 - c_\Omega)p_\Omega^k + \sqrt{c_\Omega(2 - c_\Omega)\mu_{\text{eff}}}B^k(D^k)^{-1}(B^k)^T \left(\frac{m^{k+1} - m^k}{\Omega^k} \right), \quad (\text{S1.12})$$

$$p_c^{k+1} = (1 - c_c)p_c^k + h_\Omega^{k+1}\sqrt{c_c(2 - c_c)\mu_{\text{eff}}}B^k(D^k)^{-1}(B^k)^T \left(\frac{m^{k+1} - m^k}{\Omega^k} \right) \quad (\text{S1.13})$$

and

$$\Omega^{k+1} = \Omega^k \exp \left(\frac{c_\Omega}{d_\Omega} \left(\frac{\|p_\Omega^{k+1}\|_2}{\mathbb{E}[\|\mathcal{N}(\mathbf{0}, \mathbf{I})\|_2]} - 1 \right) \right), \quad (\text{S1.14})$$

where

$$h_\Omega^{k+1} = \begin{cases} 1, & \text{if } \frac{\|p_\Omega^{k+1}\|}{\sqrt{1 - (1 - c_\Omega)^{2(k+1)}}} < \left(\frac{3}{2} + \frac{1}{\text{Dim} - \frac{1}{2}} \right) \mathbb{E}[\|\mathcal{N}(\mathbf{0}, \mathbf{I})\|_2] \\ 0, & \text{otherwise.} \end{cases} \quad (\text{S1.15})$$

The expected value belonging to a multivariate normal distribution with zero mean and covariance matrix $\mathbf{I}$ is typically approximated via

$$\mathbb{E}[\|\mathcal{N}(\mathbf{0}, \mathbf{I})\|_2] \approx \sqrt{\text{Dim}} \left(1 - \frac{1}{4\text{Dim}} + \frac{1}{21\text{Dim}^2} \right).$$

Finally, the covariance matrix $\mathbf{C}^k$ is updated according to

$$\begin{aligned} \mathbf{C}^{k+1} = & (1 - c_{\text{cov}})\mathbf{C}^k + \frac{c_{\text{cov}}}{\mu_{\text{cov}}} (p_c^{k+1}(p_c^{k+1})^T + \delta(h_\Omega^{k+1})\mathbf{C}^k) \\ & + c_{\text{cov}} \left(1 - \frac{1}{\mu_{\text{cov}}} \right) \sum_{i=1}^{\mu} w_i \left(\frac{x_{ji}^{k+1} - m^k}{\Omega^k} \right) \left(\frac{x_{ji}^{k+1} - m^k}{\Omega^k} \right)^T, \end{aligned} \quad (\text{S1.16})$$

where

$$\delta(h_\Omega^{k+1}) = (1 - h_\Omega^{k+1})c_c(2 - c_c). \quad (\text{S1.17})$$

The new matrix $\mathbf{C}^{k+1}$ determines the (co)variance of the particles' distribution in the next generation, while incorporating the knowledge about the location of the best function values from the current iteration. Together with the adjustments of m^k , this procedure aims at producing a population of particles that accumulate around the global optimum of F . The motivation behind the update of $\mathbf{C}^k$ is to find an approximation of $(\nabla^2 F)^{-1}$, the inverse Hessian matrix in case of a twice differentiable F , similar as in quasi-Newton methods. While a solid proof is still missing, empirical tests imply that, as k increases, $\mathbf{C}^k$ indeed approximates $\rho(\nabla^2 F)^{-1}$, $\rho \in \mathbb{R} \setminus \{0\}$, for many functions^{18,21}.

Our implementation included both the 2006 variant¹⁸ of the algorithm as well as the newer version¹⁷. Prior to the application to the entire subject cohort mentioned in the main text, we compared both alternatives' performance on a set of a few random test subjects. Apart from the population size Λ , we set all hyperparameters to the

recommended default values and analyzed the results with respect to convergence speed, most favorable objective function values and the final spread of particles within a population (using criteria analogous to those considered for the cost function Ψ_{cost} in the main text). For Λ , we tested 8 different values between 6 (in the 2Dim parameter space) or 8 (in the 3Dim parameter space) and 144. It turned out that the 2006 version of the algorithm in combination with $\Lambda = 24$ particles was the most favorable and numerically stable option for the problems we consider.

We handled unfeasible solutions according to an algorithm-related boundary handling procedure²². More precisely, we added a quadratic term to the objective function values that penalizes unfeasible solutions: Whenever the weighted mean m^k (Eq. (S1.11)) leaves the feasible space, a set of boundary weights is initialized as

$$\gamma_i = \frac{2\delta_{\text{fit}}}{(\Omega^k)^2 \sum_{j=1}^{\text{Dim}} \mathbf{C}_{jj}^k} \quad \forall i \in \{1, \dots, \text{Dim}\}.$$

δ_{fit} denotes the median from the last $20 + \lceil 3\text{Dim} / \Lambda \rceil$ generations of the interquartile ranges of the unpenalized objective function values. If k is not large enough yet, only the values from the generations evaluated so far are considered. We intensified the boundary weights γ_i described in the article and worked with $\tilde{\gamma}_i = 5\gamma_i$ following a set of test runs. Subsequently, specific weights are updated via

$$\tilde{\gamma}_i \leftarrow 1.2^{\min\{1, \frac{\mu_{\text{eff}}}{10 \text{Dim}}\}} \tilde{\gamma}_i$$

if the distance of the i^{th} component of $m^k \in \mathbb{R}^{\text{Dim}}$ to the feasible bound is larger than

$$3\Omega^k \sqrt{\mathbf{C}_{ii}^k} \max\left\{1, \frac{\sqrt{\text{Dim}}}{\mu_{\text{eff}}}\right\},$$

a value derived from optimization experiments on the sphere function²². The intention of this step is to obtain an even harder penalty for those critical components and thereby prevent the distribution mean from moving further away from the relevant search space. Afterwards, the penalized objective function values are computed as

$$F(x) := F(x_{\text{feas}}) + \frac{1}{\text{Dim}} \sum_{i=1}^{\text{Dim}} \frac{\tilde{\gamma}_i}{\xi_i} \left(x_{\text{feas}}^{(i)} - x^{(i)}\right)^2, \quad (\text{S1.18})$$

where

$$x_{\text{feas}} = \left(x_{\text{feas}}^{(1)}, \dots, x_{\text{feas}}^{(\text{Dim})}\right)^T \in X$$

is the feasible solution closest to

$$x = \left(x^{(1)}, \dots, x^{(\text{Dim})}\right)^T \in \mathbb{R}^{\text{Dim}}.$$

Note that the superscripts in parentheses indicate the components of the vector and not the generation number. Out-of-bound components are typically set to the respective boundary values. The quantity

$$\xi_i = \exp\left(0.9 \left(\ln(\mathbf{C}_{ii}^k) - \frac{1}{\text{Dim}} \sum_{j=1}^{\text{Dim}} \ln(\mathbf{C}_{jj}^k)\right)\right) \quad (\text{S1.19})$$

serves as a scaling factor, see the work of Hansen and collaborators for more details²². This boundary handling procedure guarantees that the minimum of F cannot be outside the feasible search space.

The optimization procedure was stopped if the best objective function value discovered so far had not improved for 50 iterations or if a maximum of 80 iterations had been reached. This selection was made in analogy with the criteria chosen for Particle Swarm Optimization. Alternatives are described by Hansen¹⁷; a stricter termination criterion would be to stop already after $10 + \lfloor 3 \text{ Dim} / \Lambda \rfloor$ iterations without improvement, for example.

Bayesian Optimization

The minimization of the objective function F starts with the evaluation of a random sample of Λ points $x_1, \dots, x_\Lambda$ which may be uniformly distributed in X . A possible choice is $\Lambda \approx 10 \text{ Dim}$ as initial sample size^{23,24}, but lower values for Λ are not uncommon. The C++ software package *BayesOpt*²⁵ uses $\Lambda = 10$ and the MATLAB routine *bayesopt* (<https://de.mathworks.com/help/stats/bayesopt.html>) works with $\Lambda = 4$ as dimension-independent default value. To distinguish between the (constant) size of the initial sample and the (increasing) number of objective function evaluations computed so far, we denote the latter by $\tilde{\Lambda}$. Before the computation of new sampling points, both quantities are equal. As a next step, a mean $m^{(0)}: X \rightarrow \mathbb{R}$ and kernel function $K^{(0)}: X \times X \rightarrow \mathbb{R}$ have to be chosen. This is essential for Bayesian Optimization since the algorithm tries to approximate the function F , which may not be available in closed form, via a stochastic model. More concretely, a nonlinear process is used to model F , typically a Gaussian Process (GP)²⁶. It can be interpreted as a quantity analogous to the function $F: X \rightarrow \mathbb{R}$, but instead of returning a scalar $F(x)$ for a certain $x \in X$, a GP returns the mean and (co)variance of a normal distribution over possible values of F at the point x . Formally, this dependence can be expressed as

$$\begin{aligned} m^{(0)}(x) &= \mathbb{E}[F(x)] \quad \text{and} \quad K^{(0)}(x, x') = \mathbb{E} \left[\left(F(x) - m^{(0)}(x) \right) \left(F(x') - m^{(0)}(x') \right) \right] \\ &\Rightarrow F(x) \sim \mathcal{N} \left(m^{(0)}(x), \theta^{(0)}(x) \right), \quad \text{where} \quad \theta^{(0)}(x) = K^{(0)}(x, x). \end{aligned} \quad (\text{S1.20})$$

At this stage, the GP serves as a prior belief about F and its possible values.

It is common to choose a constant or relatively simple function for the mean²⁷, e.g., $m^{(0)}(x) = 0$. The kernel should be positive semi-definite²⁶ and it should guarantee that two points x and x' lying close to each other in X are strongly correlated and thus generate a higher value $K^{(0)}(x, x')$ than two points that are further apart. One possible kernel is the *automatic relevance determination (ARD) squared exponential kernel*²⁸ which is given by

$$K_{\text{SE}}(x, x') = \alpha_0 \exp \left(-\frac{1}{2} r^2(x, x') \right), \quad \text{where} \quad r(x, x') = \sqrt{\sum_{i=1}^{\text{Dim}} \frac{(x^{(i)} - x'^{(i)})^2}{\alpha_i^2}}. \quad (\text{S1.21})$$

Note that $x^{(i)}$, $i \in \{1, \dots, \text{Dim}\}$, denotes the i -th component of a point $x \in X$ (in the parameter optimization considered in the main text, $x^{(1)}$ would be the coupling strength C , for example). The coefficients $\alpha_j \geq 0$, $j \in \{0, \dots, \text{Dim}\}$, represent the hyperparameters of the kernel, whose estimation we will discuss later below. α_0 can be treated as an

amplitude of the variance in the GP. Lower values favor approximations of F closer to the mean function. The remaining $\alpha_j, j \geq 1$, reflect the addendum ‘ARD’ in the name of the kernel. They assign weights to every component j and thus determine their effective contribution and relevance for the computation of the (co)variance. There also exists an unweighted variant of this kernel where $\alpha_i = 1$ for all $i \in \{0, \dots, \text{Dim}\}$. It has been described as slightly naïve, though, as divergences of all components of x affect the covariance equally²⁹. The ARD version has the advantage of being an uncomplicated function with the desired attributes (mentioned above) in combination with additional flexibility expressed via a set of hyperparameters α_i . In practice, however, its usage in a GP generates approximations of the objective function F which are unrealistically smooth²⁸. A useful alternative is therefore the *ARD Matérn class* named by Stein³⁰ after the work of Matérn³¹. Its general form is given by

$$K_{M\nu}(x, x') = \frac{2^{1-\nu}}{\Gamma(\nu)} \left(\sqrt{2\nu} r(x, x') \right)^\nu \mathcal{K}_\nu \left(\sqrt{2\nu} r(x, x') \right), \quad (\text{S1.22})$$

where Γ denotes the Gamma function and $\mathcal{K}_\nu$ is a modified spherical Bessel function of the third kind^{26,32}. Finally, $\nu > 0$ can be interpreted as a smoothness parameter²⁹. It allows for a regulation of the degree $d < \nu$ of differentiability (in the quadratic mean^{26,30}) of the approximations of the objective function F . Given the complexity of many natural processes, it has been argued that there is hardly any reasonable justification for selecting a kernel method that provides no possibility of influencing the smoothness properties of the generated output^{26,30}.

For $\nu = n + \frac{1}{2}, n \in \mathbb{N}_0$, the Bessel function $\mathcal{K}_\nu = \mathcal{K}_{n+\frac{1}{2}}$ has an easily calculable form, following from the equations (10.1.19) and (10.2.25) in the handbook by Abramowitz and Stegun³²

$$\mathcal{K}_{n+\frac{1}{2}}(z) = \sqrt{\frac{\pi}{2z}} \exp(-z) \sum_{k=0}^n \frac{(n+k)!}{k! \Gamma(n-k+1)} (2z)^{-k}. \quad (\text{S1.23})$$

Accordingly, two convenient choices in modern applications are $\nu = \frac{3}{2} (\Rightarrow n = 1)$, which leads to the *ARD Matérn 3/2 kernel*

$$K_{M32}(x, x') = \alpha_0 \left(1 + \sqrt{3} r(x, x') \right) \exp \left(-\sqrt{3} r(x, x') \right) \quad (\text{S1.24})$$

and $\nu = \frac{5}{2} (\Rightarrow n = 2)$, which, as we will demonstrate, yields the *ARD Matérn 5/2 kernel*

$$K_{M52}(x, x') = \alpha_0 \left(1 + \sqrt{5} r(x, x') + \frac{5}{3} r^2(x, x') \right) \exp \left(-\sqrt{5} r(x, x') \right). \quad (\text{S1.25})$$

We start with the computation of the Bessel function (Eq. (S1.23)) and later apply the general kernel formula (Eq. (S1.22)):

$$\begin{aligned}
\mathcal{K}_{n+\frac{1}{2}}(z) &\stackrel{n=2}{=} \mathcal{K}_{\frac{5}{2}}(z) \\
&\stackrel{(S1.23)}{=} \sqrt{\frac{\pi}{2z}} \exp(-z) \sum_{k=0}^2 \frac{(2+k)!}{k! \Gamma(3-k)} (2z)^{-k} \\
&= \sqrt{\frac{\pi}{2z}} \exp(-z) \left(\frac{2!}{\Gamma(3)} + \frac{3!}{\Gamma(2)} \frac{1}{2z} + \frac{4!}{2\Gamma(1)} \frac{1}{4z^2} \right) \\
&= \sqrt{\frac{\pi}{2z}} \exp(-z) \left(\frac{2}{2} + \frac{6}{1} \frac{1}{2z} + \frac{24}{2 \cdot 1} \frac{1}{4z^2} \right) \\
&= \sqrt{\frac{\pi}{2z}} \exp(-z) \left(1 + \frac{3}{z} + \frac{3}{z^2} \right).
\end{aligned}$$

Following Eq. (S1.22), we set $z = \sqrt{2\nu} r(x, x') \stackrel{\nu=\frac{5}{2}}{=} \sqrt{5} r(x, x')$, omit the argument of r and obtain

$$\mathcal{K}_{\frac{5}{2}}(\sqrt{5} r) = \sqrt{\frac{\pi}{2\sqrt{5} r}} \exp(-\sqrt{5} r) \left(1 + \frac{3}{\sqrt{5} r} + \frac{3}{5r^2} \right). \quad (S1.26)$$

Now we again consider Eq. (S1.22), omit the arguments of $K_{M\nu}$ and r for brevity and insert $\nu = \frac{5}{2}$. Since $\Gamma\left(\frac{5}{2}\right) = \frac{3\sqrt{\pi}}{4}$, this leads to

$$\begin{aligned}
K_{M\nu} &= \frac{2^{1-\nu}}{\Gamma(\nu)} (\sqrt{2\nu} r)^\nu \mathcal{K}_\nu(\sqrt{2\nu} r) \\
&\stackrel{(S1.26)}{=} 2^{-\frac{3}{2}} \frac{4}{3\sqrt{\pi}} (\sqrt{5} r)^{\frac{5}{2}} \sqrt{\frac{\pi}{2\sqrt{5} r}} \exp(-\sqrt{5} r) \left(1 + \frac{3}{\sqrt{5} r} + \frac{3}{5r^2} \right) \\
&= \frac{1}{\sqrt{2^3}} \frac{4}{3} \frac{5^{\frac{5}{4}} r^{\frac{5}{2}}}{\sqrt{2\sqrt{5} r}} \exp(-\sqrt{5} r) \left(1 + \frac{3}{\sqrt{5} r} + \frac{3}{5r^2} \right) \\
&= \frac{1}{3} \frac{5^{\frac{5}{4}}}{r^{\frac{5}{2}}} \frac{5^{-\frac{1}{4}}}{r^{-\frac{1}{2}}} \exp(-\sqrt{5} r) \left(1 + \frac{3}{\sqrt{5} r} + \frac{3}{5r^2} \right) \\
&= \frac{5}{3} r^2 \exp(-\sqrt{5} r) \left(1 + \frac{3}{\sqrt{5} r} + \frac{3}{5r^2} \right) \\
&= \exp(-\sqrt{5} r) \left(\frac{5}{3} r^2 + \sqrt{5} r + 1 \right),
\end{aligned}$$

which, up to the constant α_0 , corresponds to the ARD Matérn 5/2 kernel (Eq. (S1.25)). Selecting $\nu = \frac{3}{2}$ and $\nu = \frac{5}{2}$ leads to approximations of the objective function F that are once and twice differentiable, respectively^{26,30}. The limit $\nu \rightarrow \infty$ results in the ARD squared exponential kernel^{28,29}. More details about kernel functions can be found in algorithm-related works^{23,27,29}.

After having chosen the mean and kernel functions, the hyperparameters are optimized based on the knowledge that was obtained from the evaluation of the Λ initial sample points $x_1, \dots, x_\Lambda$. Importantly, the procedures of this algorithm allow for more

hyperparameters than $\alpha_0, \dots, \alpha_{\text{Dim}}$. On the one hand, it is possible to consider a constant mean $m^{(0)}(x) = \omega$ with unknown $\omega \in \mathbb{R}$, on the other hand, it can be accounted for the unknown observation noise ϑ in stochastic objective functions^{27,28}. Summarizing all considered hyperparameters in a vector

$$\xi = (\alpha_0, \dots, \alpha_{\text{Dim}}, \omega, \vartheta),$$

the easiest approach is then to maximize the likelihood of the observations $x_1, \dots, x_A$ (henceforth denoted by $x_{1:A}$) under the GP prior, i.e. for a given probability measure $\mathbf{P}$, we search for

$$\tilde{\xi} = \underset{\xi}{\operatorname{argmax}} \{ \mathbf{P}(F(x_{1:A}) | \xi) \},$$

which is known as the *maximum likelihood estimate* (MLE). Alternatively, it can be assumed that also ξ was chosen from a prior. The desired quantity $\tilde{\xi}$ is then given by the *maximum a posteriori estimate* (MAP)

$$\tilde{\xi} = \underset{\xi}{\operatorname{argmax}} \{ \mathbf{P}(\xi) | F(x_{1:A}) \} = \underset{\xi}{\operatorname{argmax}} \{ \mathbf{P}(F(x_{1:A}) | \xi) \mathbf{P}(\xi) \}.$$

It maximizes the posterior. The most exhaustive option is called the *fully Bayesian approach*, where an integration over all possible values of the hyperparameters is performed²⁷. Further details on how to obtain the desired hyperparameters practically are provided in related papers^{23,33}.

The intention of all these considerations is to obtain an adequate prior distribution over possible functions for F . Based on the function evaluations obtained so far, Bayesian Optimization tries to generate the best possible surrogate model for F .

For a new sampling point x_{A+1} , the prior distribution of F is therefore given by

$$F(x_{A+1}) \sim \mathcal{N} \left(m^{(0)}(x_{A+1}), \theta^{(0)}(x_{A+1}) \right) \quad (\text{S1.27})$$

along with the optimized hyperparameters of the (mean and) kernel. As carefully detailed by Rasmussen and Williams²⁶ (§ 2.1), Bayes' theorem can then be applied in order to derive the posterior distribution of F given the previous observations:

$$F(x_{A+1}) | F(x_{1:A}) \sim \mathcal{N} \left(m^{(\Lambda)}(x_{A+1}), \theta^{(\Lambda)}(x_{A+1}) \right). \quad (\text{S1.28})$$

The corresponding update formulas for the mean and kernel (variance) are

$$m^{(\Lambda)}(x) = K^{(0)}(x, x_{1:A}) \left(K^{(0)}(x_{1:A}, x_{1:A}) \right)^{-1} \left(F(x_{1:A}) - m^{(0)}(x_{1:A}) \right) + m^{(0)}(x), \quad (\text{S1.29})$$

$$\theta^{(\Lambda)}(x) = K^{(0)}(x, x) - K^{(0)}(x, x_{1:A}) \left(K^{(0)}(x_{1:A}, x_{1:A}) \right)^{-1} K^{(0)}(x_{1:A}, x) \quad (\text{S1.30})$$

with $K^{(0)}(x, x_{1:A}) \in \mathbb{R}^{1 \times A}$, $K^{(0)}(x_{1:A}, x_{1:A}) \in \mathbb{R}^{A \times A}$, $F(x_{1:A}) \in \mathbb{R}^{A \times 1}$, $m^{(0)}(x_{1:A}) \in \mathbb{R}^{A \times 1}$ and $K^{(0)}(x_{1:A}, x) \in \mathbb{R}^{A \times 1}$ as summarized in modern tutorials^{27,29}.

Having obtained the posterior distribution for possible values of $F(x_{A+1})$, the question arises what the most advantageous sampling point x_{A+1} might be. In order to find it, Bayesian Optimization works with an acquisition function $a: X \rightarrow \mathbb{R}$ which provides an estimation about the area where the highest gain in terms of improved objective function values can be achieved. The acquisition function is typically designed in a way that aims at making it relatively easy to maximize. Since its evaluations are much cheaper to compute than those of the objective function F , standard techniques³³ can lead to a fast

maximization of a . Frazier²⁷ recommended the quasi-Newton method *limited-memory Broyden-Fletcher-Goldfarb-Shanno Algorithm with bound constraints* (L-BFGS-B)^{34,35}, while the Nelder-Mead Algorithm³ and other methods were tested by Schonlau and collaborators²⁴.

One popular approach is to consider the *expected improvement* as acquisition function. To compute it, we define $\tilde{F}$

$$\tilde{F} = \min\{F(x_1), \dots, F(x_\Lambda)\} \text{ and } u(x) = \max\{0, \tilde{F} - F(x)\} \quad (\text{S1.31})$$

as the best value detected so far and the absolute improvement compared to it, respectively. Then, the acquisition function is given as

$$a_{\text{EI}}(x) = \mathbb{E}[u(x)], \quad (\text{S1.32})$$

for which a closed form is available²³. Another commonly used alternative is the *lower confidence bound* function

$$a_{\text{LCB}}(x) = m^{(\Lambda)}(x) - \beta \sqrt{\theta^{(\Lambda)}(x)}. \quad (\text{S1.33})$$

It creates a lower envelope of uncertainty around the posterior mean function whose width is given by the posterior standard deviation multiplied by a factor $\beta > 0$. For a minimization of F , $-a_{\text{LCB}}$ is usually maximized. The parameter β can be adjusted to tune the balance between the desire for exploitation (sampling near favorable mean values) and exploration (sampling in areas of high uncertainty). MATLAB's routine *bayesopt* works with $\beta = 2$ as default value. Other possible acquisition functions are presented by Frazier²⁷.

When a new sampling point has been found, the corresponding objective function value is computed and then added to the list of previously obtained function evaluations. Afterwards, the hyperparameters of the initial mean and kernel function can be optimized again (with $\tilde{\Lambda}$ instead of Λ) or the posterior distribution over possible values of F is updated immediately based on the knowledge gained from the new sampling point. In the formulas, Λ will be replaced by $\tilde{\Lambda}$ then. Subsequently, the acquisition function is maximized again (this time with $\tilde{\Lambda}$) to find another sampling point. This procedure is repeated until a stopping criterion is met.

Since the matrix $K^{(0)}(x_{1:\Lambda}, x_{1:\Lambda})$ (or rather $K^{(0)}(x_{1:\tilde{\Lambda}}, x_{1:\tilde{\Lambda}})$), whose size increases with every new sampling point, has to be inverted in each update step, it is recommended to either limit the number of maximum iterations to a moderate number or to gradually remove some of the initial points when a satisfactory amount of data has been collected³⁶. From the viewpoint of numerical stability and performance, it may also be favorable to work with a Cholesky decomposition of the matrix²⁵.

For our implementation, we used the C++ software package *BayesOpt*²⁵ with $\Lambda = 5$ in the 2Dim parameter space and $\Lambda = 10$ in the 3Dim case. We chose a maximum of 80 iterations and worked with the default settings to handle unfeasible points. In addition, we also used the default to model the objective function F via a GP that features a constant mean function and the ARD Matérn 5/2 kernel. Testing 8 combinations with different variants of hyperparameter learning methods and possible acquisition functions, we obtained favorable results for the fully Bayesian approach. It was used to optimize the kernel hyperparameters after every new function evaluation. Moreover, the idea of the lower confidence bound turned out as the most suitable approach for the acquisition function. All other settings were left at the default.

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6 Study 2: Exploring dynamical whole-brain models in high-dimensional parameter spaces

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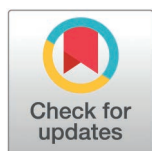
RESEARCH ARTICLE

Exploring dynamical whole-brain models in high-dimensional parameter spaces

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Data availability statement: Anonymized MRI data used for this study are available from ConnectomeDB (<https://db.humanconnectome.org/>). After signing in, the data can be accessed under 'WU-Minn HCP Data – 1200 Subjects': Open Dataset / Browse Subjects / Subject ID / MR session. The C++ source codes of our implementations of the tested optimization

Abstract

Personalized modeling of the resting-state brain activity implies the usage of dynamical whole-brain models with high-dimensional model parameter spaces. However, the practical benefits and mathematical challenges originating from such approaches have not been thoroughly documented, leaving the question of the value and utility of high-dimensional approaches unanswered. Studying a whole-brain model of coupled phase oscillators, we proceeded from low-dimensional scenarios featuring 2–3 global model parameters only to high-dimensional cases, where we additionally equipped every brain region with a specific local model parameter. To enable the parameter optimizations for the high-dimensional model fitting to empirical data, we applied two dedicated mathematical optimization algorithms (Bayesian Optimization, Covariance Matrix Adaptation Evolution Strategy). We thereby optimized up to 103 parameters simultaneously with the aim to maximize the correlation between simulated and empirical functional connectivity separately for 272 subjects. The obtained model parameters demonstrated increased variability within subjects and reduced reliability across repeated optimization runs in high-dimensional spaces. Nevertheless, the quality of the model validation (goodness-of-fit, GoF) improved considerably and remained very stable and reliable together with the simulated functional connectivity. Applying the modeling results to phenotypical data, we found significantly higher prediction accuracies for sex classification when the GoF or coupling parameter values optimized in the high-dimensional spaces were considered as features. Our results elucidate the model fitting in high-dimensional parameter spaces and can contribute to an improved dynamical brain modeling as well as its application to the frameworks of inter-individual variability and brain-behavior relationships.

algorithms are publicly available (<https://jugit.fz-juelich.de/inm7/public/par-opt-in-wbm>).

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Introduction

Over the past years, neuroimaging studies have intensively been striving to seize the full potential of mathematical models designed for the simulation of human brain dynamics. Especially the investigations of the resting-state brain activity [1] involved a plenitude of dynamical whole-brain models. These models incorporate anatomical information about the brain into the simulation of its dynamical properties either on the group or subject level [2–5]. While anatomical information in this context refers to structural connectivity (SC), i.e., physical connections in terms of axonal bundles between brain regions, dynamical properties are thought of as functional connectivity (FC), i.e., the amount of temporal coactivations between regions. SC and FC show a complex and relatively weak relationship that also depends on the considered brain parcellation [6–8]. Data-driven dynamical models equip the structural data with dynamical features [9] and can therewith shed light onto the mechanisms underlying the emergence of resting-state brain dynamics [2,10–13]. Additionally, model simulations may improve the overall interpretability by performing a certain denoising, meaning that only the relevant dynamics and phenomena are modeled, but not the unwanted effects of random noise present in the empirical data (or at least the impact can be controlled and investigated) [2,3,14–16].

As model simulations can be designed to reproduce resting-state dynamics on a personalized level, researchers strive to link the empirical observations to the ingredients and dynamical properties of the computational model [17]. That can possibly be done by approximating optimal model parameters, leading to a better mechanistic explanation of the observed brain activity [18,19]. In line with that, recent studies have reported an improved differentiation of Alzheimer's disease (AD) [20] and facilitated identification of new attention deficit hyperactivity disorder (ADHD) subtypes [21] based on model parameters of a reduced Wong-Wang model and a coupled oscillator model, respectively, and higher classification accuracy of Parkinson's disease (PD) patients versus healthy controls [22] on the basis of connectomes simulated via a reduced Jansen-Rit model to give a few examples. Personalized virtual brain models could also assist at the estimation of the epileptogenic zone and simulation of the virtual neurosurgery [23].

However, the precondition for all mentioned advantages and applications is a proper model validation against empirical data. Model validation is also referred to as model fitting or model inversion [24–27]. The approximation of optimal model parameters remains a challenge because a complete parameter space scan on a dense grid (grid search) poses exponentially growing computational requirements for every single subject. Simulations introducing region-specific model parameters, i.e., parameter heterogeneity, may however involve more than 100 free parameters [27,28]. In such cases, a grid search is unfeasible, which constitutes a major limiting factor for the aspirations of personalized brain modeling mentioned above.

Several works were already focusing on the investigation of regional heterogeneity [28–31]. However, only a few model parameters were actually optimized. By incorporating anatomical information in form of the myelin content [29], gene expression profiles [30] or the T1-weighted/T2-weighted ratio [31] into the model, a function can

be derived from empirical brain imaging data that returns the parameter values of every brain region. This function in turn depends on only a few free global parameters (6 [29] or 3 [30], for example), which greatly simplifies a genuine regional parameter heterogeneity and does not require its optimization in high-dimensional parameter spaces. Similarly, Kong and colleagues [28] suggested to constrain the regional heterogeneity of a parametric mean-field model by both anatomical and functional gradients and therefore reduced their original model featuring 205 free parameters to a simpler one with only 10.

The precise replication of personalized resting-state dynamics may nevertheless require the transition to high-dimensional model parameter spaces [18,23,27]. In this scenario, optimal parameters can comprise degenerate manifolds that ideally would be sampled systematically by Monte Carlo approaches [23,29,32–34]. With respect to computational resource consumption and tractability, however, the more practical solution is often given by the use of mathematical optimization algorithms [28,35–40]. These methods suggest new sampling points iteratively and aim at convergence to an optimal parameter configuration [41,42].

In this study, we investigate the behavior of a whole-brain model when the model fitting to subject-specific empirical data is performed in a high-dimensional parameter space. We illustrate this on a simple model of coupled phase oscillators when the similarity between simulated and empirical FC was maximized by simultaneous optimization of about 100 model parameters via two dedicated optimization algorithms: Bayesian Optimization (BO) and the Covariance Matrix Adaptation Evolution Strategy (CMAES). The latter were selected as efficient approaches for model validation in low-dimensional parameter spaces in our previous study [42]. Our ambition in the current study was to fully exploit the algorithms' superiority over a grid search [42] and explore the benefits and challenges that arise with real high-dimensional parameter spaces. We wanted to assess the practical value for more precise replications of the resting-state brain dynamics and possible relations to phenotypical data as additional values for the application and validation of the modeling results. This may contribute to the existing literature on brain modeling and show that the mathematical methods allow us to validate whole-brain models that feature a genuine, unconstrained parameter heterogeneity.

Below, we demonstrate that the high-dimensional model validation can indeed strongly improve the quality of the model fitting with a respective (moderate) increase of the required computational resources. We also inspect and document the properties of the optimized model parameters, the corresponding matrices of simulated FC (sFC) as well as their reliability and potential utility for further applications. Despite persistent fluctuations within the approximated optimal model parameters, the sFC remains relatively stable. Finally, we take phenotypical data of individual subjects into account and analyze the impact of the parameter space's dimension on the extent of differences between males and females observed in simulated data. We find enhanced sex differences in the modeling results for high-dimensional parameter spaces, leading to significantly higher classification accuracies than for the low-dimensional model fitting, which can serve as further indications of the applicability and validity of the employed modeling approaches and reported results.

Methods

In the present study, we considered neuroimaging data of $S = 272$ healthy, unrelated subjects (age 28.5 ± 3.5 years, 128 males) from the Human Connectome Project (HCP) S1200 public dataset release [43]. The local ethics committee of the HCP WU-Minn gave its approval for the project, and written, informed consent was obtained from all subjects. All experiments were performed in accordance with the relevant guidelines and complied with the principles expressed in the Declaration of Helsinki.

For our investigations, the brain was parcellated (according to a given brain atlas) into separate brain regions used for the calculation of SC and resting-state FC. A simple dynamical whole-brain model of coupled phase oscillators was then applied to simulate the resting-state brain dynamics of every subject based on the individual structural data. We inferred sFC from the model output and compared it to the empirical FC (eFC). By the use of the Pearson correlation coefficient, we assessed their similarity, i.e., the quality of the model fit, and searched for model parameter values that maximize it.

We will also refer to this procedure as model validation. Further, we investigated the impact of the number of free model parameters used for simultaneous optimization and therefore considered various parameter spaces for model validation.

Our goal was to extract information about the results of the model validation in the high-dimensional parameter spaces. We wanted to evaluate the properties of the optimized model parameters, sFC and the extent of similarity between empirical and simulated data. In particular, we were interested in (i) the presence of multiple optima in the high-dimensional parameter spaces and (ii) the identifiability of the simulation results, which could be affected by the convergence to different optima in repeated algorithm executions. We therefore implemented two mathematical optimization methods, BO and CMAES, to search for optimal parameter values (model validation) which put the model output in the closest possible correspondence with empirical data. After performing several repetitive model validations for different initial conditions for the same subject, we analyzed the modeling outcomes with respect to their variability, reliability and practical utility. Finally, we inspected the applicability of the modeling results to phenotypical data. We were especially interested in how much high-dimensional model validation can reveal sex differences in the modeling results, compared to the cases of low-dimensional model fitting as well as purely empirical brain imaging data.

Empirical and simulated data

MRI data preparation. The considered HCP dataset included complete T1-weighted and diffusion-weighted magnetic resonance imaging (dwMRI) as well as resting-state functional MRI (fMRI) data for every subject. The extraction of SC was performed with a publicly available pipeline (https://github.com/inm7/vbc_dwmri). We refer to our related works [8,44] for further details about the utilized software tools. The reconstructed, parcellation-based SC comprised two matrices: one featuring the number of streamlines between individual regions, i.e., the streamline count, henceforth referred to as SC, and another one providing the average length of streamlines between regions, termed path lengths (PL). We considered the functional Schaefer atlas [45] with $N = 100$ cortical regions (Sch100) as well as the anatomical Harvard-Oxford atlas [46] featuring $N = 96$ regions and a probability threshold of 0% (HO0Thr).

The calculation of eFC in turn was based on the resting-state fMRI data provided by the HCP repository [43]. Time series of the blood-oxygen-level-dependent (BOLD) fluctuations were extracted as mean signals averaged over all voxels of individual brain regions parcellated according to the considered brain atlases. A subsequent calculation of the Pearson correlation for each pair of linearly detrended and z-scored BOLD time series from the respective cortical areas then yielded the desired eFC matrix. In this setting, four fMRI sessions comprising 1200 volumes each (sampled with a repetition time of $TR = 0.72$ s) were available for every subject. Scans were performed twice using different phase-encoding directions on two days. A concatenated BOLD signal was generated by combining the z-scored BOLD time series from the mentioned sessions. We focused on the eFC matrix derived from this concatenation (and eventual cross-correlation of the regional signals) for the optimization of model parameters in terms of the best fit between simulated and empirical data, i.e., between sFC and eFC.

Model simulations. To obtain sFC, we implemented the Kuramoto model of coupled phase oscillators [47–49]. In the model, each of N oscillators represented one brain region defined by the underlying parcellation ($N \in \{96, 100\}$ in this study). Their temporal dynamics served as a basis to compute simulated BOLD signals that were then cross-correlated in order to derive sFC. More precisely, the phase dynamics of the mean BOLD signal of a brain region $i \in \{1, \dots, N\}$ can be described by the following differential equation:

$$\dot{\theta}_i(t) = 2\pi f_i + \sum_{j=1}^N k_{ij} \sin(\theta_j(t - \tau_{ij}) - \theta_i(t)) + \sigma \eta_i(t). \quad (1)$$

For a given time t , $\theta_i(t)$ denotes the phase of the i^{th} oscillator that oscillates with a natural frequency $2\pi f_i$ if left uncoupled ($k_{ij} = 0$) from the other oscillators. This assumption considers that the ensemble of neurons contained within a cortical

area behaves coherently, leading to a well-defined average phase, whose dynamics is described by the natural frequency [50,51]. For the low-dimensional cases, the frequency parameters $f_1, \dots, f_N$ were estimated from the maximal spectral peaks (restricted to the frequency range from 0.01 Hz to 0.1 Hz) of the empirical BOLD time series. In the model simulations and validations with high-dimensional parameter spaces in turn, we treated them as free parameters restricted to the same range.

Apart from intrinsic oscillations, the phase dynamics is influenced by delayed interactions with the other oscillators. The individual coupling strengths k_{ij} and delay values τ_{ij} were derived from the empirical matrices $SC = (SC_{ij})_{1 \leq i,j \leq N}$ and $PL = (PL_{ij})_{1 \leq i,j \leq N}$, respectively:

$$k_{ij} = \frac{SC_{ij}}{\langle SC \rangle} \frac{C}{N}, \quad \tau_{ij} = \frac{PL_{ij}}{\langle PL \rangle} \tau. \quad (2)$$

In this context, $\langle \cdot \rangle$ indicates the mean over all matrix elements, excluding the diagonals. C and τ are global weighting factors that influence the strength and delay of the interactions between individual oscillators, respectively. These quantities were treated as free parameters in all considered scenarios. Another variable for optimization can be the intensity σ of the independent noise $\eta_i(t)$ which is sampled from a uniform distribution over $[-1, 1]$ and perturbs the individual oscillators. While C and σ are dimensionless quantities, τ is measured in seconds.

We solved Eq. (1) numerically using Heun's method for stochastic differential equations [52] with a discrete time step of $\Delta t = 0.06$ s. Here, we simulated phase dynamics for 3500 s after skipping 500 s as a transient. The calculated phases were down-sampled to 0.72 s in order to match the repetition time of the fMRI data provided by the HCP. With the model at hand, we generated simulated BOLD time series by computing $\sin(\theta_i(t))$ for all $i \in \{1, \dots, N\}$ corresponding to the regions in the respective brain parcellation. As mentioned above, sFC was then derived from the Pearson correlation coefficients across all pairs of simulated time series. We assessed the similarity between simulated and empirical data by correlating the matrices of sFC and eFC, where the former depended on the model parameters C, τ, σ and $(f_i)_{1 \leq i \leq N}$.

