

Sensitivity Analysis and Uncertainty Quantification with Uncertainpy

Computational Statistics

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Uncertainpy

- **Open-source Python toolbox:** Sensitivity Analysis and Uncertainty Quantification on black-box models.
- Tailored for neuroscience application by recognizing **characteristic features**.
- No need to write complex code.

Mathematical Framework

Consider the following problem model:

$$Y = U(\mathbf{x}, t, \mathbf{Q}) \quad (1)$$

where \mathbf{x} is the space, t is the time, \mathbf{Q} is the set of uncertain input parameters, and Y is the output. The following methods can be used:

- **Uncertainty Quantification:** describe unknown distribution of the model output with statistical tools.
- **Sensitivity Analysis:** quantify relation between uncertainty of each model input and model output \implies Sobol indices.

Mathematical Framework

Sobol indices can be of first order or total:

$$S_i = \frac{\mathbb{V}[\mathbb{E}[Y|Q_i]]}{\mathbb{V}[Y]} \quad S_{Ti} = 1 - \frac{\mathbb{V}[\mathbb{E}[Y|Q_{-i}]]}{\mathbb{V}[Y]} \quad (2)$$

Where S_i quantifies the influence of the only i_{th} parameter on the output, while S_{Ti} takes into account also the interaction with the other parameters. To obtain them, two different possibilities arise:

- **Quasi-Monte Carlo methods;**
- **Polynomial Chaos Expansion.**

Project's outline

- **Hodgkin-Huxley model** for the action potential of the neuron using **Valderrama's** previous analysis: paper results and deeper study.
- **Hodgkin-Huxley original model** for the action potential of the neuron: *Uncertainpy* and *CellML* models, I/O models.
- **Maleckar model** for heart cell membrane: comparison with paper results and use of features.
- **Mitchell model**: uncertainty quantification for a simpler model, using features.

The Hodgkin-Huxley model

Action potentials are characterised by a sharp increase in the membrane potential (**depolarisation** of the membrane) followed by a less sharp decrease towards the resting potential (**repolarisation**). The equivalent electrical circuit of the model is the following:

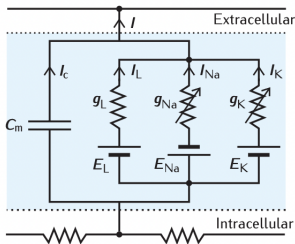


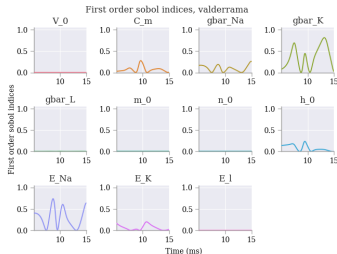
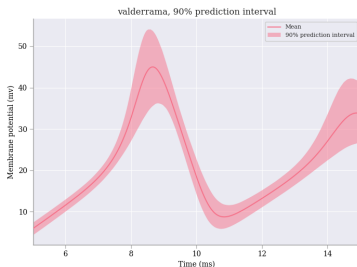
Figure: Hodgkin-Huxley equivalent electrical circuit

(source: Sterratt, D., Graham, B., Gillies, A., and Willshaw, D. (2011). Principles of Computational Modelling in Neuroscience. Cambridge, UK: Cambridge University Press.)

This model presents **11 parameters** to be considered for the analysis.

Valderrama model - paper results

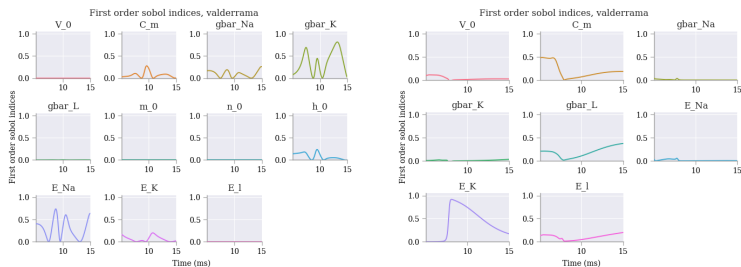
The action potential and the 11 first order Sobol indices are the following.



