Sensitivity and uncertainty analysis of cardiac cell models with Gaussian process emulators

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1. Introduction

Models of electrical activation in cardiac cells and tissue have become accepted as research tools that can be used alongside experiments to gain insights into physiological mechanisms. More recently, there is the prospect that these tools could be used to inform clinical decision making [1] and for in-silico drug safety assessment [2]. As a result, the behaviour of cardiac models under uncertainty in model parameters, initial conditions, and boundary conditions has become an area of active interest [3].

2. Emulators for computer models

The effects of uncertainties in cardiac models can be explored by running the model many times, each with different sets of model parameters or other conditions. While this approach can yield useful insight, cardiac models have a high-dimensional parameter space, and a thorough exploration can be computationally expensive. Emulators, sometimes called surrogate models or metamodels, have been used in other domains where computational models are expensive to run. If the computational model or simulator is described as a function $\boldsymbol{y}_s = f(\boldsymbol{x})$, where $\boldsymbol{y}_s$ is a vector of model outputs, and $\boldsymbol{x}$ a vector of model inputs, then the emulator is a function $\boldsymbol{y}_e = f'(\boldsymbol{x})$ where the emulator output $\boldsymbol{y}_e \approx \boldsymbol{y}_s$.

3. Gaussian process emulators for cardiac cell models

A Gaussian process (GP) is a distribution over functions that can be composed of a mean function and a covariance [4]. The GP has hyperparameters that can be fitted by maximising their log-likelihood over design data, which are a series of model runs that sample the possible input space. For each vector of inputs $\boldsymbol{x}$, a corresponding vector of outputs $\boldsymbol{y}$ are obtained, and these are used in the fitting process.

Once fitted, the emulator can be evaluated cheaply to estimate the mean and variance of the output(s) $\boldsymbol{y}$, for new vectors of inputs $\boldsymbol{x}$ that were not used in the design data. It is also possible to calculate variances on the outputs given variances on one or more of the inputs, if all the distributions are assumed to be Gaussian. A variance-based sensitivity index can be calculated for each combination of input and output, which is the proportion of the output variance that can be accounted for by variance on each input.

4. Emulators for cardiac cell models

Cardiac cell models are typically a set of stiff and nonlinear ordinary differential equations, which describe the flow of current through voltage-gated ion channels, pumps, and exchangers embedded in the cardiac cell membrane. A numerical solution of the model yields an action potential time series.

5. Emulators for models of the human atrial action potential

We have used GP emulators to investigate the Courtmanche-Ramirez-Nattel model of the human atrial action potential. We selected 9 features of the action potential and two features of the intracellular [Ca^{2+}] transient as outputs. For inputs, we selected 9 ion channel maximum conductances, 3 pump exchange maxima, 4 external boundary conditions, and 4 parameters relating to [Ca^{2+}] storage, uptake, and release. To obtain design data, we ran the model code 300 times, each with a different set of inputs drawn using a Latin hypercube from a uniform distribution bounded by 50% and 150% of the default value of the input. In 5/300 runs the model displayed pacemaking behaviour or a failure to repolarise, and these runs were excluded from the design data. The emulators were validated against a further 150 model runs using mean average percentage error.

6. Sensitivity and uncertainty analysis

Sensitivity indices showed that the action potential upstroke and amplitude have a strong dependence on maximum Na^+ channel conductance, as would be expected. The maximum conductances of I_{CaL} and I_{Kur} both had a strong influence on action potential shape and duration. Some of the other inputs, for example the maximum conductance of I_{Ks} had surprisingly little influence on the model output. Action potential duration was sensitive to many of the inputs. The effect of uncertainties in the inputs was examined by increasing the variance on all of the inputs, and observing the change in uncertainty on the outputs. The coefficient of variation in action potential duration increased to 30% when the standard deviation on all the inputs was 20% of the range used in design data.

7. Conclusions

GP emulators are a valuable tool with which to undertake sensitivity and uncertainty analysis of cardiac cell models.

References

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