Parameter optimization. As mentioned above, the model was validated by optimization of the model parameters for the best correspondence between sFC and eFC. The case, where the two model parameters of global coupling and delay were optimized, corresponds to the model validation in a two-dimensional (2D) parameter space, see also [49,53]. Besides, a three-dimensional (3D) parameter space was considered, where also the noise intensity was treated as a free parameter, see also [3]. These two scenarios can be described as the low-dimensional cases. In our preceding work [42], we performed a systematic comparison of optimization methods applied to individualized whole-brain models in such low-dimensional parameter spaces (for fewer subjects than here and only one brain atlas). After investigating the stability and computational expenses of several approaches, we identified the best performing algorithms (BO, CMAES) for further usage. Here, we additionally worked with two high-dimensional parameter spaces for two brain atlases, in which we adapted the idea of region-specific model parameters that had already been motivated in [27], for example. We therefore applied our previously tested methods, circumvented the unsurmountable resource requirements of a potential grid search and optimized the frequency parameters for all brain regions. This extends previous attempts to introduce regional heterogeneity, in which the natural frequencies in the Kuramoto model were based on anatomical node strengths, i.e., row sums in the SC matrix [54–56]. Taking into account the three previously mentioned parameters of global coupling, delay and noise intensity, this ultimately led to 99-dimensional (99D) and 103-dimensional (103D) parameter spaces for the Harvard-Oxford atlas and the Schaefer atlas, respectively. We note here that the consideration of local model parameters for all brain regions appeared as the most logical step for introducing regional heterogeneity in the considered phase oscillator model.

Applying two mathematical optimization methods instead of one appeared reasonable since we could not always use a grid search as a baseline for result verification. Our confidence in both methods was based on previous successful

applications and analyses [28,42,57–59]. In the current study, however, we did not intend to compare the methods as such very extensively. We treated them more as a mutual reassurance to minimize the risk of biased result interpretations due to algorithm peculiarities. Instead, we inspected the differences between models validated in low- and high-dimensional parameter spaces. We therefore investigated the approximated optimal parameters and obtained fitting quality together with the sFC and computational requirements in all tested dimensions.

We repeat at this point that we worked with several model parameter spaces. In the simplest case (2D), we fixed the noise intensity at $\sigma = 0.3$ and extracted the frequency parameters $f_1, \dots, f_N$ from the empirical BOLD signals. The free parameters were then the global coupling strength $C \in [0, 1]$ and the global delay $\tau \in [0, 100]$. In the 3D scenario, we increased the dimension of the parameter space by adding $\sigma \in [0, 2]$ as a free variable. The motivation of the considered parameter ranges and the efficacy of the considered optimization algorithms on such problems are detailed in our preceding work [42]. For the high-dimensional simulations, which constitute the essence of this study, we further included all remaining free parameters of the model, namely the natural frequencies $f_1, \dots, f_N \in [0.01, 0.1]$ as parameters for simultaneous optimization. This resulted in the 99D and 103D parameter spaces for HO0Thr and Sch100, respectively. The range for C was increased to $[0, 2]$ here in order to enable a more global search in the high-dimensional cases.

All model fitting simulations for this study were performed on the CPU partition of the high-performance supercomputing cluster JURECA-DC at Forschungszentrum Jülich. Every computation node featured two AMD EPYC Rome 7742 processors with 64 cores each, and each core supported two hardware threads, so that one computation node ultimately offered $2 \times 2 \times 64 = 256$ threads for simultaneous computations, see [60] for further details about the configuration of JURECA-DC.

Optimization algorithms. The BO method is a sequential design strategy suited for optimization problems with an unknown goal function F that is expensive or time-consuming in its evaluation. After computing the goal function values for a random sample of $\Lambda \in \mathbb{N}$ candidate solutions in the parameter space, the obtained information is used to construct a probabilistic surrogate model for F [61]. This approximation of F can be updated based on the knowledge obtained from further function evaluations. Ideally, the surrogate model will eventually deliver a close approximation of the goal function, thereby enabling its efficient optimization. Detailed descriptions of all relevant steps can be found in algorithm-related papers [42,62,63]. We used the C++ software package *BayesOpt* [64] for our simulations. After analyzing the gradual development of the correlation between sFC and eFC for a saturation (depending on the number of performed iterations), we applied a stopping criterion in the form of a maximal number of iterations. We worked with 80 and 230 iteration steps in the low- and high-dimensional cases, respectively, see also Supplementary Materials. For every subject and parameter space, we performed $R_{\max} = 30$ executions of BO with random initial data. Some results of the convergence tests are shown in **Supplementary Fig 1** in [S1 Appendix](#).

The CMAES constitutes a global, population-based search procedure. In every iteration, a sample of Λ candidate solutions is drawn from a multivariate normal distribution. We refer to it as the *search distribution*. CMAES works with a weighted mean of $\lfloor \frac{\Lambda}{2} \rfloor$ solutions which yield the lowest values of the goal function (in a minimization problem). Afterwards, a new generation of candidates is obtained by taking Λ new samples from the search distribution centered around the weighted mean of these most promising points. That is how the search distribution is adapted iteratively towards a concentration around the optimal solutions, see [42,65,66] for more details. In accordance with the setting for BO, we also executed CMAES $R_{\max} = 30$ times for every subject and parameter space, see also Supplementary Materials. The initial search distribution mean was selected uniformly randomly within the considered parameter ranges. The correlation of sFC and eFC showed a saturation after 80 and 150 iteration steps in the low- and high-dimensional parameter spaces, respectively. Some examples of the performed convergence tests are shown in **Supplementary Fig 1** in [S1 Appendix](#).

Analysis of modeling results

As indicated above, we assessed the quality of the model fit by computing the Pearson correlation coefficient between the matrices of sFC and eFC, where the former depended on the selected model parameters. The highest correlation

between such two matrices (found by the optimization of the model parameters) was termed the model's *goodness-of-fit* (GoF). We collected and analyzed the approximated optimal model parameters as well as the respective GoF values and sFC matrices for each of 30 independent runs of the optimization methods for all subjects and parcellations. In particular, we analyzed the test-retest reliability of the optimized model parameters, GoF values and sFC edges, for which we defined reliability as the intraclass correlation (between-subject variance relative to total variance [67]). Hereby, we deliberately deviated from the classical procedure of considering the variability within subjects across repeated empirical measurements (test-retest) and worked with the variability across repeated optimization algorithm initializations instead. Our intention was to see how variable the modeling output is across independent executions of the validation procedure for the same subject as well as between subjects. Particular attention was devoted to the high-dimensional cases.

Intra-subject variability of approximated optimal frequency parameters. We stress that we had added the frequencies $f_1, \dots, f_N$ to the list of parameters for optimization in the high-dimensional cases (99D, 103D). Due to such an increase in the dimension of the parameter space and the related complexity of the corresponding model validation procedure, we had to elaborate more on the properties of the optimized model parameter values. Besides the optimized triple (C, τ, σ) , we obtained N optimized frequency values $(f_i)_{1 \leq i \leq N}$ after every algorithm execution with random initial conditions for a given subject. This means that in addition to the three global parameters of delay, coupling and noise intensity, the simulations yielded specific local parameters related to every brain region. An analysis of the distributions and structure of the latter parameters was performed to inspect the variability within subjects and check for potential subject-specific characteristics in the optimized values. In search of such common patterns across any two executions $q_1, q_2 \in \{1, \dots, R_{\max}\}$, $q_1 \neq q_2$, we correlated all pairs of vectorized frequency sets $(f_i)_{1 \leq i \leq N}^{q_1}$ and $(f_i)_{1 \leq i \leq N}^{q_2}$. For every subject $s \in \{1, \dots, S\}$, we then saved the obtained correlation values to a matrix $A_s \in \mathbb{R}^{R_{\max} \times R_{\max}}$ and applied the k -means clustering method [68] to the rows of A_s . Additionally, we computed the sum of all squared distances between the cluster elements and their cluster centroids. The final number of clusters k was then selected by the “elbow method” as the one for which the sum of distances showed the strongest decrease as compared to the previous case $k - 1$, and where the larger number of clusters $k + 1$ did not reduce it notably. As a quantification of the cluster size, we considered the number of elements in the largest cluster. The number and size of clusters were however set to zero if the absolute mean of the off-diagonal elements in the correlation matrix A_s was below 0.25.

As an extension to the clustering procedure, we also investigated whether a principal component analysis (PCA) of the obtained model parameters can provide additional insights about the structure of the solutions.

Reliability of modeling outcomes. We analyzed the test-retest reliability of the simulation results with the intraclass correlation coefficient (ICC) [67,69–71]. In this approach, we considered the optimized model parameters and the obtained GoF values as well as the elements/edges of the sFC matrices. The ICC quantifies the between-subject variance of the mentioned values relative to the total variance, i.e., between and within subjects. As stated above, we treated repeated executions of the optimization algorithms as proxies for different scanning sessions. Higher ICC scores imply more reliable results.

There exist many different definitions of the ICC in the literature, all of them being suitable for particular problems [67]. We worked with the ICC that is also known as ICC(1) or ICC(1,1) and can be described as the original ICC without bias or systematic error [67]. It is defined as follows:

$$ICC = \frac{o_{\text{subject}}^2}{o_{\text{subject}}^2 + o_{\text{residual}}^2} \quad (3)$$

where o_{subject}^2 denotes the variance of the considered quantity that is related to the variance among subjects and o_{residual}^2 represents the remaining residual variance that may be induced by different measurements of a given subject, for instance. It has been proposed to use this definition in cases where the sources of fluctuations within subjects are unspecified and no structured variability can be assumed [70,71]. This was adequate for our setting since we only changed the

random initial data of every algorithm execution for a given subject. To compute the ICC, we used the approximative sample ICC recommended in [67]. It allowed us to inspect the ratio of the fluctuations of the simulation outcomes between subjects relative to the fluctuations between algorithm executions across and within subjects. We adapted the quality gradation suggested in [72,73], see also Supplementary Materials.

As an extension of the analyses pertaining to the fluctuations within and between subjects, we also computed the *subject specificity* [74–76] derived from the differences between intra- and inter-subject (i) FC correlations and (ii) FC matrix norm distances. The details are provided in the Supplementary Materials. GoF-based specificity measures were computed as well, see also Supplementary Materials.

Relations to phenotypical data

As mentioned above, the cohort in this study consisted of $S = 272$ healthy subjects, with 128 males and 144 females. Our intention was also to extend the application of the modeling results beyond neuroimaging data, and we investigated phenotypical differences in the simulated data. After controlling our results for GoF outliers, we repetitively selected a random execution number $q_s \in \{1, \dots, R_{\max}(s)\}$, $R_{\max}(s) \leq 30$, separately for every subject $s \in \{1, \dots, S\}$ and subsequently defined a vector $u \in \mathbb{R}^S$ containing the corresponding optimal parameter or GoF values detected in these algorithm executions. We then split the data of males and females and computed the effect size (ES, see next section) of the differences in the parameter or GoF values. This procedure was repeated 1000 times for all parameter spaces and optimization methods, so that we ultimately obtained 1000 estimates of the actual ES. We wanted to see whether the simulation outcomes could reveal pronounced sex differences, which appeared to us as the most suited initial practical application and validation of our considered modeling approach.

When investigating the phenotypical differences in the simulated data, we took into account that the intracranial brain volume (brain size) usually tends to be larger for males than for females [77]. We therefore regressed out the brain size from the simulation results like GoF and also assessed the sex differences in the residuals. Such an analysis can provide further insights if the sex differences observed in the simulation results were caused by the differences in brain size.

As a purely empirical alternative to the simulated data, we also briefly inspected the ES of the differences in the correlations between SC and eFC and compared them to the values that we observed for the modeling results.

To bolster the practical utility of our results in case of fluctuating solutions, we further analyzed suited alternatives to select *one* final outcome per subject out of the 30 available solutions of the algorithm executions. We therefore compared the results for the selection of the algorithm runs yielding

- the highest GoF (option 1),
- the median GoF (option 2),
- the minimal $\|sFC - eFC\|_F$ (option 3),

where $\|\cdot\|_F$ denotes the Frobenius norm, see Supplementary Materials. For the optimization problem considered in this work, these three options represent mathematically intuitive selection strategies. Note that our models were fitted to maximize the correlation between sFC and eFC, but not to minimize the matrix norm of their difference.

For the mentioned alternatives, we analyzed the extent of sex differences in the FC edges (above the diagonal) and also computed balanced accuracies [22] for a machine learning sex classifier being trained on either the GoF values or the optimized model parameters.

For the sex classification, we resorted to a publicly available classification script developed at our lab (<https://github.com/kyesam-jung/model-based-prediction/>). It applied a nested 5-fold cross-validation (CV) scheme, where every outer CV loop included five embedded inner loops as a nested CV (inner 5-fold CV) for training the prediction model (a logistic regressor, see below). The training procedure started with a random splitting of the entire subject cohort into five

subgroups of equal size, while maintaining the ratio of females and males in each subgroup. Subsequently, in every outer loop, one subgroup was selected after another as a test set, and the other four subgroups were united into a training set. In the inner loop with the training set, a confound removal (CR) was performed to eliminate the effect of brain size on the sex classification from the features, *i.e.*, GoF values or model parameters. Finally, the approach used a logistic regression with an L2 penalty for the training in the nested CV. The regularizing parameter was optimized by the *Limited memory Broyden-Fletcher-Goldfarb-Shanno algorithm* (L-BFGS) [78]. After the training in the nested CV, the best model was selected and applied to the test set to classify the unseen subjects as either males or females. Here, the respective CR and z-scoring with parameters obtained for the training set were applied beforehand. Such a CV-CR scheme prevents a data leakage as no information from the test set was used during the training [79]. This prediction process was repeated 100 times for different random subject splits into five subgroups. Finally, a balanced accuracy [22] was calculated using predicted probability values and target variables (male or female).

Statistical tests and effect sizes. In this work, we utilized two non-parametric tests to assess statistical significance. When dealing with two related samples (e.g., the GoF for the same subjects, atlas and algorithm, but for a different dimension of the parameter space), we applied the Wilcoxon signed-rank test. In case of two independent samples (e.g., the GoF for males and females in the same parameter space), we used the Wilcoxon rank-sum test. For the latter method, we further assessed the ES of statistical differences with Rosenthal's formula [80]:

$$ES = \frac{Z}{\sqrt{S}} \quad (4)$$

where Z denotes the z-score of the test statistic and S represents the total sample size (number of males + number of females, for example). We used this formula in accordance with related works [22,81] and adapted the quality gradation from *very low* to *very strong* according to [82], see also Supplementary Materials.

Results

In this section, we present our findings with increasing complexity of involved analysis and result interpretation. We put particular emphasis on the results of the model validation in the high-dimensional parameter spaces, from which we derive the majority of novel insights. Our goal was not only to examine the mere increases in fitting quality (GoF) that constitute an important result of the model validation in a high-dimensional parameter space. In fact, we also wanted to investigate the extent of intra- and inter-subject variability of the modeling outcomes in the high-dimensional cases. We aimed to show and suggest the utility of such simulations for future applications related to phenotypical data and, also, to the link between brain and behavior. To design our flow of thoughts most effectively, we start with the “directly” observable effects which include the reporting on the detected GoF values, the invested computational resources and the approximated optimal model parameters. Then, we inspect the underlying structure of the model parameters and the corresponding matrices of sFC as well as their variability and reliability. Finally, we demonstrate how the dimension of the model parameter space may influence the extent of differences between the groups of males and females in simulated data.

[I] Model validation outcomes

GoF, computation time and optimized model parameters. The quality of the model validation (GoF values) is influenced by the number of free model parameters (dimension of the model parameter space) being simultaneously optimized for the best correspondence between simulated and empirical data. We compared the detected GoF values across all subjects and observed that for both tested atlases, more free parameters led to a higher fitting quality [Fig 1, Supplementary Table 2 in S1 Appendix]. Indeed, increasing the dimension from 2D to 3D resulted in a moderate median improvement of 11% – 15% [Fig 1] and a low ES of 0.3–0.4 for the GoF differences [Supplementary Table 2 in S1 Appendix]. However, the transition to the high-dimensional cases caused a remarkable jump, where the median

GoF could double [Fig 1A, CMAES for the Schaefer atlas (Sch100)]. It demonstrated a strong effect of 0.7–0.8 for the GoF differences between the 2D and high-dimensional cases for both considered atlases [Supplementary Table 2 in S1 Appendix].

Similarly, a respective increase of required computational resources can be observed when comparing the median consumption of low- and high-dimensional optimizations [Supplementary Fig 3 in S1 Appendix]. We however note here that more iteration steps were performed in the high-dimensional cases (see Methods and Supplementary Materials), meaning that also additional time-consuming evaluations of the goal function were made.

When inspecting the model parameters optimized in the high-dimensional space, we found large fluctuations across different algorithm executions even for the same subject [Fig 2, Supplementary Fig 4 in S1 Appendix]. Especially the optimized frequency parameters $(f_i)_{1 \leq i \leq N}$ seem to cover the entire plausible range of values in [0.01, 0.1] Hz for the vast majority of brain regions $i \in \{1, \dots, N\}$ [Fig 2E,F, Supplementary Fig 4 in S1 Appendix]. Compared with this variance, the spread of the GoF values obtained in 30 algorithm executions appears to be low [Fig 2D, Supplementary Fig 4 in S1 Appendix]. Indeed, for the considered example of the 103D parameter space with CMAES and the Schaefer atlas [Fig 2, Supplementary Fig 4 in S1 Appendix], we found that the GoF values are narrowly distributed around the median 0.59 with interquartile range (IQR) 0.03, i.e., about 5% of the relative variability as given by the fraction IQR/median [Fig 2D]. On the other side, such a variability reaches on average 90% for the optimized frequencies [Fig 2E,2F], as well as 43% and 41% for the optimized parameters of coupling C and noise intensity σ , respectively [Fig 2B,2C]. Probably the largest variability is manifested by the optimized parameter of delay τ with IQR around 57.60 at zero median [Fig 2A]. The

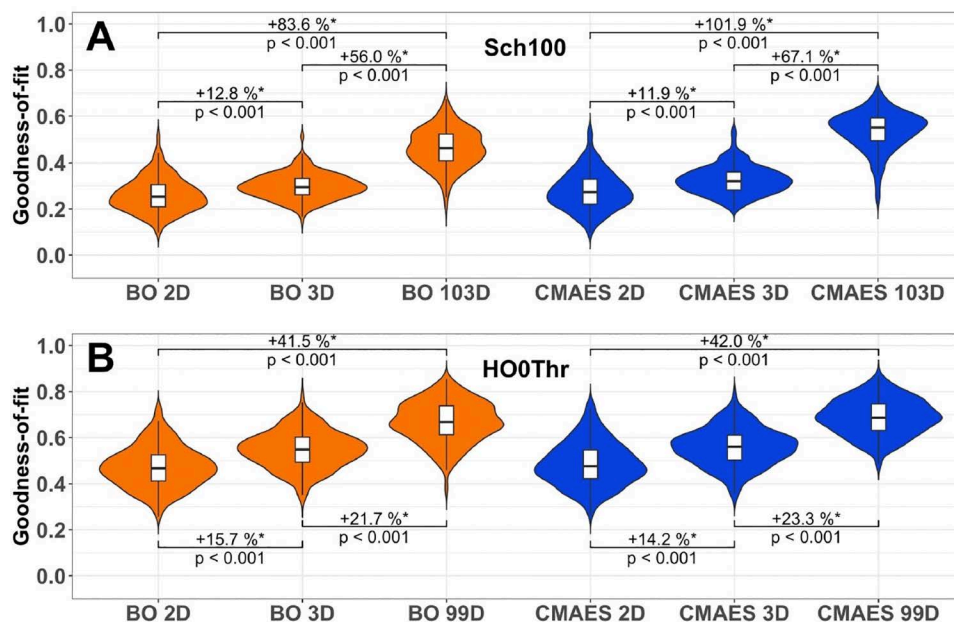


Fig 1. Distributions of the goodness-of-fit (GoF) values for all tested approaches and parameter spaces. The considered optimization methods and the respective dimensions of the parameter spaces are indicated on the horizontal axes (BO 2D, CMAES 2D, BO 3D and CMAES 3D in the low-dimensional cases and BO 103D, CMAES 103D, BO 99D and CMAES 99D in the high-dimensional ones) along with the detected GoF values on the vertical axes. Violins show the distributions of the median GoF values obtained for all subjects across 30 algorithm executions with random initial data (option 2, see Methods). The medians (across subjects) of the relative increase between the results obtained in different parameter spaces for a given algorithm are indicated in the plots together with p -values of the Wilcoxon signed-rank test and the considered atlas: (A) the Schaefer atlas (Sch100) and (B) the Harvard-Oxford atlas (HO0Thr). Statistically significant differences are marked with an asterisk. The significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons.

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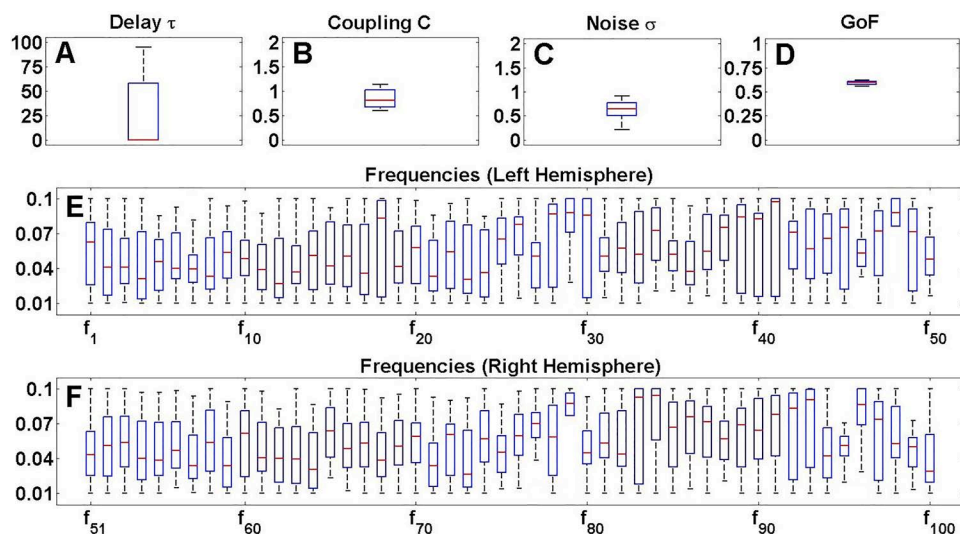


Fig 2. Example of the results of the model fitting in the 103-dimensional parameter space. Boxplots illustrate the distributions of the values for the optimal (A) delay τ , (B) coupling C , (C) noise intensity σ , (D) goodness-of-fit (GoF) and (E,F) frequency parameters (f_i) $_{1 \leq i \leq N}$ found in 30 executions (with random initial data) of the CMAES algorithm for one subject. The considered modeling quantities are indicated in the titles of each plot, while their considered ranges are given on the vertical axes. Plot (E) shows the first half of the frequency parameters, belonging to the brain regions in the left hemisphere in the Schaefer atlas, and (F) shows the second half, which represents the right hemisphere. This figure was created with MATLAB R2021a (www.mathworks.com).

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median value of zero however indicates that more than half of the performed algorithm executions for this subject yielded an optimal delay of $\tau = 0$.

We verified the above findings for the entire subject cohort. Therefore, we evaluated the variability (IQR) of the approximated optimal model parameters and GoF values across algorithm executions for all subjects, see Supplementary Materials. We observed a persistently high variability of the model parameters for both atlases and optimization algorithms [Supplementary Fig 5 in S1 Appendix]. Compared with the regional model parameters, i.e., frequencies (f_i) $_{1 \leq i \leq N}$, the global parameters of delay τ , coupling C and noise intensity σ may show a slightly lower variability, but still a much higher one than that of the GoF values, see Supplementary Materials.

Correlations of optimized frequency distributions. We found that, despite the fluctuations, the values of the optimized frequency parameters are by no means entirely random across different algorithm executions. To illustrate this, we calculated the correlations between the values of the model parameters obtained for different optimization runs (with different initial conditions) for the same subject. More precisely, the N -dimensional vector (f_i) $_{1 \leq i \leq N}^{q_1}$ of optimal frequencies obtained for one optimization run q_1 may show a pattern that tends to be strongly (anti)correlated with the optimal frequencies (f_i) $_{1 \leq i \leq N}^{q_2}$ calculated for another optimization run q_2 for the same subject [Supplementary Fig 4 in S1 Appendix, Fig 3A]. An example that visualizes such an (anti)correlation based on the optimized frequency parameter values is provided in Supplementary Fig 4 in S1 Appendix. We observed (anti)correlated clusters of frequency patterns obtained for different optimization runs for individual subjects. All ($R_{\max} = 30$) runs can be split into two groups (clusters), where the vectors of the optimized frequencies strongly correlate with one another within the same cluster, but negatively correlate with those from the other cluster [Fig 3A]. The clusters may however vary in size for different subjects [Fig 3B–3I]. This means that one frequency pattern may be dominant for a given subject, and there is just one cluster of optimized frequency parameters, where all obtained frequency realizations strongly correlate with one another [Supplementary Fig 6 in S1 Appendix]. For another subject, two anticorrelated frequency patterns (and respective clusters) can occur with

almost equal or different probabilities [Fig 3A]. It may also happen that there are no clusters, and different optimization trials lead to weakly correlated frequency constellations [Supplementary Fig 6 in S1 Appendix]. A PCA of the frequency patterns revealed that strong anticorrelations might be reflected by clear differences (separation) regarding the scores of the first principal component in the PC space [Supplementary Fig 7 in S1 Appendix]. Weak correlations or the presence of just one dominating pattern in turn may align with increased variation in the second principal component but seem harder to be described by the PC scores [Supplementary Fig 7 in S1 Appendix]. The fraction of explained variation by a given number of principal components differs considerably across subjects, while 13–16 components are on average needed to explain 80% of variation [Supplementary Fig 7 in S1 Appendix]. This indicates that the space dimension of

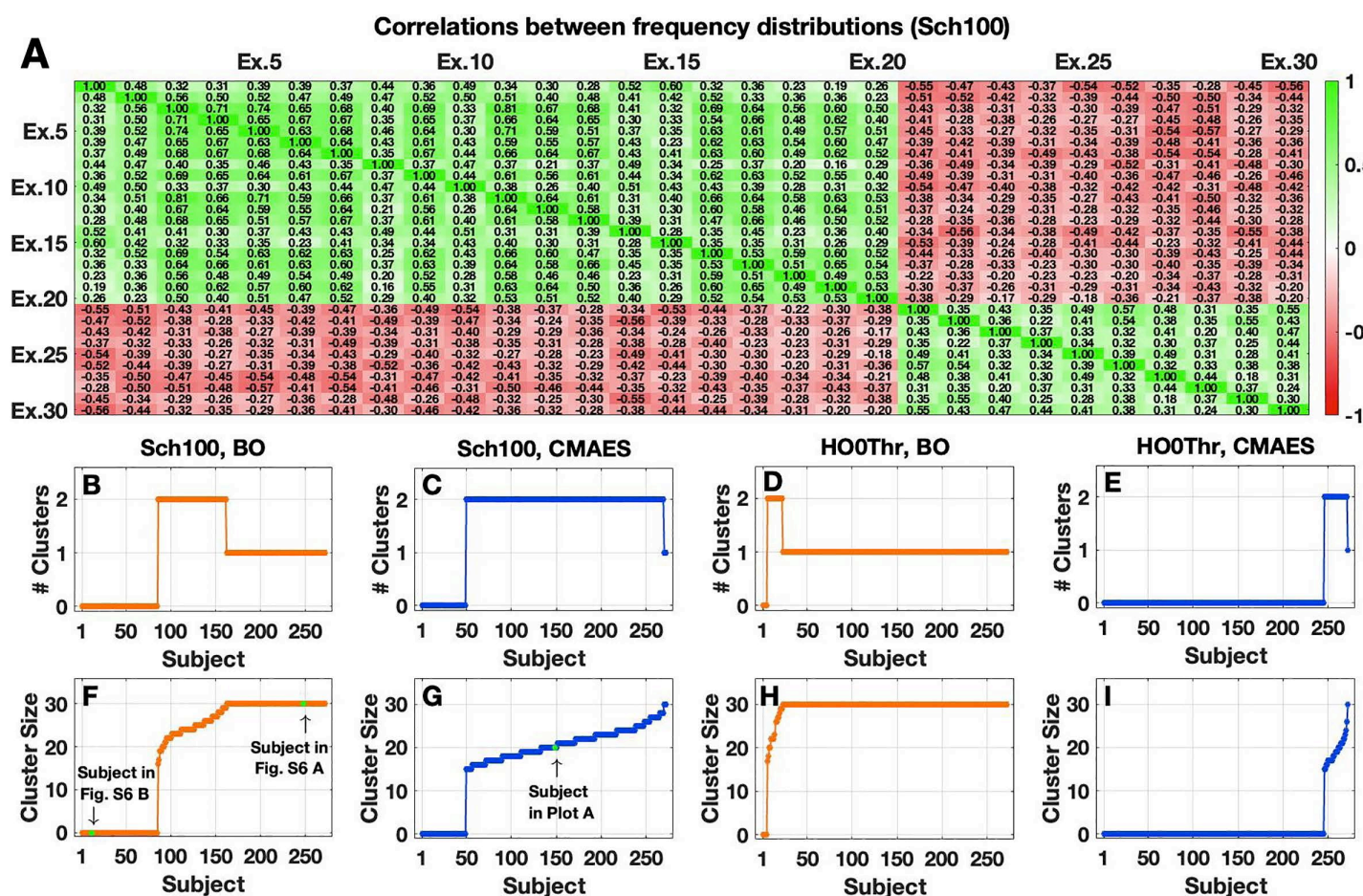


Fig 3. Structure of optimized model parameters in the high-dimensional cases. (A) Example of the correlations between optimized frequency parameter sets obtained at the model validation in the 103-dimensional parameter space via CMAES for the Schaefer atlas (Sch100). For a given subject, the correlations between any two sets of optimized frequency parameters (f_i)_{1≤i≤N} obtained in different algorithm executions (Ex.) were calculated and then indicated in the table cells also highlighted in color. The algorithm executions were sorted, so that the cluster structure becomes observable. (B–I) Number of clusters and cluster size for all subjects and optimization approaches. (B–E) Subject-dependent number of the frequency clusters (# Clusters) for the atlases (Sch100 and HO0Thr) and methods (BO and CMAES) indicated in the titles. In each plot, the subjects were sorted according to the number of elements in the largest cluster as illustrated in the bottom plots. (F–I) Cluster size for all subjects, i.e., the number of algorithm executions in the largest frequency cluster. The number and size of the clusters were determined with help of the k -means clustering method. Both were set to zero if the absolute mean value of the off-diagonal elements in the correlation matrix (cf. (A)) was below 0.25 (corresponding to weak correlations between different frequency sets). The subjects considered in (A) and Supplementary Fig 6 in S1 Appendix are highlighted in the plots (F) and (G). This figure was created with MATLAB R2021a (www.mathworks.com).

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the optimized frequency parameters may be around 15 or higher. In general, the tendency to obtain two anticorrelated frequency patterns is more pronounced for the Schaefer atlas than for the Harvard-Oxford atlas, as more subjects exhibit two-cluster frequency realizations for the former parcellation than for the latter [Fig 3B and 3I]. Coming back to the analysis of the (GoF and parameter) variability across repeated algorithm executions for same subjects, we want to highlight that the IQR of GoF values was relatively low [Supplementary Fig 5 in S1 Appendix] even when almost no clusters of frequency patterns could be observed across subjects [Fig 3E].

Nevertheless, the presence of anticorrelated frequency patterns, which reflect the discussed variability of the optimized model parameters, together with relatively small GoF changes can still be observed in cases where the high-dimensional optimization was informed by the results of the low-dimensional one [Supplementary Fig 8 in S1 Appendix]. We confirmed the reported conclusions by taking into account the optimal parameter values approximated during the low-dimensional model fitting as starting points for the high-dimensional optimization problems (instead of random initial conditions that were considered above) [Supplementary Fig 8 in S1 Appendix]. We also note here that the model includes a random noise term that can be an additional source of the observed variability at the optimization in the high-dimensional spaces.

Based on these findings, we suspect that the optimal solutions for a model validation in high-dimensional parameter spaces are located on a certain subspace of the domain of the goal function. We may refer to it as a *characteristic manifold of model fitting*, whose properties (such as a degeneracy) require a deeper investigation that builds on the methodological scope presented here.

[II] Test-retest reliability of modeling results

In the following, we analyze how reliable the results of the model simulations are. We define the test-retest reliability of the modeling results as the ICC computed across repeated executions of the utilized optimization algorithms (see Methods). After investigating the reliability of the approximated optimal model parameters, we proceed to the corresponding sFC and GoF.

Reliability of model parameters. At first, we considered the optimized parameters of global delay τ , coupling C and noise intensity σ , and found that their reliability is influenced by the employed brain atlas and optimization method [Fig 4]. The reliability of parameter τ decreases for an increasing number of free model parameters. While it varies between *fair* (BO) and *good* (CMAES) for both atlases in 2D, it drops to a *poor* reliability for all other conditions that we tested [Fig 4A, 4D]. For the coupling parameter C , we also observed the highest values in 2D (BO: *fair*, CMAES: *excellent*), and subsequent drops for the other dimensions of the parameter space [Fig 4B, 4E]. The only exception is given for BO and the Schaefer atlas, where the ICC reliability of C is smallest in the 3D case [Fig 4B]. The reliability of the noise intensity σ remains nearly unchanged for the transition from 3D to the high-dimensional cases for BO, staying within the *fair* (Schaefer atlas) or within the *good* range (Harvard-Oxford atlas) [Fig 4C, 4F], which is in contrast with that of the delay and coupling parameters (but see Fig 4B). However, for CMAES, the reliability of the parameter σ clearly drops from the *excellent* to the *fair* range during the same transition to the high-dimensional spaces [Fig 4C, 4F].

In the latter cases, we also evaluated the reliability of the frequency parameters $(f_i)_{1 \leq i \leq N}$. We found that their ICC reliability hardly ever exceeds the threshold of 0.4 and can therefore be considered *poor* for all methods and parcellations [Fig 5A, 5B, 5D, 5E, gray histograms].

In summary, the reliability of the three model parameters of delay τ , coupling C and noise intensity σ shows a rather complex behavior as measured by the ICC. We can, however, conclude that the reliability of the parameters τ , C and σ becomes lower when the number of free model parameters increases for CMAES. For BO, this is also the case, except for C (Schaefer atlas) and σ (both atlases). In the high-dimensional cases, the optimal delay, coupling and frequency parameters mainly demonstrate a *poor* reliability. Nevertheless, the optimal noise intensity can still be obtained with *fair* or even *good* (BO, Harvard-Oxford atlas) reliability, which indicates that its variability within subjects can be lower than between subjects for multiple executions of the optimization methods.

Reliability of sFC and GoF. In this step of our analyses, we investigated the ICC reliability of the optimal sFC matrices generated in each algorithm execution. Here, the reliability of every individual matrix element above the diagonal was calculated across subjects (see Methods), and the distributions of the obtained values were inspected. We started with the high-dimensional cases, where it turned out that the sFC matrices feature reliable edges ranging mainly between a *fair* and *good* quality [Fig 5A,5B,5D,5E, orange and blue histograms]. These matrices can nevertheless be outperformed by their equivalents from the 2D and 3D cases which, for their part, may even reach an *excellent* reliability, except for BO with the Schaefer atlas [Supplementary Fig 9 in S1 Appendix].

We further evaluated the ICC reliability of the GoF values obtained for repeated runs of the optimization procedures. Here, we observed a decreasing trend for both algorithms and the Schaefer atlas, with the highest reliability in the case of the two-dimensional parameter space (*excellent*), followed by 3D (*excellent*) and 103D (*good*) [Fig 5C]. For the Harvard-Oxford parcellation, the GoF values reached an *excellent* reliability in all considered cases, including the high-dimensional ones [Fig 5F].

In summary, we observed an sFC reliability of *good* quality together with high ICC values for the GoF (*good* and *excellent* reliability) even for the high-dimensional model fitting. These findings are in alignment with the low GoF variability for single subjects described above but needed to be verified given the remarkable fact that the optimized model parameters, which generate such sFCs and GoF values, tend towards a *poor* reliability [Figs 4,5].

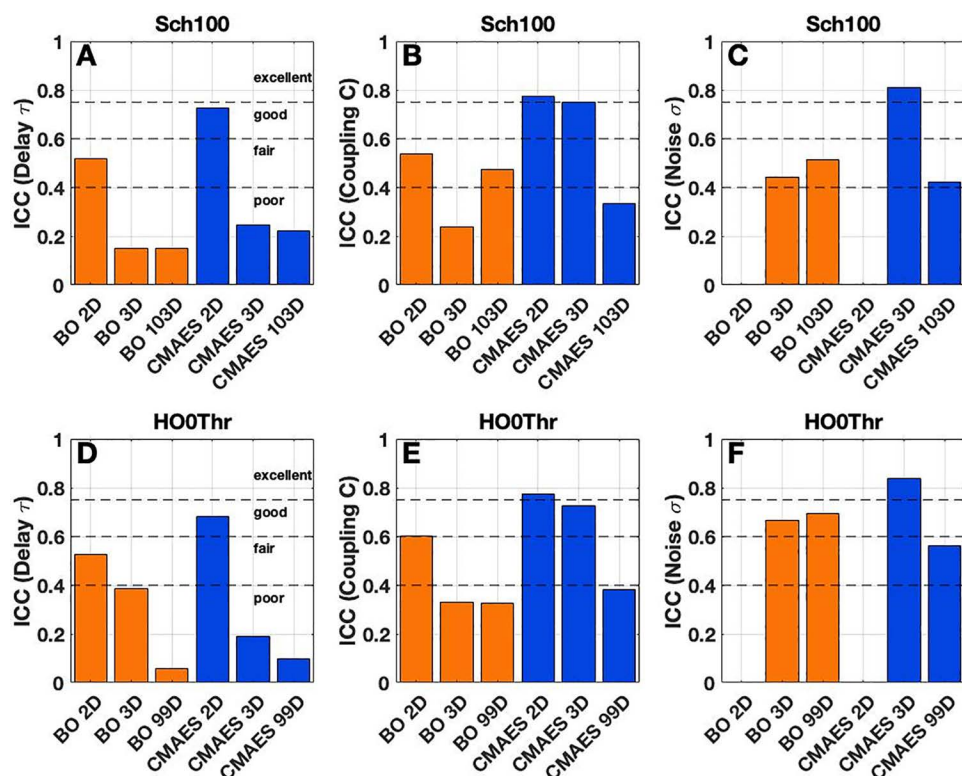


Fig 4. Reliability of the optimized model parameters of delay τ , coupling C and noise intensity σ . Colored bars illustrate the reliability of the modeling results as measured by the intraclass correlation coefficient (ICC). The considered optimization algorithms and parameter spaces are indicated on the horizontal axes along with the ICC scores on the vertical axes. Results are shown for (A-C) the Schaefer atlas (Sch100) and (D-F) the Harvard-Oxford atlas (HO0Thr). Dashed horizontal lines indicate the levels of *poor*, *fair*, *good* and *excellent* reliability in terms of the ICC as suggested in [72,73]. This figure was created with MATLAB R2021a (www.mathworks.com).