It is possible to note that the trends of the Sobol indices reflect the physical characteristics of the model.

Valderrama model - further analysis 1

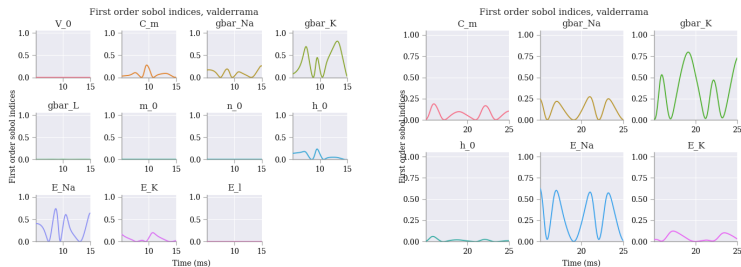
In this first case, the **current** through the membrane is fixed to a **null** value.



Analyzing the resulting Sobol indexes it is possible to deduce some physical characteristics which are in accord with the expected behavior.

Valderrama model - further analysis 2

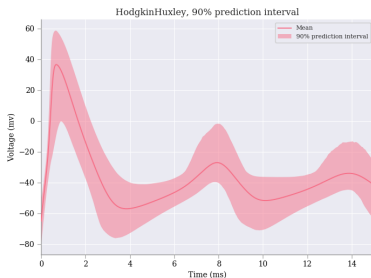
In order to consider only the relevant parameters, the ones with low Sobol index are fixed at their mean value.



The second analysis was done by considering a longer time interval, in order to check the influence of the initial Na^+ inactivation state (h_0).

Hodgkin-Huxley original model

To simulate this model, two different codes have been used: the one included in the *Uncertainpy* library, and a second one from the *CellML* repository.



Although the formulation of the two models are different, we notice that the results of the analyses are similar.

Maleckar Model

Models of the cardiac action potential typically comprise a system of coupled, non-linear ordinary differential equations, therefore the relationship between model parameters and model outputs is difficult to establish. The model representation is the following:

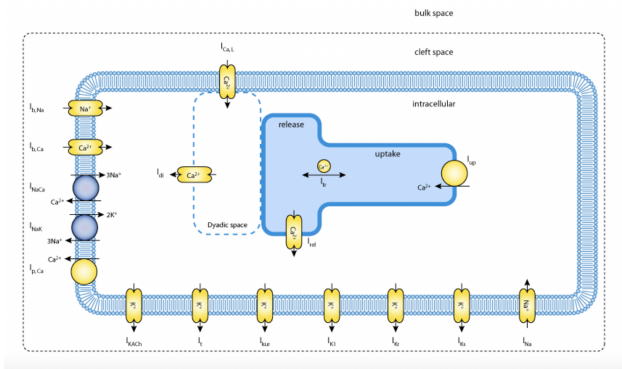
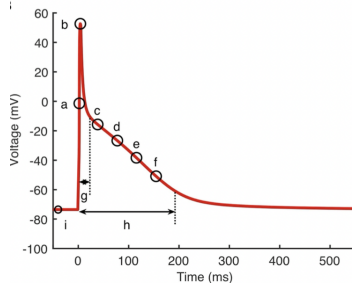
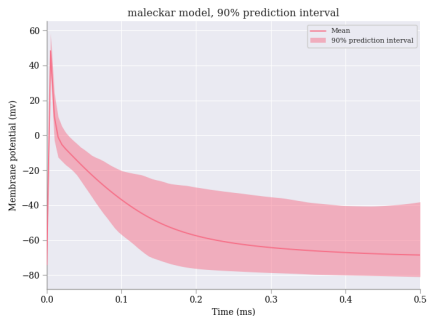


Figure: Maleckar model representation

(source: CellML.org)

