Statistical design of in silico experiments for the robustness analysis of electrophysiologic response simulators

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Statistical Design of *in silico* Experiments for the Robustness Analysis of Electrophysiologic Response Simulators.

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Background. To assess the risk of Torsade de Pointes, the CiPA initiative has proposed to test in silico models able to reconstruct electrophysiologic responses and analyze mechanistic causes of specific toxicological events such as TdP. One example of such simulators is the O'Hara Rudy's model [1], used herein as a benchmark model.

Objectives

Such in silico models are composed of a large number of biological parameters. Their values are never fully known and they are generally estimated with a substantial uncertainty. So, what happens if the values of some parameters are wrong? Can we still trust the simulated responses? In this application context, our objective is to firstly identify the critical modeling parameters.

Methods

To reduce the computation time, we propose a statistical approach suited to the screening of model parameters. Our approach relies on a Placket-Burman design of numerical assays. 79 models parameters have been tested and only 80 numerical experiments were carried out. The action potential response was split up into five phases and three statistics (duration, AUC and amplitude) were computed for each phase. Accordingly, 15 response variables were analyzed. A Pareto analysis is finally used to rank the most critical parameters.

Results

Results show that all the tested modeling factors have the same order of effect on the global response. In other terms, no parameter can be neglected. Two parameters appear as more critical than the other ones: the stimulus current and the initial temperature of the cell. The effects of all the parameters on each of the five beating phase are also estimated and ranked.

Conclusion

This study analyzes the sensitivity of the simulated potential action response with respect to uncertainty on 79 modeling parameters. All of them have significant effects on at least one part of the response, which emphasizes the relevance to accurately estimate them to trust simulations. As a consequence, another crucial question is worth asking and deals with the model identifiability, i.e. the possibility to learn the true values of the model parameters after obtaining an infinite (theoretical identifiability) or a finite (practical identifiability) number of *in vitro* observations [1]

[1] T. O'Hara, L. Virág, A. Varró, and Y. Rudy, Simulation of the undiseased human cardiac ventricular action potential: Model formulation and experimental validation, PLOS Computational Biology, vol. 7, pp. 1–29, 05 2011.

[2] S. Dobre, T. Bastogne, C. Profeta, M. Barberi-Heyob, and A. Richard, "Limits of variance-based sensitivity analysis for non-identifiability testing in high dimensional dynamic models," Automatica, vol. 48, pp. 2740–2749, Aug. 2012.

Fig.1: Example of Plackett-Burman design of experiments used to identify the most critical modeling parameters of the O'Hara-Rudy's model [1]. 80 simulations (tests) were carried out on Matlab™ to estimate the additive effects of 79 model parameters (factors). Each of them took 2 values: ± 10% nominal values.
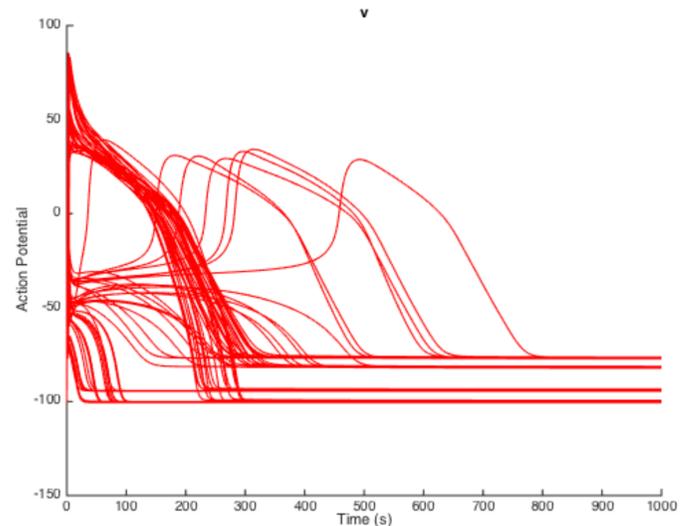

Fig.2: Superposition of simulated action potential responses provided by the O'Hara-Rudy's model [1].
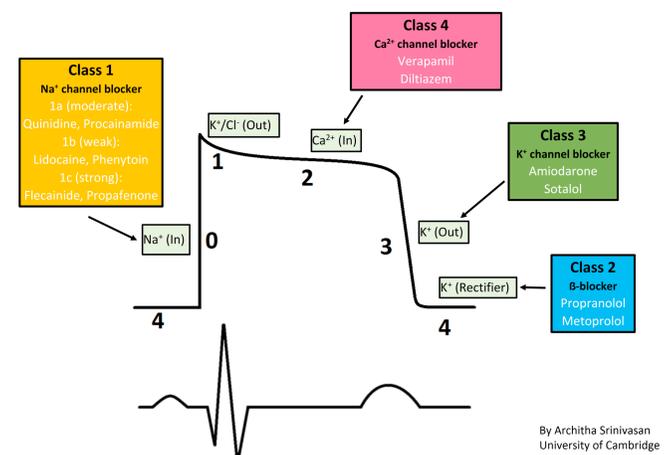

Fig.3: Each response is split up by an algorithm into 5 phases (0,1,2,3,4) and 4 statistics: duration, AUC, min & max values are computed
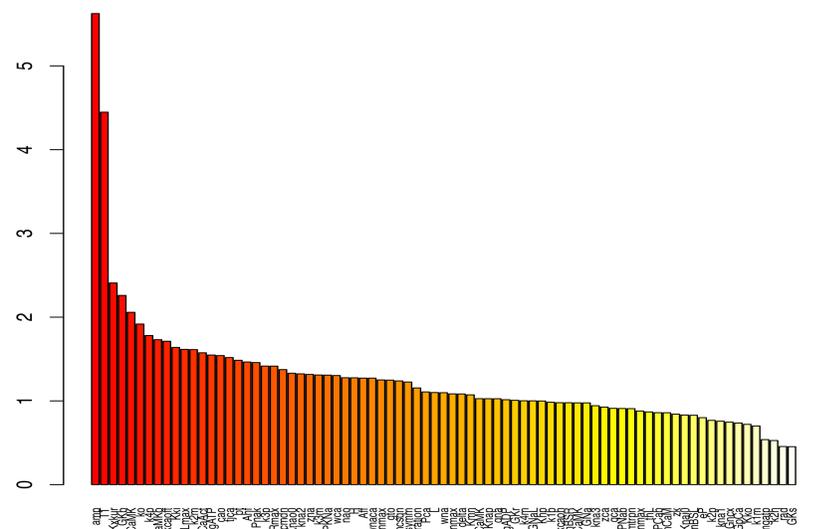

Fig.4: Pareto's Diagram of the model parameters and their effect on the AUC of the complete action potential response