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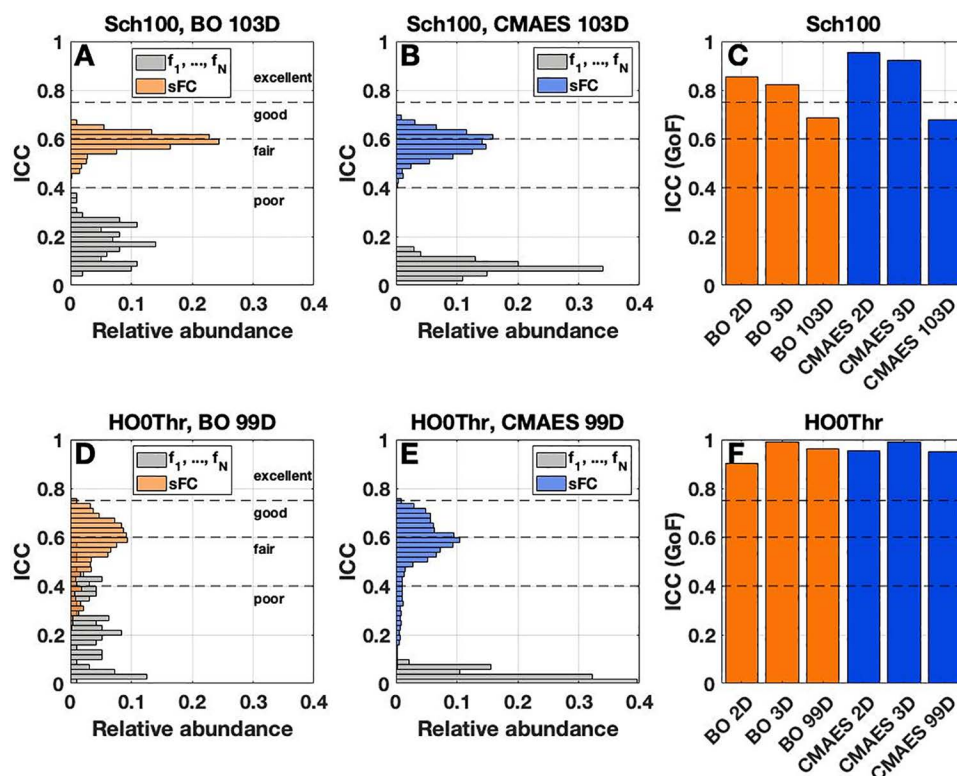


Fig 5. Reliability of the optimized frequency parameters and sFC matrix edges in the high-dimensional cases as well as of the GoF. (A-B,D-E) Colored, horizontal histograms visualize the distributions of the intraclass correlation coefficients (ICC) for the model parameters (f_i) $_{1 \leq i \leq N}$ (gray) as well as for the above-diagonal edges of the matrices of sFC (orange and blue for BO and CMAES, respectively). The considered atlases, i.e., (A-B) the Schaefer atlas (Sch100) and (D-E) the Harvard-Oxford atlas (HO0Thr), are provided in the titles together with the utilized optimization algorithms and parameter spaces, which are indicated on the horizontal axes. The names of the atlases are again provided in the titles. Dashed horizontal lines indicate the levels of *poor*, *fair*, *good* and *excellent* ICC reliability as suggested in [72,73]. This figure was created with MATLAB R2021a (www.mathworks.com).

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To deeper investigate the two modeling results (sFC, GoF) that turned out as the most reliable ones across optimization runs, we used them to compute the subject specificity, see Supplementary Materials. The specificity characterizes the similarity/discrepancy between intra- and inter-subject properties like average FC correlations within subjects vs. average FC correlations between subjects, for instance. We tested ES- and difference-based approaches to compute the specificity and analyzed the impact of the dimension of the parameter space.

We found that the specificity indices frequently remained within narrow ranges of values, and we did not find a clear trend that would indicate an enhancement or reduction of the specificity depending on the dimension of the model parameter space considered for the model validation [Supplementary Figs 10,11,12,13 in S1 Appendix].

At this point, we emphasize that the model validation in high-dimensional parameter spaces much better approximates the measured brain activity as the simulated data (sFC) closely replicate the empirical ones (eFC). A comparably low correspondence between empirical and simulated data in the low-dimensional parameter spaces can be balanced by an enhanced reliability of the model parameters and connectivity patterns. While the reliability of sFC edges and GoF values can reach the fair, good and excellent ranges also for the model validation in the high-dimensional parameter spaces, there remains the high variability of the approximated optimal model parameters. This may play a role in further applications, where it may often be desirable to extract *one* final outcome per subject. However, as we will see in the next part,

sampling from parameter distributions or selecting one solution based on given characteristics may open up new possibilities for further successful usage of the simulated data. Our results for the high-dimensional cases do bear a potential for a better detection of inter-individual differences despite the observed variability of model parameters.

[III] Application of modeling results to phenotypical data

In this section, we focus on the potential benefit of the whole-brain model simulations for the detection of phenotypical differences in the data. Therefore, we split our cohort of subjects into males and females and analyze the modeling results separately for both groups (see Methods).

Sex differences in GoF distributions. We observed significantly higher GoF values for males during the model fitting procedure, with a regular exception given by the 3D cases with the Schaefer atlas [Fig 6A,6B]. Among the optimization algorithms, we obtained mostly consistent results, where the sex-related GoF differences are significantly stronger for the high-dimensional model fitting than for the low-dimensional cases (except for BO with the Schaefer atlas) [Fig 6C,6D].

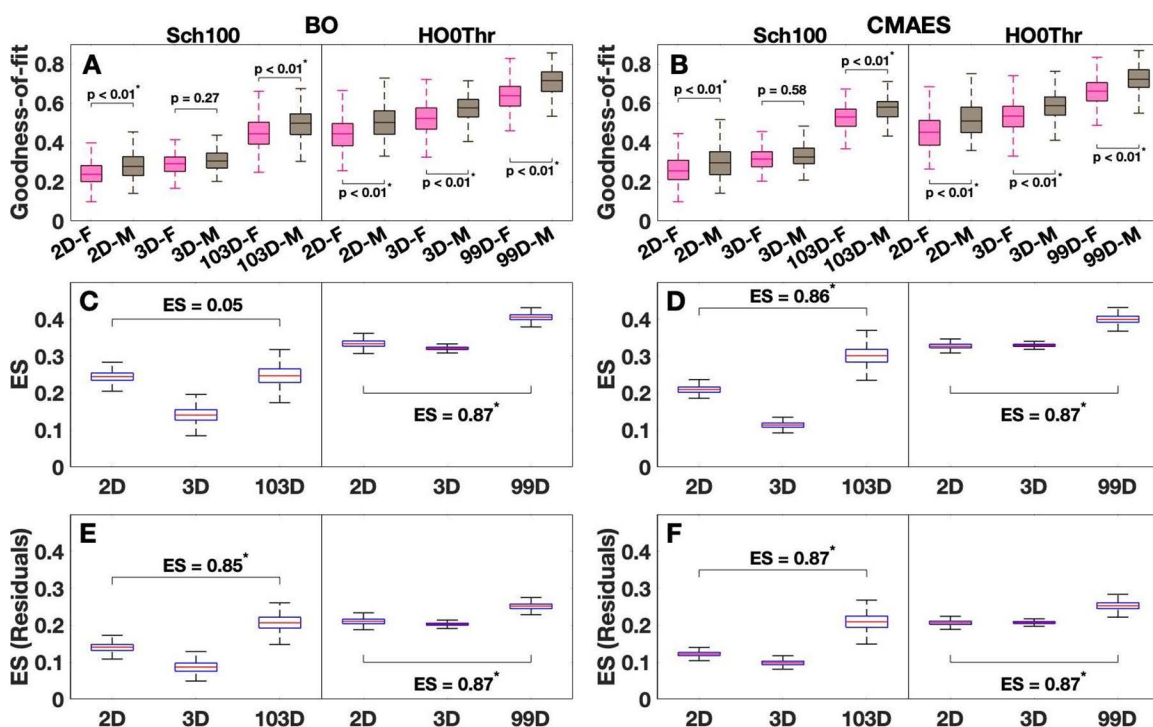


Fig 6. GoF values for males and females together with the corresponding effect sizes (ES) of the observed differences. (A-B) Colored boxplots show the distributions of the median model fits obtained for males (brown) and females (pink) in 30 algorithm executions with random initial data (option 2, see Methods). The considered dimensions of the parameter spaces combined with the group abbreviations of males (M) or females (F) are indicated on the horizontal axes along with the detected GoF values on the vertical axes. Solid vertical lines separate the results for the Schaefer atlas (Sch100) and the Harvard-Oxford atlas (HO0Thr). The names of the utilized optimization algorithms are given in the titles. Statistically significant sex differences as assessed by the Wilcoxon rank-sum test are marked with an asterisk. The significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons. The corrected p -values of the sex differences are indicated in the plots. (C-D) Boxplots illustrate the distributions of the ES for the sex differences observed during a random selection of one of the 30 available algorithm executions for every subject and a subsequent comparison of the corresponding GoF values across both groups (1000 repetitions). The ES of the changes in ES from the low- (2D) to the high-dimensional (99D, 103D) cases are indicated in the plots. The Wilcoxon rank-sum test was applied. Statistically significant differences are marked with an asterisk. The significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons. (E-F) Same as (C-D), but the ES of the sex differences were computed for the GoF residuals obtained by regressing out the intracranial volume of the individual subjects from the GoF values. This figure was created with MATLAB R2021a (www.mathworks.com).

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To be more precise, the median ES of the differences between males and females for the Schaefer atlas ranges around 0.21 in the 2D case and climbs to roughly 0.3 for CMAES (ES=0.86 between 2D and 103D) in the high-dimensional model fitting [Fig 6D], but not for BO, where it remains at the approximate level it had in 2D [Fig 6C]. The situation is different for the Harvard-Oxford atlas, where the ES of the sex differences are in general higher (around 0.33 in both 2D and 3D [Fig 6C,6D]) than their counterparts for the Schaefer atlas. An obvious increase of the GoF differences between males and females was observed in the high-dimensional case [Fig 6C,6D]. It approaches a moderate ES around 0.4 for both algorithms (ES=0.87 between 2D and 99D). So, except for BO with the Schaefer atlas, the high-dimensional model validations seem to strongly enhance the observed differences between males and females in GoF values (with very strong ES of the differences between the low- and high-dimensional cases [Fig 6C,6D]).

Subsequently, we investigated whether the sex differences in GoF could be related to the differences in intracranial brain volume between males and females. We therefore applied linear regression to regress out the intracranial volume from the GoF values and repeated the analysis from above for the respective GoF residuals (see Methods). Here, we indeed observed a reduction of the differences between males and females, which is indicative of an impact of the intracranial brain volume on sex differences in GoF values [compare Fig 6C,6D with Fig 6E,6F]. Nevertheless, we also confirmed that the sex differences in the modeling results are more pronounced when the model validation is performed in high-dimensional parameter spaces [Fig 6E,6F]. Even for BO with the Schaefer atlas, which previously did not confirm the trend, we observed a very strong increase of the differences between males and females when comparing the low- and high-dimensional cases (ES=0.85 between 2D and 103D) [Fig 6E].

Sex differences in empirical data, model parameters and FC strength. To assess the actual benefit of the data generated by whole-brain model simulations, we also searched for similar patterns in empirical data. We therefore considered the structure-function relationship as given by the correlation between SC and eFC. It appeared as the most straightforward empirical alternative to the GoF of the modeling results. Here, we found larger correlation values for the females than for the males for both atlases [Supplementary Fig 14 in S1 Appendix], in contrast to the GoF values, see also [81]. However, the absolute ES of the sex differences did not exceed 0.2 (-0.13 for the Schaefer atlas and -0.19 for the Harvard-Oxford atlas), which was regularly surpassed in the modeling outcomes [Fig 6C,6D]. This result provides further evidence of the practical utility of whole-brain model simulations, which can, as in the considered case, reveal differences between males and females that are hardly observable in empirical brain imaging data.

We note that our data do not yet show equipollent differences between males and females when the analysis was based on the optimized values of the model parameters instead of the GoF values. The ES remained very low in most cases. Significant and relatively strong increases in the (still low) ES could only be observed during the transition from low- to high-dimensional parameter spaces for the coupling parameter C for both atlases and optimization methods and slight increases for the noise intensity σ for the Schaefer atlas and both methods [Supplementary Fig 15 in S1 Appendix]. For the other cases and model parameters, the sex differences can even decrease for the high-dimensional model fitting [Supplementary Figs 15,16 in S1 Appendix]. Especially the frequency parameters $(f_i)_{1 \leq i \leq N}$ did not seem to contain information suitable for differentiating between subjects [Supplementary Fig 16 in S1 Appendix]. By contrast, the sex differences in the GoF values can frequently and strongly increase for the high-dimensional model fitting, where the ES may reach up to 0.4 in the median [Fig 6].

Nevertheless, as the approximated optimal parameters constitute one major source of new, model-based information regarding the brain dynamics of a given subject, we investigated the practical utility of the model parameters further. We attempted to suggest a justified strategy of selecting one of the 30 fluctuating solutions per subject and find relations to other properties of the neuroimaging and behavioral data. In this endeavor, we could repeatedly detect slightly higher coupling values for males in the high-dimensional cases [Fig 7A,7C] when selecting one of the available 30 solutions per subject based on the following three options: Choose the algorithm solution from the execution yielding (1) the highest GoF, (2) the median GoF or (3) the minimal $\|sFC - eFC\|_F$, see also [Supplementary Figs 17,18 in S1 Appendix]. We controlled our results for GoF outliers.

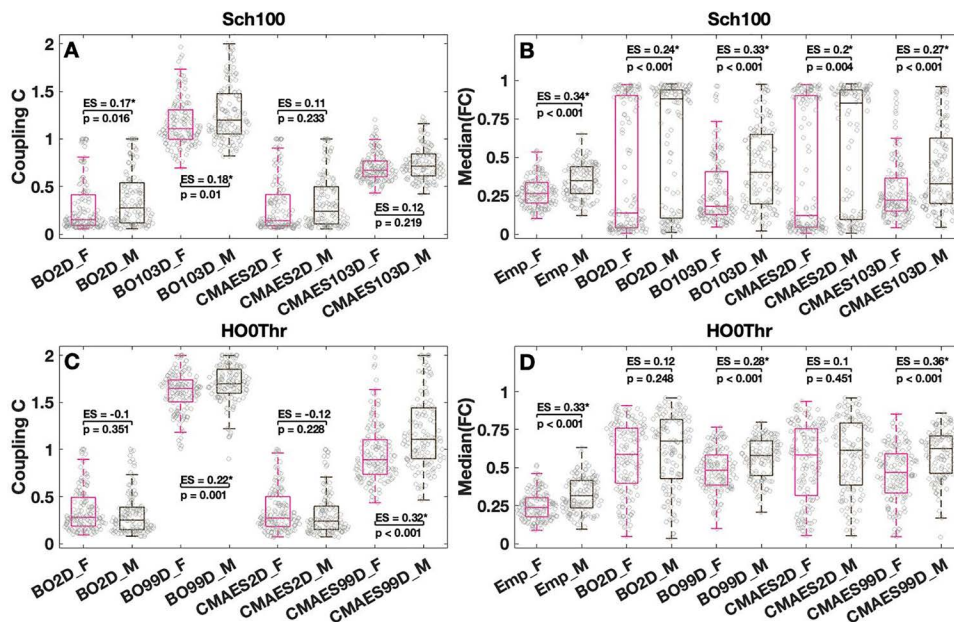


Fig 7. Distributions of optimized coupling parameters and median FC strengths for males and females. Colored boxplots together with gray circles in the background show the distributions of (A,C) the values of approximated optimal coupling parameters C and (B,D) the median connectivity strength in the FC matrices for males (brown) and females (pink). Empirical (eFC, Emp) as well as simulated (sFC) data were considered. For every subject, the eFC from the concatenated sessions as well as the sFC matrix and coupling parameters yielding the highest GoF across algorithm executions were selected (option 1, see Methods). We refrained from including the 3D cases in the figures as we found no remarkable differences to the 2D cases. The names of the utilized optimization algorithms and considered dimensions of the parameter spaces combined with the group abbreviations of males (M) or females (F) are indicated on the horizontal axes along with the median FC and optimal C values on the vertical axes. The names of the considered atlases are given in the titles, i.e., (A,B) the Schaefer atlas (Sch100) and (C,D) the Harvard-Oxford atlas (HO0Thr). Statistically significant sex differences as assessed by the Wilcoxon rank-sum test are marked with an asterisk. The significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons. The effect sizes (ES) and corrected p -values of the sex differences are indicated in the plots. This figure was created with MATLAB R2021a (www.mathworks.com).

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Trying to relate the pattern of higher coupling parameter values for males to the practical role of the coupling parameter in the considered whole-brain model, we inspected whether there are also sex differences in the FC strength. We therefore compared the respective median FC values when we selected one FC matrix per subject from the three mentioned options. Here, we indeed found that the connectivity seems to be significantly stronger for males than females despite a wide overlap [Fig 7BD,]. For the eFC, we observed a significant ES of 0.34 and 0.33 for the Schaefer and Harvard-Oxford atlas, respectively. While the ES of sFC in the low-dimensional cases are clearly lower (0.1 to 0.24 for option 1) across all tested scenarios, they approach or even exceed (ES = 0.36 for CMAES with HO0Thr, option 1) the empirical values in the high-dimensional cases. Very similar trends can be identified for option 2 [Supplementary Fig 17 in S1 Appendix] and 3 [Supplementary Fig 18 in S1 Appendix]. So, higher values for the optimized model parameter of coupling C in the high-dimensional cases seem to align with higher values of the median connectivity strength in the FC matrices, which may explain the observed stronger FC in males also in empirical data.

Model-based sex classification. Finally, we inspected the applicability of the modeling outcomes to a sex classification task as an example of the investigation of inter-individual variability. We trained the machine learning classifier, a logistic regressor, separately on the GoF values as well as on the optimized model parameter values and inspected the performance changes between low- (2D) and high-dimensional (99D, 103D) parameter spaces. (The 3D cases did not show outstanding differences to the 2D cases.) It turned out that the GoF and optimized coupling parameter values are useful features for classification in the high-dimensional cases, while the remaining parameters are not. We

found balanced prediction accuracies centered mostly around the chance level of 50% for the model parameters of delay τ , noise intensity σ and frequencies $(f_i)_{1 \leq i \leq N}$ (not shown), which resonated with a poor practical utility of these quantities. For the features of GoF and coupling C , we however observed median accuracies reaching up to 62% and 57% in the high-dimensional cases, respectively, when the GoF or coupling parameter value obtained from the algorithm execution yielding the highest GoF (option 1) were selected [Fig 8]. The ES between low- and high-dimensional scenarios can reach 0.53 and 0.78, respectively [Fig 8]. We also tested the classification performances for the options 2 and 3 of solution selections [Supplementary Figs 19,20 in S1 Appendix] and found that option 1 might exhibit the most consistent and pronounced classification improvements for the high-dimensional cases, especially for the coupling parameter C . Option 1 therefore appears to be most suited for the applications presented here.

We conclude that the validation of the whole-brain models in high-dimensional parameter spaces is beneficial for studying differences between males and females in simulated resting-state data. For selected modeling quantities, the extent of observable sex differences exceeded those that are present in purely empirical data. We found in particular that the gap in the respective GoF value distributions between male and female subject groups can be expanded with a very strong ES of about 0.87 when the model validation is performed in high-dimensional parameter spaces. This conclusion still holds after regressing out the intracranial brain volume of the individual subjects. Additionally, we found significantly higher classification accuracies for a sex classifier trained on the modeling output from the high-dimensional cases, where one out of 30 available algorithm solutions was selected as the final output for a given subject. Our results indicate beneficial effects of the model validation in high-dimensional parameter spaces and a general importance of involving modeling results in the analyses and interpretations of brain and behavior.

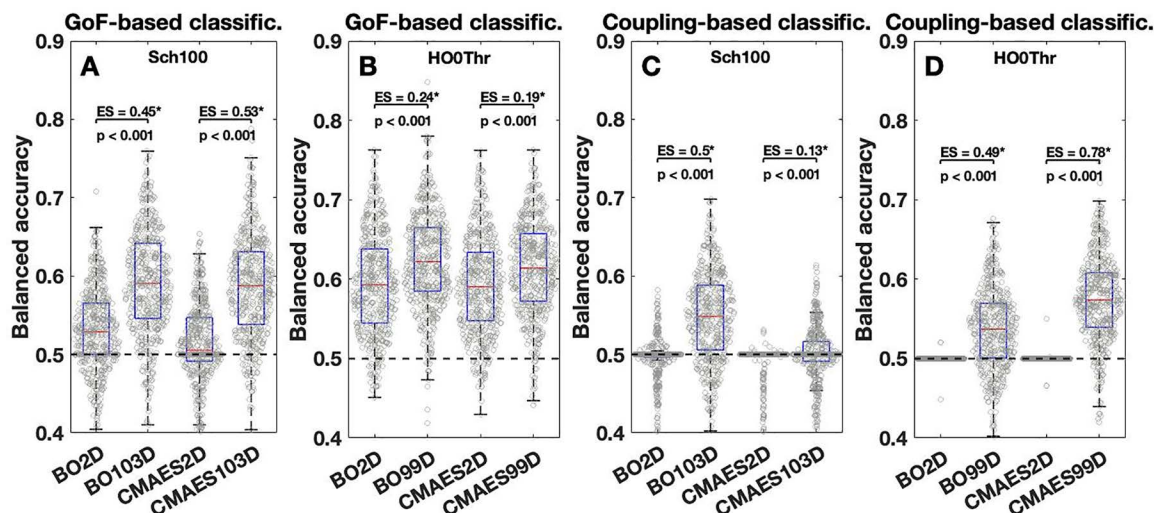


Fig 8. Model-based sex classification accuracies. (A-D) Boxplots together with gray circles in the background visualize the balanced accuracies of a logistic regressor trained for sex classification based on (A-B) the GoF or (C-D) the optimized values of the coupling parameter C . For every subject, the GoF and parameter values derived from the algorithm execution yielding the highest GoF were selected (option 1, see Methods). We refrained from including the 3D cases in the figures as we found no remarkable differences to the 2D cases. The names of the utilized parameter optimization algorithms and parameter spaces are provided on the horizontal axes along with the balanced accuracy values on the vertical axes. Dashed horizontal lines indicate the chance level of 50%. Indications of which property (GoF or coupling parameter) was used for classification (classific.) are provided in the titles. The names of the considered atlases (Sch100 for the Schaefer atlas and HOOThr for the Harvard-Oxford atlas) are given in the plots. Statistically significant performance gains between low- and high-dimensional parameter spaces as assessed by the Wilcoxon rank-sum test are marked with an asterisk. The significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons. The effect sizes (ES) and corrected p -values of the increases are indicated in the plots. This figure was created with MATLAB R2021a (www.mathworks.com).

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Discussion

In this work, we demonstrated that selected mathematical optimization algorithms allow for precise model simulations of resting-state brain activity. Remarkably, the validation of whole-brain models featuring high-dimensional model parameter spaces can be performed even for large subject cohorts. We showed that the transition from low- to high-dimensional parameter spaces improved the observed model fitting quality (GoF) dramatically [Fig 1]. This enhancement was accompanied by an increased intra-subject variability of optimized model parameters [Fig 2], which constitutes an issue that requires further attention. We however found that despite the fluctuating parameters, the obtained GoF and also sFC remained relatively stable and reliable [Fig 5]. Finally, we could show that the sex differences in simulated data became much more pronounced when the fitting of the whole-brain models to empirical data was performed in the high-dimensional parameter spaces. The resting-state brain dynamics of males could be better replicated by the employed model than those of females [Fig 6], which was particularly evident in the high-dimensional cases, where we observed significantly higher classification accuracies compared to the low-dimensional cases [Fig 8]. Altogether, this highlighted the practical utility of the high-dimensional model fitting. It depicted the used optimization approach and dynamical model as useful complements to empirical data when dealing with phenotypical differences and brain-behavior relationships.

We want to stress an important finding, which pertains to the location of approximated optimal model parameters. We observed that both algorithms frequently converged to more than one optimal solution when the high-dimensional cases were considered, while the GoF and sFC often varied only slightly. This let us speculate about the presence of a manifold of optimal model parameters in the high-dimensional cases. We cannot yet provide a mathematical proof of the existence of a manifold, which is far from trivial. However, such a notion was supported by the fact that the reliability (as measured by the ICC across repeated algorithm executions) of the GoF as well as of the edges in the sFC matrices ranged mainly between *good* and *excellent* despite a *poor* to *fair* reliability for the majority of model parameters in the high-dimensional optimizations [Figs 4,5]. The two mentioned quantities (GoF and sFC) therefore appear much more reliable than the model parameters that generate them and can thus be considered as modeling outcomes qualified for further employments of model application (studying phenotypical differences, for instance). The low, but still present intra-subject variability of GoF and sFC may be related to the interplay of stochastic factors such as the noise term in the considered whole-brain model and the random numbers generated and processed by the algorithms during their iterative optimization procedures.

We infer that it is indeed possible and also favorable to perform the model validation in high-dimensional model parameter spaces by employing relatively simple mathematical optimization algorithms. As an initial way to cope with the observed variability of the approximated optimal model parameters, we proposed to either sample (GoF and parameter) values from the solution distributions obtained by repeated optimization runs or to select one final solution based on the highest GoF or other options, for example. The insights deduced from the optimized model parameters may, admittedly, still require deeper investigations, but the obtained GoF and sFC already provided solid results for the replicability of human brain dynamics and differentiability of individual phenotypical properties.

Computational resources

We stress that a considerable (but still tractable) amount of computational resources is necessary to perform the model fitting in the high-dimensional parameter spaces for both algorithms [Supplementary Fig 3 in S1 Appendix]. This might limit the applicability of such an optimization approach in case of low-budget computational resources. Nevertheless, both considered optimization methods outperformed the grid search parameter optimization starting from the 3D cases in this respect [42]. While more computational time is required for the high-dimensional cases as compared to the low-dimensional ones, the amount necessary to optimize in a 99D or 103D parameter space is still comparable to that of a 3D grid search [Supplementary Fig 3 in S1 Appendix], not to say about more dimensions. In view of the growing technological progress and current practices to work with *big data*, however, we are convinced that more computational resources

will be dedicated to the brain research and modeling. This means that the discussed computation time may be no longer a great issue in the nearest future. Combining the presented gains in phenotypical differences with the much-improved quality of the model validation, we conclude that the invested computational costs are justified.

Selection of whole-brain model, atlases and optimization algorithms

We worked with the Kuramoto model of coupled phase oscillators, which is one of the simplest models suited for simulating the features of resting-state brain activity [83]. Given our intention to study the effect of a drastic increase in the number of optimized model parameters (and herewith the complexity of the model), it appeared reasonable to select this basic modeling approach for our study. In addition, its simple structure made it easier to investigate the immediate impact of the number of free parameters on the simulated dynamics. In line with numerous studies [54,55,84] that praised the Kuramoto model for providing a balanced tradeoff between complexity and plausibility in whole-brain modeling, we therefore decided to work with this model. We do not suspect that our qualitative results (e.g., increase in GoF for high-dimensional cases) depend on the selected modeling approach. However, we cannot provide any statement on whether or not the pattern of anticorrelated parameter constellations would generalize to other model validations in high-dimensional parameter spaces, especially for other regional model parameters than the considered natural oscillation frequencies. That should be tested in future studies. The GoF differences between males and females, for their part, were also observed for a network model of limit-cycle oscillators in a related work [81], which supports our expectations that the results reported in this study for the phenotypical data can be generalized to other models.

We considered two paradigmatically distinct brain atlases. They define how the brain is parceled into distinct brain regions that are treated as network nodes in the model. While the Schaefer atlas [45] is based on functional MRI data, the Harvard-Oxford atlas [46] is inspired by the human brain anatomy, i.e., the presence of sulci and gyri on the cortical surface. Our motivation was to study the modeling results for a sample of both the functional and the anatomical parcellation approach with comparable numbers of brain regions, similarly as in [44]. Related works [8,85] deal with systematic atlas variations and the resulting impacts on the whole-brain modeling. An important extension of our work might encompass the comparison of coarser and finer parcellations from the same paradigmatic approach and the impact on the obtained GoF, for instance. The cited works have shown that the quality of the model fit does not depend on the selected paradigmatic approach alone. Indeed, it was reported that the anatomical Harvard-Oxford atlas outperformed the functional Schaefer parcellation in terms of GoF for many applications of FC simulation. Interestingly, in our study, this was also observed in the high-dimensional cases, where the model for HO0Thr featured 99 parameters and therefore 4 less than the one for Sch100 (103 parameters). Conversely, it has been shown that the (functional) Shen atlas [86] may yield a very high GoF as compared to Sch100 [8,85]. While we cannot provide a clear answer on what causes a particular atlas to perform better or worse than others, we know that selected properties of empirical data variables such as the empirical structure-function relationship strongly correlate with the obtained GoF [8]. Differences in the values of these variables for different parcellations may align with the observed differences in GoF.

The selection of the utilized mathematical optimization algorithms was based on our previous work [42], where we thoroughly discussed the advantages and drawbacks of several approaches for model validation. BO and CMAES emerged as the best methods in the tested low-dimensional parameter spaces and therefore had the greatest potential for the high-dimensional cases. While CMAES, the population-based algorithm, generated the most stable results with respect to the spread of solutions, BO, the global probabilistic approach, could convince potential users with its most efficient use of computational resources. Having applied both methods for the high-dimensional model validation in this study, we can conclude that they are indeed applicable for such kinds of optimization problems. We however note that, in terms of the rise in the invested resources [Supplementary Fig 3 in S1 Appendix], the transition to the high-dimensional cases seemed to be a smaller problem for CMAES than for BO, which is deemed most successful in optimization problems featuring up to 20 free variables [63]. Also, CMAES seemed to give quite a better fit for the Schaefer atlas in the

high-dimensional cases than BO [Fig 1]. Therefore, together with a recommendation for CMAES, we note here that another exhaustive comparison of both algorithms might be necessary, which was not the main intention of this study though. The observed results for the parameter variability, reliability and, also, application to phenotypical data did not evoke any solid impression that one of the applied methods is clearly better or worse than the other one.

In this study, we assessed the quality of the model validation with help of the well-established and commonly used Pearson correlation coefficient between static sFC and eFC, see also recent works [87–89]. One may also aim to apply the algorithms to newer, more elaborate measures that include dynamic FC (dFC), for instance.

Optimal manifolds and concerns about overfitting and overparameterization

Observing several parameter constellations that all lead to comparable values of the goal function in a mathematical model is a known issue. Indeed, the so-called problem of parameter identifiability in dynamical systems has been known for a long time already [90–96]. In general, a distinction can be made between structural and practical identifiability [97]. While the former pertains to the more fundamental impossibility of estimating unique optimal model parameters under perfect experimental conditions (continuous and noise-free data), the latter applies to all cases, where the condition of a perfect experimental setting cannot be fulfilled because of noise-related inaccuracies, for instance. Several approaches to tackle identifiability problems have been suggested in the literature [98–101]. Typically, they are applied to reduce the number of model parameters based on their mutual interdependencies and/or the information extracted from the Fisher Information Matrix [35,36]. In view of our results, we can suppose that the positively correlated frequency patterns yielding similar GoF values and sFC matrices may be related to a form of practical identifiability: Across repetitions, the algorithms may produce several approximations of the same optimal point, which are variable in their quality (distance to the actual optimum). The observed anticorrelations between the solutions of repeated algorithm executions for the same subject may however go beyond the standard parameter identifiability issue. Besides the matter of a potential degeneracy [75,102,103], previous studies have reported a so-called *neural redundancy* in the brain, meaning that different patterns of neural activity generate the same outcome [104,105]. It is indeed possible that the algorithm solutions constitute distinct samples of optimal points which are all located on a high-dimensional manifold. In that sense, the anticorrelation between two solutions may indicate that such two points are found on opposite or reflected (mirrored) locations. Both of them still generate the same (or very similar) outcomes in terms of simulated resting-state FC and quality of the model validation. Our work thus also contributes to the existing literature by providing useful insights which are in alignment with the idea of neural redundancy in the brain. Optimal model parameters being located on a subject-specific manifold in the parameter space might characterize an individual subject's personal profile.

Further, we note that the considered model parameters, e.g., the frequencies of the oscillators, are motivated by considering the brain as a network of active units (regions). A possible reduction of the parameter space dimension by an irreversible parameter change, redefinition and compression whatsoever would inevitably cause challenges of result interpretability. Based on that, we argue that overparameterization is not much of an issue in the scenarios we analyzed. The sets of model parameters that appear to be natural for the brain dynamics should be analyzed as they are if the interpretability of the derived conclusions is important.

A similar reasoning applies to the question of overfitting. Kong and colleagues [28] reported a significantly worse fit when 205 model parameters optimized in a training set were applied to a test set for a mean-field model based on group-averaged SC and FC data. The authors therefore advocated for a constraint of high-dimensional model parameter spaces as the model parameters should not be too flexible and free. They proposed to parameterize local circuit properties with help of both anatomical and functional gradients. In our study, we were working with personalized models that were derived from and validated against neuroimaging data of individual subjects. There were no models for an entire subject group here, which could be overfitted to the data of this given group and then would fail if applied to another group. In our approach, we are interested in the best possible model for every single subject individually, which can be

considered a digital twin for brain investigation *in silico* [23]. We however recognize that the high-dimensional parameter optimization considered in this study may pose a limitation due to a potential risk of overfitting when the approximated optimal model parameters were to be used for fitting whole-brain models for other (groups of) subjects. While the still relatively moderate fraction of variance explained by the model [Fig 1] may not immediately indicate such a problem, additional investigations might be necessary in this respect.

At this point, we stress that the variability in optimized parameters observed across repeated algorithm executions for same subjects does not yet allow for an unambiguous selection of one specific solution that shall be used for further applications. Our reflections on the clustering of different frequency patterns can be seen as a first step to group together solutions with equivalent properties. Additionally, we offered three simple options on how to select one from the available algorithm executions as the final outcome for a given subject. We may advocate for choosing the solution yielding the highest GoF for subsequent analyses as it provided the best results in our applications. All results were however obtained during an optimization procedure which aimed at the maximization of the Pearson correlation between sFC and eFC (i.e., GoF) only. As we have seen, this condition leaves the parameters a certain amount of freedom since they “only” have to be located somewhere on the presumed high-dimensional manifold of optimal parameters. We suspect that an inspection of the results with focus on other features of interest such as graph-theoretical network properties in combination with norm-based distances to the empirical data (cf. option 3) may help in further reducing the variability in the solutions that can be treated as distributions (comparable in their mean, median etc.) for now, as in related studies [23,34]. Another approach would be to intensify the work with a PCA of the optimized model parameters. This might provide another way to estimate the dimensionality of the parameter space occupied by the parameters and select leading variables of the parameter distributions.

Phenotypical differences

The observed sex differences in model fitting quality (GoF), which persist even after the regression of the intracranial volume, constitute an important finding of this study. With one exception given by BO for the Schaefer atlas, we have observed very strong and significant increases in the ES between GoF distributions for males and females when transitioning from the model validation in the two-dimensional to the high-dimensional parameter spaces [Fig 6]. This implies that the model-based connectome relationship of the function-to-function fitting (sFC to eFC) may be helpful in distinguishing between males and females in brain research. The GoF of dynamical whole-brain models provides a measure that quantifies how easy/difficult it is under the given modeling conditions to mimic the resting-state brain dynamics of a given human being. Pronounced differences in this quantity (or others, like the model parameters) provide supplementing information going beyond that encoded in purely empirical data and can thus enhance the differentiability between subjects. Especially the models optimized in high-dimensional parameter spaces emerge as useful complements to empirical observations. Our improved classification results underline this claim.

In fact, the extraction of well-pronounced differences between males and females from functional brain imaging data has been far from trivial for a long time. Many studies reported no or only very small and inconsistent findings especially when dealing with functional data related to cognitive tasks in psychological domains [106–109]. But also for resting-state fMRI data, it has been claimed that no differences between males and females can be detected [110]. At roughly the same time, however, other researchers published results which indeed indicated the presence of sex differences in certain resting-state networks and other elements of the functional brain organization [111–114]. In the course of time, the technological progress led to deeper insights into this topic. On the one hand, more complex methods such as machine learning approaches for classification could be applied and, on the other hand, studies over longer time periods as well as studies including larger subject cohorts could be conducted [79,115–120]. Our rationale for applying the modeling results to sex differences was based on one of these latter works, where intriguing classification results based on resting-state FC were obtained, despite the absence of a clear-cut dimorphism between males and females in the functional data [118]. It has

been argued that, with the availability of new methodological approaches such as statistical learning, the general question should not be whether or not differences between males and females exist in the brain, but rather how large and meaningful they are compared to the overall intra- and inter-individual brain variability of subjects [121].

We regard our findings as an important contribution to this topic. The model validation in high-dimensional parameter spaces opens new perspectives for more personalized models that can reflect additional subject-related properties. In particular, we observed that the replication of resting-state FC by model simulations appeared to be easier (larger GoF) for the whole-brain model when the data of male participants were utilized as compared to those of females. This trend was mostly pronounced in the high-dimensional cases, regardless of which of two inspected optimization algorithms and brain atlases were considered. So, while our fitted results approached the empirical data more and more closely from one side, we were also able to outperform the empirical data from another side, here by revealing increased differences between males and females (which, if desired, could be mitigated by considering males and females separately throughout the entire modeling approach or by applying linear regression on the sex-related GoF values prior to further applications, for example). Further, we stress that our applied regressor was relatively simple and reached a classification accuracy of 62% based on one scalar value (GoF or optimal coupling strength, i.e., always one feature regardless of the dimension of the parameter space) only. This accuracy is not very high, and multivariate analyses on empirical data might likely outperform our results. However, analyses combining both empirical and simulated data may prove superior to approaches that resort to only one of the mentioned data types. In this way, empirical approaches might benefit from considering the simulated data obtained at the model fitting in the high-dimensional parameter spaces as additional features. Especially the conflation of several features that we treated in isolation so far may bear a huge potential. We therefore suppose that the personalized validation of mathematical whole-brain models in high-dimensional parameter spaces can potentially contribute to further explorations in the field of phenotypical differences in the brain as well as other research topics focusing on the link between brain and behavior. In the considered example of sex differences, our results confirmed and extended the insights extractable from empirical data, which might be favorable for the long-term idea of individualized care and precision medicine [122,123].

