Uncertainty and Sensitivity Analysis of the Courtemanche-Ramirez-Nattel Human Atrial Cell Model Using Gaussian Process Emulators

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Abstract

Models of cardiac cellular electrophysiology are highly detailed with many input parameters. However, the effect of input parameters on model outputs is often not well characterised. Uncertainty and sensitivity analysis using Monte Carlo techniques require large numbers of model runs. In this study we investigated Gaussian Process (GP) emulators, which provide a computationally cheap way to assess uncertainty and sensitivity analysis.

We constructed GP emulators for 6 metrics of action potential shape (max dV/dt, max voltage, dome voltage, action potential duration to 90% repolarisation (APD90), resting voltage and APD to 50% repolarization), as a function of maximal conductance. The emulators were fitted to design data obtained from 150 model runs where the input parameters varied within a range of $\pm 1/3$ of their default value, and where each point in parameter space was selected using Latin hypercube sampling. The emulators were then used to calculate variance based sensitivity indices.

Variance based sensitivity indices describe the proportion of output variance that can be attribute to variance in an input. We found that action potential upstroke (max dV/dt) and maximum voltage were both highly sensitive to GNa, with sensitivity indices of 0.75 and 0.89 respectively. Dome voltage was sensitive to GKur (0.2) and GCaL (0.51), and GK1 had a strong effect on APD90 (0.35) and resting voltage (0.41). APD50 was most sensitive to GCaL (0.35). These sensitivity indices were comparable to sensitivity determined from partial least squares regression.

We conclude that GP emulators provide a computationally efficient way to undertake sensitivity analysis in cardiac cell models. Both parameters and outputs are treated explicitly as normal distributions, with means and variances. Thus it is possible to undertake uncertainty quantification as well as sensitivity analysis using this approach.

1. Introduction

Models of cardiac cellular electrophysiology have, over the last few decades, become valuable research tools which allow us to quantify our understanding of biophysical mechanisms underlying the cardiac action potential. These models have become increasingly detailed with subsequent iterations, and promise to encapsulate information from the genome scale all the way to models of cardiac function. As a result, the number and variety of input parameters has increased significantly, even when the effect of input parameters on model outputs is often not well characterised.

The traditional technique to carry out Uncertainty and Sensitivity Analysis of complex models is to use Monte Carlo techniques, requiring large numbers of model runs which is a time consuming and non-exhaustive process. The need to complete accurate yet efficient analyses of electrophysiology models has led to a growing interest in the field of Uncertainty Quantification, which are a collection of techniques to formalise and address the uncertainties brought about by complex models in an efficient manner. One such technique is the use of Gaussian Process (GP) emulators, which provide a computationally cheap way to assess uncertainty and sensitivity analysis based on the training of a *surrogate-* or *meta-* model based on a small number of model runs.

In this study, we sought to carry out uncertainty and sensitivity analysis of the Courtemanche-Ramirez-Nattel [1] (CRN) human atrial cell model by building a GP emulator, and using the emulator to derive sensitivity indices describing the relative contribution of inputs to a given emulator output.

2. Methods

An emulator is a statistical model built to estimate the output of a model given a set of input values. A Gaussian Process (GP) emulator is constructed using normal distributions to represent both inputs and outputs. Under the

assumption that model inputs follow a multivariate normal distribution, it is possible to analytically compute the output distributions.

We constructed separate GP emulators for 6 metrics of action potential shape (max dV/dt, max voltage, dome voltage, action potential duration to 90% repolarisation (APD90), resting voltage and APD to 50% repolarization), as a function of 13 maximal conductances published within the CRN model. We first generated design data to train the emulators, which were obtained from 150 model runs, where the input parameters varied within uniform distributions centred on the published parameter value in the original value and a range of $\pm 1/3$ of this value. This total range was and scaled normalised to range from 0 to 1, such that 0.5 represented the default value. The 150 points in the full parameter space were selected using Latin hypercube sampling (LHS).

In each run, we paced a single cell for 20 beats at 1Hz, and calculated metrics from the final action potential. The cell model was directly exported from the CellML repository, and we chose to fix the concentrations of $[Na^+]_i$ and $[K^+]_i$ following Cherry et al [2] to eliminate long-term drift. Simulations and analysis were carried out in Matlab (Mathworks, UK).

The GP emulators were then built according to Chang et al [3], and the fit of the emulator was assessed using test data from a set of 20 further model runs. We also compared the quality of the emulator fit using fewer design points (25, 50 and 100) and these showed consistency.

3. Results

3.1. CRN design data

In Figure 1, we visualise 100 action potentials from the design data, coloured by values of G_{CaL}, G_{Kr}, G_{Kur} and G_{Ks} which were varied between 0 and 1. A variety of action potentials shape metrics were observed and there was no clear correlate between any single conductance and a corresponding shape metric. Further quantitative analysis could be obtained through construction of the GP emulator based on the design data.

