

# Hodgkin-Huxley Sensitivity Analysis with Arbor

## Reproducing Torres Valderrama et al. 2015: Uncertainty Propagation in Nerve Impulses Through the Action Potential Mechanism

Sebastian Schmitt (University of Göttingen), Nora Abi Akar, Ben Cumming, Stuart Yates (CSCS);

Thorsten Hater, Brent Huisman, Anne Küsters (Forschungszentrum Jülich)

We present a reimplementation of a study performed by Torres Valderrama et al. [7], "Uncertainty Propagation in Nerve Impulses Through the Action Potential Mechanism". This study was conducted to establish the utility of Arbor and to be able to verify the results and claims of the original publication. In it, the sensitivity of the membrane voltage to variation in the parameters of the Hodgkin-Huxley model are investigated using the Sobol method.

### Where to find us

Website [arbor-sim.org](http://arbor-sim.org)  
Source code [github.com/arbor-sim/arbor](https://github.com/arbor-sim/arbor)  
Documentation [docs.arbor-sim.org](https://docs.arbor-sim.org)  
Contact [contact@arbor-sim.org](mailto:contact@arbor-sim.org)

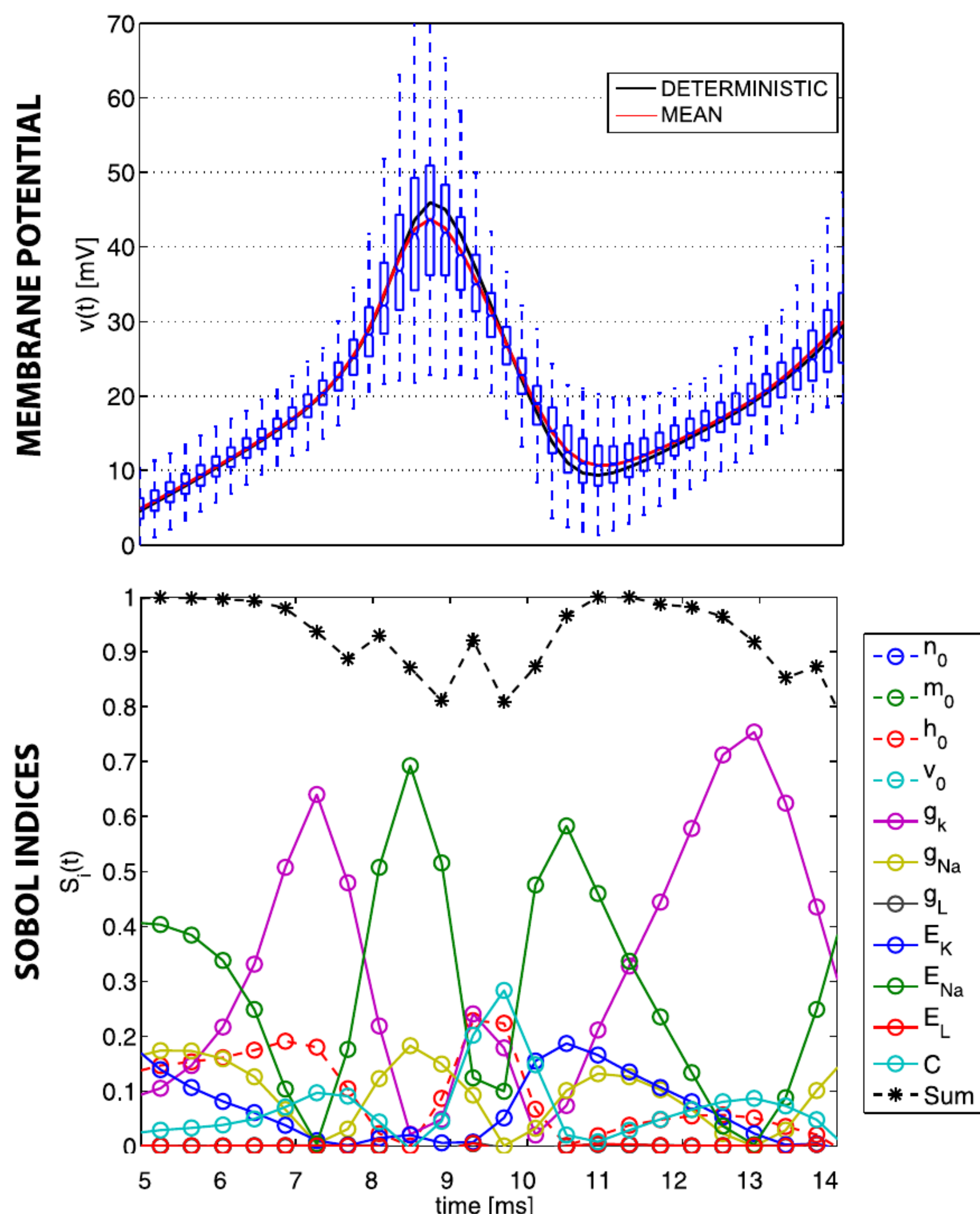


Figure 1: Reproduced from figure 1a in Torres Valderrama et al. 2015. Top: Membrane potential as function of simulation time. Bottom: the evolution of the individual Sobol indices and their sum. From this the conclusion is drawn that maximum conductance  $\bar{g}_K$  and Nernst equilibrium potential  $E_{Na}$  are together enough to estimate the variance of the original model to within 10% difference for all time points.