Conclusions

We have shown that practical and efficient tools for model validation in high-dimensional parameter spaces are available nowadays. Their computational feasibility and economy rendered them suitable for applications even on large subject cohorts. The transition from the low- to the high-dimensional parameter spaces was marked by significant increases in the fitting quality of the whole-brain models. In the best case, the GoF could even double. The reliability of sFC and GoF remained high even after a high-dimensional model validation, which suggests the usage of these quantities for further applications. We also observed that differences in GoF values and optimized model parameters of coupling strength were more pronounced between males and females in the high-dimensional cases and therefore led to significantly higher sex classification accuracies. Our study can contribute to an improved, personalized modeling of human brain dynamics, which could be helpful for a deeper understanding of the latter. Whole-brain models validated in high-dimensional parameter spaces may play a supporting role in personalized medical decision making as they may be used as a risk-free test bench for clinical research and application.

Supporting information

S1 Appendix. Supplementary Materials.
(DOCX)

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Supplementary Materials

for the manuscript

Exploring dynamical whole-brain models in high-dimensional parameter spaces

by

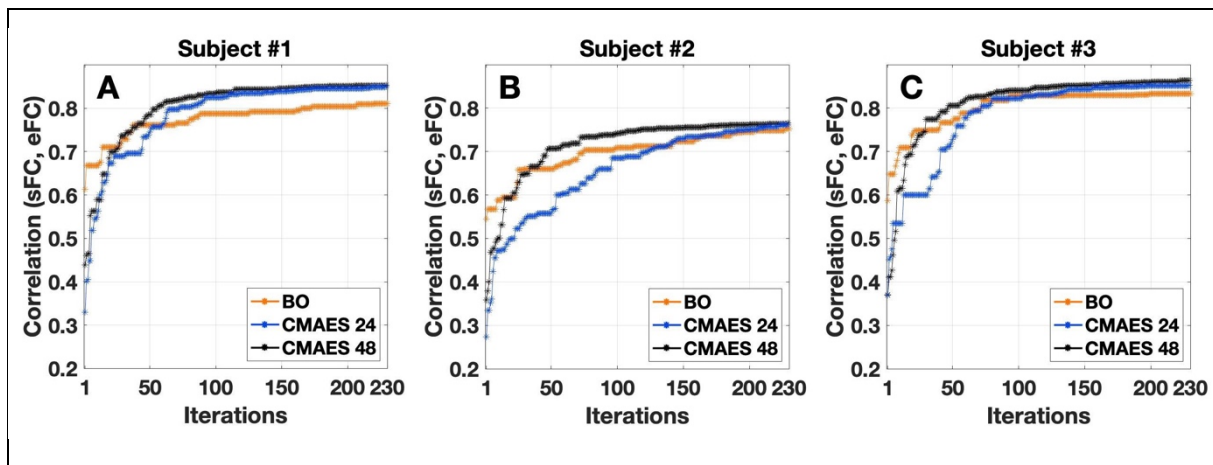
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Supplementary Fig 1. Examples of the algorithms' convergence as given by the values of the goodness-of-fit versus the iteration number. The plots show the gradual development of the obtained correlation between simulated and empirical FC (colored lines) for one run of the methods indicated in the legends (BO, CMAES 24 and CMAES 48, where the latter two correspond to an execution of the CMAES method with $\lambda = 24$ and $\lambda = 48$ candidate solutions in every iteration, respectively). The presented results pertain to the model parameter optimization in one of the considered high-dimensional parameter spaces (99 model parameters) for three randomly selected subjects, which are mentioned in the titles. This figure was created with MATLAB R2021a (www.mathworks.com).

Here we provide some reasoning about the mathematical optimization algorithms (BO, CMAES) which we applied for model validation in the presented article.

BO

After an extensive testing of the C++ software package *BayesOpt* [1], we worked with $\Lambda = 10$ initial sampling points followed by 80 iteration steps in the low-dimensional cases (2D, 3D), see [2] for additional illustrations and details about the tested criteria. The only difference compared to the setting from our previous work was that we selected the default value of $\Lambda = 10$ sampling points also in 2D (instead of $\Lambda = 5$). This did not cause considerable increases in computational costs, but made the simulations in the low-dimensional cases congruent prior to the intended comparisons with the high-dimensional ones (99D, 103D). In the latter, we selected $\Lambda = 200$ initial samples with 230 subsequent iterations. Increasing Λ became necessary for the establishment of a more plausible first approximation of the unknown objective function depending on such a high number of parameters. However, this served primarily as an initial orientation and, undoubtedly, the number of the following iteration steps had to be increased as well. Since a comparison with the results of a dense grid search was not possible, the choice of 230 steps was based on a tradeoff between computation time and the convergence of the observed fitting quality [Supplementary Fig 1]. We had to take into account that the supercomputer JURECA-DC [3] enforces a simulation time limit of 24 hours for one job script. Similarly, as we could not compute a *success probability* [2] to reach a fitting quality obtained via a grid search, we doubled the number of total algorithm executions for every subject from $R_{\max} = 15$ in our previous work to $R_{\max} = 30$ here. This appeared reasonable, because we could not anticipate the model behavior in high-dimensional parameter spaces beforehand. Further, the surrogate model for the objective function F (i.e., correlation(sFC,eFC)) was updated after every single or after every 15th new function evaluation in the low- and high-dimensional scenarios, respectively. This less frequent updating in the latter cases became necessary due to the increased time demands, which otherwise let our executed scripts (containing several algorithm executions running in parallel) come close to the simulation time limit of 24 hours.

CMAES

For the low-dimensional cases, we adapted the setting that we utilized and recommended previously [2], i.e., 80 iterations with $\Lambda = 24$ candidate solutions in every step. We highlight that this exceeded the recommended minimal sample size ($\Lambda = 6$ in 2D and $\Lambda = 7$ in 3D), which typically scales with the number of parameters for optimization [4]. Before applying the algorithm for model validation in the high-dimensional scenarios, we tested the values $\Lambda = 24$ and $\Lambda = 48$ for random test subjects. The latter case implies a doubled amount of invested computational resources compared to the former. (The recommended minimal sample size would be $\Lambda = 17$ for both the 99D and the 103D case.) From our tests we concluded that, after approximately 150 iteration steps, a saturation of the observed fitting quality sets in frequently and the differences between the CMAES executions with $\Lambda = 24$ and $\Lambda = 48$ do not differ so much that the expenditures for the latter case would be justified [Supplementary Fig 1]. We therefore worked with $\Lambda = 24$ candidate solutions in every iteration and also executed the CMAES method with this setting $R_{\max} = 30$ times to ensure comparability with BO.

For a gradation of the intraclass correlation coefficient (ICC), we adapted the following table as suggested in [5, 6]:

$[0, 0.4[$	poor
$[0.4, 0.6[$	fair
$[0.6, 0.75[$	good
$[0.75, 1[$	excellent

Subject specificity of simulated connectivity and GoF (Methods)

Correlation-based variability and specificity of FC patterns

To address the similarity of sFC matrices within and between subjects, we used the Pearson correlation of the vectorized matrices. More precisely, to compare two sFC matrices across different algorithm executions for the same subject and across different subjects, we randomly selected two subjects $s_1, s_2 \in \{1, \dots, S\}$, $s_1 \neq s_2$ and three execution indices $q_1, q_2, q_3 \in \{1, \dots, R_{\max}\}$, $q_1 \neq q_2$. We then computed the correlation for the following sFC pairs:

- sFC (s_1, q_1), sFC (s_1, q_2): within subjects (intra-subject)
- sFC (s_1, q_1), sFC (s_2, q_3): between subjects (inter-subject)

This allowed us to investigate in how far the optimal sFC derived from several algorithm executions fluctuated within and across subjects. Overall, the discussed calculation of the similarity within and between subjects was repeated 1000 times in order to obtain adequate estimates of the underlying distributions.

For eFC, we also calculated the correlation-based similarity within and between subjects. A direct comparison with the sFC-related results could then be made for the correlations between subjects, i.e., eFC(s_1), eFC(s_2). For the variability within subjects, we utilized the data from the four available resting-state fMRI sessions per subject (provided by the HCP) to calculate different realizations of eFC as proxies for sFCs calculated from the repeated algorithm executions for the same subject. The respective indices q_1, q_2, q_3 were therefore randomly selected from these four fMRI sessions. This may however prevent a straightforward comparison of the fluctuations in eFC within subjects with those of sFC because the latter was always fitted to the same eFC calculated from the concatenated BOLD signals for the same subject.

Based on that, we also calculated the index of subject specificity of the simulated or empirical FC, which reflects the similarity of sFC or eFC within subjects relative to that between subjects [7-9]. In this study, we considered two different ways of its calculation for FC:

1. Effect size (see Methods) of statistical differences between the distributions of correlations within and between subjects;
2. Difference between the mean correlation within subjects and the mean correlation between subjects.

With this, we extended the specificity approach pursued in [7, 9], which was based on option 2 exclusively. Such a specificity measure is however based on the difference of the mean values only and does not take into account the other properties of the within- and between-subject distributions of similarity. We therefore put more focus on option 1.

Difference-based variability and specificity of FC patterns and GoF

Besides the Pearson correlation coefficient, which we used just above (and also as the sole measure for assessing the fitting quality of the model), we also quantified the similarity of two connectivity matrices $A, B \in \mathbb{R}^{N \times N}$, $N \in \mathbb{N}$, by the Frobenius norm $\| \cdot \|_F$ of the difference matrix $C = A - B$. The norm is defined as follows:

$$\|C\|_F = \sqrt{\sum_{i=1}^N \sum_{j=1}^N c_{ij}^2} = \sqrt{\sum_{i=1}^N \sum_{j=1}^N (a_{ij} - b_{ij})^2}. \quad (\text{S2.1})$$

We used both approaches (correlation and norm of the difference) as two stand-alone measures when investigating the FC variability within and between subjects, i.e., across different algorithm executions and fMRI measurements for sFC and eFC, respectively, for the same subject and across different subjects, accordingly. Note that this pertains only to a comparison of sFC with sFC or eFC with eFC, but not across modalities.

We stress here that in the norm-based approach, we applied the Fisher z-transformation to the elements of the sFCs (and eFCs) to render them normally distributed before computing the differences. The Fisher z-transformation is defined as follows:

$$z = \text{artanh}(r) = \frac{1}{2} \ln \left(\frac{1+r}{1-r} \right) \quad \text{for } |r| < 1. \quad (\text{S2.2})$$

It is typically used when statistical tests are intended to be applied on arithmetic operations of correlations, which are not interval-scaled and often show a skewed distribution when close to 1 or -1 [10].

The same procedure of a random selection of subjects and indices of optimization runs/fMRI measurements, which was employed for the correlation-based similarity above, was also used for the similarity based on the matrix differences. Accordingly, we calculated the index of subject specificity of the simulated or empirical data based on the FC differences:

1. Effect size of statistical differences between the distributions of the $\| \cdot \|_F$ -norms of the (Fisher z-transformed FC matrix) differences between and within subjects;
2. Difference between the mean $\| \cdot \|_F$ -norm of the differences between subjects and the mean $\| \cdot \|_F$ -norm of the differences within subjects.

Here, we also concentrated more on option 1 featuring the effect sizes. Since the norm of the calculated (within- or between-subject) matrix differences is a measure of sFC (eFC) dissimilarity, the positions of the intra- and inter-subject difference distributions were exchanged as compared with those for the FC correlations. This guarantees a positive specificity index in the case when the intra-subject variability is smaller than inter-subject one, as expected.

Additionally, we calculated the subject specificity for the GoF values:

3. Effect size of statistical differences between (Fisher z-transformed) absolute GoF differences between and within subjects.

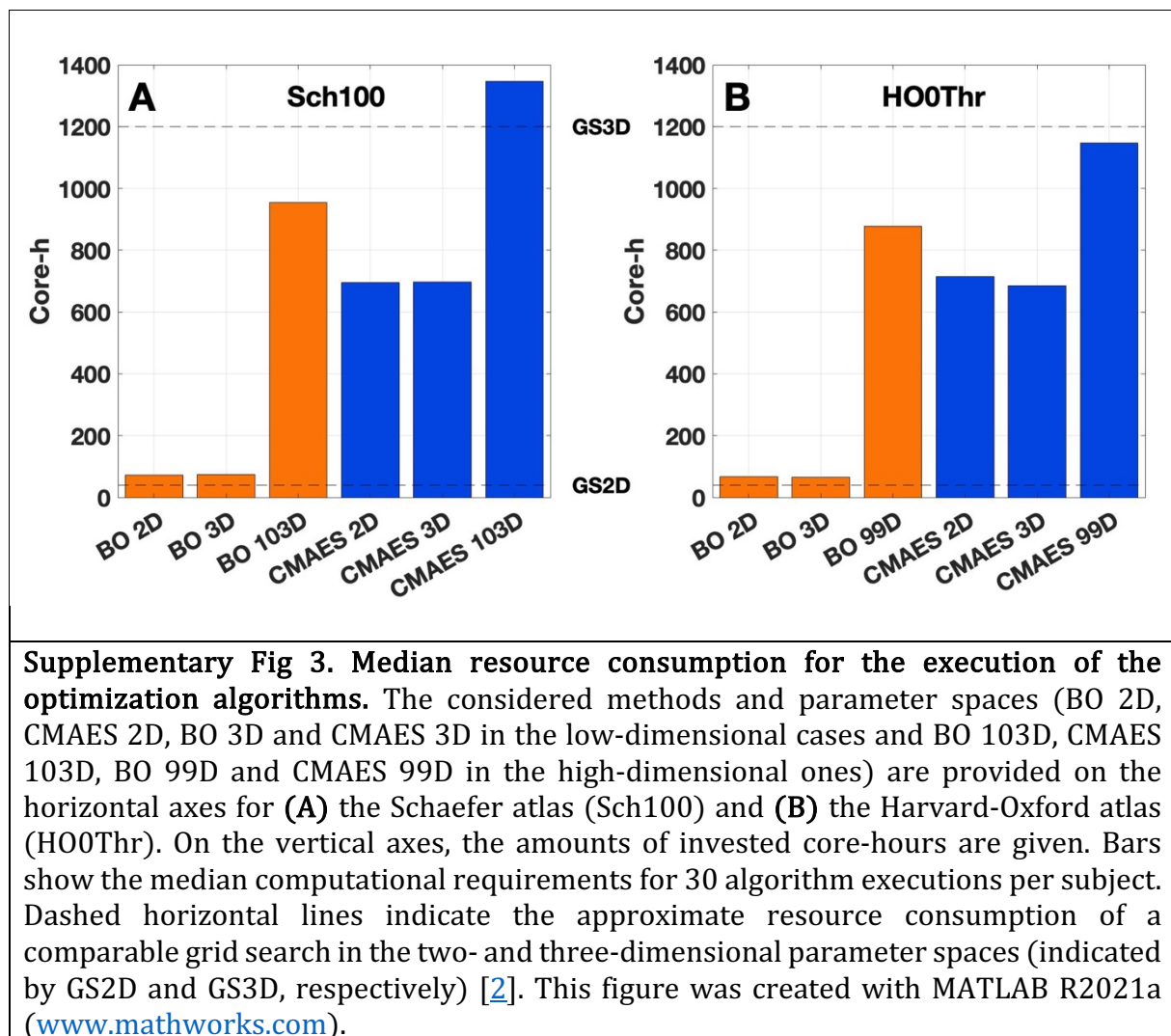
In summary, we computed the FC variations, i.e., correlations and difference norms, both within and between subjects for the repeated parameter optimizations. This allowed us to calculate several measures of reliability and subject specificity pertaining to the observed differences (within subjects vs. between subjects). We wanted to assess the variability of sFC patterns across subjects for all tested dimensions of the parameter space. The same applies to the fitting quality (GoF), for which we also calculated a related measure. We were eager to investigate the impact of a varying number of free model parameters on the simulation outcomes.

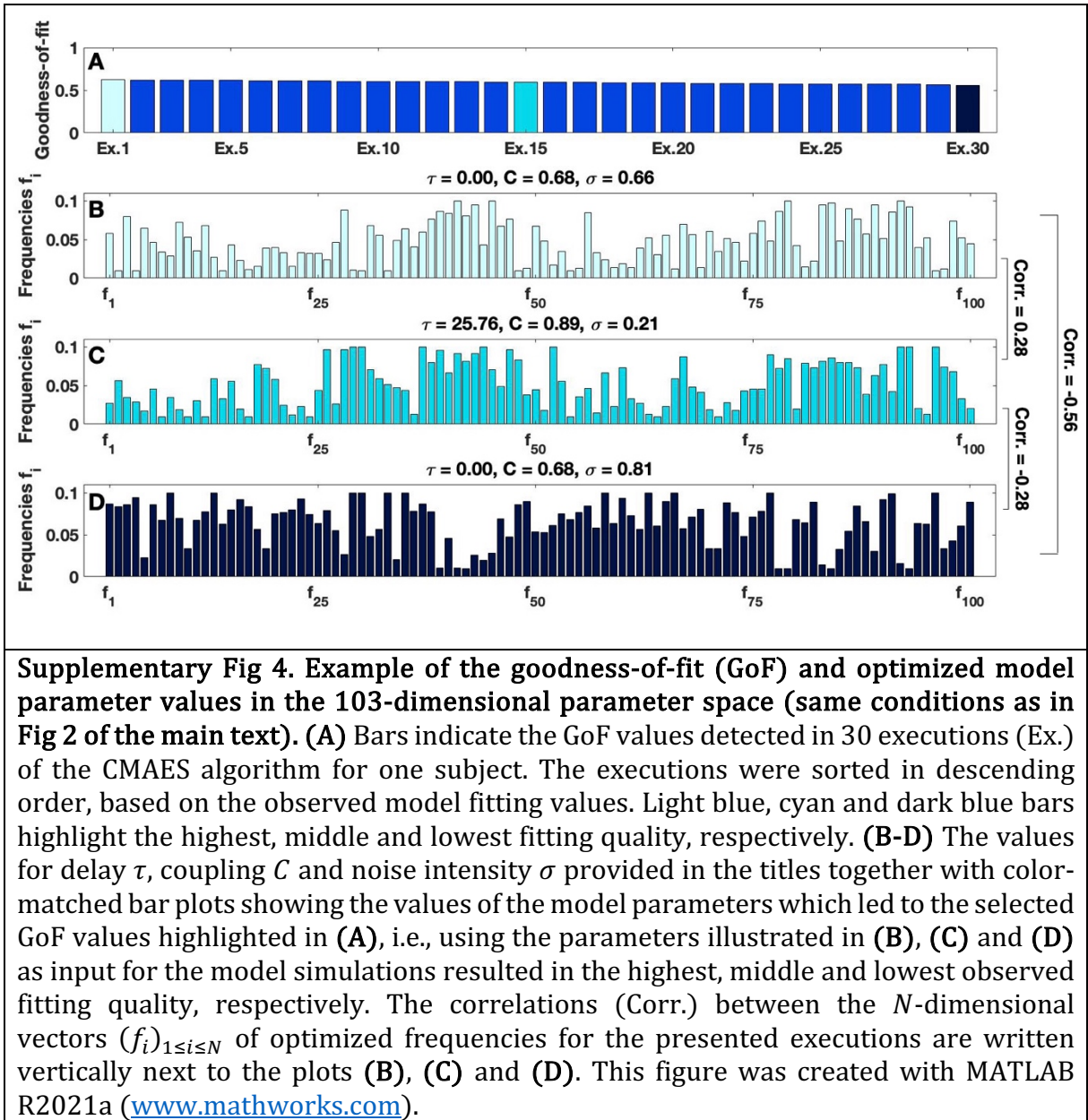
For the effect size (ES) of statistical differences computed with Rosenthal's formula [11], we can adapt the gradation suggested in [12]:

[0, 0.2[	very low
[0.2, 0.4[	low
[0.4, 0.6[	moderate
[0.6, 0.8[	strong
[0.8, 1]	very strong

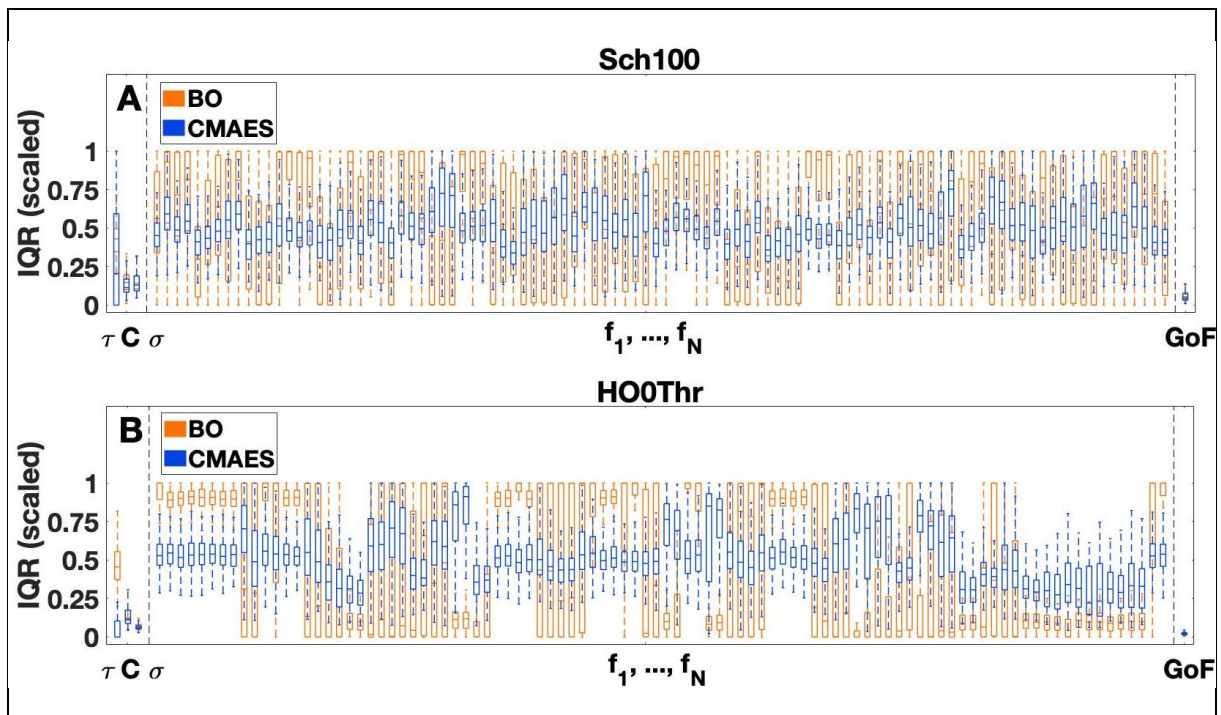
	Sch100			HO0Thr		
	<i>2D - 3D</i>	<i>3D - 103D</i>	<i>2D - 103D</i>	<i>2D - 3D</i>	<i>3D - 99D</i>	<i>2D - 99D</i>
BO	0.30	0.78	0.79	0.32	0.80	0.82
CMAES	0.41	0.59	0.75	0.39	0.64	0.77

Supplementary Table 2. Intensity of the goodness-of-fit (GoF) changes across parameter spaces. For the GoF distributions shown in Fig 1 of the main text, the values in the table indicate the effect size (ES) of the GoF increases observed for the transitions from one to another parameter space. All numbers were calculated with Rosenthal's formula [11]. The notations in the second line of the table, for example, "*2D - 3D*" indicate the two parameter space dimensions used for comparison. Results are shown for both considered optimization algorithms (BO, CMAES) and atlases (Sch100, HO0Thr).

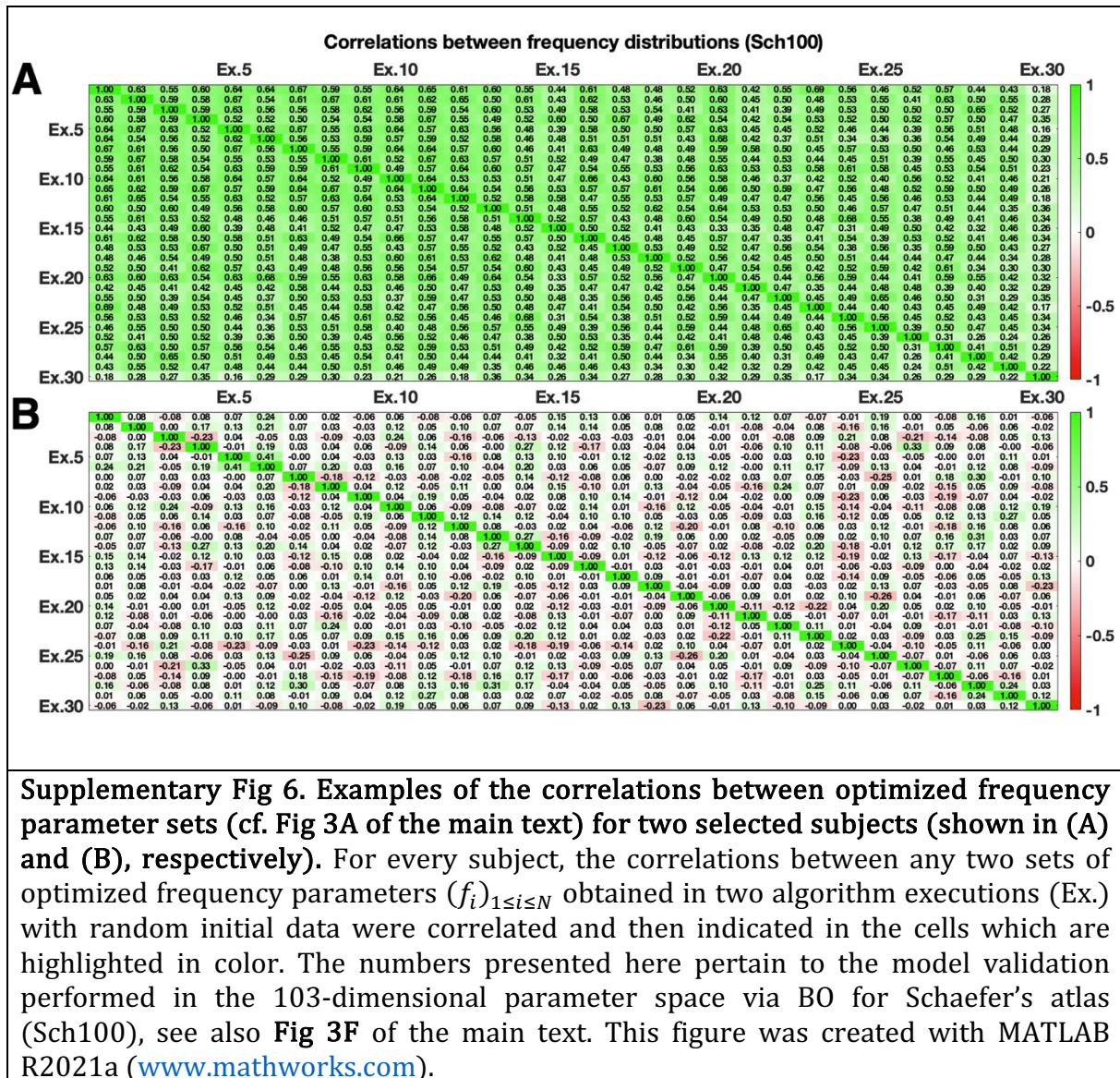


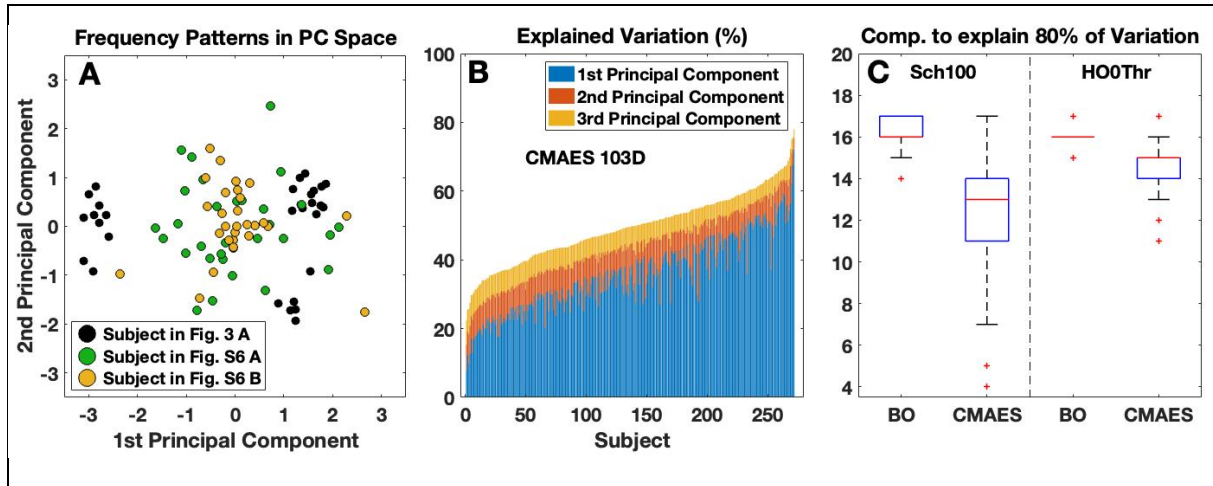


We evaluated the variability (interquartile range, IQR) of the approximated optimal model parameters and GoF values across algorithm executions for all subjects. Lower values of the IQR reflect smaller intra-subject variability. For the sake of visual comparability of the spreads of parameters, which varied along values of different orders of magnitude (e.g., $\tau \in [0, 100]$ and $\sigma \in [0, 2]$), we divided the computed IQR values by the maximal value that the respective parameter could reach as specified by the considered parameter ranges (1 for GoF). This approach delivered the illustration closest to the unscaled data treated in separate parameter ranges. We stress that a division by the median might distort the illustration in cases where the median of optimal values is (close to) zero. When optimized with the CMAES method for the Schaefer atlas, the parameters of delay τ show a relatively broad spread of fluctuations across optimization trials for all subjects. The scaled (by maximum parameter value) IQR is distributed around its median of approximately 0.20 [Supplementary Fig 5A]. However, the boxplot including whiskers covers the entire range from 0 to 1, meaning that very high as well as very low fluctuations of delay values may frequently be observed for a certain portion of subjects. For the Harvard-Oxford atlas, the spread of IQR values appears to be somewhat lower together with zero median. Unlike CMAES, the BO method shows a similar spread of the optimized delay τ fluctuations for both considered atlases, where the distributions of the scaled IQR are centered around medians in the range of 0.43-0.46 [Supplementary Fig 5]. This indicates that the extent of fluctuations within subjects tends to be on a nearly constant level for BO. A persistent variability can be observed for the frequency parameters $(f_i)_{1 \leq i \leq N}$ optimized by CMAES, where (i) the scaled median IQR remains between 0.22 and 0.91 across brain regions, and (ii) the spreads of the frequencies obtained for individual subjects concentrate narrowly around their medians in most cases [Supplementary Fig 5, blue boxes for the frequencies $(f_i)_{1 \leq i \leq N}$]. The situation is much more heterogeneous for the BO method, especially for the Harvard-Oxford atlas [Supplementary Fig 5B, orange boxes for the frequencies $(f_i)_{1 \leq i \leq N}$], where the scaled median IQR of the optimized frequency parameters can be very different across brain regions. Furthermore, the individual subjects may also exhibit a rather distinct frequency spread and broadly deviate from their scaled median IQR for many brain regions. The other model parameters of coupling C and noise intensity σ demonstrate much more consistent optimization results with narrow distributions of the scaled IQR across trials and subjects with medians between 0.06 and 0.15 [Supplementary Fig 5]. Most reproducible are however the GoF values, where the median of the scaled IQR is close to 0.05 (Sch100) and 0.02 (HO0Thr) for both considered optimization methods [Supplementary Fig 5], despite the broadly distributed (delay and) frequency parameters.

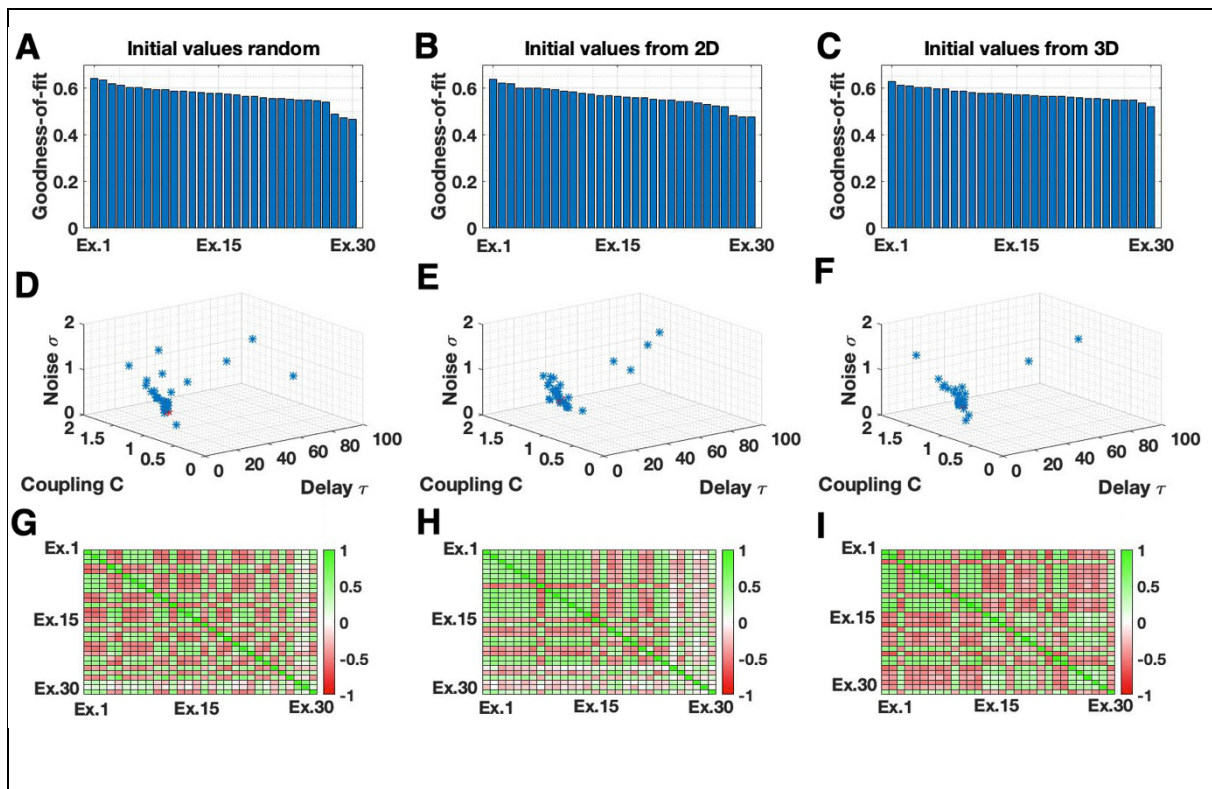


Supplementary Fig 5. Variability of the optimized model parameters and GoF values across algorithm executions for all subjects. The considered model parameters (delay τ , coupling C , noise intensity σ , frequencies $(f_i)_{1 \leq i \leq N}$ and also GoF) are indicated on the horizontal axes along with the values of their scaled interquartile range (IQR) on the vertical axes. For every subject, the IQRs of the model parameters and GoF values found in 30 optimization executions with random initial data were computed and then separately divided by the respective, highest possible parameter values as specified by the considered parameter ranges. Boxplots visualize the resulting, visually comparable distributions of the scaled IQRs of all parameters (including GoF) for the optimization approaches based on BO (orange boxes) and CMAES (blue boxes). The results pertain to **(A)** the Schaefer atlas (Sch100) and **(B)** the Harvard-Oxford atlas (HO0Thr). This figure was created with MATLAB R2021a (www.mathworks.com).

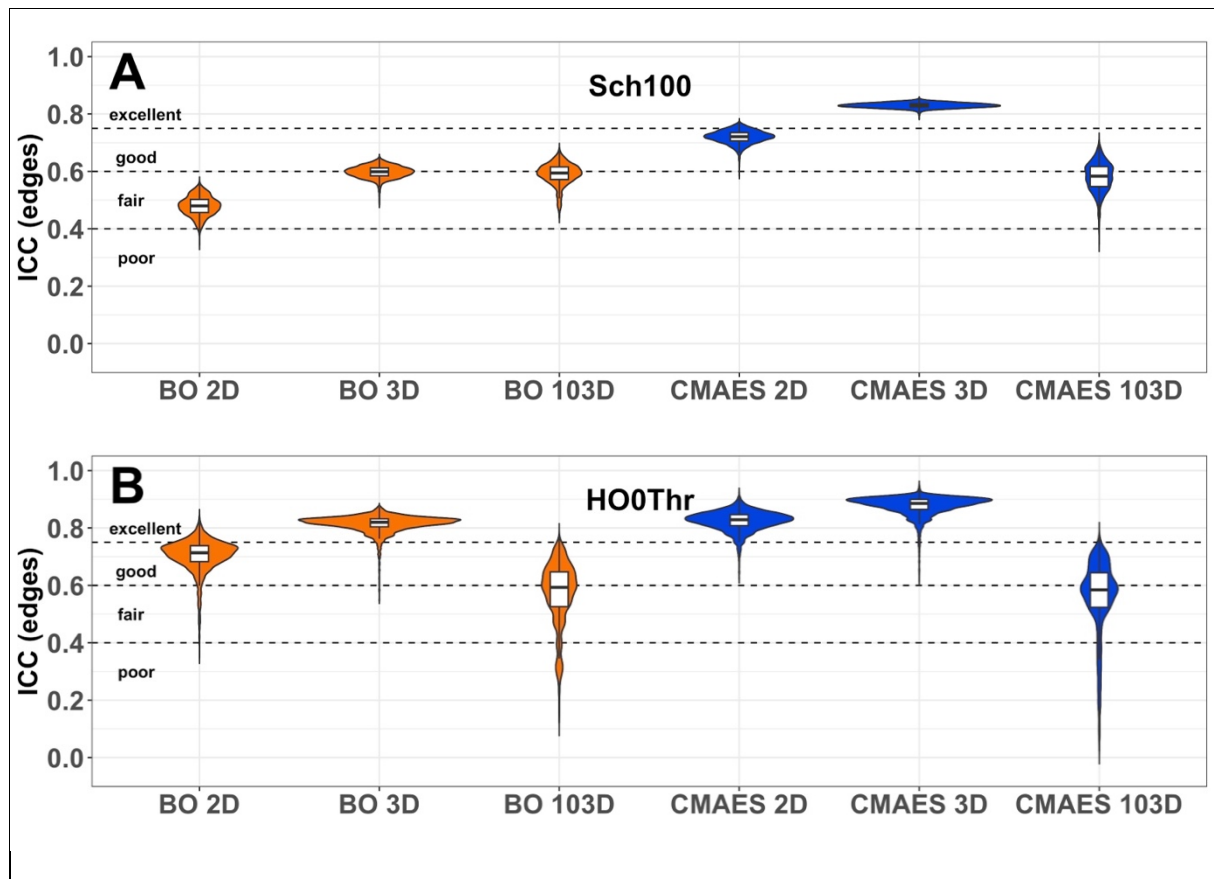




Supplementary Fig 7. Principal component analysis (PCA) results for the optimized model parameters. (A) Scatter plots visualize the PC scores of the optimized frequency parameters $(f_i)_{1 \leq i \leq N}$ derived from 30 algorithm executions. Results are shown in the PC space spanned by the first two principal components indicated on the axes. Black, green and sand-colored dots represent the values for three subjects. The same subjects were also used as examples in **Fig 3** of the main text as well as in **Supplementary Fig 6**. (B) Color-stacked bar plots show the fraction of variation explained by the first three principal components for all subjects. The numbers of the subjects are provided on the horizontal axis along with the percentages of explained variation on the vertical axis. As indicated in the plot, the parameter optimization was performed via CMAES in the 103-dimensional parameter space (Sch100). (C) Boxplots visualize the distributions of principal components (Comp.) required to explain at least 80% of variation in the optimized frequency parameters for all considered high-dimensional cases. The names of the utilized algorithms are provided on the horizontal axis along with the number of components on the vertical axis. A dashed line separates the results for the different atlases (Sch100, HO0Thr) indicated in the plot. This figure was created with MATLAB R2021a (www.mathworks.com).