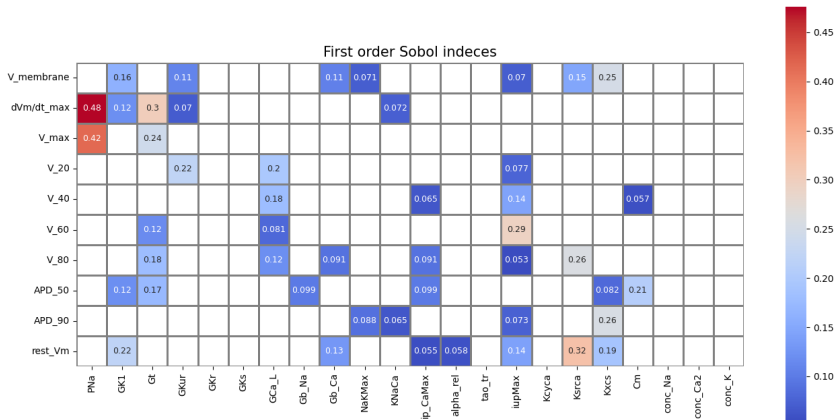
Maleckar Model



1) On the left: simulation of Maleckar Model (*CellML*) using *Uncertainpy*; 2) On the right: (a),(b),(c),(d),(e),(f) represent the features we want to study.

Maleckar Model

While *Coveney et al.* used Gaussian Processes to perform the statistical study, we again analyzed the Sobol indices using *Uncertainpy*. The results are the following:



Mitchell Model

In order to reduce the number of parameters on which to perform the analysis, we finally considered a model with **less parameters** for the potential through the heart membrane.

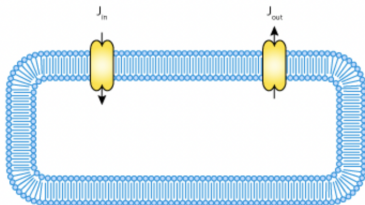


Figure: Mitchell model representation
(source: CellML.org)

The simplicity of this model allows the use of the **features** tool.

Performance comparison

To obtain this plot: Exact QMC with 200000 model evaluations (for mean and var) and 100000(d+2) for Sobol. 50 re-run using QMC method; Poly-Chaos with point collocation.

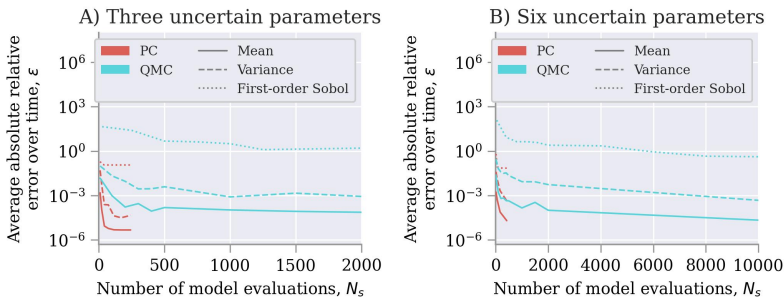


Figure: Comparison between MonteCarlo and Polynomial Chaos Expansion

Final Considerations

- **Uncertainpy** proved to be easy to use and versatile: any I/O mathematical model can be used, provided the corresponding code.
- **Features** have been used in order to perform a deeper analysis of the models, giving some more interesting information.
- From uncertainty quantification and sensitivity analysis it is possible to extrapolate physical characteristics of the system.
- Nevertheless, some models presented in the paper were not working well (i.e. NEST, NEURON).

References

- [1] Sam Coveney and Richard H. Clayton. "Sensitivity and Uncertainty Analysis of Two Human Atrial Cardiac Cell Models Using Gaussian Process Emulators". In: *Frontiers in Physiology* 11 (2020).
- [2] Mary Maleckar, Joseph Greenstein, Natalia Trayanova, and Wayne Giles. "Mathematical simulations of ligand-gated and cell-type specific effects on the action potential of human atrium". In: *Progress in biophysics and molecular biology* 98 (2009), pp. 161–170.
- [3] Colleen C. Mitchell and David G. Schaeffer. "A two-current model for the dynamics of cardiac membrane". In: *Bulletin of Mathematical Biology* 65.5 (2003), pp. 767–793.
- [4] David Sterratt, Bruce Graham, Andrew Gillies, and David Willshaw. *Principles of Computational Modelling in Neuroscience*. Cambridge University Press, 2011, pp. 47–71.
- [5] Simen Tennøe, Geir Halmes, and Gaute T. Einevoll. "Uncertainpy: A Python Toolbox for Uncertainty Quantification and Sensitivity Analysis in Computational Neuroscience". In: *Frontiers in Neuroinformatics* 12 (2018).
- [6] Aldemar Torres Valderrama, Jeroen Witteveen, Maria Navarro, and Joke Blom. "Uncertainty Propagation in Nerve Impulses Through the Action Potential Mechanism". In: *The Journal of Mathematical Neuroscience* 5.1 (2015).