### Abstract of Torres Valderrama et al. 2015

We investigate the propagation of probabilistic uncertainty through the action potential mechanism in nerve cells. Using the Hodgkin–Huxley (H-H) model and Stochastic Collocation on Sparse Grids, we obtain an accurate probabilistic interpretation of the deterministic dynamics of the transmembrane potential and gating variables. Using Sobol indices, out of the 11 uncertain parameters in the H-H model, we unravel two main uncertainty sources, which account for more than 90 % of the fluctuations in neuronal responses, and have a direct biophysical interpretation. We discuss how this interesting feature of the H-H model allows one to reduce greatly the probabilistic degrees of freedom in uncertainty quantification analyses, saving CPU time in numerical simulations and opening possibilities for probabilistic generalisation of other deterministic models of great importance in physiology and mathematical neuroscience. We reproduce a plot of the main results in fig. 1.

### Methods: Sobol Indices

Variance-based sensitivity analysis (often referred to as the Sobol method or Sobol indices, after Ilya M. Sobol[4, 5]) is a form of global sensitivity analysis. Working within a probabilistic framework, it decomposes the variance of the output of the model or system into fractions which can be attributed to inputs or sets of inputs.

From a black box perspective, any model may be viewed as a function  $Y = f(X)$ , where  $X$  is a vector of  $d$  uncertain model inputs  $X_1, X_2, \dots, X_d$ , and  $Y$  is a chosen univariate model output. A direct variance-based measure of sensitivity  $S_i$ , called the "first-order sensitivity index", or "main effect index" is the contribution to the output variance of the main effect of  $X_i$ , therefore it measures the effect of varying  $X_i$  alone, but averaged over variations in other input parameters. It is standardised by the total variance to provide a fractional contribution. Higher-order interaction indices  $S_{ij}, S_{ijk}$  and so on can be formed by dividing other terms in the variance decomposition by  $\text{Var}(Y)$ . In the present study, we limit ourselves to first order indices.

### Methods: Tools

The two software components used in this replication are Arbor and SALib.

Arbor [1] simulates networks of spiking neurons, particularly multi-compartment neurons. In these networks, the interaction between cells is conveyed by spikes and gap junction and the multi-compartment neurons are characterized by axonal delays, synaptic functions and cable trees. Each cell is modeled as a branching, one-dimensional electrical system with dynamics derived from the balance of transmembrane currents with axial currents that travel through the intracellular medium, and with ion channels and synapses represented by additional current sources. SALib [6] is an open source library written in Python for performing sensitivity analyses. Instead, SALib is responsible for generating the model inputs, using one of the sample functions, and computing the sensitivity indices from the model outputs, using one of the analyze functions.