Supplementary Fig 8. Examples of the model fitting results for different starting points in the 103-dimensional parameter space. For one subject, the CMAES method was executed 30 times, where the parameter values for the initial search distribution mean were taken **(A,D,G)** randomly and uniformly from the respective parameter intervals (see Methods); **(B,E,H)** from the results of parameter optimization in the 2D space; and **(C,F,I)** from the results of parameter optimization in the 3D space. For the latter two cases, the parameters of noise intensity and frequencies in 2D as well as frequencies in 3D had the initial values that were considered in the corresponding low-dimensional model validations (e.g., $\sigma = 0.3$ in 2D, see Methods). **(A-C)** Bars indicate the goodness-of-fit (GoF) values detected in 30 algorithm executions (Ex.). The executions were sorted in descending order, based on the observed model fitting values. **(D-F)** Blue asterisks show the location of the approximated optimal parameters of coupling, delay and noise intensity in the 3D subspace of the 103D parameter space. The configuration yielding the highest GoF is marked in red (may be covered by other solutions). **(G-I)** Correlations between optimized frequency parameter sets for different optimization runs (Ex.) (cf. **Fig 3A** of the main text, **Supplementary Fig 6**). This figure was created with MATLAB R2021a (www.mathworks.com).



Supplementary Fig 9. Reliability of the matrix edges for all considered conditions. Violins show the distributions of the intraclass correlation coefficients (ICC) for the off-diagonal edges of the matrices of sFC in the low- and high-dimensional cases. Dashed horizontal lines indicate the levels of *poor*, *fair*, *good* and *excellent* reliability in terms of the ICC as suggested in [5, 6]. The presented distributions reflect the results obtained during the model validation for **(A)** the Schaefer atlas (Sch100) and **(B)** the Harvard-Oxford parcellation (HO0Thr). The employed optimization approaches are listed on the horizontal axes along with the ICC scores of the sFC edges on the vertical axes.

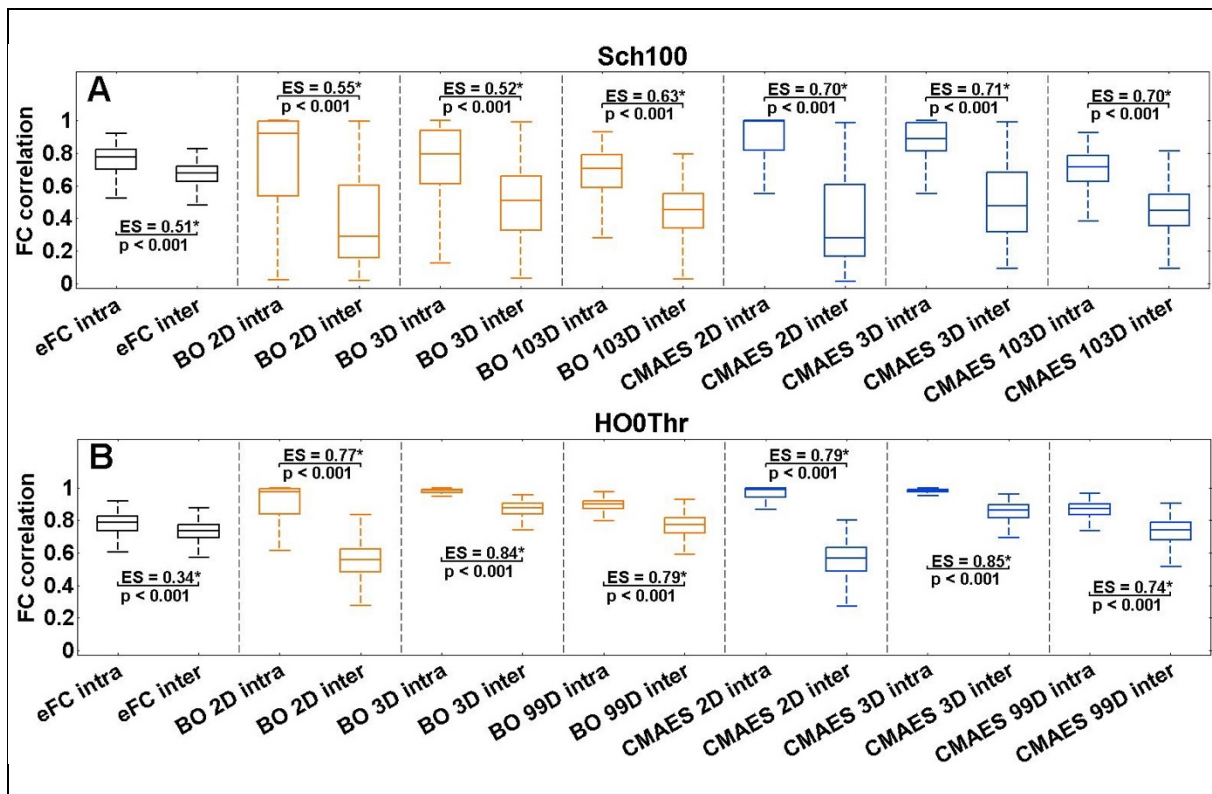
Subject specificity of simulated connectivity and GoF (Results)

This section is dedicated to a deeper investigation of those two modeling results that turned out to be the most reliable ones across optimization runs, namely the sFC and GoF.

Correlations between connectivity patterns

We compared the sFC matrices obtained for different executions of the optimization methods. The corresponding matrix correlations were calculated within (intra) and between (inter) subjects (see Methods above). Here we found that the sFC correlations within subjects are higher (sFC is more similar) than those between subjects, which is consistent across the considered optimization methods and brain atlases [Supplementary Fig 10]. For the Schaefer atlas, however, the inter-subject sFC correlations display relatively broad distributions (IQR on average around 228% higher) as compared with those for the Harvard-Oxford atlas [Supplementary Fig 10]. This may indicate a non-uniform inter-individual variability of sFC for the former atlas, where the sFC correlations between subjects are widely spread from small to large values.

The discussed correlations can also be calculated for the eFC. A few eFC realizations for the same subject are extractable from the repeated fMRI measurements in the considered HCP dataset (see Methods above). The distributions of the intra- and inter-subject eFC correlations are illustrated in **Supplementary Fig 10** (black boxes in the leftmost sections) indicating a higher intra-subject eFC similarity as compared to that between subjects.

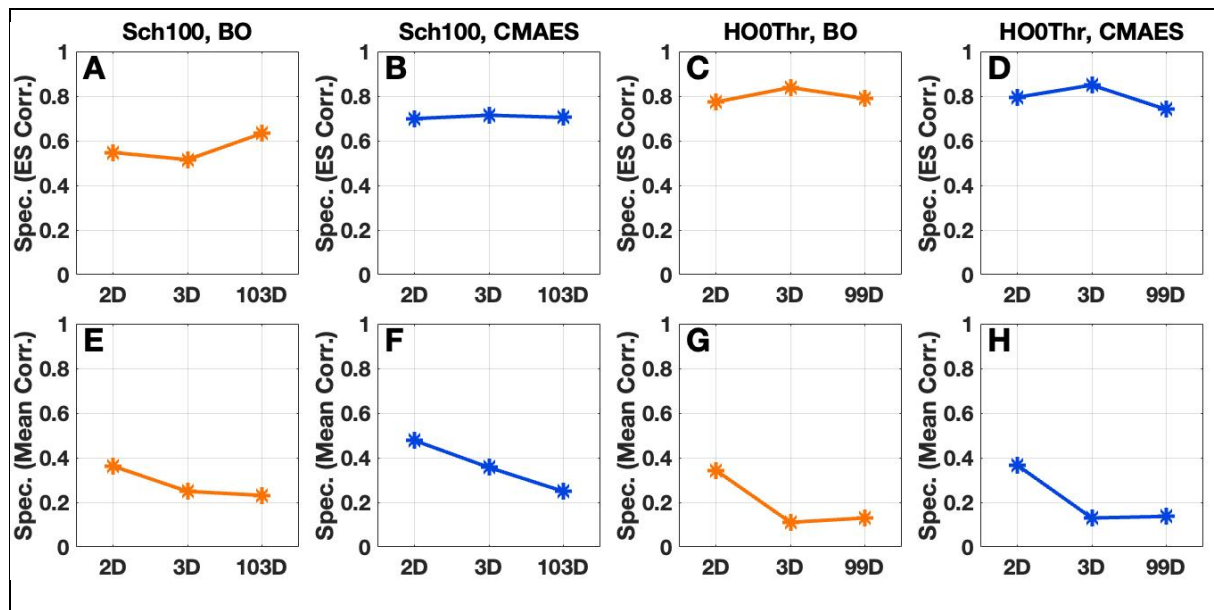


Supplementary Fig 10. Correlations of the FC matrices within and between subjects. For two randomly selected different subjects, two different algorithm solutions for one subject together with one solution for the other subject were randomly chosen in order to compute the correlations of any two sFC matrices, i.e., within (intra) and between (inter) subjects, respectively (see Methods above). For the correlations of eFC, data from the four available resting-state fMRI sessions per subject were considered. This procedure was repeated 1000 times. Boxplots show the distributions of the resulting matrix correlations for the algorithms and parameter spaces listed on the horizontal axes. The correlations presented on the vertical axes pertain to **(A)** the Schaefer atlas (Sch100) and **(B)** the Harvard-Oxford atlas (HO0Thr). Outliers are not shown in this figure. The effect sizes (ES) of the deviations between the intra- and inter-subject distributions of the FC correlations in all considered parameter spaces are indicated in the plots together with p -values of the Wilcoxon rank-sum test. Statistically significant differences are marked with an asterisk. The significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons. This figure was created with MATLAB R2021a (www.mathworks.com).

An important property that can be calculated from the intra- and inter-subject FC (dis)similarities is the *subject specificity*. It reflects whether the results are more similar to each other within than between subjects. We characterize the subject specificity of FCs principally by the ES between the distributions of their intra- and inter-subject correlations (see Methods above). The specificity indices derived from the intra- and inter-subject correlations of sFCs are highest in the high-dimensional case for the Schaefer atlas with BO, but remain almost constant across parameter spaces for CMAES [Supplementary Fig 11]. For the Harvard-Oxford atlas, both algorithms seem to be characterized by a specificity from the same narrow range of values for all dimensions [Supplementary Fig 11]. Further, the model simulations generated connectivity matrices which are more subject-specific than the empirical ones for both atlases and optimization methods [Supplementary Fig 10].

We however note here that the calculated intra- and inter-subject variability and subject specificity of eFC and sFC cannot always be directly compared to each other. Indeed, for sFC, these quantities were calculated for different runs of the optimization methods, where the sFC was always fitted to the same eFC of a given subject. This may allow for a comparison of the inter-subject similarity and variability of eFC and sFC. It however prevents a straightforward comparison of the intra-subject variability and thus subject specificity of eFC and sFC, unless we assume that the repeated model simulations, fittings and sFC optimizations for different initial conditions may correspond to separate (fMRI) measurements of empirical data. We also note here that the observed low inter-subject correlations of sFC relative to those for eFC [Supplementary Fig 10] may indicate that the considered modeling approach enhances the inter-individual variability of the functional connectomes.

An additional measure of the subject specificity based on the differences of the mean values (see Methods above) is illustrated in **Supplementary Fig 11**. Only for a few considered cases, we may observe some monotonic decline of the subject specificity for sFC with increasing dimension of the parameter space, such that the illustrated results to a large extent agree with those discussed above. We however note here that such a specificity measure based on the mean values only does not take into account the other properties of the intra- and inter-subject similarity distributions, in contrast to the ES-based specificity index.



Supplementary Fig 11. Subject specificity derived from the differences between the intra- and inter-subject distributions of similarities of sFCs obtained after several executions of the optimization algorithms. The sampling approach was chosen as in **Supplementary Fig 10**. The considered atlases and methods are provided in the titles of the plots, while the parameter spaces are listed on the horizontal axes. **(A-D)** Specificity indices defined as the effect sizes (ES) between the distributions of the intra- and inter-subject correlations of sFCs (Spec. (ES Corr.)). **(E-H)** Specificity indices based on the differences between the mean values of the intra- and inter-subject distributions of sFC correlations (Spec. (Mean Corr.)). This figure was created with MATLAB R2021a (www.mathworks.com).

Differences between connectivity patterns

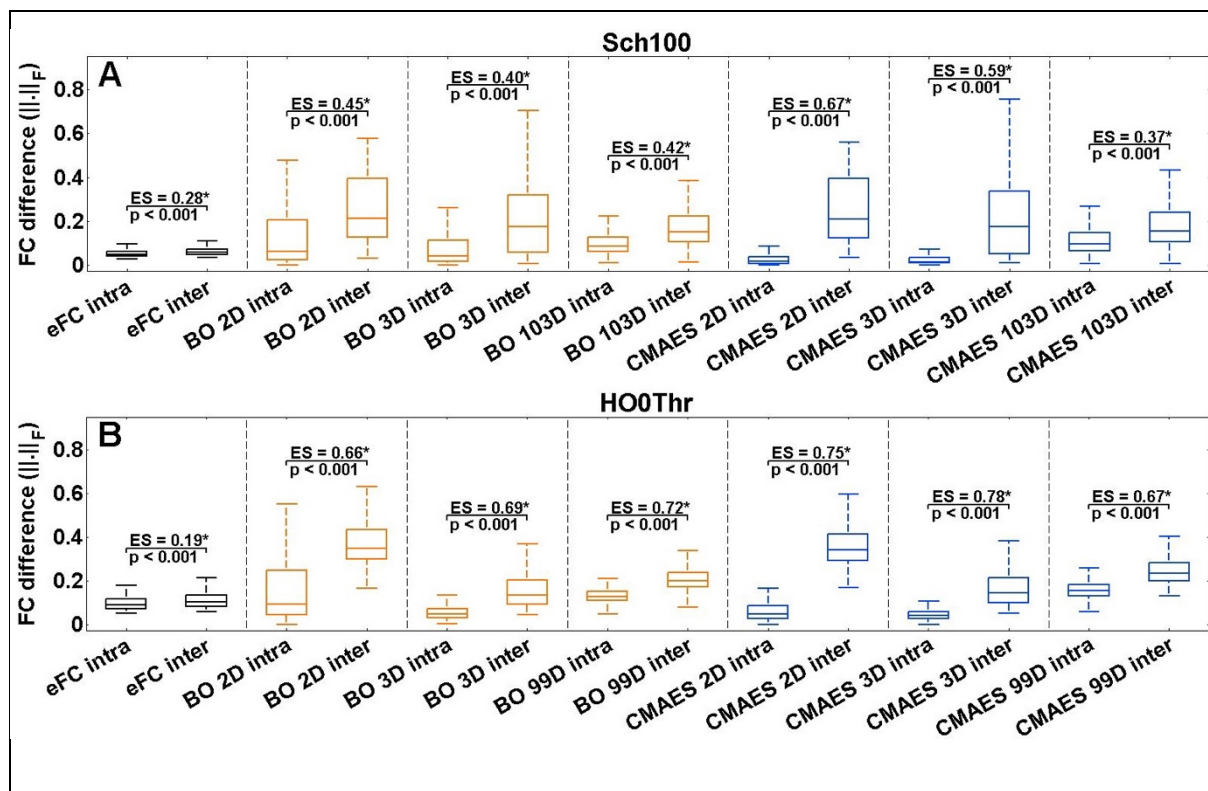
The situation is very similar when the resemblance of the FC matrices within and between subjects is evaluated by the matrix differences measured by the Frobenius norm $\| \cdot \|_F$ (see Methods above). Analogously, the intra-subject sFC differences appear to be lower than the inter-subject differences [Supplementary Fig 12]. We also observed the patterns of broad distributions of the sFC similarity for the Schaefer atlas, where the IQR of the inter-subject sFC differences is on average around 108% larger than that for the Harvard-Oxford atlas [Supplementary Fig 12].

We found a relatively high subject specificity of sFC for all considered conditions, where the ES ranges from moderate to strong with somewhat stronger results for the Harvard-Oxford atlas [Supplementary Fig 12]. For the Schaefer atlas, we observed a drop in the specificity accompanying the transition to the high-dimensional cases for CMAES [Supplementary Figs 12,13]. For the other conditions, no such clear trend can be reported, because the specificity values are gathered in a narrow range for all dimensions of the parameter space [Supplementary Figs 12,13]. Therefore, increasing the dimension of the model parameter space may not consistently lead to a reduction or an enhancement of the subject specificity of sFC.

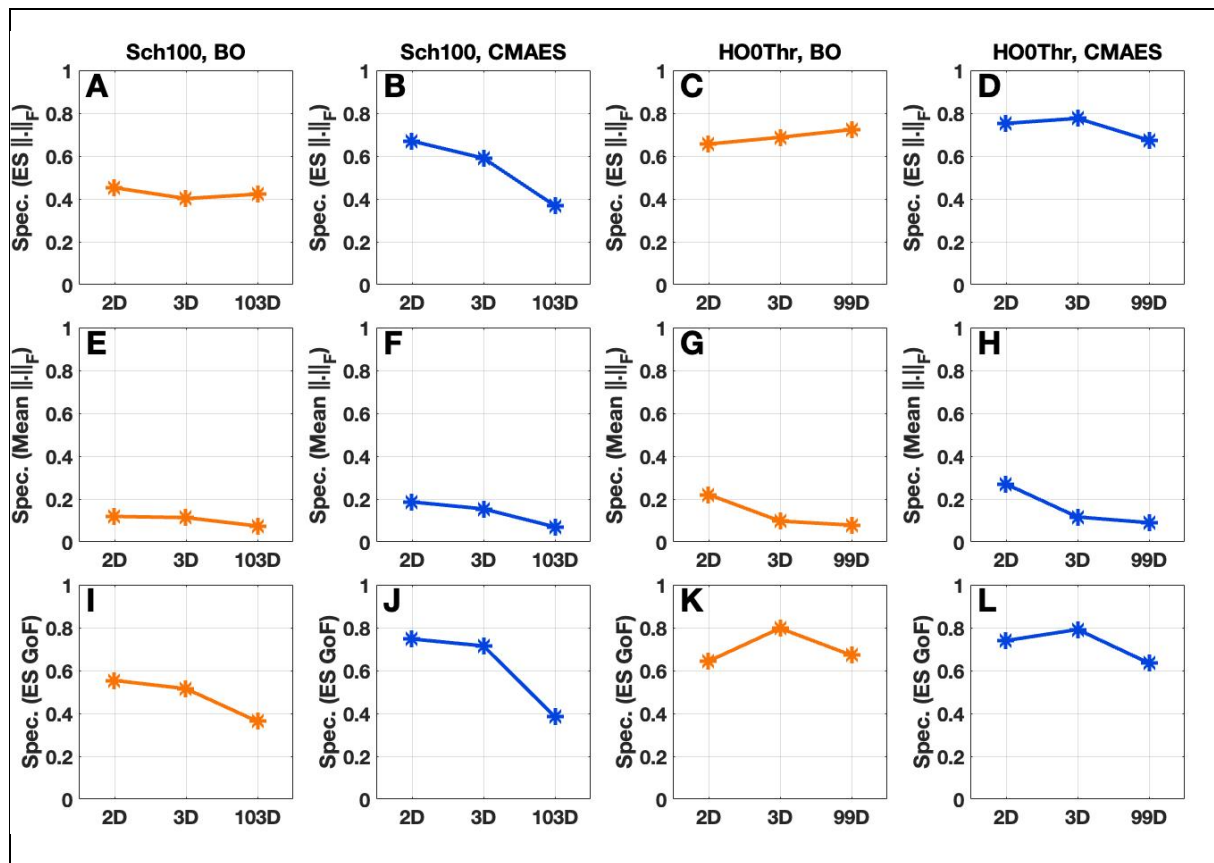
For the specificity based on the differences of mean values, we observed only very small changes across parameter spaces [Supplementary Fig 13]. We stress that the ES-based approach might be a more appropriate specificity measure especially in the cases of heterogeneous intra- and inter-subject variability of similarity values as in our study [Supplementary Figs 10,12].

The reported findings thus demonstrate that only for the Schaefer atlas, CMAES and difference-based similarity of sFC, we may observe a considerable drop in the subject specificity for model fitting in a high-dimensional parameter space [Supplementary Fig 13]. For the other considered conditions, the extent of the specificity varied only slightly across parameter dimensions with a possible small enhancement for more free parameters in some cases.

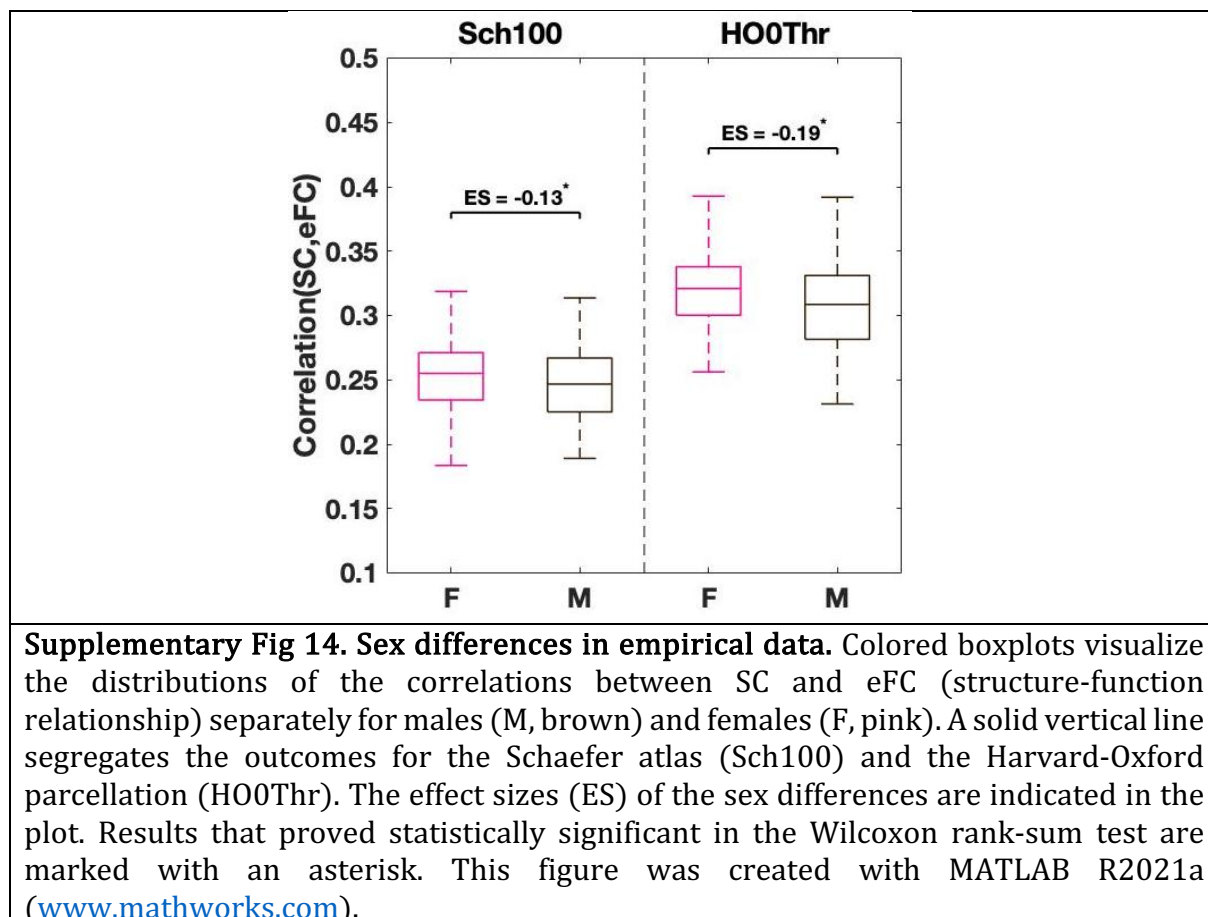
We also calculated the specificity of the GoF values (see Methods above). For this quantity, we observed a monotonically decreasing trend for the Schaefer atlas as the dimension of the model parameter space increases. The specificity for the Harvard-Oxford atlas, however, does not consistently decay for more free parameters, such that the high-dimensional model validation does not necessarily imply a lower subject specificity here either [Supplementary Fig 13].

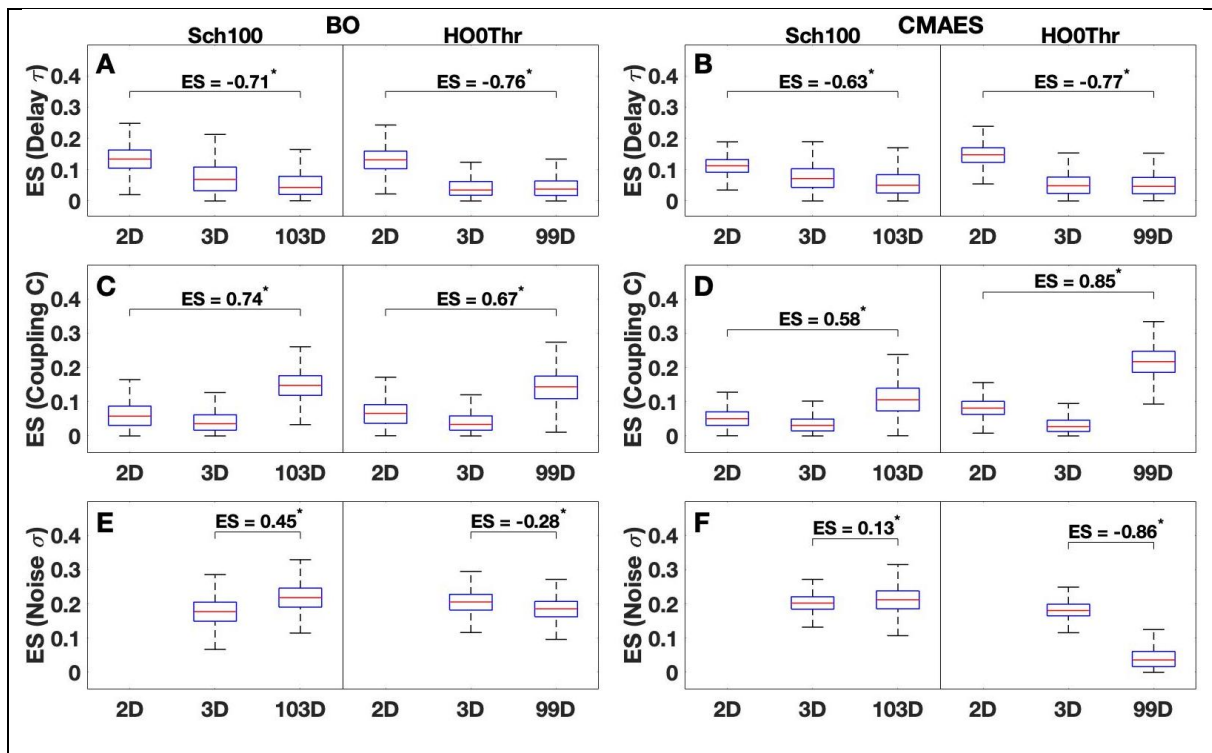


Supplementary Fig 12. Differences of the FC matrices within and between subjects. The same approach and notations as in **Supplementary Fig 10** were used, but for the Frobenius norm $\| \cdot \|_F$ of the differences of any two (Fisher-transformed) FC matrices. The differences presented on the vertical axes were normalized by one maximum value calculated separately for each atlas. The ES was calculated between inter- and intra-subject distributions of FC correlations, see Methods above. This figure was created with MATLAB R2021a (www.mathworks.com).

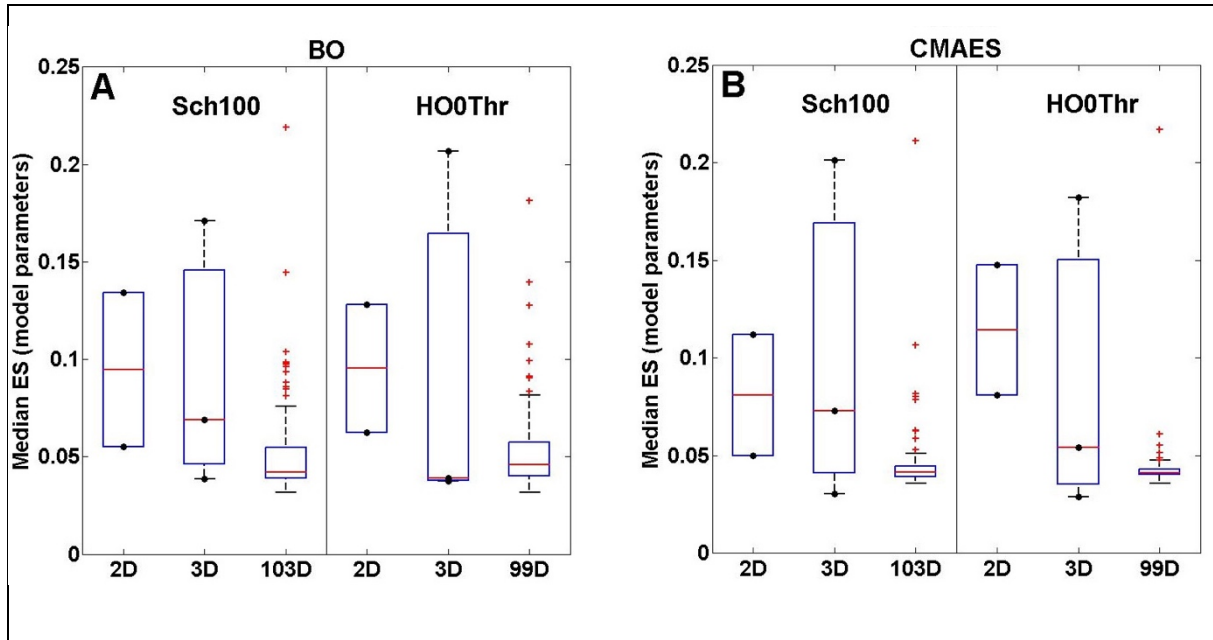


Supplementary Fig 13. Subject specificity based on the differences between the inter- and intra-subject similarity distributions of sFC and GoF values obtained after several executions of the optimization algorithms. The sampling approach was chosen as in **Supplementary Fig 10**. The considered atlases and methods are provided in the titles of the plots, while the parameter spaces are listed on the horizontal axes. **(A-D)** Specificity indices defined as the ES between the distributions of the inter- and intra-subject sFC differences measured by the Frobenius norm (Spec. (ES $\| \cdot \|_F$)). Since the calculated matrix difference is a measure of sFC dissimilarity, the positions of the intra- and inter-subjects difference distributions were exchanged in order to obtain positive ES, see Methods above. **(E-H)** Specificity indices derived from the differences between the mean values of inter- and intra-subject sFC differences measured by the Frobenius norm (Spec. (Mean $\| \cdot \|_F$)). **(I-L)** GoF-based specificity defined as the ES between the inter- and intra-subject differences of GoF values. This figure was created with MATLAB R2021a (www.mathworks.com).

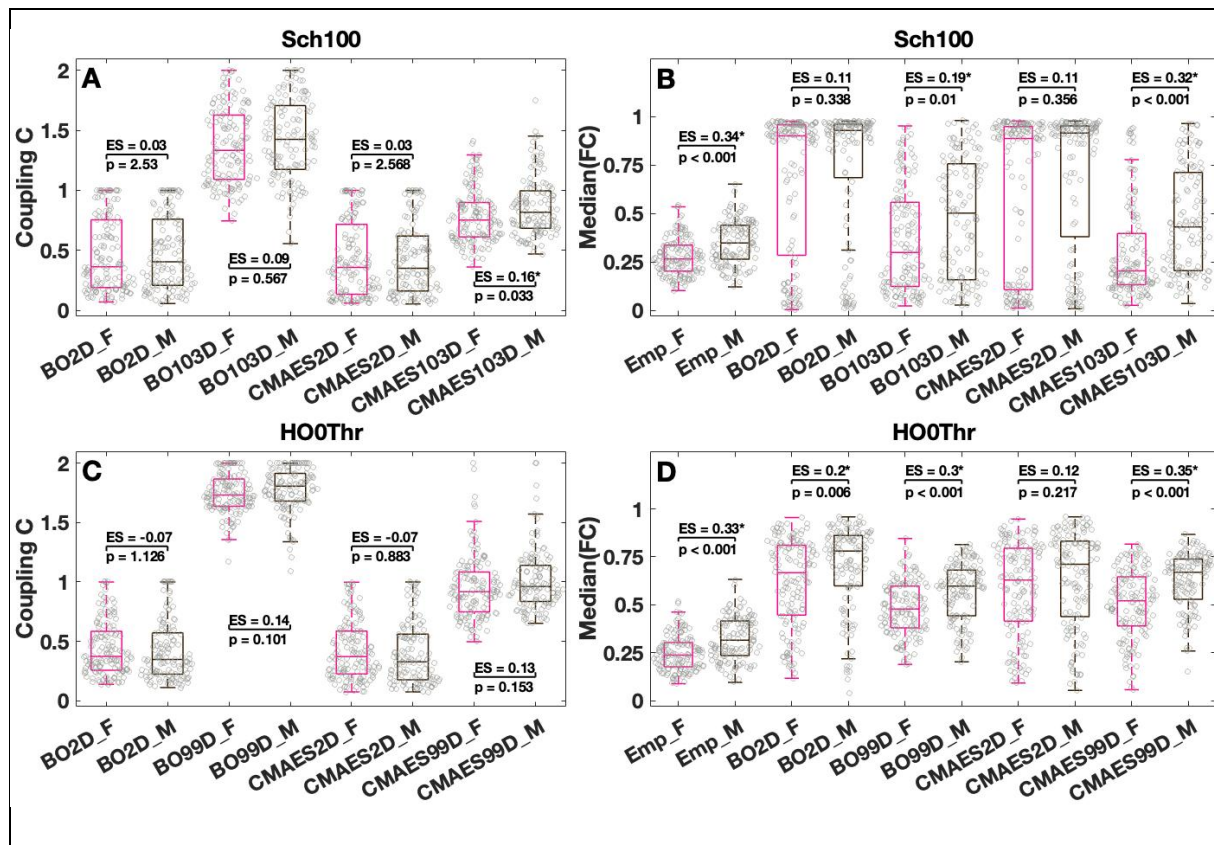




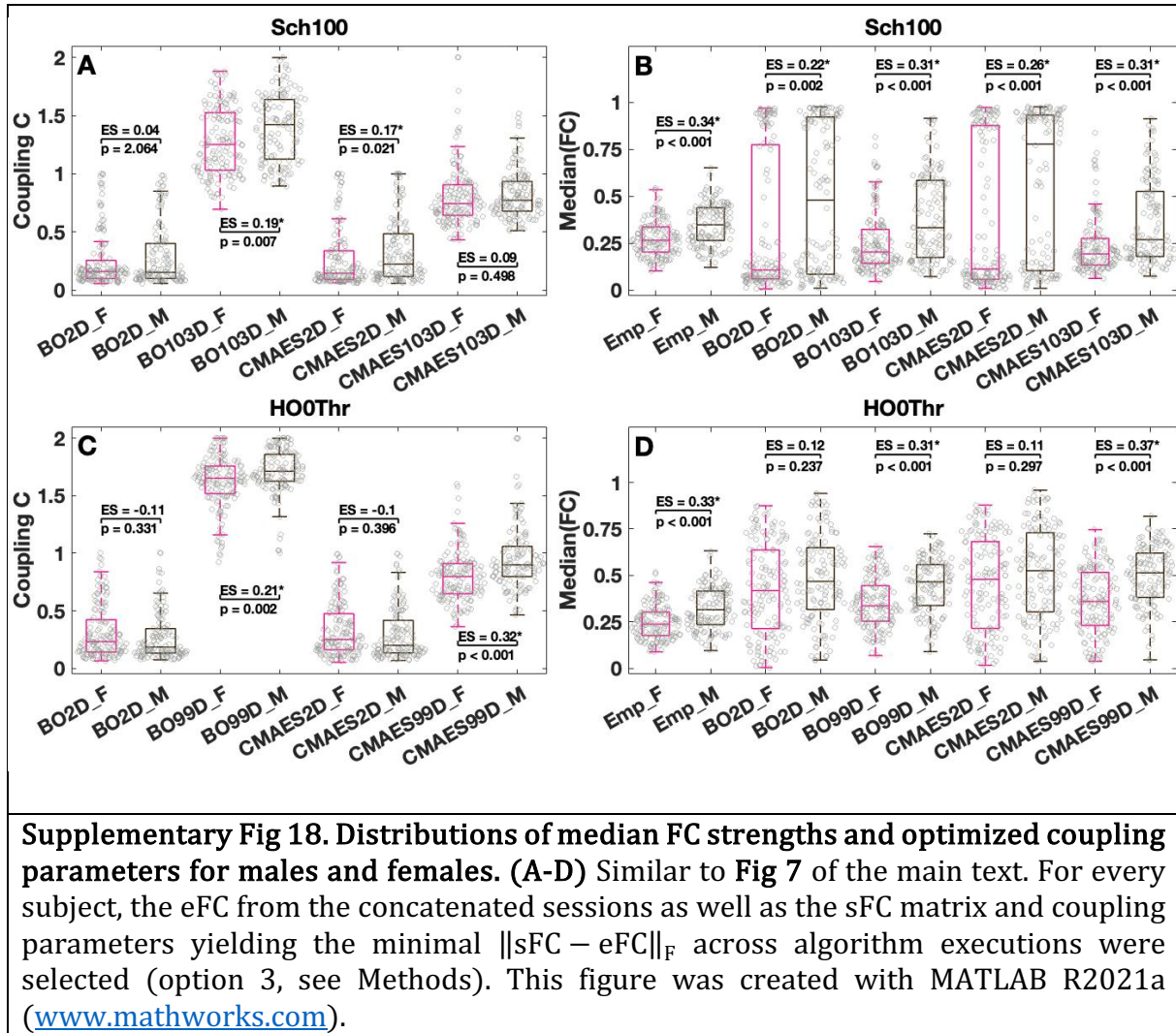
Supplementary Fig 15. Sex differences in the optimized model parameters of delay τ , coupling C and noise intensity σ . Boxplots illustrate the distributions of the effect sizes (ES) for the sex differences in (A-B) delay τ , (C-D) coupling C and (E-F) noise intensity σ observed during a random selection of one of the 30 available algorithm executions for every subject and a subsequent comparison of the respective parameter values across both groups (1000 repetitions). The utilized optimization methods and brain atlases are provided in the titles, while the considered parameter spaces are listed on the horizontal axes. On the vertical axes, the ES of the sex differences are depicted for the indicated model parameter. The changes (in ES) of the detected sex differences between the low- (2D, 3D) and the high-dimensional (99D/103D) cases are also indicated in the plots. Statistically significant changes (detected by the Wilcoxon rank-sum test) are marked with an asterisk. The significance level of 5%, $p < 0.05$, has been Bonferroni-corrected for multiple comparisons. This figure was created with MATLAB R2021a (www.mathworks.com).

