Validation of dynamical whole-brain models in high-dimensional parameter spaces

Kevin J. Wischnewski[1,2,3], Simon B. Eickhoff[1,2], & Oleksandr V. Popovych[1,2]

[1]Institute of Neuroscience and Medicine (INM-7: Brain and Behaviour), Research Centre Jülich, Jülich, Germany;
[2]Institute of Systems Neuroscience, Heinrich Heine University Düsseldorf, Düsseldorf, Germany;
[3]Institute of Mathematics, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

Email: k.wischnewski@fz-juelich.de **Website:** www.fz-juelich.de/inm/inm-7

OHBM 2023
Poster 559

Introduction

- The link between resting-state brain dynamics and structural brain data can be investigated via mathematical **whole-brain models**, which describe a subject's brain activity by **interpretable model parameters** and **simulated functional connectivity**.
- However, computational **challenges in parameter optimization** constrain high-dimensional model studies and their level of **model personalization**.
- We apply 2 **mathematical optimization algorithms** to explore high-dimensional parameter spaces at moderate computational costs, and validate **whole-brain models** by optimizing between 2 and 103 free model parameters simultaneously.

➢ Aim: To gain an insight into the model validation in high-dimensional parameter spaces and its potential utility for **personalized simulations** of human brain dynamics.

Methods

- **272 subjects** (Human Connectome Project [1]) with **individual** empirical **structural** and **functional connectivity** (eSC and eFC, resp.)
- **Brain atlases:** Schaefer 100 (Sch100) [2] and Harvard-Oxford 0% (HO0Thr) [3] atlases with $N = 100$ and $N = 96$ cortical regions, resp.
- **Computational model:** Kuramoto model [4] of coupled phase oscillators
- Phase dynamics of brain region $i \in \{1, \ldots, N\}$:

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

➡ **simulated BOLD signals** ➡ **simulated FC** (sFC)

Model variables	Description	Model variables	Description
$\theta_i(t)$	Phase of region i at time t	$\tau_{ij} = \frac{PL_{ij}}{< PL >}\tau$	Coupling delay (signal transmission time) between region i and j
f_i	**Free parameter** of natural frequency ($0.01 - 0.1$ Hz) of region i	PL_{ij}	Average fiber path length between region i and j
C	**Free parameter** of global coupling strength	τ	**Free parameter** of global delay
$k_{ij} = \frac{SC_{ij}}{< SC >}$	Relative coupling strength between region i and j	σ	**Free parameter** of noise intensity
SC_{ij}	Number of streamlines between region i and j in the eSC matrix	$\eta_i(t)$	Independent noise perturbation of region i at time t
$< . >$	Averaging operator	$\sin(\theta_i)$	Simulated BOLD signal of region i

Model validation:
Pearson Correlation (sFC,eFC) ❯ *MAXIMIZATION*

Detecting optimal, subject-specific model parameters:

- C and τ free, $\sigma = 0.3$ fixed, f_i from empirical BOLD: **2D**
- C, τ and σ free, f_i from empirical BOLD: **3D**
- C, τ, σ and f_i free: **103D (Sch100) / 99D (HO0Thr)**

Optimization methods:

Covariance Matrix Adaptation Evolution Strategy (CMAES) [5]: Global population-based optimization technique, best trial solutions from every iteration (generation) are selected to form the distribution mean of the population for the next step

Bayesian Optimization (BO) [6]: Sequential design strategy for global optimizations of black-box functions, probabilistic surrogate model for the goal function, adjusted after every new function evaluation