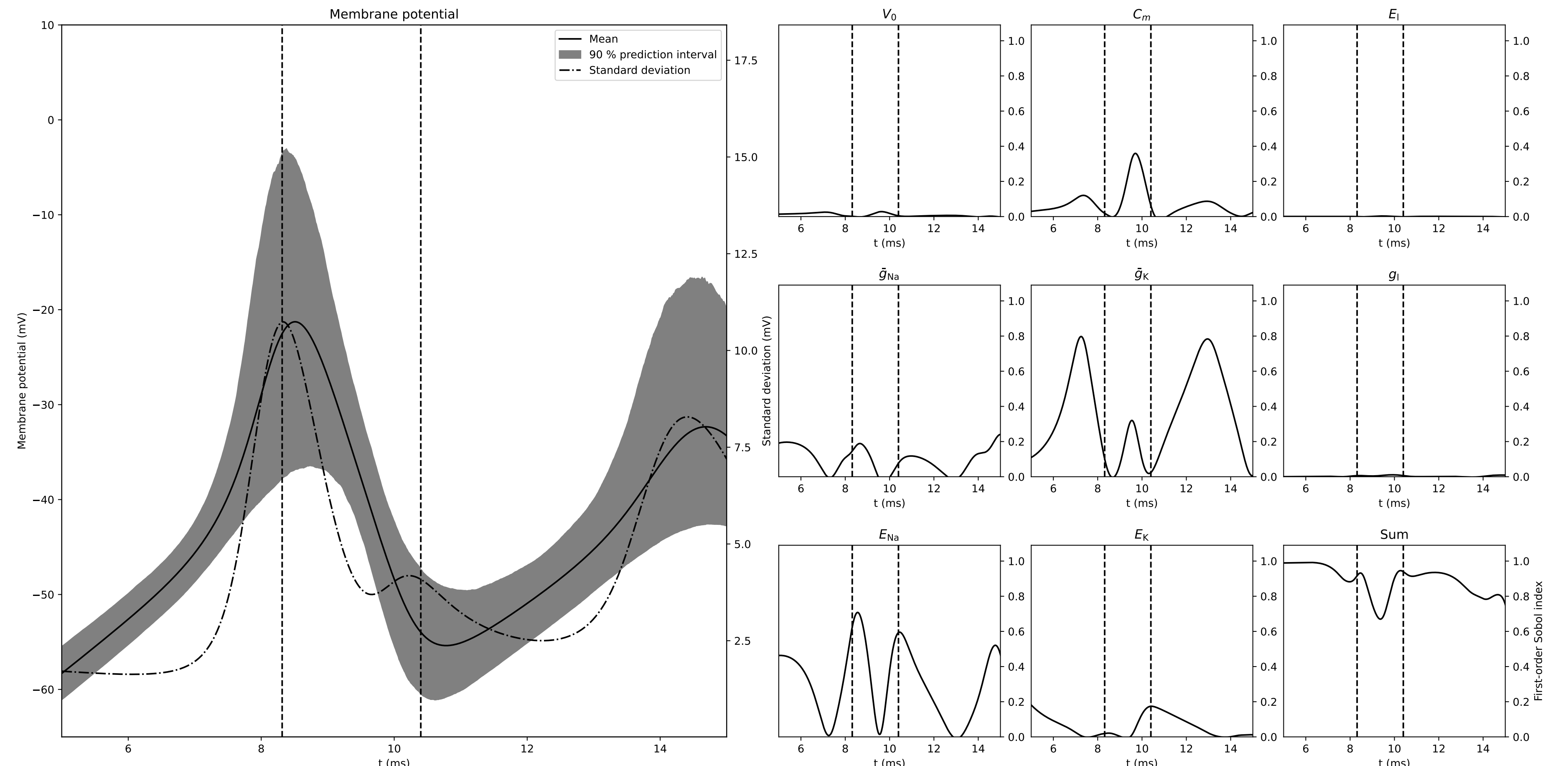


Figure 2: Results reproduced for this poster. Left: Membrane potential as function of simulation time. Right: panels showing the evolution of the Sobol indices for the eight variables and their sum, as reproduced with Arbor and SALib.

### Method: Procedure

A typical sensitivity analysis using SALib follows four steps:

- 1 Determine the model inputs (parameters) and their sample range.
- 2 Run the sample function to generate the model inputs.
- 3 Evaluate the model using the generated inputs, saving the model outputs.
- 4 Run the analyze function on the outputs to compute the sensitivity indices.

The parameters chosen are the same as in Torres Valderrama et al. 2015, minus the initial conditions  $n_0, m_0, h_0$ :

$$\xi = [V_0, C_m, E_L, \bar{g}_{Na}, \bar{g}_K, g_L, E_{Na}, E_K] \quad (1)$$

The parameter space of a 20% variability in the nominal values of the eight parameters is sampled 256 times using Saltelli's[3] extension of the Sobol' sequence;

`SALib.sample.saltelli.sample()`.

The present study is about the parameters of the Hodgkin–Huxley model. In Arbor, Hodgkin–Huxley is a mechanism that is 'painted' on (parts of) a cell's morphology. Since the morphology in this case is not relevant, a cylindric cell with diameter and length of  $2 \mu\text{m}$  is created. The variables in formula eqn. 1 are parametrized and set for each simulation of the in the previous step generated values. A current clamp of  $140 \mu\text{A}/\text{cm}^2$  applied for 15 ms.  $m, n, h$  and the membrane voltage are probed every  $10 \mu\text{s}$  and stored to disk.

Finally, a (first order) Sobol index is calculated for every timestep of every parameter, giving an indication of the relative contribution of each parameter; `SALib.analyze.sobol.analyze()`.

### Results and Conclusions

The results are plotted in fig. 2. Comparing the membrane potential and the Sobol indices with those in the original paper, excellent agreement is readily apparent. This strengthens the observations made in the original publication, as well as demonstrates the accuracy and capability of Arbor for serious study in general, and the creation of a quick toy simulation for verification of results. We have demonstrated how to setup and replicate a study using Arbor and SALib. Sources for the reproduction of the result are available at [2].

### References

- [1] Nora Abi Akar et al. "Arbor – a Morphologically-Detailed Neural Network Simulation Library for Contemporary High-Performance Computing Architectures". In: *2019 27th Euromicro International Conference on Parallel, Distributed and Network-Based Processing (PDP)* (Feb. 2019), pp. 274–282. DOI: 10.1109/EMDP.2019.8671560. arXiv: 1901.07454.
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- [3] A. Saltelli, ed. *Sensitivity Analysis in Practice: A Guide to Assessing Scientific Models*. Hoboken, NJ: Wiley, 2004.
- [4] I.M. Sobol'. "Sensitivity Analysis for Nonlinear Mathematical Models". In: *Mathematical Modeling and Computational Experiment* (1993).
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- [7] Aldemar Torres Valderrama et al. "Uncertainty Propagation in Nerve Impulses Through the Action Potential Mechanism". In: *The Journal of Mathematical Neuroscience* 5.1 (Dec. 2015), p. 3. DOI: 10.1186/2190-8567-5-3.

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