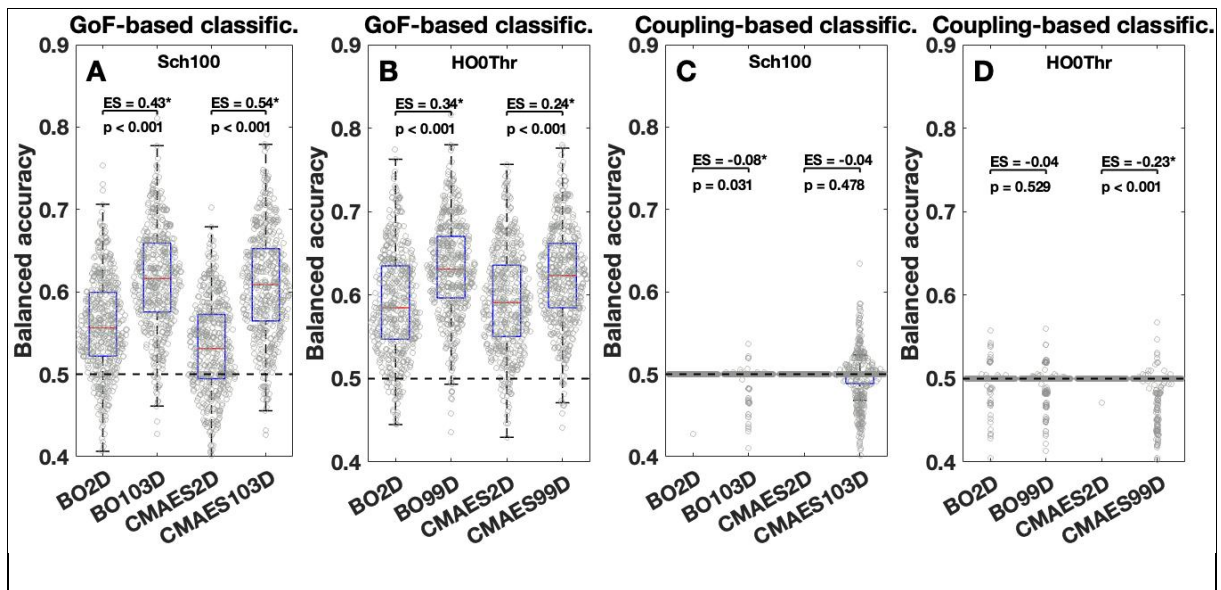


Supplementary Fig 16. Median sex differences for all model parameters together. For the optimization approaches based on (A) BO and (B) CMAES, boxplots visualize the distributions of the median effect sizes (ES) of the differences between males and females for all optimized model parameters. The medians were computed in analogy to the results presented in **Supplementary Fig 15**. In every considered parameter space, a random selection of one of the 30 available algorithm executions for every subject and a subsequent comparison of the respective parameter values across the groups of males and females were repeated 1000 times. This led to 1000 values of ES of sex differences for every model parameter in all considered parameter spaces. For the parameters of delay, coupling and noise intensity, these distributions are shown in **Supplementary Fig 15**. Here, only the medians of the individual distributions for every parameter were considered and assigned to the corresponding parameter space dimensions. In the low-dimensional cases (2D, 3D), the boxplots therefore depict only 2 or 3 values (for delay τ , coupling C and, additionally, the noise intensity σ). These are highlighted by black dots and correspond to the red lines presented in the boxplots in **Supplementary Fig 15**. The boxes corresponding to the high-dimensional cases (103D, 99D) illustrate the median extent of sex differences observable throughout all model parameters considered in this study, i.e., delay τ , coupling C , noise intensity σ and frequencies $(f_i)_{1 \leq i \leq N}$. Solid vertical lines segregate the results for the Schaefer atlas (Sch100) and the Harvard-Oxford atlas (HO0Thr). This figure was created with MATLAB R2021a (www.mathworks.com).

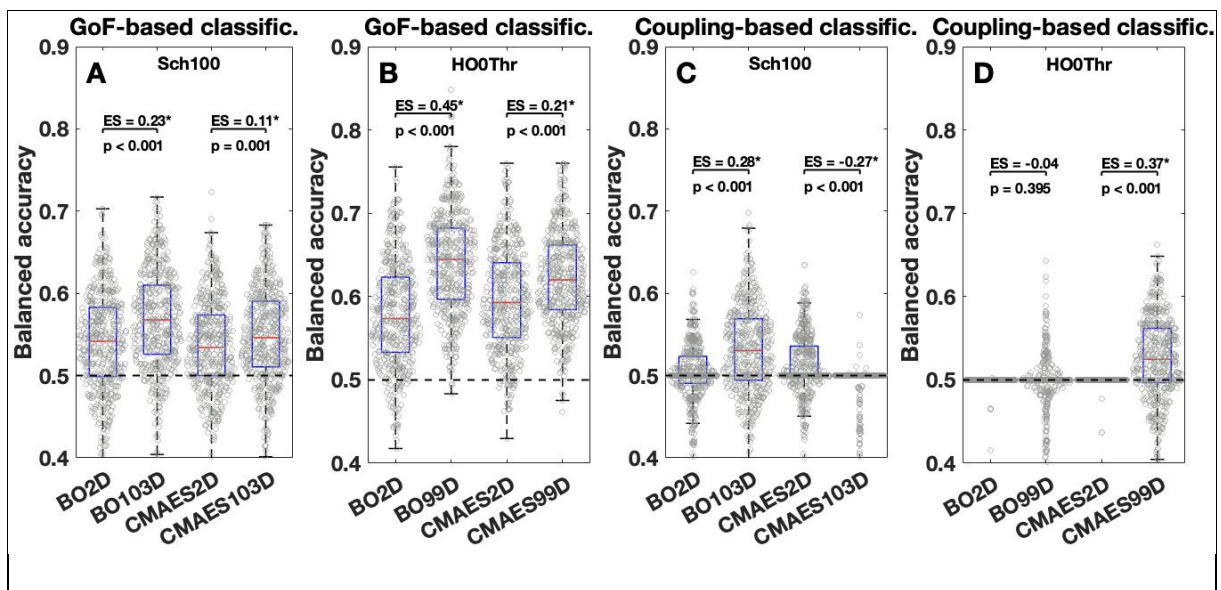


Supplementary Fig 17. Distributions of median FC strengths and optimized coupling parameters for males and females. (A-D) Similar to Fig 7 of the main text. For every subject, the eFC from the concatenated sessions as well as the sFC matrix and coupling parameters yielding the median GoF across algorithm executions were selected (option 2, see Methods). This figure was created with MATLAB R2021a (www.mathworks.com).





Supplementary Fig 19. Model-based sex classification accuracies. (A-D) Similar to Fig 8 of the main text. For every subject, the GoF and parameter values derived from the algorithm execution yielding the median GoF were selected (option 2, see Methods). This figure was created with MATLAB R2021a (www.mathworks.com).



Supplementary Fig 20. Model-based sex classification accuracies. (A-D) Similar to Fig 8 in the main text. For every subject, the GoF and parameter values derived from the algorithm execution yielding the minimal $\|sFC - eFC\|_F$ were selected (option 3, see Methods). This figure was created with MATLAB R2021a (www.mathworks.com).

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7 Study 3: Effective workflow from multimodal MRI data to model-based prediction

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OPEN Effective workflow from multimodal MRI data to model-based prediction

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Predicting human behavior from neuroimaging data remains a complex challenge in neuroscience. To address this, we propose a systematic and multi-faceted framework that incorporates a model-based workflow using dynamical brain models. This approach utilizes multi-modal MRI data for brain modeling and applies the optimized modeling outcome to machine learning. We demonstrate the performance of such an approach through several examples such as sex classification and prediction of cognition or personality traits. We in particular show that incorporating the simulated data into machine learning can significantly improve the prediction performance compared to using empirical features alone. These results suggest considering the output of the dynamical brain models as an additional neuroimaging data modality that complements empirical data by capturing brain features that are difficult to measure directly. The discussed model-based workflow can offer a promising avenue for investigating and understanding inter-individual variability in brain-behavior relationships and enhancing prediction performance in neuroimaging research.

Keywords Brain MRI, Whole-brain modeling, Parameter optimization, Machine learning, Classification, Prediction

Since the concept of the human connectome¹ was proposed almost two decades ago, whole-brain connectivity derived from neuroimaging data has been employed to address questions across various topics including cognitive functions² and brain disorders³. An important characteristic of magnetic resonance imaging (MRI) data is their multi-modality that has enabled the researchers to view the brain connectivity from multiple perspectives of structural and functional connections between brain regions⁴. For instance, diffusion-weighted MRI (dwMRI) can be used to investigate the microstructure of white matter as well as to estimate axonal fibers connecting brain regions via tracking streamlines. The latter are interpreted as anatomical connectivity and also referred to as structural connectivity (SC)⁵. On the other hand, resting-state functional MRI (rsfMRI) provides a way to obtain the degree of similarity of activity patterns between brain regions over time, representing functional connectivity (FC)⁶. These two connectivities (SC and FC), constructed in different ways, evidently have different meanings and interpretations and, accordingly, can be utilized in several ways. For example, temporal changes of brain activity will be represented in FC^{7,8}, while anatomical white matter changes in long-term periods can be revealed through SC^{9,10}. Furthermore, comparing these connectomes and calculating their similarity led to the notion of the brain structure-function relationship as a possible methodological approach to explore the interdependence between structure and function of the human brain¹¹. However, the strength of the structure-function relationship is usually relatively low, might depend on many factors including brain parcellation into separate regions, and its mechanism is still unclear^{12,13}.

Integration of model-based approaches into whole-brain connectome research can expand the scope of investigation to understand the brain. The models can, for example, be used to generate simulated FC that together with the fitted model parameters can serve as an additional data modality. This approach provides further attributes that characterize brain dynamics in great detail¹⁴. In the framework of the whole-brain dynamical modeling, the models were suggested as a possible mediator between brain structure and function, where the empirical SC and FC are used for the model derivation and validation¹⁵. A natural output of such models is the relationship between simulated and empirical connectomes, which can in particular be used for investigation of the brain structure-function relationship. One of the main advantages of a model-based approach is a great freedom of considering many in silico models, ranges of their parameters and the respective

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brain activity that may be hidden in a few in vivo measurements¹⁶. The modeling results may thus contain the information going well beyond that of empirical data and can also validate the biophysical properties of the brain that have been discovered so far or even provide new insights¹⁷. In addition, with increased power of high-performance computational clusters, a variety of experimental and data-processing conditions can be simulated including modeling of virtual brain interventions in order to identify and test the optimal conditions and parameters, which is hardly possible in vivo^{18,19}.

In this study we suggest a framework that advances the applicability of the model-based approach for neuroimaging research and outline an effective workflow for applying simulated data to machine-learning analysis (Fig. 1). With the suggested framework, we illustrate a few examples of model-based machine learning applied to sex classification and prediction of behavioral scores by employing the data simulated by whole-brain dynamical models. This approach proved beneficial for the performance compared to using solely empirical neuroimaging data. Since the simulated FC and its relationship to empirical FC are among the main outputs of the models, we consider connectome relationships as features for predictions. Purely empirical connectome relationship (empirical SC vs. empirical FC) is used as empirical feature and simulated connectome relationship (empirical FC vs. simulated FC) is used as simulated feature which involves simulated data. We then compare the cases of using empirical features, simulated features, and their combination. Such an enhancement of model applicability might be of relevance, for example, in medical research, where the classification of subjects into patients and healthy individuals might be well assisted by models²⁰.

The simulated and empirical connectome relationships exhibit weak similarity between each other with low or even negative correlations across individuals²¹. This indicates that the simulated data showing stronger relationships might contain additional and possibly useful information for the machine-learning prediction analysis if included as features. Along this line, we recently reported that model-based simulated connectomes show higher correlation with clinical scores than that of empirical connectomes, thereby outperforming the latter in this respect¹⁸.

Including simulated data as an additional data modality in the mentioned studies was motivated by several previous results demonstrating distinct properties of simulated and empirical data in spite of the fact that the models were fitted to the latter. One of the important issues in brain MRI research is the low reliability of findings. This problem has particularly been brought up in the resting-state functional imaging of the whole-brain connectome²². However, model-based connectome relationships can offer relatively good reliability and improved subject specificity compared to a fair reliability and low specificity of empirical functional data²³. Enhanced data reliability might also be important for the prediction analysis²⁴. Therefore, applying model-based simulated connectome features, which exhibit distinct patterns along with enhanced reliability and inter-subject variability, to machine learning could lead to consistent results and potentially improved prediction performance as we illustrate in a few examples in this study.

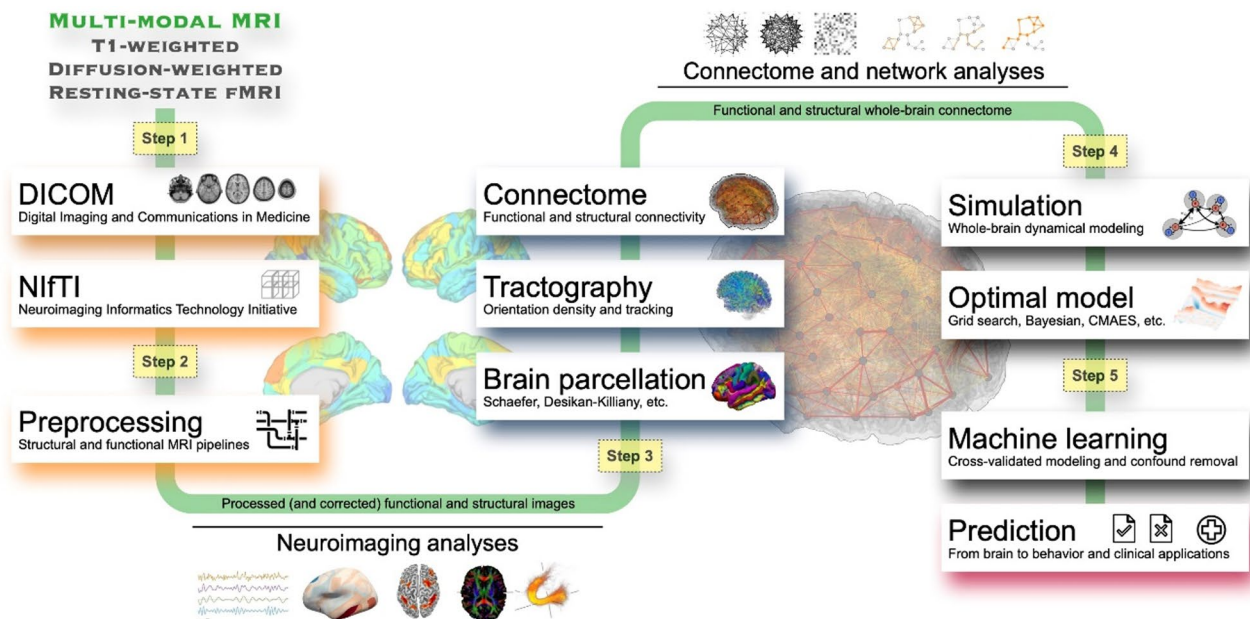


Fig. 1. A workflow for model-based prediction research. It can be divided into five steps. The first step is the acquisition of multi-modal MRI data (T1-weighted, diffusion-weighted, and resting-state functional MRI). The second step is preprocessing the acquired MRI data, which can be used for neuroimaging analysis. The third step is to calculate whole-brain tractography and apply a brain parcellation to reconstruct the whole-brain structural and functional connectomes. The fourth step involves whole-brain dynamical modeling including parameter optimization, where the optimal whole-brain model is identified and used to simulate and investigate the brain dynamics in silico. The final step is applying the simulated data for machine-learning analyses.

Methods

In the suggested workflow (Fig. 1), the first step of the model-based approach required multi-modal MRI data, including T1-weighted, dwMRI, and rsfMRI scans. The second step involved processing the MRI data, which included inhomogeneous field/motion corrections, tissue segmentation, cortical rendering, and image registration. In the next step, we applied brain parcellation schemes and computed the whole-brain connectome, including both SC and FC. The fourth step consisted of selecting a dynamical model for the research objectives and optimizing model parameters by fitting simulated data to empirical data. Finally, machine learning was performed using features derived from both the measured and model-based data. We utilized empirical human connectomes, i.e., SC derived from the white-matter fiber tracking and FC calculated by Pearson's correlation between resting-state Blood Oxygenation Level-Dependent (BOLD) signals of parcellated brain regions. Subsequently, simulated BOLD signals were generated via the considered whole-brain model informed by empirical neuroimaging data and validated by parameter optimization, where the model showed the highest similarity, i.e., Goodness-of-Fit (GoF) between simulated and empirical FCs, and GoF is considered as simulated features which involved simulated data. Then the connectome relationships between empirical and simulated brain connectomes were calculated by Pearson's correlation between empirical SC (eSC), empirical FC (eFC) and simulated FC (sFC). These connectome relationships were considered as brain features and utilized by machine-learning techniques for prediction of behavioral characteristics of individual subjects, for instance, sex classification or prediction of cognitive scores and five personality traits. The subsections below describe details of each step in the workflow. All methods were performed in accordance with the relevant guidelines and regulations.

Multi-modal MRI data: step 1

The current study used the Human Connectome Project (HCP) S1200 young adult dataset²⁵ including 270 unrelated subjects of 142 females and 128 males with ages in 28.5 ± 3.5 (mean $\pm$ standard deviation) years. HCP data were acquired using MRI protocols approved by the Washington University institutional review board (IRB #20124036). Informed consent was obtained from all subjects. Anonymized data are publicly available (<https://db.humanconnectome.org>). Multi-modal MRI data including T1-weighted MRI (T1w), rsfMRI, and dwMRI were used in the current workflow.

MRI processing: step 2

A pipeline of MRI processing that consists of structural and functional modules was applied to the multi-modal MRI data, i.e., T1w, rsfMRI, and dwMRI. The pipeline is available via a public repository (<https://jugit.fz-juelich.de/inm7/public/vbc-mri-pipeline>). The pipeline uses functions in AFNI²⁶, ANTs²⁷, FreeSurfer²⁸, FSL²⁹, MRtrix3³⁰, and Connectome Workbench³¹. The entire MRI pipeline was aiming at obtaining the whole-brain human connectome. The Schaefer atlas with 100 parcels⁷ and the Harvard-Oxford atlas with 96 parcels³² were utilized in this study for brain parcellation in the MNI space. T1w was employed for preprocessing and co-registration between rsfMRI and dwMRI, although it was not directly included in the connectome analysis. However, cortical volumes extracted from T1w were used as a confounding factor in machine learning to classify males and females.

Resting-state BOLD signals were extracted from the rsfMRI processed with FMRIB's ICA-based X- noiseifier (ICA-FIX) provided by a pipeline of the HCP repository³³. There were four rsfMRI sessions (1200 volumes, TR = 720 ms) conducted over two different days and consisting of two different phase-encoding directions on each day. In order to obtain the mean regional BOLD signals, the brain was parcellated according to a given brain atlas, and the voxel-wise BOLD signals in every brain region were averaged over all voxels of the region at each time point. A concatenated BOLD signal was then generated by combining all four z-scored BOLD signals from the four rsfMRI sessions.

For the whole-brain tractography (WBT) calculation, response functions were estimated for spherical deconvolution using the constrained deconvolution algorithm³⁴. Fiber oriented distributions (FODs) were estimated from the dwMRI using spherical deconvolution³⁵, and WBT including 10 million streamlines was created through the fiber tracking by second-order integration over the FOD by a probabilistic algorithm³⁶.

Whole-brain connectome: step 3

For eFC, Pearson's correlation coefficients between the concatenated regional BOLD signals of each pair of brain regions of the considered brain parcellation were calculated, resulting in the whole-brain resting-state FC. For eSC, the atlases were transformed from the MNI space to the native space of dwMRI. Following the transformation, labeled voxels masked within gray matter were selected for seed and target regions and applied to the WBT. Subsequently, streamlines connecting the seed and target regions were selected for each pair of brain regions, and we ultimately obtained the whole-brain SC matrices including streamline counts and average path lengths of them. With eFC and eSC, we can apply connectome and graph-theoretical network properties for further analyses.

Mathematical whole-brain model and model fitting: step 4

We simulated a whole-brain dynamical model of N coupled phase oscillators^{37,38}. Their temporal dynamics can be described by the following set of differential equations:

$$\dot{\phi}_i(t) = 2\pi f_i + \frac{C}{N} \sum_{j=1}^N k_{ij} \sin(\phi_j(t - \tau_{ij}) - \phi_i(t)) + \sigma \eta_i, \quad i = 1, 2, \dots, N. \quad (1)$$

The number of oscillators N corresponds to the number of brain regions as defined by a given brain atlas, where $\phi_i(t)$ models the phase of the mean BOLD signal of the corresponding region, and the simulated BOLD was calculated as $\sin\phi_i(t)$. C is a global coupling which scales the level of couplings of the whole-brain network. η_i is an independent noise perturbing oscillator i , which is sampled from a random uniform distribution from the interval $[-1,1]$. $\sigma = 0.3$ denotes the noise intensity. The natural frequencies f_i were estimated from the empirical data as frequencies of the maximal spectral peaks (restricted to the frequency range from 0.01 Hz to 0.1 Hz) of the empirical BOLD signals of the corresponding brain regions. k_{ij} stands for the coupling strength between oscillators i and j , and τ_{ij} approximates the time delay of the signal propagation between oscillators i and j . They were calculated from the streamline counts and average path-length matrices and determined by the following equations:

$$k_{ij} = \frac{w_{ij}}{\langle W \rangle}, \quad (2)$$

where w_{ij} is the number of streamlines between the i^{th} and j^{th} parceled region, and $\langle W \rangle$ is an average number of streamlines over all connections except self-connections. The delays were calculated as

$$\tau_{ij} = \frac{L_{ij}}{\langle V \rangle} = \tau L_{ij}, \quad (3)$$

where L_{ij} is the average path length of the selected streamlines connecting the i^{th} and j^{th} region, and τ is a global delay, which is a reciprocal of an average speed of signal propagation $\langle V \rangle$ through the whole-brain network. The time step of the numerical integration of Eq. 1 by the stochastic Heun method was fixed to 0.04 s, and the simulated signals were generated for 3,500 s after skipping 500 s of the initial transient. The simulated BOLD signals and the corresponding sFC matrices were calculated from the phases down-sampled to TR = 0.72 s, which is the repetition time of the current rsfMRI acquisition.

The considered mathematical model (Eq. 1) has two global parameters: global coupling C and global delay τ . These were optimized within the ranges $C \in [0,1]$ and $\tau \in [0,100]$ with the aim to maximize Pearson's correlation between eFC and sFC. We will refer to this setting with two free parameters as the low-dimensional parameter optimization. Further, we also considered the model fitting in high-dimensional spaces of model parameters, where the noise intensity σ and additional local (regional) parameters of natural frequencies f_i (see Eq. 1) of the brain regions were included in the optimization process. For both scenarios, we applied the Covariance Matrix Adaptation Evolution Strategy (CMAES) for parameter optimization^{39,40}. At the parameter optimization by CMAES, the number of particles sampled per generation was chosen as $\lambda = 24$ based on the previous study⁴¹. To account for a possible result variability of such a parameter optimization, we performed CMAES 30 times for every subject with different initial conditions and selected the optimal model parameters corresponding to the largest GoF for further analyses.

Machine learning for model-based prediction: step 5

To illustrate the benefits in machine learning via including simulated data into the features, we used the empirical connectome relationship (Pearson's correlation between eFC and eSC) and the simulated connectome relationship (Pearson's correlation between eFC and sFC, that is the best GoF of the model to eFC). The empirical and simulated connectome relationships were used for sex classification ($n=270$) as well as the prediction of cognitive composite scores ($n=268$, 2 subjects had no cognitive scores) and personality traits ($n=269$, 1 subject had no data on personality traits) by using machine learning. We also merged the two features (empirical and simulated) and used them for the same machine-learning approach for the classification and prediction analyses. Afterward, we compared the performances with feature conditions of empirical only, simulated only, and merged features.

For the sex classification, we used a nested 5-fold cross-validation (CV) scheme, where every outer CV loop ($k=5$) included the embedded 5 inner loops as a nested CV (inner 5-fold CV) for training the prediction model using hyperparameter optimization. The training procedure started with a random splitting of the entire subject sample into 5 equally-sized subgroups while maintaining the ratio of female/male in each subgroup. Subsequently, in every outer loop, one subgroup was selected after another as a testing set, and the other 4 subgroups were united into a training set. In the inner loop with the training set, we performed a confound removal (CR) to remove the effect of brain volumes on the sex classification from the features, i.e., connectome relationships. For this we used the univariate linear regression with the brain volumes (sum of cortical, subcortical and white matter volumes), estimated the parameters of the linear model, and z-scored the obtained residuals across subjects in the training set. Finally, we used a logistic regression with an L2 penalty for the training in the nested CV, and the regularizing parameter was optimized by the Limited memory Broyden-Fletcher-Goldfarb-Shanno algorithm (L-BFGS). After the training in the nested CV, the best model was selected and applied to the testing set to classify the unseen subjects as females or males. Here, the respective CR and z-scoring with parameters obtained for the training set were applied beforehand. Such a CV-CR scheme prevents a data leakage, where no information from the testing set was used during the training⁴². We repeated this prediction process 100 times for different random subject splits into 5 subgroups. Finally, we calculated a balanced accuracy using predicted probability and target variables (female or male).

The CV-CR scheme (5-fold nested CV and CR with brain volumes and ages) was used for predicting the total cognitive function composite score (*CogTotalComp_Unadj*) as general intelligence acquired in the NIH toolbox (<https://www.nihtoolbox.org>) and also the Five-Factor Model⁴³ known as the big five personality traits including openness, conscientiousness, extraversion, agreeableness and neuroticism. The entire group was

split into training and testing sets as before while keeping the shape of scores' distributions for the training and testing sets for an efficient and reliable CV performance⁴⁴. Here, the training and testing sets were created by stratifying the subjects among 7 subgroups balanced within 7 intervals of each target score (cognitive and personality traits) in order to mimic the distribution of the entire cohort. We applied a ridge regression with an L2 penalty for training the prediction model, and the optimal regularizing parameter values were selected among several discrete values of 10^{-6} , 10^{-5} , ..., 10^5 , and 10^6 . The model with the optimal regularizing parameter was selected, which demonstrated the highest Pearson's correlation coefficient between predicted values and the target scores across subjects in the training set. Consequently, the best model trained through the nested CV on the training set was applied to the testing set to predict the target scores of unseen subjects. We repeated this CV-CR prediction 100 times with each iteration having different stratified subject splits. Finally, we calculated Pearson's correlation between predicted and measured scores for prediction performance.

For the machine-learning approach, we used Python version 3.11 with modules including Scikit-learn version 1.3.0⁴⁵, NumPy version 1.24.4⁴⁶, and SciPy version 1.11.1⁴⁷.

Statistical analysis

Effect sizes of the difference between prediction performance of feature conditions were calculated by the Rosenthal formula⁴⁸ which used z-statistics also utilized for calculation of the *p*-values of Wilcoxon rank-sum two-tail test. Bonferroni correction was applied for corrected *p*-values in multiple comparisons. Principal component analysis (PCA) was performed for features, and loadings of each principal component were estimated. All statistical tests and data visualizations were performed in MATLAB (R2024a; MathWorks).

Code availability

The features for machine learning in this study can be found in the GitHub repository including Python scripts for training prediction models and a MATLAB script to analyze results and generate figures illustrated in this study (<https://github.com/kyesam-jung/model-based-prediction>).

Results

By leveraging empirical whole-brain connectomes for the whole-brain dynamical modeling, we successfully generated sFC that can be used alongside the eFC. This allows us to characterize whole-brain dynamics through connectome relationships, highlighting inter-individual variability. Both empirical and simulated connectome relationships can be considered as individual features of whole-brain dynamics and used to classify subjects into different categories or predict their behavioral characteristics using machine-learning approaches. Here, simulated data can complement empirical neuroimaging data or serve as stand-alone features, which can improve the prediction performance. As an example of the proposed framework, we demonstrate that the modeling results can effectively classify subjects by sex (male vs. female) and predict their general intelligence as well as personality traits, showing improved performance compared to using empirical features alone.

Model-based connectome relationships as leveraged feature information

To calculate brain connectomes and their relationships, we utilized two brain parcellation schemes. One is the Schaefer atlas with 100 regions⁷, where the cortical surface was divided based on functional characteristics of the brain. The other one is the Harvard-Oxford atlas with 96 regions³², where structural brain characteristics were used for cortical parcellation. The connectome relationships as given by the Pearson's correlation between the respective connectivity matrices were calculated for every subject leading to distributions of their values for a given subject cohort (Fig. 2a). We observed that the two considered parcellation schemes yielded different distributions for the empirical structure-function connectome relationships $\text{corr}(\text{eFC}, \text{eSC})$ (Fig. 2a, Emp.). In particular, the Harvard-Oxford atlas supported a somewhat stronger structure-function relationship as compared to the Schaefer atlas. Similarly, the simulated connectome relationships $\text{corr}(\text{eFC}, \text{sFC})$ also produced different ranges of values depending on the parcellation scheme applied (Fig. 2a, Sim.). The considered functional connectome relationship involving the simulated data sFC is important in the brain modeling and frequently used in the literature as a measure of the best fitted model to empirical functional data¹⁵. We observed that the simulated connectome relationships (eFC vs. sFC) exhibited a much broader spread as compared to the empirical connectome relationships (eFC vs. eSC) including an enhanced inter-individual variability when the simulated data were involved (interquartile ranges, empirical vs. simulated features: 0.033 vs. 0.104 for the Schaefer atlas, and 0.044 vs. 0.136 for the Harvard-Oxford atlas). The effect size of the difference between the atlases was similarly large for both empirical and simulated data (effect size: 1.088 vs. 1.077 for empirical data and simulated data, respectively). Furthermore, the difference between the mean values of each atlas is larger for the simulated data (effect size: 0.679 vs. 1.189 for the Schaefer and Harvard-Oxford atlas, respectively, see Fig. 2a).

The illustrated empirical and simulated connectome relationships can be considered as features for the machine-learning prediction approaches, where the enhanced inter-subject variability of the simulated features (larger spread of the feature distributions) might be a good indication for involving the simulated data in the analyses. To examine the extent of overlap and difference in the feature information under the considered four conditions (2-by-2) shown in the legend in Fig. 2a, we performed PCA using empirical and simulated features of the connectome relationships. Interestingly, we found that the first two principal components (PC1 and PC2), which deliver the largest fraction of the explained variance of all connectome relationships, primarily related to the simulated features (Fig. 2b-c), while the next two components (PC3 and PC4) explained the empirical features. Furthermore, PC1 and PC3 represented common contributing factors in the simulated and empirical connectome relationships, respectively, of the two parcellation schemes (Fig. 2b). In contrast, PC2 and PC4 distinguished the parcellation schemes in the respective simulated and empirical feature conditions (Fig. 2b).

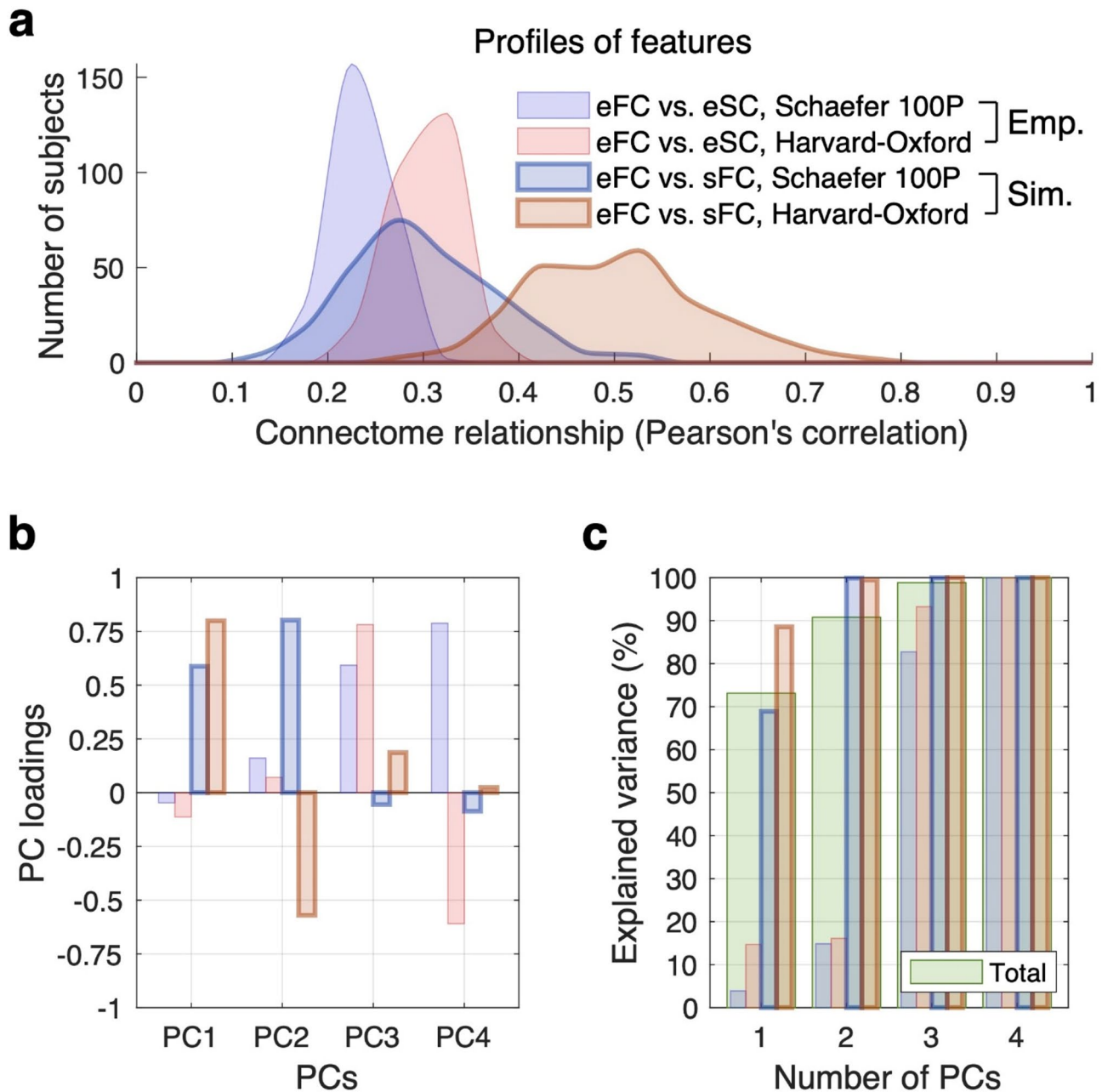


Fig. 2. Empirical and simulated features (connectome relationship) for machine learning. **(a)** Feature distributions across individual subjects for two brain parcellations given by the Schaefer atlas (100 regions) and the Harvard-Oxford atlas (96 regions) as indicated in the legend. **(b,c)** Principal component analysis (PCA) of the feature variability across 4 feature conditions: empirical, simulated and the two considered brain parcellations. The loadings and the fractions of the explained variance by different principal components are illustrated in plots **(b)** and **(c)**, respectively. The color and line schemes are as in plot **(a)**. The cumulative explained variance across all conditions is depicted in plot **(c)** by bars in light green color. *eFC* empirical functional connectivity, *eSC* empirical structural connectivity, *sFC* simulated FC, *PC* principal component.

The two first PCs with the loading by simulated data cumulatively explained up to 90% of the variance of all features (Fig. 2c). The observed segregation of the empirical and simulated features into different PCs as well as the leading role of the latter features in PCA further support the expectations of a positive contribution of the simulated features to prediction results, which can be used either as stand-alone features or as a complement to empirical ones.

Classification and prediction performance

Since the empirical and simulated connectome relationships exhibit distinct variabilities across individuals (Fig. 2), these two types of connectome relationships might contribute differently to a machine-learning

prediction process. To investigate this, we prepared three distinct feature sets: empirical (Emp.), simulated (Sim.), and combined empirical and simulated (Emp. & Sim.) features. Here, the first feature set (Emp.) includes the empirical structure-function relationships (Pearson's correlation between eSC and eFC), the second feature set (Sim.) includes the relationships between eFC and sFC (GoF values), and the third feature set (Emp. & Sim.) includes both the empirical and simulated features. We then performed two machine-learning analyses using these features to (i) classify the individual subjects as females or males and (ii) predict a continuous behavioral score as given by the general intelligence based on the total cognitive function composite score⁴⁹. For both cases and under each feature condition, we calculated prediction performance on the training set and after applying the model to the testing set of unseen subjects (Fig. 3a, b). Sex classification on the test subject sets shows that the balanced accuracy was significantly enhanced, when the simulated features were employed in the classification analysis as compared to the case of the empirical features (Bonferroni-corrected $p < 0.05$) (Fig. 3c, compare "Emp." to "Sim."). The machine-learning analysis applied to predict the general intelligence also exhibited improved performance with features that contain the simulated data. This was confirmed by statistical tests demonstrating a significant improvement of the prediction performance for the simulated features (Sim.) as well as for a combination of the empirical and simulated features (Emp. & Sim.) compared to the case of the empirical features (Emp.) (Fig. 3d).

Enhanced performance with high-dimensional parameter optimization

We also fitted the model to empirical data in high-dimensional parameter spaces, where around 100 model parameters were simultaneously optimized by the CMAES algorithm. In such a way we obtained an increased GoF, where the simulated FCs closely approached the empirical FCs of individual subjects leading to a higher model personalization. For example, the mean GoF = 0.607 and 0.724 for high-dimensional model fitting of the Schaefer and Harvard-Oxford atlases, respectively, may be compared to the respective GoF = 0.299 and 0.501 for the low-dimensional model fitting (Fig. 2a). We then applied the simulated connectome relationships of the high-dimensional model fitting as features to machine learning. Interestingly, the results showed that involving the simulated features obtained through high-dimensional optimization yielded the best outcome in the sex classification (Fig. 4a). Likewise, the low-dimensional optimization condition showed the best prediction of cognition (Fig. 4b). Additionally, in the prediction of personality traits (Fig. 4c–g), the simulated features showed the best results in four out of five traits, except for the openness, where the empirical features demonstrated the best performance (Fig. 4g). These findings indicate that whole-brain dynamical modeling can enhance the performance of machine learning. This is especially evident in predictions of cognitive ability and personality traits, where the empirical features mainly showed correlations near zero, whereas the simulated features demonstrated clearly improved results. To assess the extent to which the results presented in this study align with those predicted by traditional statistical methods, we conducted group comparisons between males and females, as well as linear regression analyses for each feature condition: Emp., Sim. (Low dim.), and Sim. (High dim.). The results demonstrated that the relationships between measured and predicted scores consistently aligned with those obtained through out-of-sample machine learning (Supplementary Figures S1 and S2). Moreover, a permutation test was applied to evaluate the robustness of the current approach (Supplementary Figure S3). We observed that the empirical features can be predictive for sex classification and the openness personality trait only. On the other hand, the performance of the machine learning with simulated features showed a significant and relatively large positive difference from the null distributions except for the openness and neuroticism (Supplementary Figure S3), which is in agreement with Fig. 4.