Results

Fig.1: Goodness-of-fit for personalized model simulations

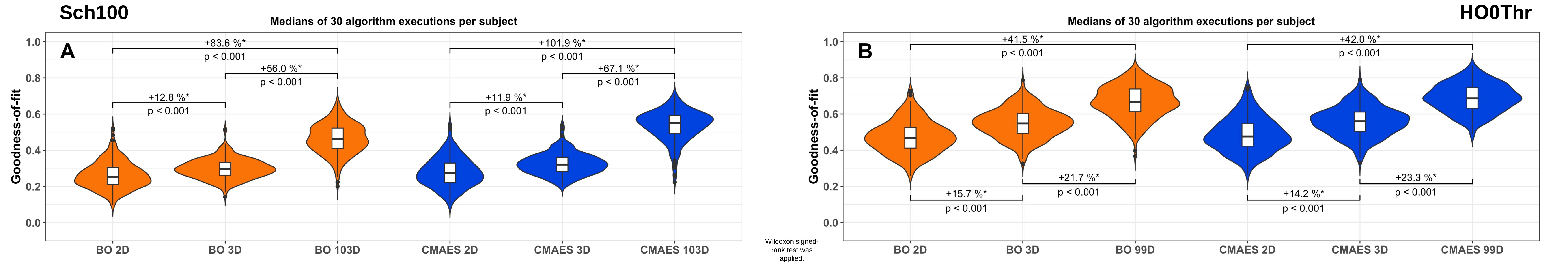


Fig.2: Mean resource consumption per subject for 30 algorithm executions