Mitchell Model - extras

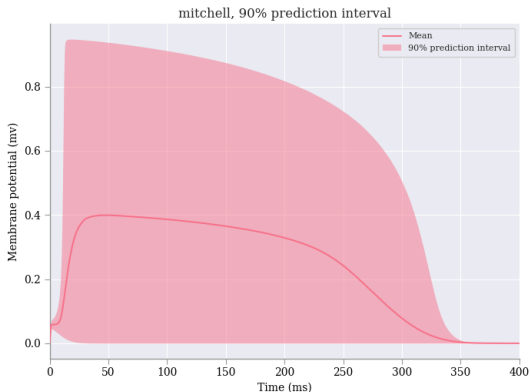


Figure: Mithcell model prediction interval. This explains why we need to fix *IstimApp* (intensity of the applied stimulus).

Mitchell Model - extras

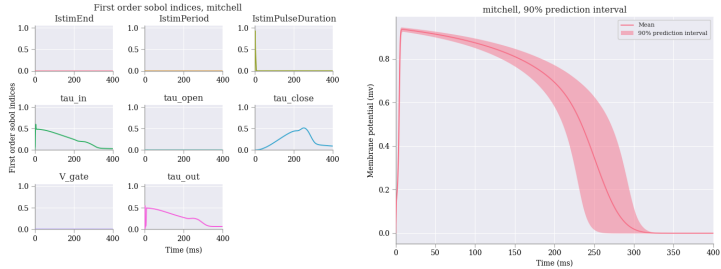


Figure: $IstimApp > 0.05$ ($=0.15$).

Mitchell Model - extras

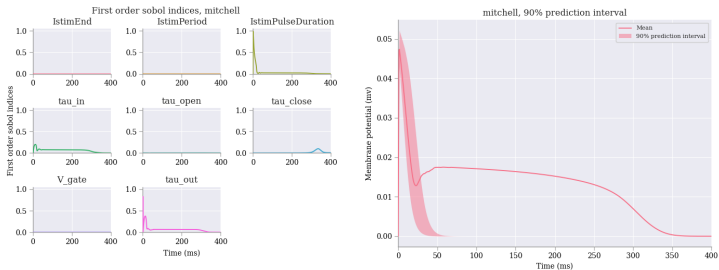


Figure: $IstimApp < 0.05$.

Mitchell Model - extras

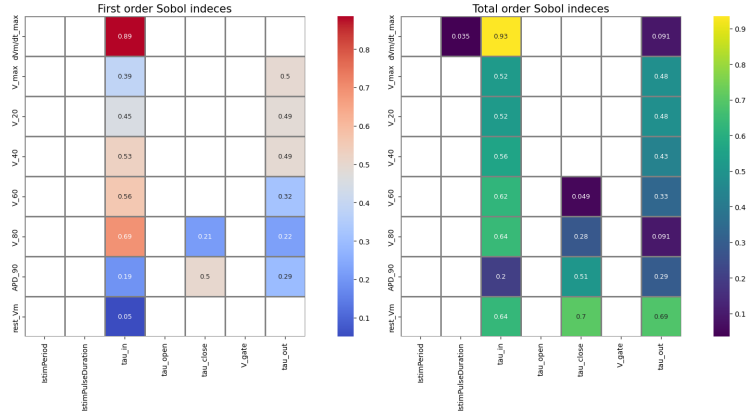


Figure: Sobol indexes for the features case.