Finally, when looking at the overall concatenated results of predicting all five personality traits, the simulated features obtained through the high-dimensional parameter optimization showed the highest prediction correlation (Fig. 5), and the difference from the results based on the empirical features was especially large (effect size is 0.836).

The contribution of individual features to prediction results can be examined by analyzing the coefficients of the trained machine-learning models (logistic and ridge regressions, see Methods). This can for example be approached by considering the distributions of the regression coefficients and their contribution to prediction accuracy across all CV loops for all individual empirical and simulated features for the two considered brain atlases (Supplementary Figures S4 and S5). We observe that the feature contributions vary based on the atlas and type of features (empirical or simulated) confirming our conclusions (Fig. 4). In many cases, the good or bad predictability of individual features can clearly be distinguished, see Supplementary Figures S4 and S5 and discussion therein.

Another approach to understanding feature contributions relates to Shapley additive explanation (SHAP) values⁵⁰ that we calculated for the best predictors of each target (Fig. 6). The latter are empirical features for openness, simulated features of the low-dimensional parameter optimization for cognition and simulated features of the high-dimensional parameter optimization for the other five tasks including sex classification, and prediction of agreeableness, conscientiousness, extraversion, and neuroticism, see Fig. 4 (note the negative mean prediction correlations in Fig. 4f). A comparison between the distributions of SHAP values (Fig. 6) and the distributions of model coefficients (Supplementary Figures S4 and S5) revealed consistent trends. For example, in the case of the agreeableness prediction, the regression coefficients for features derived from the Harvard-Oxford atlas are mostly negative and strongly contributing to prediction (Supplementary Figure S5k). Correspondingly, the distributions of SHAP values under the same condition show the importance of the Harvard-Oxford atlas, where the SHAP values shift from positive to negative as the feature values increase, which is in contrast to the Schaefer atlas (Fig. 6, Agreeableness). As such, all best predictors exhibited a consistent alignment between the distributions of the model regression coefficients and the distributions of SHAP values. We also calculated the mean of absolute SHAP values that reflects the importance of each feature for the prediction results. In summary,

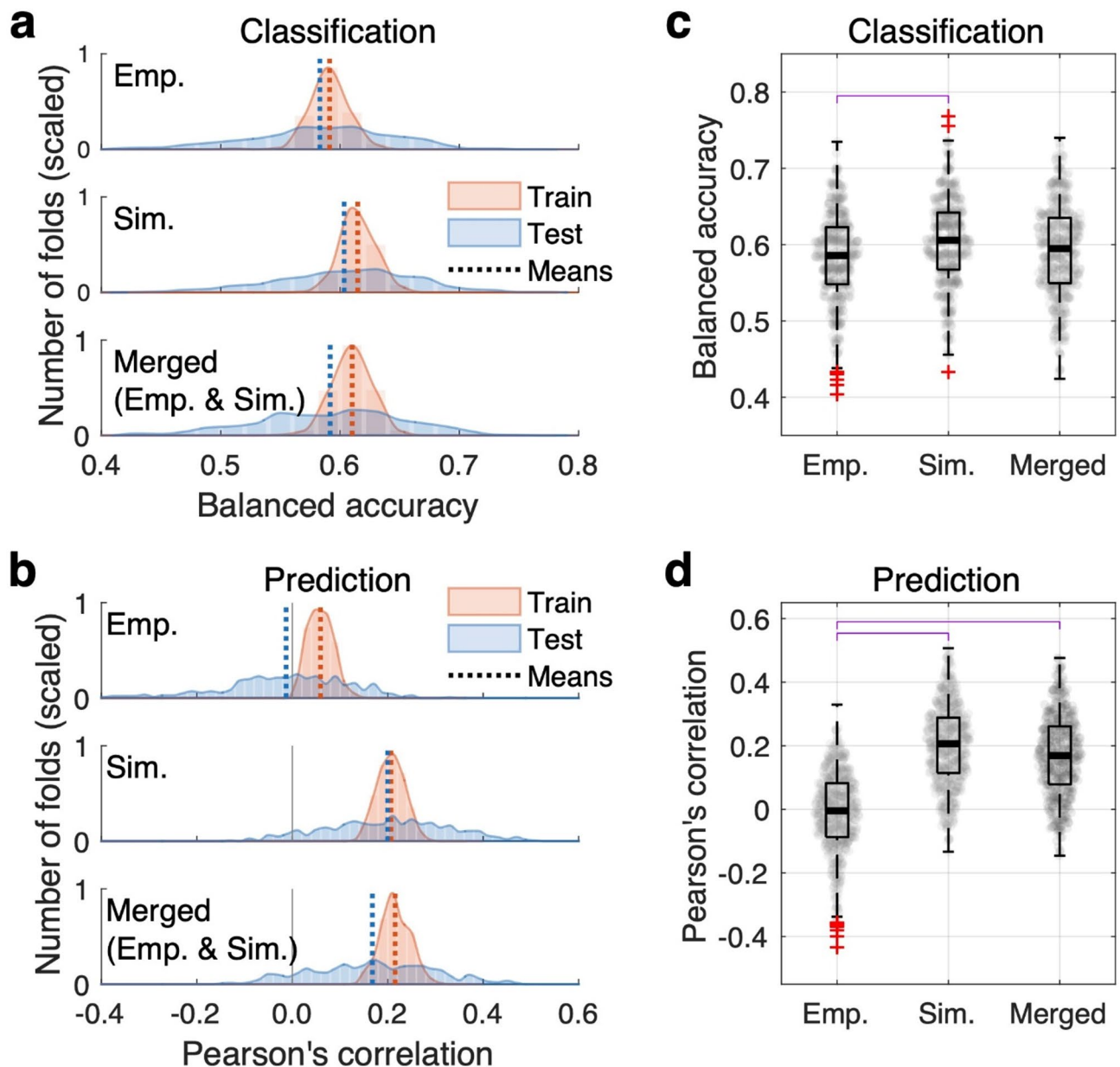


Fig. 3. Machine-learning performances in sex classification and prediction of general intelligence. **(a)** Accuracy of sex classification as given by the fraction of correctly classified subjects for the training and testing sets as indicated in the legend. Distributions of balanced accuracy across cross-validation (CV) folds are shown. The mean values of the distributions are indicated by vertical dashed lines. The three plots illustrate the cases of (from top to bottom) the empirical features (Emp.), the simulated features (Sim.), and combination of the empirical and simulated features (Emp. & Sim.). The features of the two parcellations were merged in each condition. **(b)** Prediction of the total cognitive function composite scores (Pearson's correlation between predicted and empirical scores) for training and testing sets with the same scheme of **a**. **(c)** Comparison of the sex classification and **(d)** prediction performance of the three feature conditions. The magenta bars depict statistically significant differences (with $p < 0.05$ of the Wilcoxon rank-sum two-tail test Bonferroni-corrected for multiple comparisons) in the distribution of prediction between the feature conditions indicated on the horizontal axis.

the SHAP-based and coefficient-based interpretations can offer complementary insights about the mechanisms of the machine-learning prediction procedure, which can contribute to its better understanding.

Discussion

In this report, we demonstrated that connectome relationships derived from the whole-brain dynamical modeling can represent individual variability of brain dynamics in a distinct way compared to empirical

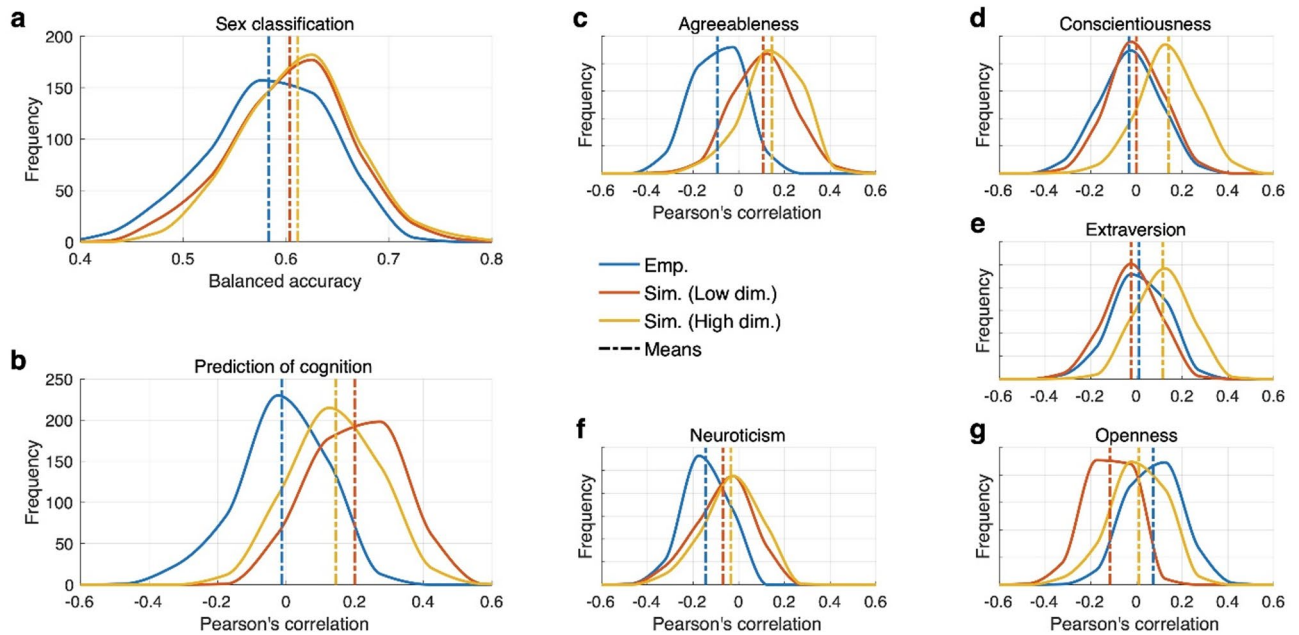


Fig. 4. Prediction results with different feature conditions based on empirical features: Emp., simulated features with low-dimensional parameter optimization: Sim. (Low dim.) and high-dimensional parameter optimization: Sim. (High dim.). **(a)** Results of sex classification with five different feature conditions shown in the figure legend in the center. Dashed vertical lines indicate mean values of performance in each feature condition. **(b–g)** Results of prediction for cognition (**b** general intelligence) and five personality traits (**c–g** agreeableness, conscientiousness, extraversion, neuroticism, and openness).

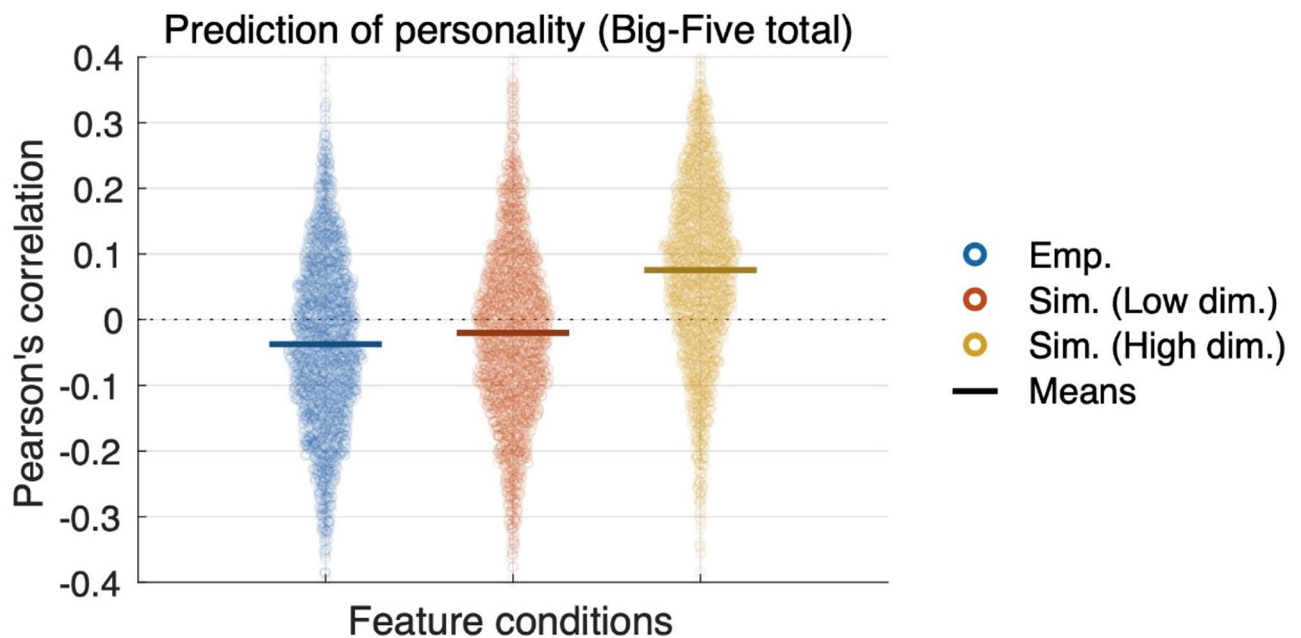


Fig. 5. Overall concatenated prediction of personality traits. Each distribution includes Pearson's correlation coefficients between predicted and measured personality of all five traits in machine learning with 100 iterations and 5 folds cross-validation scheme, leading to 2,500 points.

connectome relationships. We also showed that involving simulated connectomes in the machine-learning prediction analysis can enhance its prediction performance. Furthermore, machine learning using simulated and empirical features in a complementary way exhibited comparable or even improved performance in relation to a separate utilization of these feature configurations. Our results suggest that incorporating model-based

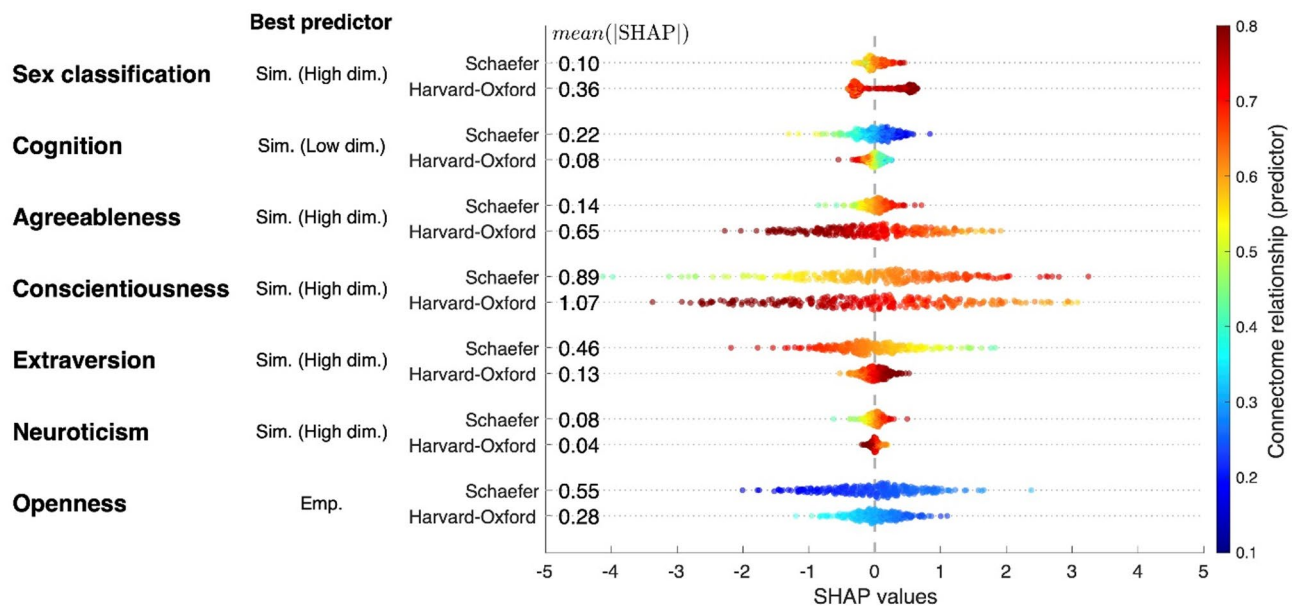


Fig. 6. Beeswarm plots of SHAP values for the best predictors of each target. Data points are reflecting the individual subjects, where the SHAP values were averaged across 100 iterations of the nested 5-fold cross-validation for each individual. The vertical axis includes the prediction target (leftmost column), the feature type (middle column) and the brain atlas (rightmost column). Colors of the dots depict feature values of the best predictors with the scaling given on the color bar. The numbers in the plot indicate the mean absolute SHAP values ($\text{mean}(|\text{SHAP}|)$) reflecting the SHAP feature importance. The abbreviation ‘Emp.’ is for empirical features, ‘Sim. (Low dim.)’ and ‘Sim. (High dim.)’ are for the simulated features of the low- and high-dimensional parameter optimizations, respectively.

features alongside empirical ones can enhance the extent of information extracted from the features provided by neuroimaging data. Building on these findings, it is important to delve into the specific advantages offered by the model-based approach.

The framework for the effective workflow proposed in this study consists of five steps, and the necessary procedures and possible approaches for each step are as follows:

- **Step 1:** For the whole-brain dynamical modeling, three types of MRI data are required: T1w, dwMRI, and resting-state fMRI. For neuroimaging research, raw data, i.e., Digital Imaging and Communications in Medicine (DICOM)⁵¹ can be converted to a standard format such as Neuroimaging Informatics Technology Initiative (NIfTI)⁵². In addition, the data can be organized according to a consensus data organization called Brain Imaging Data Structure (BIDS)⁵³. Nowadays, many published datasets exist, which provide brain MRI necessary for the workflow such as OpenNeuro (<https://openneuro.org>) or other data collections, e.g., ADNI (<https://adni.loni.usc.edu>), AOMIC⁵⁴, PPMI⁵⁵ and research projects like 1000BRAINS⁵⁶, HCP²⁵, MOUS⁵⁷, PNC⁵⁸, etc.
- **Step 2:** This step of the workflow involves completing the preprocessing of MRI data and signal extractions through a pipeline. In this step, a careful selection of the data processing parameters with high quality control is necessary to check for errors or missing information in the acquired data. Small differences at the early stages can have a significant impact in the final stage of data modeling^{20,21,23,59–62}. The pipeline for processing MRI provided in this study (<https://jugit.fz-juelich.de/inm7/public/vbc-mri-pipeline>) can be configured in various ways depending on the purpose of the study. Alternatively, public pipelines such as fMRIPrep⁶³, MRtrix3³⁰, QSIprep⁶⁴, SPM⁶⁵, and FreeSurfer⁶⁶ can be used. The processed data can be utilized to study the functional or structural characteristics of the brain through imaging analysis, as well as for modeling.
- **Step 3:** This step involves parcellating the brain into multiple regions according to a given brain atlas considering various schemes^{7,32,67–69} and calculating functional and structural connectivity of each pair of regions in order to construct the human brain connectome¹. At this stage, the data necessary for the modeling (step 4) will finally be prepared. A few datasets of BOLD signals, SC and FC calculated for many brain parcellations are available on the EBRAINS (<https://www.ebrains.eu>) platform ready for analysis and modeling^{70–72}. Furthermore, since the structural and functional connectivities between brain regions can be interpreted as underlying structures of the information flow and its processing within the brain networks⁷³, studies can be conducted to explore the relationships between network characteristics of SC and FC and behavioral, cognitive and clinical scores^{2,3}.
- **Step 4:** A whole-brain dynamical model can be constructed based on the empirical whole-brain connectomes and used to simulate brain dynamics such as electrical neuronal activity and BOLD signals. By varying the model parameters, one can analyze the simulated brain dynamics in comparisons with empirical data using

BOLD signals⁷⁴, FC¹⁵, dynamic FC that captures evolution of FC over time⁷⁵, SC²¹, metastability⁷⁶, behavioral or clinical scores^{18,20}, etc. This allows us to find optimal model parameters, where the model best replicates empirical brain dynamics and behavior depending on the study objectives. Several software packages are available for the modeling of neuronal brain dynamics, for example, The Virtual Brain⁷⁷, NEST⁷⁸ and DCM⁷⁴ to mention a few. Furthermore, by employing dedicated parameter optimization algorithms⁴¹, we can obtain fine-tuned models for an improved replication of empirical data. Such a whole-brain dynamical modeling approach provides personalized optimal model parameters after model fitting toward specific target neuroimaging or behavioral scores of individual subjects, thereby showing the strongest relationship between simulated results of optimal models and clinical characteristics^{18–20} or cognitive functions as demonstrated in the present study.

- **Step 5:** This stage involves conducting machine-learning prediction analysis using model-based data obtained from the previous steps. In this step, the cross-validated model-based scheme²⁰ extracts effective simulated features derived from personalized optimal models, and their predictive performances are evaluated using machine-learning techniques. This approach allows us to incorporate additional model-based features into the machine-learning process while keeping the established protocols of conventional machine-learning methodologies based on neuroimaging empirical data such as Julearn (<https://juaml.github.io/julearn>)⁷⁹. The cross-validated model-based machine-learning approach has demonstrated improved prediction performance, as evidenced by medical data²⁰ and this study.

In this study, the suggested workflow was applied to sex classification and prediction of behavioral scores for the healthy population of young adults. We report on improved sex classification and prediction of cognition scores by simulated connectome relationship compared to empirical structure-function relationship. Furthermore, the discussed workflow of the model-based prediction led to significant improvement in the prediction of personality traits that were only weakly predicted by empirical structural connectomes⁸⁰ or by the empirical structure-function relationship as shown in this study. In order to better explain the feature contributions to the machine-learning models and prediction results, we calculated the distributions of the regression coefficients of the trained models (Supplementary Figures S4 and S5) and the SHAP values⁵⁰ (Fig. 6), which confirmed our conclusions that the simulated features appeared to be important in most considered prediction cases and also illustrated the role of the considered brain parcellations in the prediction analysis.

The primary objective of this study was to illustrate a model-based prediction approach incorporating personalized whole-brain modeling, where the models were derived from and fitted to neuroimaging data of individual subjects. Within this framework, researchers may utilize either their own models or established ones; however, careful consideration should be given to model-specific dynamics when applying and interpreting the results. For instance, in the present study, high-dimensional parameter optimization may pose a limitation due to potential risk of overfitting if the optimized model parameters obtained for one subject were to be tested on another one. Additionally, the choice of initial parameters for optimization may still have influenced the fitting and prediction results, although we conducted repeated optimizations using different initial parameters to mitigate the variability in the outcomes.

In this study, we propose to consider the simulated data as an additional neuroimaging data modality that captures distinct properties compared to empirical data and can be leveraged for machine learning. In the previous studies, theoretical justifications were demonstrated, where the simulated data clearly exhibited an enhanced inter-individual variability, test-retest reliability and subject specificity compared to empirical data^{21,23}. This was in particular demonstrated for a personalized whole-brain dynamical model of coupled phase oscillators, which motivated its consideration in this study and possibly contributed to the improved prediction results. The use of oscillator models is supported by their relevance to brain oscillatory dynamics^{81,82}. Biophysical models can also be considered for dynamical modeling potentially leading to translational applications^{18–20,83,84}. Beyond this, various studies have used simulated brain dynamics to draw neurobiological interpretations^{85,86}. These findings can contribute to a growing body of work using simulated brain dynamics for neurobiological insights and may inform future research on personalized whole-brain modeling and its application to investigation of brain-behavior relationships.

The discussed model-based approach can effectively be used for testing a variety of experimental and data-processing conditions applicable to many topics of brain research^{14,19}. This approach has several advantages including enhanced reliability and flexibility as well as cost efficiency as it eliminates the burden to repeatedly acquire whole-brain dynamics from participants under different experimental conditions in the scanner. Additionally, given the diversity of approaches for the whole-brain modeling^{87–90}, researchers can select and utilize models that best align with their research objectives, thereby facilitating model-based connectome investigation. For example, we can also apply the proposed model-based prediction approach to other modeling techniques such as behavioral model fitting based on graph-theoretical network properties demonstrating an enhanced correlation with clinical scores when compared to empirical data¹⁸.

A critical aspect of this modeling process is the selection of data processing pipelines, including brain parcellation schemes and other parameters, which can significantly influence the modeling outcomes⁹¹. More than 20 brain parcellation schemes have been employed in neuroimaging research, contributing to the diversity of empirical and simulated brain dynamics as well as connectivity^{13,21,60} including the reliability and specificity of the results²³. Consequently, there is no ground truth or well-justified recommendation for atlas selection for a given neuroimaging analysis, whether based on empirical data or modeling studies. The choice of atlas can also influence machine-learning outcomes, resulting in performance alterations^{20,80,92}. It is therefore advisable to involve several brain atlases in contemporary studies in order to confirm and compare the results for other parcellations. In this study, we considered two atlases based on the structural and functional brain properties and providing comparably good reliability and subject specificity for simulated FC²³. Additionally, merging multiple

atlases within the feature space may further enhance performance²⁰, which we utilized also in this study. Moreover, variations in neuroimaging processing pipelines can substantially affect research outcomes^{59,61,62}, and multiple strategies of model fitting can be applied to optimizing whole-brain models in different ways^{18,20,41,93}. The variability of simulated connectomes across subjects can also provide more personalized data across a broader range of perspectives compared to analyses based solely on empirical results²³.

This workflow has been applied to clinical data as well, where an improved classification performance was reported when simulated features were included in the machine learning²⁰. We therefore expect that the suggested model-based approach can be generalized to small clinical cohorts with possibly low-quality neuroimaging data as has already been tested for classification of patients with Parkinson's disease and correlation with clinical scores^{18,20}. The applicability to other datasets still has to be explicitly demonstrated.

By incorporating model-based features alongside empirical data, we can extensively explore brain connectomes and their relationships, offering enhanced performance and other benefits. At the same time, researchers can gain a deeper understanding of the brain dynamics. Given the recent advancements in digital brain research, integrating and expanding brain models⁹⁴, the systematic model-based approach proposed in this report represents a promising method for advancing brain models and their applications. Furthermore, considering modern deep learning methods with enough features extracted from various stages of the proposed workflow including voxel-wise, region-wise and network-wise approaches may enhance the prediction performance, where the models can provide additional features based on the space of model parameters hardly accessible for empirical data. Consequently, this approach underscores the potential for leveraging integrated data to provide comprehensive insights and improved predictive capabilities in neuroimaging research.

Data availability

The features for machine learning in this study can be found in the GitHub repository including Python scripts for training prediction models and a MATLAB script to analyze results and generate figures illustrated in this study (<https://github.com/kyesam-jung/model-based-prediction>).

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Author contributions

KJ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing - original draft, Writing - review & editing; KJW: Data curation, Methodology, Software, Validation, Writing - review & editing; SBE: Conceptualization, Funding acquisition, Resources, Project administration, Writing - review & editing; OVP: Conceptualization, Funding acquisition, Methodology, Resources, Project administration, Software, Supervision, Validation, Writing - review & editing.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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Supplementary Materials

for the manuscript

Effective workflow from multimodal MRI data to model-based prediction

by

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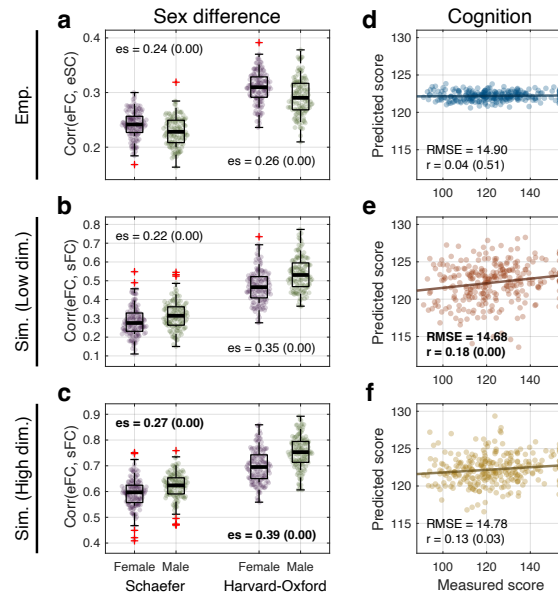


Figure S1. Comparison of the connectome relationships between females and males and linear regression analysis of cognition. (a-c) Distributions of the empirical (Emp.) and simulated (Sim.) connectome relationships for each subject group (females and males) and conditions of the low- and high-dimensional parameter optimizations (Low dim., High dim.) as well as Schaefer and Harvard-Oxford brain atlases indicated on the horizontal axes. Effect size (es) between the groups is shown in the plots with its *p*-value in the parentheses. **(d-f)** Scatter plots of the cognition scores predicted by the multiple linear regression versus the measured scores. The independent variables of the regression were the same empirical and simulated features used for the machine-learning prediction in the main text (Methods and **Fig. 4b**). Root-Mean-Squared-Error (RMSE) and Pearson's correlation coefficient *r* with its *p*-value (in parentheses) are indicated in each plot for each feature condition (Emp., Sim. Low-dim, Sim. High dim.), and the best performance is highlighted in boldface.

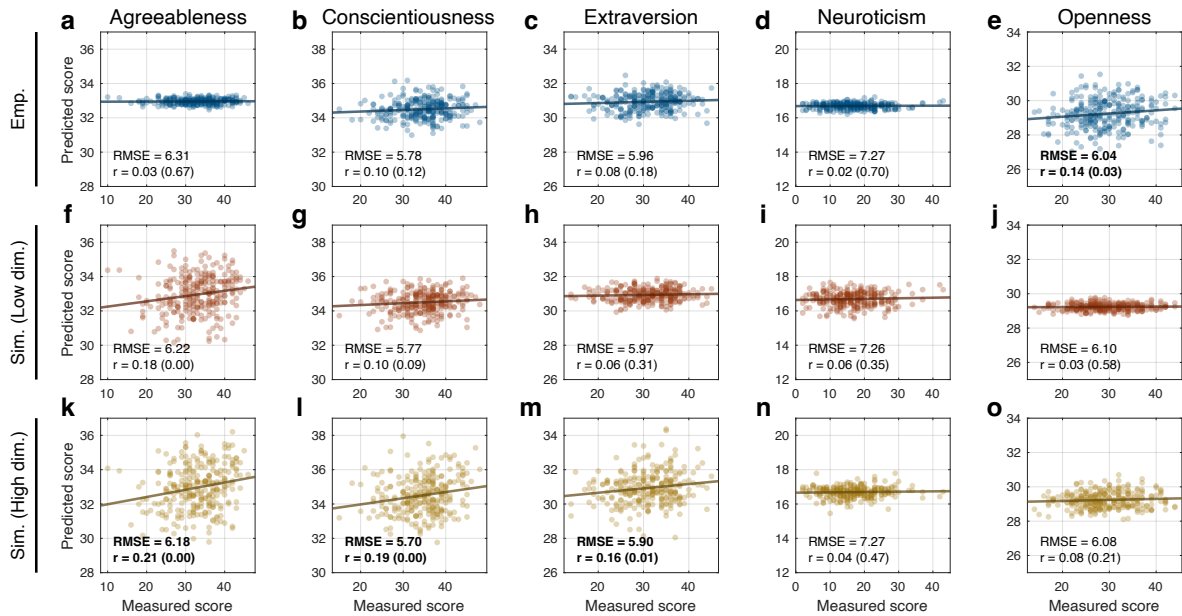


Figure S2. Linear regression analysis on each trait of the personality. (a-o) Scatter plots of predicted scores from linear regression against measured scores. Root-Mean-Squared-Error (RMSE) and Pearson's correlation coefficient r with its p -value are shown on each plot for each feature condition, respectively.

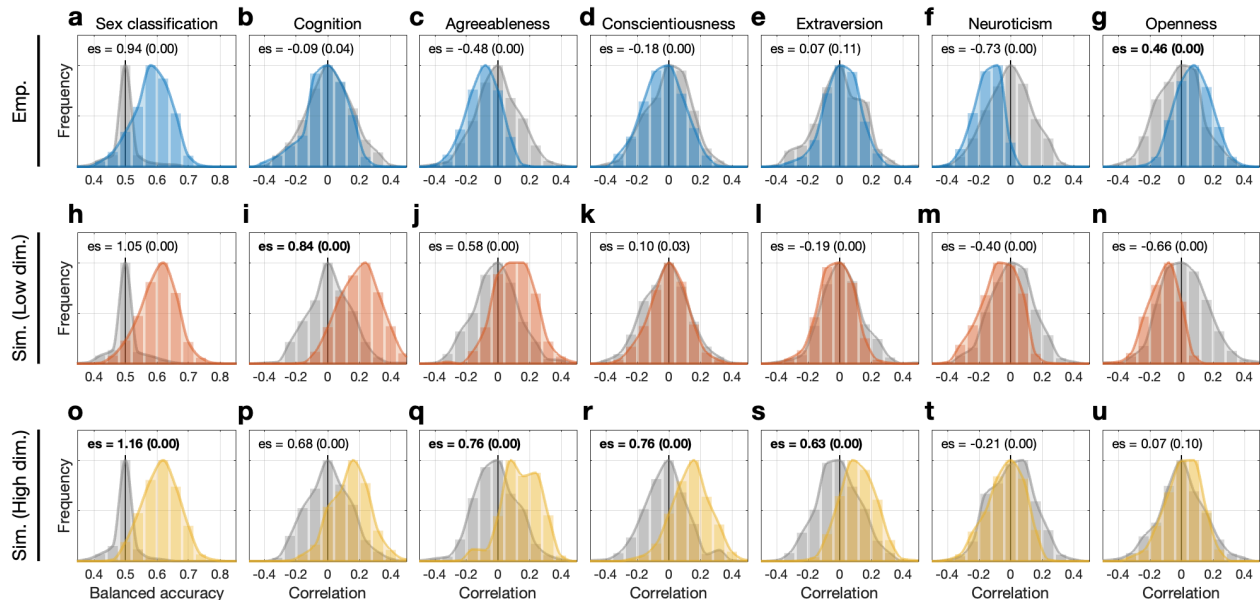


Figure S3. Comparison between permutation tests and prediction results. The null distributions of the permutation tests (gray histograms) were obtained by repeatedly randomly shuffling the target scores among subjects before the machine-learning prediction. The respective permutation tests were compared to the original prediction results (colored histograms) of the balanced accuracy for sex classification (leftmost column) and correlations for cognition and five personality traits for (a-g) empirical feature (Emp.), (h-n) simulated features (Sim.) for the low-dimensional (Low dim.) parameter optimization and (o-u) simulated features for the high-dimensional (High dim.) parameter optimization. Effect size (es) between permutation and prediction data is indicated in the plots together with its p -value in the parentheses. Bold font indicates the largest positive and significant effect size for a given target score.

Feature contributions to models based on coefficients of machine-learning models.

To examine the contributions of individual features to prediction, we can investigate coefficients of the regression models applied in this study. In the case of sex classification, the empirical features based on the Schaefer atlas appear to contribute more than that of the Harvard-Oxford atlas. On the other hand, when using simulated features, the Harvard-Oxford atlas seems to be the main contributor to performance [Fig. S4a–c]. Similarly, examining the distribution of models' coefficients for prediction of cognition reveals that, for empirical features, both positive and negative values are mixed, while the simulated features consistently show negative values. Moreover, the Schaefer atlas appears to be more prominently utilized in this case [Fig. S4d–f]. In a similar manner, the predictive models for personality traits can also be analyzed [Fig. S5]. A consistent observation is that models with better performance tend to have coefficient values concentrated either positively or negatively, whereas models with lower performance show coefficients more evenly mixed between positive and negative values. An interesting finding is that, even with the same analytical approach, the manner in which features contribute to prediction can vary depending on the atlas used. In addition, we can elucidate feature contributions to models that show good performance via estimating SHAP values. This metric allows us to interpret the best model how features contribute to the model.

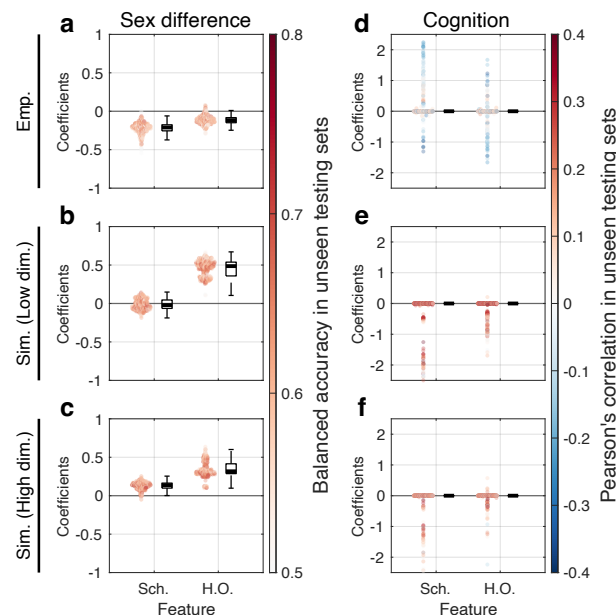


Figure S4. Distributions of the optimized regression coefficients in machine learning for sex classification and cognition prediction. (a-c) Coefficients of the trained models for sex classification. Each distribution reflects separate feature conditions of the two considered atlases indicated on the horizontal axes ('Sch.' for the Schaefer atlas and 'H.O.' for the Harvard-Oxford atlas) for empirical features (Emp.) and simulated features of the low- and high-dimensional parameter optimizations ('Sim. (Low dim.)' and 'Sim. (High dim.)'), respectively. The color gradients of the dots indicate the balanced accuracy obtained for the testing sets. **(d-f)** The same analysis for cognition prediction. The color gradients of the dots here indicate Pearson's correlation between the measured and predicted target scores in testing sets.