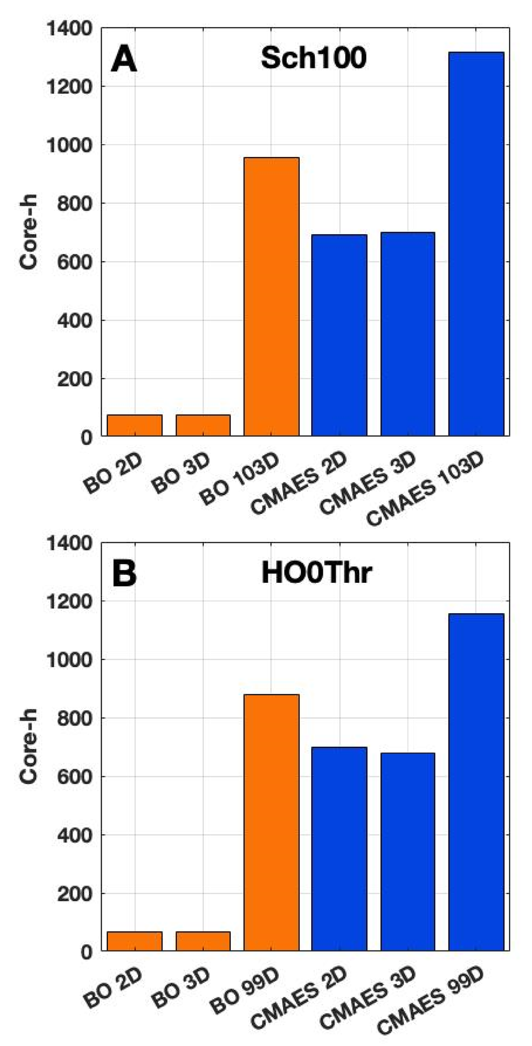


Fig.3: Example of high-dimensional simulation outcomes for one subject

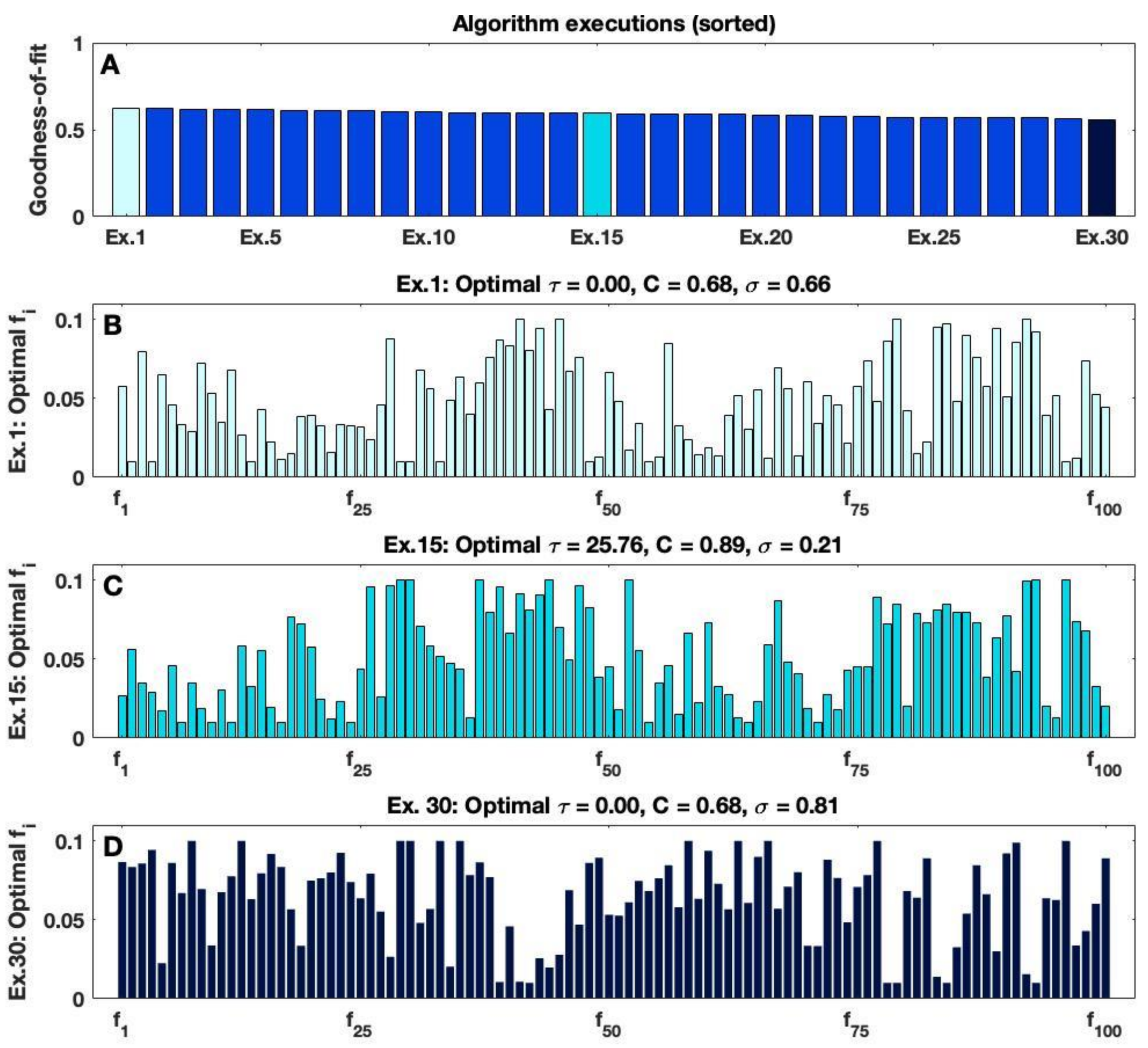
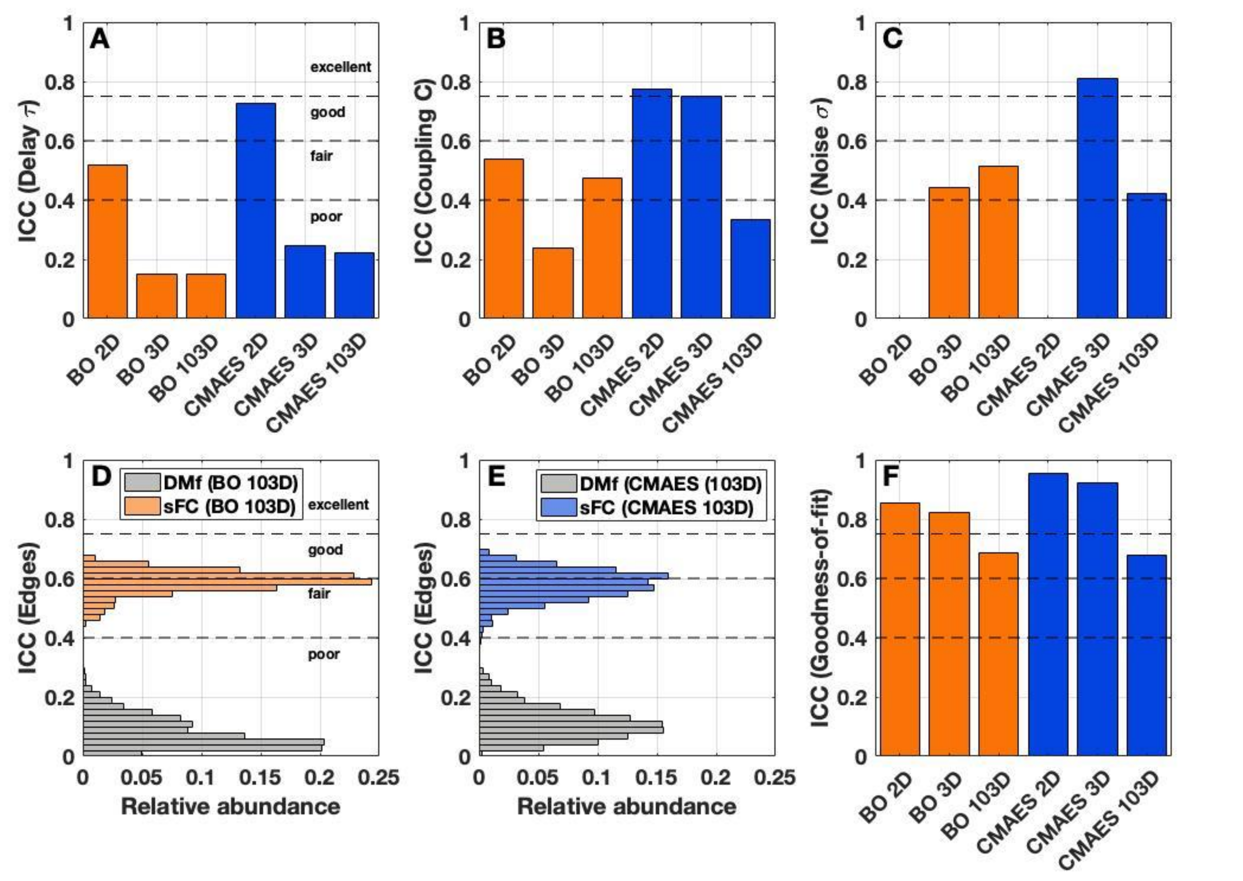