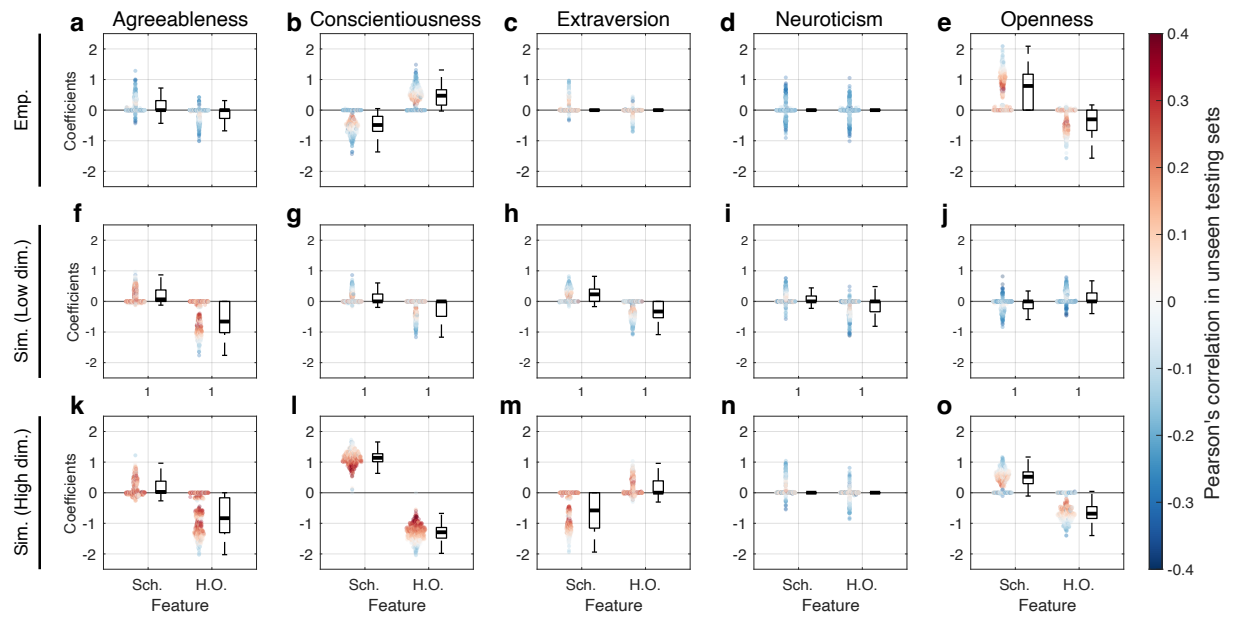


Figure S5. Distributions of optimized regression coefficients in machine learning for prediction of personality traits. (a-e) Coefficients of the trained models using empirical data for the five personality traits. Each distribution shows separate feature conditions of the two atlases. (f-j) The same analysis using simulated features of the low-dimensional parameter optimization. (k-o) The same analysis using simulated features of the high-dimensional parameter optimization. The color gradients of data indicate Pearson's correlation between measured and predicted scores in testing sets. Other notations are as in Figure S4.

8 Discussion

Dynamical whole-brain models offer a riskless and insightful experimental way to simulate and study distinct properties of human brain activity both on the group and single-subject level. In particular, modeling results can reveal hidden characteristics of brain dynamics that are inaccessible via in vivo measurements. The main ambition for conducting this research project was to leverage more of this potential for the analysis and possible understanding of inter-individual variability in the brain. Methods from the field of mathematical optimization here constitute the key ingredient to a proper fitting of the dynamical models to empirical data. However, the virtual lack of ground truth values for optimal model parameters necessitated a systematic evaluation of efficient search techniques for their approximation. This was done in study 1, where we extensively compared the performance of four derivative-free optimization methods (NMA, PSO, CMAES and BO) and put it in relation to the results of a thorough parameter space exploration on a dense grid of two and three model parameters. Our evaluation criteria included

- the observed GoF and its spread across repeated algorithm executions within subjects,
- the invested computational resources as well as
- the spread of the approximated model parameters across repeated executions and their respective distance to the putative optima extracted from the dense GS.

The solutions of the GS can serve as a good approximation of ground truth values. Provided that the grid is dense enough, there is a low risk of missing relevant optima. It turned out that CMAES delivered the most stable results while BO manifested the most efficient use of resources in the two- and three-dimensional model parameter spaces. Consequently, these approaches were most frequently recommended when we assessed the costs of all methods and the probability to reach the approximate result quality of a dense GS. In the three-dimensional setting, this was confidently achieved with around 5.6% (CMAES) and 1.1% (BO) of the computational resources. In sum, study 1 demonstrated how much time can be saved with optimization algorithms as compared to grid-based approaches. It highlighted CMAES and BO as promising tools for further applications involving higher-dimensional model fitting to neuroimaging data.

Exponentially increasing time demands for every new dimension added soon reflect unsurmountable challenges for a dense GS. That is why nearly no profound statements could be made about any model behavior and fitting procedure when the number of free parameters exceeded five or six, for example. In study 2, we therefore applied CMAES and BO to parameter optimization problems that included up to 103 free model parameters. While the search for optimal parameter values is not new in mathematical neuroscience, this step towards high-dimensional search spaces and the subsequent utilization of the results constituted the main novelties investigated in this research project. Study 2 here revealed an increased variability and reduced reliability of the parameters approximated via repeated random algorithm initializations within subjects. This was often manifested by relatively high spreads and reduced *intraclass correlation coefficients* (ICC) of test-retest reliability in the high-dimensional settings. The presence of several near-optimal points called for adequate solution selection strategies which we investigated by considering the *Frobenius norm* as an additional quality measure for the model fit and by applying a clustering approach as well as a *principal component analysis* (PCA) on the

obtained parameter sets. On the positive side, the study also demonstrated far more precise replications of the resting-state brain dynamics. These were reflected by significantly increased GoF values (up to +102%) that remained comparably stable across algorithm executions. The study could further shed light on possible relations to phenotypical data. Compared to the low-dimensional cases, somewhat higher classification accuracies for a subject's sex were observed when GoF (62%) or coupling parameter (57%) values found in the high-dimensional settings were considered as predictive features. While this accuracy by itself is not sufficient for a classification task, the result constituted a statistically significant increase in accuracy compared to the settings in low-dimensional parameter spaces. Altogether, study 2 helped assess the practical value of high-dimensional search spaces in whole-brain modeling and intensified differences between males and females in the simulation outcomes.

The observations related to phenotypical differences in study 2 prompted the design of study 3, where the results of parameter optimizations in both low- and high-dimensional search spaces were incorporated into a systematic workflow from raw MRI data to model-based predictions of phenotypical properties. In particular, we extended the pool of methods from study 2 and used the simulated connectome relationships as given by the GoF values not only to classify a subject's sex but also to predict reported scores of cognitive ability and personality traits. Here we compared the results with those using only empirical connectome relationships as given by the Pearson correlation coefficient between the matrices SC and eFC . It turned out that the prediction performance was significantly higher in most cases when the simulated data features were considered. While the observed correlations of almost 0.2 between true and approximated scores are not seminal as such, it must be noted that the empirical alternatives regularly failed in the prediction and centered around an accuracy of zero. The inclusion of only one simple quantity derived from model simulations therefore led to a considerable amelioration of the machine learning performance. Study 3 thereby highlighted important advantages of whole-brain modeling for the investigation of inter-individual variability.

All in all, this research project demonstrated the benefits of efficient parameter optimization strategies for the study of links between the brain and behavior of humans.

8.1 Whole-brain modeling and model selection

Our results fit well into the overall framework of personalized whole-brain modeling which comes along with a list of many benefits as well as some challenges with space for improvements ([Bansal et al., 2018](#)). In general, it may be seen as a drawback that the model fitting procedure is typically performed based on a specific scientific question with given objective function, which can hamper the generalizability of the results. However, the multitude of available models poses no restrictions whatsoever on the objective function, so that the models' adaptivity on given problems can conversely be seen as an advantage. In fact, the considered Pearson correlation coefficient between the matrices sFC and eFC describes just one possible way to assess the model output. While it is still a very popular measure that is used in the modern neuroscientific literature ([Bandyopadhyay et al., 2026](#); [Ma et al., 2026](#)), some researchers also add other optimization criteria and study their models with respect to graph-theoretical measures ([Goñi et al., 2014](#); [Stam et al., 2016](#); [Tewarie et al., 2014](#)), behavioral data ([Jung et al., 2023](#)), EEG power spectra ([Hartoyo et al., 2019](#); [Hashemi et al., 2018](#)) or properties of time-varying FC (*dynamic FC*, *dFC*) ([Hoheisel et al., 2025](#)), for example. This suggests that the models offer a great freedom for specialization in various domains.

Another critical point states that every model is a simplification of a complex phenomenon, and its output does not necessarily depict realistic brain activity. This can be reflected by comparably low correlation coefficients (< 0.2) between the matrices of *sFC* and *eFC* as sometimes seen in the low-dimensional model parameter spaces studied primarily in study 1, for example. Here we argue that the observed GoF does not always depend on the selected model, but can be heavily influenced by the underlying data preprocessing strategy ([Jung et al., 2021](#)) and parcellation scheme ([Domhof et al., 2021](#)). Even certain properties of empirical data variables such as the correlation coefficient between *SC* and *eFC* show a strong relationship with the obtained GoF ([Popovych et al., 2021](#)). Importantly, study 2 demonstrated how an increased dimension of the model parameter space can dramatically enhance the similarity between simulated and empirical data. Top correlations regularly exceeding 0.6 signify decent replications of subject-specific FC patterns in the human brain during the resting-state.

A critic may assert that models lack neurophysiological foundations and that their predictive capability can be limited. This was demonstrated by some low prediction accuracies in study 2 and 3, even for high-dimensional model parameter spaces. While we acknowledge this point, we must also see the bigger picture and evaluate what purely empirical approaches with a comparable number of predictive features offer in terms of accuracy. Applying the WW model (section 3.2.3), it has been shown that modeling results (here optimized parameter sets) can outperform the empirical connectomes of *SC* and *FC* in the prediction of cognitive clinical scores ([Zimmermann et al., 2018](#)). In study 2 and 3, we observed significantly increased accuracies when comparing simulated connectome relationships (GoF values) with empirical ones (correlation values between the matrices *SC* and *eFC*). Here, the former were derived from a phenomenological model. But, most importantly, we emphasize that it is by no means intended to present model simulations as rivals to empirical investigations. Both approaches deserve credit for their advantages and should not compete. On the contrary, as we stressed in all included studies, we regard the simulated connectome as an additional data modality in brain research. Its incorporation into neuroscientific analysis pipelines can enhance the performance and lead to benefits for both the empirical and simulated side of the coin. In accordance with that, recent envisionments of digital brain research in the future endorse the role of simulation models and highlight the translation of *digital twins* into clinical practice ([Amunts et al., 2024](#); [Hashemi et al., 2026](#); [Jirsa, 2025](#)).

We underline that computational models are sensitive to the underlying network structure and that they provide a plausible relationship between the brain anatomy and function ([Cabral et al., 2022](#); [Wein et al., 2021](#)). This is particularly useful since many brain abnormalities and disorders such as schizophrenia and autism may be a result of an altered connectivity between brain regions ([Bullmore & Sporns, 2012](#); [Karbowski, 2014](#)). Here, models allow for *in silico* experiments simulating brain lesions or regional resections by removing edges ([Aerts et al., 2016](#); [Alstott et al., 2009](#)) or nodes ([Hutchings et al., 2015](#); [Khambhati et al., 2016](#)), respectively, of the structural brain network ([Bansal et al., 2018](#)). This is often termed *virtual neurosurgery* ([Aerts et al., 2020](#); [Jirsa et al., 2023](#)).

As briefly mentioned when introducing the Kuramoto (section 3.3.1) and limit-cycle model (section 3.3.3), deliberate modifications to the SDEs impact the simulated brain activity and can be considered as effects of external brain stimulations ([Deco et al., 2019](#); [Gollo et al., 2017](#); [Schmidt et al., 2015](#)). Studying the effects of local perturbations on the

global dynamics is relevant for the investigation and potential treatment of diseases like attention deficit hyperactivity disorder, epilepsy and Parkinson's, for example ([Iravani et al., 2021](#); [Jirsa et al., 2017](#); [Muldoon et al., 2016](#); [Popovych & Tass, 2018](#)). The candidate regions for brain stimulation and surgery detected in a study on epilepsy using a neural population model (called *Epileptor model* ([Jirsa et al., 2014](#))) corresponded well with the regions that are typically considered in medicine as those evoking epileptic seizures ([Jirsa et al., 2023](#)). In this setting, the presence of interpretable model parameters can be vital for clinical considerations ([Woolrich & Stephan, 2013](#)) as they may reflect patterns not directly observable in empirical data. One such example is the capacity of the coupling parameter C in the Kuramoto model to predict a subject's sex above chance level as seen in study 2. Properties of this type may prove useful not only for studying inter-individual variability with links between the brain and behavior, but also for clinical applications with early disease detection. In this endeavor, researchers can either use their own implementation of specific models or resort to public platforms containing ready-to-use implementations of popular approaches for personalized simulations of multi-faceted brain activity. Examples are *The Virtual Brain* (TVB) ([Ritter et al., 2013](#); [Sanz-Leon et al., 2015](#)), the *Neural Simulation Tool* (NEST) ([Gewaltig et al., 2012](#)), *Dynamic Causal Modeling* (DCM) ([Friston et al., 2003](#)) and *CUDA-accelerated Brain Network Modeling* (cuBNM) ([Saber, Wan, et al., 2025](#)), with parts of the latter being developed in collaboration with the authors of the studies included in this thesis.

We worked with the Kuramoto model of coupled phase oscillators which shows a resemblance to a swarm model of interacting, self-propelled particles studied in an earlier career step ([Chepizhko et al., 2013](#); [Wischniewski, 2019](#)). As explained in section 3.3.1, the Kuramoto model constitutes one of the simplest approaches to simulate brain activity. It aims at the phenomenological reconstruction of oscillatory signal patterns. Here, the dynamical variable of interest is the region-specific phase $\theta_i, i \in \{1, \dots, N\}$, from which simulated BOLD signals are inferred, see subchapter 3.4. Unlike more biologically motivated neural population models, the Kuramoto model does not consider any properties like firing rates or action potentials. A more advanced, but still phenomenological approach is given by the limit-cycle model (section 3.3.3) which contains an additional time-dependent variable regulating the amplitude of oscillations. We selected the Kuramoto model, because its relative simplicity from a biological perspective allowed us to concentrate on the role of the mathematical parameter tuning and the impact of the dimension of the parameter space X on the simulated output. Our focus laid on the systematic comparison of optimization methods (study 1), for which an overly complicated brain model was not necessary. At the same time, it enabled us to control the degree of complexity and increase it effectively via the transition to high-dimensional search spaces (study 2). Independently, we do not reckon that our presented observations are highly model-specific. Deep biological details related to mechanistic explanations play an inferior role for powerful predictive outcomes ([Bansal et al., 2018](#)) since most models can provide similar results ([Ghosh et al., 2008](#)). Indeed, previous works have reported Kuramoto results similar to those of more advanced models ([Bhowmik & Shanahan, 2013](#); [Cocchi et al., 2016](#)). This was vividly demonstrated in two studies investigating the impact of brain parcellations on the model fitting to empirical data and related modalities ([Domhof et al., 2021](#); [Popovych et al., 2021](#)). One of them tested both the Kuramoto and limit-cycle model ([Popovych et al., 2021](#)). Besides the optic similarities of simulated and empirical connectome relationships in **Figs. 3A,E** and **4A,E** therein, especially **Fig. 5C** illustrates the high correlations between the GoF values obtained from both models throughout all tested parcellations (of which there were 11).

In the other one, **Fig. 6C** confirms the impression of high correlations also for a GoF comparison between the Kuramoto and the WC model (section 3.2.1) across 19 brain parcellations ([Domhof et al., 2021](#)).

We summarize that the essential aspects under consideration can equally be captured by the simpler Kuramoto model. No concrete recommendation for either the limit-cycle or WC model being an advanced phenomenological or biologically inspired neural population model, respectively, could be formulated. Thus, the application of the Kuramoto model is justified for our presented parameter optimizations maximizing the correspondence between simulated and empirical data in both low- and high-dimensional search spaces. The existence of recent studies ([Barnes et al., 2026](#); [Myrov et al., 2026](#); [Zhao et al., 2026](#)) that implement the Kuramoto model as a simple starting point for more sophisticated, hierarchical analyses supports this claim.

In general, we can say that mathematical whole-brain models have many useful properties as delineated above. We worked intensively with the Kuramoto model from which we inferred useful insights about the pros and cons of a transition to high-dimensional model parameter spaces. Naturally, a great extent of such new observations is derived from the presence of optimized parameters that increase the similarity between simulated and measured data. We however repeat that the purpose of our approach is not merely a blind replication of empirical signals to the highest achievable level. Instead, we aim at extracting a benefit from the simulations that facilitates the investigation of personalized brain activity. This can be an enhanced differentiability between subjects based on a model parameter even without immediate biological equivalent, cf. the potential of the coupling strength C in study 2, for instance.

Before formulating an outlook on future directions in model-based brain research, we reflect on some of the mathematical aspects that played a critical, technical role in this research project.

8.2 Role of numerical solver

When evaluating the utility of any dynamical whole-brain model, it must be kept in mind that the simulated output reflects a numerical approximation of the (generally) unknown solutions of the model SDEs. This means that the question of how “good” a given modeling approach and its output will be, cannot be answered conclusively when looking at the model only. On the contrary, before starting any simulations, it is crucial to reflect on how closely the observed solution can approximate the exact one. The selection of an adequate numerical solver therefore plays a role of utmost importance when researchers aim to model specific aspects of human brain activity.

We applied the stochastic generalization of the Heun method (Eq. (48)) to approximate the solutions of the Kuramoto SDEs (see section 3.3.2 for the complete problem formulation). For general SDEs, it has the same order of strong and weak convergence ($\beta = \gamma = 1$) as the Milstein method (Eq. (47)) but is slightly cheaper from the implementational perspective.

The construction of methods of higher order has proven cumbersome due to several reasons. First, such methods often require the evaluation of derivatives of the coefficients f and g present in the SDE (Eq. (8)-(11)), cf. $\frac{\partial}{\partial x} g$ in the Milstein method (Eq. (47)). This constitutes an additional computational burden since the derivatives must be implemented on top of the coefficients f and g for every SDE. Naturally, it is possible to avoid the derivatives and approximate them via finite differences, involving more function evaluations instead. This leads to *Runge-Kutta* type methods for SDEs ([Burrage](#)

et al., 2004; Kloeden & Platen, 1993). However, Rümelin showed that the order of such schemes cannot be increased arbitrarily if the noise increments ΔW_t are to be the only random variables included in the update rules (Kloeden & Platen, 1993; Rümelin, 1982). The information extracted from the increments is not sufficient to guarantee very accurate approximations to the solution of an SDE. Accordingly, the stochastic generalization of the Heun method (Eq. (48)), which is derivative-free, cannot reach order 2 as in the deterministic setting, but is bounded to $\beta = \gamma = 1$ (Kloeden, 2011; Mannella, 2025; McShane, 1974). That is why additional and potentially more complicated random variables would have to be included (Kloeden & Platen, 1993).

Second, a continuation of the Taylor-like expansion (section 2.3.2) leads to a plenitude of (stochastic) multi-integrals, whose evaluation may be problematic. During the derivation of the Milstein method (Eq. (47)), we have already seen triple-integrals, which would grow to quadruple-integrals in the subsequent step of the expansion and so on. No general formulas are known for computing such integrals. This applies to Itô and Stratonovich integrals alike. We demonstrated the derivation of the Milstein method suited for Itô SDEs, whereas other methods may be derived from performing related expansions in the Stratonovich sense (Burrage et al., 2004; Kloeden, 2011). In order to apply a Stratonovich method to an Itô SDE with multiplicative noise, the drift f would have to be modified as presented in Eq. (25) (Arnold, 1974; Rümelin, 1982). The stochastic Heun method is one of those methods (Rümelin, 1982).

Third, an approximation of the multi-integrals via (moderately complicated) random variables, as done during the design of schemes prioritizing the weak order, may be overly simplistic (Burrage et al., 2004; Higham, 2001; Kloeden & Platen, 1993). The *weak Euler method*, for instance, has been designed as follows: Instead of working with a normally distributed random variable $\Delta W_t \sim \mathcal{N}_{0,\Delta t}$ in the update rule of the EM method (Eq. (40)), the much simpler variable $\Delta \widetilde{W}_t$ satisfying

$$\mathbf{P}(\Delta \widetilde{W}_t = \pm \sqrt{\Delta t}) = \frac{1}{2}$$

is used. This corresponds to $\eta_{t_k} = \pm 1$ with equal probability in Eq. (40). It fulfills

$$\begin{aligned} \mathbb{E}[\Delta \widetilde{W}_t] &= \mathbf{P}(\Delta \widetilde{W}_t = \sqrt{\Delta t}) \sqrt{\Delta t} + \mathbf{P}(\Delta \widetilde{W}_t = -\sqrt{\Delta t}) (-\sqrt{\Delta t}) \\ &= \frac{1}{2} \sqrt{\Delta t} - \frac{1}{2} \sqrt{\Delta t} = 0 = \mathbb{E}[\Delta W_t], \\ \mathbb{E}[\Delta \widetilde{W}_t^2] &= \frac{1}{2} \Delta t + \frac{1}{2} \Delta t = \Delta t \\ \Rightarrow \text{Var}(\Delta \widetilde{W}_t) &= \mathbb{E}[\Delta \widetilde{W}_t^2] - (\mathbb{E}[\Delta \widetilde{W}_t])^2 = \Delta t - 0 = \Delta t = \text{Var}(\Delta W_t) \end{aligned}$$

and ensures the same order of weak convergence as the EM method ($\beta = 1$), but it offers no strong convergence anymore (Higham, 2001). This problem can transfer to methods offering a higher weak order, which are therefore unsuited for cases where strong solutions, or solution paths, are needed.

Based on experimental integration tests and the observed interplay between numerical and stochastic inaccuracies, some authors have voiced doubts about the practical utility of higher order methods for SDEs. This pertains in particular to those approaches originating from generalizations of better deterministic schemes. The use of the methods we explained so far (EM, Milstein and Heun, see section 2.3.2) has therefore been

advocated ([Fahrmeir, 1976](#); [Kloeden, 2011](#); [Mannella, 2002](#); [Mannella, 2025](#)). However, this does not mean that higher order methods are not worth considering depending on a given SDE and research question. The interested reader is referred to the provided works ([Burrage et al., 2004](#); [Kloeden & Platen, 1992](#); [Kloeden & Platen, 1993](#); [Platen, 1999](#)) and the references therein for a thorough collection of numerical methods with low/high weak/strong order, including those from categories that we did not address here such as implicit and multi-step methods. Many approaches simplify considerably in case of additive noise (cf. the correspondence between the EM (Eq. (40)) and Milstein method (Eq. (47)) discussed in section 2.3.2).

In the studies presented in this thesis, we first model the trajectories of individual oscillators reflecting the activity of brain regions. Subsequently, we compute their pairwise Pearson correlation coefficients, which is a summarizing measure. This procedure aligns with the ideas of both strong and weak convergence (section 2.3.1). Further, the noise perturbation in our models is always additive, so that Itô and Stratonovich solutions coincide. Applying the stochastic adaptation of the well-known Heun method thus appeared reasonable. It provides an advantageous tradeoff between implementational complexity and convergence order in strong and weak sense ($\beta = \gamma = 1$). Moreover, it outperforms the Euler and therefore Milstein method in deterministic computations where the parameter of noise amplitude $g(t, x) \equiv \sigma$ is set to zero in the models.

8.3 Some aspects about algorithm convergence

We applied a series of optimization algorithms to approximate the model parameters that maximize the correspondence between simulated and empirical data. This similarity was mainly assessed via the Pearson correlation coefficient between the matrices of *sFC* and *eFC* (studies 1-3), but we also considered the Frobenius norm of the matrix difference as an additional quality measure (study 2). The fact that none of the presented algorithms (NMA, PSO, CMAES, BO) can guarantee convergence to a global optimum (if it exists at all) in a tractable amount of time and *F*-evaluations, rendered several repeated executions with different initial conditions necessary. We began with low-dimensional ($\text{Dim} \in \{2, 3\}$) model parameter spaces, for which we intensively compared the algorithm output with the results of a dense GS (study 1). Although a full elimination of any uncertainty was not possible, the systematic comparison with the GS allowed us to confidently estimate the presence and location of optima as well as the algorithms' capability to approximate them. With the gained experience, we applied the two most reliable methods (CMAES, BO) to optimization problems in high-dimensional ($\text{Dim} \in \{99, 103\}$) model parameter spaces, where no ground truth values could be approximated any longer. Here we could infer that the provided methods, together with a state-of-the-art computational infrastructure, allow us to overcome the immense time demands and related practical unfeasibility of a thorough parameter search on a dense grid. Although drawing neuroscientific conclusions as to why we observe certain phenomena in simulated data does not always appertain to us, we provided insightful mathematical tools that can reveal hidden dynamics and previously unknown data patterns, whose inclusion will be vital for future investigations of brain activity. The inspection of the algorithms' convergence properties is crucial here, since all derived statements rest on the parameter and objective function values approximated by the performed iterative optimization procedures. Too early terminations or a frequent convergence to local optima pose risks that ought to be minimized, particularly in cases where no reference values for comparison are available.

All simulations were performed on supercomputing clusters at Forschungszentrum Jülich. In study 1, one computation node of the cluster JURECA ([Krause & Thörnig, 2018](#)) featured two processors (CPUs) with 12 cores each. Every core supported two hardware threads, so that one computation node eventually offered $2 \times 12 \times 2 = 48$ threads for simultaneous computations. For the experiments in study 2, the technically upgraded cluster JURECA-DC ([Jülich-Supercomputing-Centre, 2021](#)) could be used. Here, one computation node contained two processors (CPUs) with 64 cores each, and two hardware threads per core. One computation node thus offered $2 \times 64 \times 2 = 256$ threads for simultaneous computations.

We investigated all methods with respect to the occurrence of a saturation of the objective function values depending on the executed iterations. NMA has the advantage that it offers several options for the updates of candidate solutions during the optimization procedure. Its ability to flip, shrink and expand the current simplex enables it to adapt its search procedure to the observed shape characteristics of the objective function. Also the fact that it requires at most $\text{Dim} + 1$ F -evaluations per iteration can be beneficial in low-dimensional parameter spaces. However, as a local, deterministic search method, it is susceptible to local optima, and its efficiency reduces with increasing dimension of the search space ([Hicken et al., 2012](#); [Rios & Sahinidis, 2012](#)). False convergence has already been reported for a four-dimensional optimization problem in the algorithm's introductory work ([Nelder & Mead, 1965](#)). Our tests performed in two- and three-dimensional model parameter spaces (study 1) showed a tendency to converge to local optima as well. In fact, it has been proven that, under certain conditions for the initial simplex, NMA converges to a non-optimal solution even for a convex and twice differentiable objective function ([McKinnon, 1998](#); [Rios & Sahinidis, 2012](#)). That is one reason why we did not consider this method for the high-dimensional optimization problems in study 2 (and 3). Under the configuration applied in study 1, one isolated execution of NMA took on average 1.5 hours (h) and 2.5 h for $\text{Dim} = 2$ and $\text{Dim} = 3$, respectively. These runs were parallelizable, so that one effectively consumed less than 2% of the core-h (number of cores per node $\times$ wall time in h) required for the GS in the two-dimensional (40 core-h, 100 minutes, $48 \times 64 = 3072$ F -evaluations) and three-dimensional (1200 core-h, 50 h, $22 \times 48 \times 81 = 85536$ F -evaluations) cases. Formally, the stopping criterion of 80 iterations corresponded to $80(\text{Dim} + 1) \in \{240, 320\}$ F -evaluations per run. However, the actual number of performed objective function evaluations was far lower since, first, not all $\text{Dim} + 1$ candidate solutions must be updated in every step (only the worst, mainly) and second, the simplex shrank to a small size terminating the optimization before 80 iterations in most cases.

Swarm approaches like PSO pursue a different search and updating strategy. Here, PSO is superior to NMA in the sense that it has a lower risk of premature convergence to local optima. The considered candidate solutions are distributed over the search space throughout the iterations and enable a global search with the ability to escape suboptimal solutions. In alignment with that, we consistently observed better results for PSO than NMA in the tests performed in study 1, particularly for the criteria considering the location and spread of candidate solutions. Nevertheless, a relatively big swarm size appears to be one determinant factor for stable results. This means that more F -evaluations are required to enable a powerful exchange of information between the particles and make the heuristic search for optima effective. More than 30 years after its introduction, the study of the algorithm's theoretical convergence properties is still an active topic ([Huang et al., 2023](#); [Tarekegn Nigatu et al., 2024](#)), while a generally valid proof

cannot be provided, as for most heuristic, non-deterministic methods. We observed that one execution of PSO with $\lambda = 60$ particles per iteration took slightly less than 4 h on average, regardless of the considered parameter space. This corresponds to around 231% and 8% of the core-h invested in a GS for $\text{Dim} = 2$ and $\text{Dim} = 3$, respectively. In approximatively 89% of the tested scenarios, 80 iterations resulting in $60 \times 80 = 4800$ F -evaluations were needed until a saturation of the function values set in.

The fact that every F -evaluation demands an expensive simulation of the time series of phases in the tested model, rendered methods from the field of kriging, and particularly the related BO attractive. For this method, which was designed with the aim to reduce the number of costly F -evaluations, we observed a far more efficient use of computational resources combined with relatively stable results for $\text{Dim} \in \{2,3\}$. Similar as for NMA, one isolated BO execution took roughly 1.5 h and 2.5 h for $\text{Dim} = 2$ and $\text{Dim} = 3$, respectively. The relative amount of required resources in comparison to a dense GS also corresponded to that reported for NMA. BO however turned out as less susceptible to local optima than NMA, which was manifested by lower cost values assigned to BO when investigating the location of the approximated optimal model parameters in study 1. Finally, computing up to 10 initial samples followed by 80 iteration steps corresponded to 90 F -evaluations per run. We also applied BO to the high-dimensional problems considered in study 2. Here, more F -evaluations (230 initial samples followed by 200 consecutive iterations) were needed to ensure a saturation of the function values. Generally valid statements about convergence of the method to a global optimum are still under investigation, though ([Bull, 2011](#)). The repeated incorporation of new F -values into the updated surrogate model for F let the computation time surge to around 20 h per run. In fact, reduced performance speed in high-dimensional parameter spaces as well as the invariably sequential, i.e., non-parallelizable evaluation of samples throughout the optimization have been listed as weaknesses of BO which is best suited for problems with $\text{Dim} \leq 20$ variables ([Brochu et al., 2010](#); [Frazier, 2018](#)). Fortunately, we could parallelize 80 to 120 separate algorithm executions, so that the computational burden remained tractable. (Theoretically, 256 parallel algorithm runs would be possible on the utilized computational cluster ([Jülich-Supercomputing-Centre, 2021](#)), but the parallelization overhead let the execution time approach the admissible limit of 24 h per job on the cluster in some cases.)

Seen across all experiments in study 1 and 2, CMAES emerged as the most recommendable optimization method tested in this project. It features useful invariance properties (against, e.g., monotonic and angle-preserving transformations of the objective function and search space, respectively) and shares the benefits of a global, swarm-like exploration of the parameter space ([Hansen, 2016](#); [Hansen et al., 2009](#)). The updates are designed with the aim to increase the probability of previously successful steps. To this end, the mean vector and covariance matrix of the search distribution are adapted based on F -evaluations, so that, ideally, the search distribution approximates the contour lines of the objective function ([Hansen, 2016](#)). A multivariate normal distribution is considered as underlying probability distribution. The normal distribution offers the largest entropy, i.e., uncertainty in the realizations across all continuous probability distributions with specified variance ([Cover & Thomas, 2005](#)), which renders it particularly useful for global explorations of (high-dimensional) parameter spaces ([Hansen, 2016](#)). The issue that we may raise about this algorithm is that, like for the other heuristic methods considered, a rigorous convergence proof is missing, and most assertions in this direction originate from empirical experiments only ([Hansen, 2006](#); [Hansen & Ostermeier, 1997](#)). The reported costs to adapt to the topography of a given objective function range between

$\mathcal{O}(\text{Dim})$ and $\mathcal{O}(\text{Dim}^2)$ in the associated literature ([Hansen, 2016](#); [Hansen et al., 2003](#); [Hansen et al., 2009](#)). In the tests performed in study 1, one isolated execution of CMAES with $\Lambda = 24$ candidate solutions per iteration lasted for slightly less than 2 h on average, regardless of the dimension of the parameter space. The cluster configuration available at that time allowed for a parallelization of two such runs, so that the required core-h corresponded to approximately 56% of the resources consumed by a dense GS for $\text{Dim} = 2$. This fraction plummeted to around 2% for $\text{Dim} = 3$. In around 76% of the executions we performed for $\text{Dim} \in \{2,3\}$, 80 iterations resulting in $24 \times 80 = 1920$ F -evaluations were necessary to observe a saturation of the objective function values. This corresponded to 40% of the F -evaluations made for PSO, where more candidates ($\Lambda = 60$) were sampled per iteration. The high-dimensional scenarios considered in study 2 enforced an increase of the performed iterations (150 instead of 80), so that in most cases $24 \times 150 = 3600$ F -evaluations were made per execution, lasting for 3.5 h on average.

Other methods that we did not include, but might also perform well in our tested scenarios, are the algorithm of *Simulated Annealing* (SA) ([Kirkpatrick et al., 1983](#)) and the software package *Stable Noisy Optimization by Branch and Fit* (SNOBFIT) ([Huyer & Neumaier, 2008](#)). A theoretical convergence statement can be derived for the former, albeit for unpractically many iteration steps. The latter is particularly suited for noisy optimization problems but comes along with a relatively expensive optimization procedure independent of the considered objective function.

We summarize that no single algorithm is perfect for all problems. In study 1, where ground truth values could be approximated up to a certain degree, CMAES and BO turned out as the most recommendable options. The transition to high-dimensional cases (study 2) was less of an issue for CMAES than for BO, so that the former could be considered as the most effective method we tested. In alignment with that, CMAES has been incorporated into the whole-brain modeling and parameter optimization package cuBNM ([Saber, Wan, et al., 2025](#)), a joint project involving some of the authors of the studies presented in this thesis.

8.4 Future paths for handling parameter variability

The previous subchapter provides a documentation of the convergence behavior observed when applying the considered optimization algorithms to the whole-brain model fitting to empirical data. Here, in turn, we extend the preceding discussion and address the issue that finding a heuristic method converge to a certain solution in the search space, does not necessarily imply that this solution is optimal. While we can be relatively confident about the optimality of solutions in study 1, where a dense GS served as a benchmark, the parameter variability frequently observed across repeated algorithm executions in high-dimensional search spaces in study 2 deserves further attention. Indeed, the lack of reference values of the objective function F renders it hard to say whether one global optimum exists and whether it has been found by the algorithms. The presence of several solutions that are objectively equally valid has already been reported in the field of whole-brain modeling ([Irsa et al., 2023](#)). However, this phenomenon can originate from an intrinsic property of the model, the applied numerical solver or the tested optimization algorithm, which all influence the observed F -values. It must be kept in mind that a numerical integration scheme is used to solve the model SDEs, whose output is fed into the optimization method. This means that several factors contribute to the observed result.

As a first step, improving the accuracy of the numerical solution by applying, for instance, an SDE solver of higher order could lead to better results in the optimization problem. This strategy might diminish the risk of errors during the transition from the theoretical model equations to the practical application of optimization methods. Second, the impact of noisy F -evaluations on the fitting procedure should be investigated and reduced where possible. Averaging multiple F -values obtained for repeated evaluations with the same input arguments is a valid technique here. In fact, we tested this approach for NMA in the initial stage of the project but abandoned it for the sake of more algorithm executions with different initial data, which turned out to consume fewer computational resources. Other variants however keep the additional computational costs low thanks to an adaptive averaging approach, where the noise impact is assessed, and users control the fraction of F -values considered for reevaluation and subsequent averaging ([Hansen et al., 2009](#)). This strategy of handling noise-induced uncertainty was demonstrated to prevent premature convergence of CMAES and could potentially support the interpretation of our observations of several near-optimal solutions. Together with an increased number Λ of candidate solutions per iteration, which is referred to as *implicit averaging* ([Hansen et al., 2009](#); [Jin & Branke, 2005](#)) and has been applied in a related work ([Saber, Wischniewski, et al., 2025](#)), this could lead to less variation in the optimized model parameters. Lastly, the consideration of additional criteria like the Frobenius norm as suggested in study 2 can offer a way to select one solution from a pool of candidates showing little variation for the primary objective function.

Here we stress that our experiments were carefully designed and calibrated to the challenges of model fitting. In fact, we worked with larger population sizes in CMAES than considered necessary ([Hansen, 2016](#)) and applied a numerical method that outperforms the standard EM ([Acebrón et al., 2005](#)). The mentioned technical suggestions provide additional means to reduce the risk of misinterpretations due to possible inaccuracies from the numerical and optimization side. Thus, we conclude that the presence of multiple near-optimal solutions for the correspondence between simulated and empirical data may indeed relate to a certain extent to the principles of neural redundancy, meaning that several configurations lead to the same or comparable output in the model ([Hennig et al., 2018](#); [Mizusaki & O'Donnell, 2021](#)). The similar GoF values observed across repeated algorithm executions in combination with the high ICC scores for GoF support this claim. Extending the performed PCA and clustering analyses may show that the space dimension of the optimized model parameters is lower than Dim, the total number of considered parameters. So, the existence of a subject-specific, lower-dimensional subspace containing the parameters deemed approximately optimal, as postulated in study 2, remains a plausible conjecture. Future studies that investigate ways to prove and parameterize it will be very valuable for the personalized modeling of human brain activity and the effect of inter-individual differences.

For now, we have seen that the inclusion of simulated data can have a positive impact on the predictive power of machine learning approaches (study 2 and 3). This pertains in particular to the features extracted from the high-dimensional model fitting. While the prediction accuracy as such is not high and the insights derived from most model parameters are currently limited by the observed variability within subjects, the GoF values as well as the optimized coupling parameter values C already led to significant accuracy enhancements in comparison to the low-dimensional cases. It remains to be investigated whether the available data allow for precise predictions at all or whether the encoded information is limited to target-specific trends or patterns that can yield only

modest improvements over chance level. We stress that the described settings refer to scenarios where one single quantity is used as a predictor for a given target such as a subject's sex, for instance. Here, the utilized data should mainly be considered a useful complement to current approaches based on empirical neuroimaging data. However, following the presented suggestions for handling parameter variability, all parameters can potentially be considered as input for predictive approaches. When inserting the simulation output as features into a predictive model, a proper feature selection strategy and a possible regularization will be vital to extract the components that lead to robust results. From the perspective of whole-brain simulations, the optimized model parameters (including GoF) can then be regarded as an individual's personal profile. Recent developments from mathematics ameliorate state-of-the-art techniques and render methods such as support vector machines for classification more powerful, see also ([Jarre, 2026](#)). One idea might be to test whether such concepts enable a clearer differentiation between brain health and disease based on model parameters optimized on a personal level. We believe that together with the required neuroscientific expertise, modeling results can be meaningfully integrated into analysis pipelines paving the way towards a better understanding of human brain activity both on the group and subject level.

8.5 Conclusion

The results of the presented studies demonstrate the benefit of efficient model parameter optimization strategies for personalized simulations of human brain activity. Unlike in grid-based approaches, the computational resources required by the considered derivative-free optimization algorithms remain tractable for increasing numbers of parameters for optimization. The tested methods thus allow for model fitting procedures in high-dimensional search spaces featuring around 100 free parameters. Comparing several algorithms, the present work highlights their distinct strengths during the effective maximization of the correspondence between simulated and empirical data which reflect the structural and functional brain organization. Focus is put on the transition from low- to high-dimensional model parameter spaces and the resulting implications for model-based predictions of phenotypical data. Here, the included studies offer methodological recommendations for analyzing the algorithm output and applying it to the estimation of inter-individual variability expressed by a subject's sex, cognitive scores and character traits. Future studies may extend the findings of the presented work by designing new research pipelines that incorporate both simulated and empirical data into the prediction workflow. Establishing links between optimized model parameters and a subject's brain activity can likely be a determinant factor for early disease detection and the study of the interplay between an individual's brain and behavior.

9 References

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