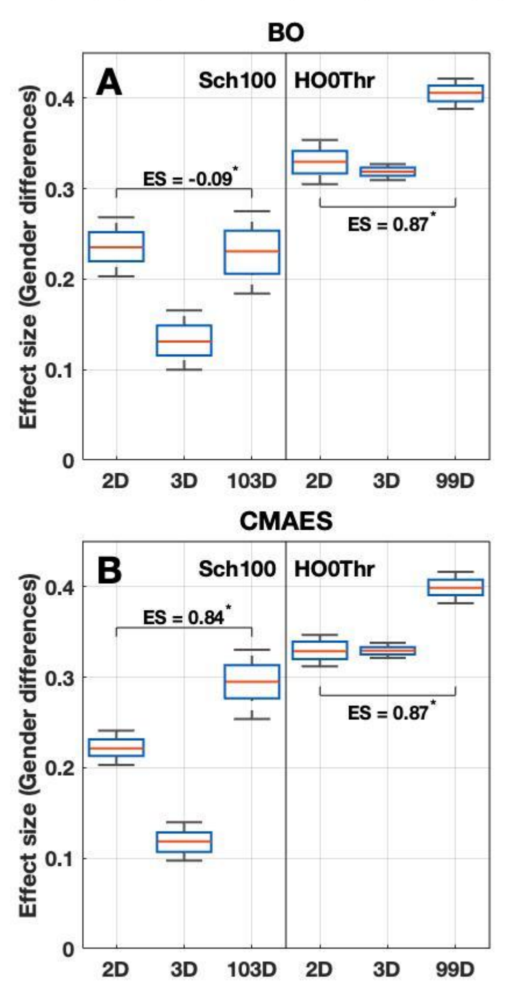
Fig.4: Reliability of modeling results across repeated algorithm executions (Sch100)



Reliability assessed via intraclass correlation (**ICC**, [7]):
Between-subject variance relative to total variance (between and within subjects).

DMf: Matrix of differences in optimized frequency parameters f_i ($\text{DMf}_{ij} = |f_i - f_j|$).

Fig.5: Higher goodness-of-fit for males than for females



128 males and 144 females. Effect sizes computed with Rosenthal's formula [8] for Wilcoxon rank-sum test.

Discussion

Summary:

- Empirical measurements can be replicated best by models validated in high-dimensional parameter spaces.
- A high goodness-of-fit (GoF) can be obtained for **several configurations of "optimal" model parameters**, which are less reliable than the observed sFC and GoF.
- **Differences between males and females** appear to be **more pronounced** when the model validation is performed in high-dimensional parameter spaces.

Conclusions:

- New horizons for personalized brain modeling can be opened up by mathematical **optimization algorithms** which **enable the exploration of whole-brain models in high-dimensional parameter spaces**.
- Multiple algorithm executions per subject are necessary in view of the complexity of high-dimensional parameter spaces and the unfeasibility of a confirmatory grid search.

Outlook:

- Whole-brain models properly validated bear a huge potential for **more precise and personalized studies**.
- The model validation in high-dimensional parameter spaces can potentially contribute to the exploration of phenotypical differences in brain research.
- Models that closely replicate empirical brain imaging data may serve as a **risk-free test bench for medical interventions**.

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Acknowledgements: This study was supported by the Helmholtz Portfolio Theme "Supercomputing and Modeling for the Human Brain" and the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 785907 (HBP SGA2), 945539 (HBP SGA3) and 826421 (VirtualBrainCloud). The authors gratefully acknowledge the computing time granted through JARA on the supercomputer JURECA at Forschungszentrum Jülich.