3.2. Variance based sensitivity analysis

Sensitivity indices describe the proportion of the output variance that can be attributed to variance from a given input, and this is typically calculated in different ways. Using the GP emulator approach, the expectation and variance of each emulator output can be directly calculated by assigning a mean and variance to model input parameters. In Figure 2, we plot the mean effects plots of each output, showing how the expectation of the output changes as each input is assigned a fixed value that varies across the range 0 to 1 in normalised units, while other inputs were assigned a fixed mean of 0.5 and a variance of 0.04.

The overall pattern of the mean effects is consistent with existing knowledge of the CRN model. G_{Na} had a strongly influence on the action potential upstroke metrics, max dV/dt and max voltage, whilst the metrics contributing to the action potential shape (dome voltage, APD50 and APD90) were influenced by a balance of maximal conductances modulating K^+ and Ca^{2+} currents such as G_{CaL}. The transient outward current G_{to} had an effect on APDs and resting voltage, whilst the potassium related conductances had a stronger effect on resting voltage as well. We subsequently calculated a matrix of sensitivity indices which is a generalisation of the mean effects plots in Figure 3. In each row, which corresponds to a single emulator output, the index and colour indicated the proportion of variance that can be attributed to variance in the input conductance corresponding to that column. This allowed us to obtain a clearer breakdown of relative contributions to a single output. Using this matrix of indices, we found that AP upstroke (max dV/dt) and maximum voltage were highly sensitive to G_{Na}, with sensitivity indices of 0.79 and 0.85 respectively. Dome voltage was most sensitive to G_{Kur} (0.2) and G_{CaL} (0.51), whilst G_{K1} had a strong effect on APD90 (0.35) and resting voltage (0.41). APD50 was most sensitive to G_{CaL} (0.35). We compared these these sensitivity indices to sensitivities determined using a partial least squares regression method [4] and the results were comparable.

4. Discussion

We have demonstrated that GP emulators provide a computationally efficient way to undertake sensitivity analysis in cardiac cell models. This is possible because both parameters and outputs are treated explicitly as multivariate normal distributions with means and variances, allowing uncertainty quantification as well as sensitivity analysis to be calculated directly throughout parameter space but based on a relatively small number of design data. However an assumption of GP emulators requires that the output surface is smooth. We have so far worked with the CRN model under steady 1Hz pacing, and have not considered emergent behaviours, such as restitution properties or APD alternans at short cycle length, which could be of further interest.

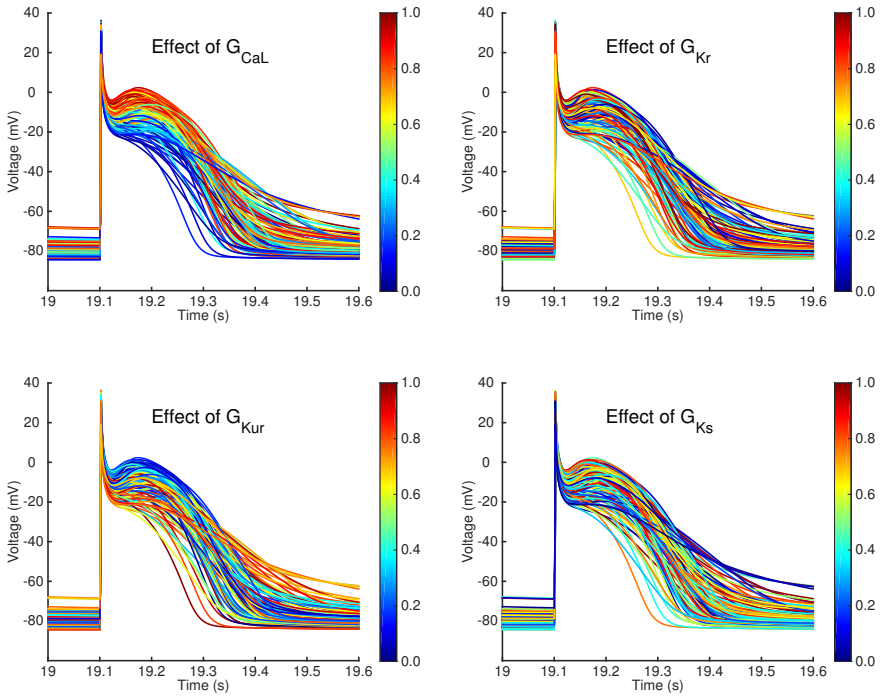

Figure 1: Simulated Courtemanche-Ramirez Nattel action potential traces coloured by maximal conductances G_{CaL}, G_{Kr}, G_{Kur} and G_{Ks}, which were varied within $\pm 1/3$ of the default value. The data range is rescaled from 0 to 1, with 0.5 representing the maximal conductance in the original model.

Acknowledgements

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References

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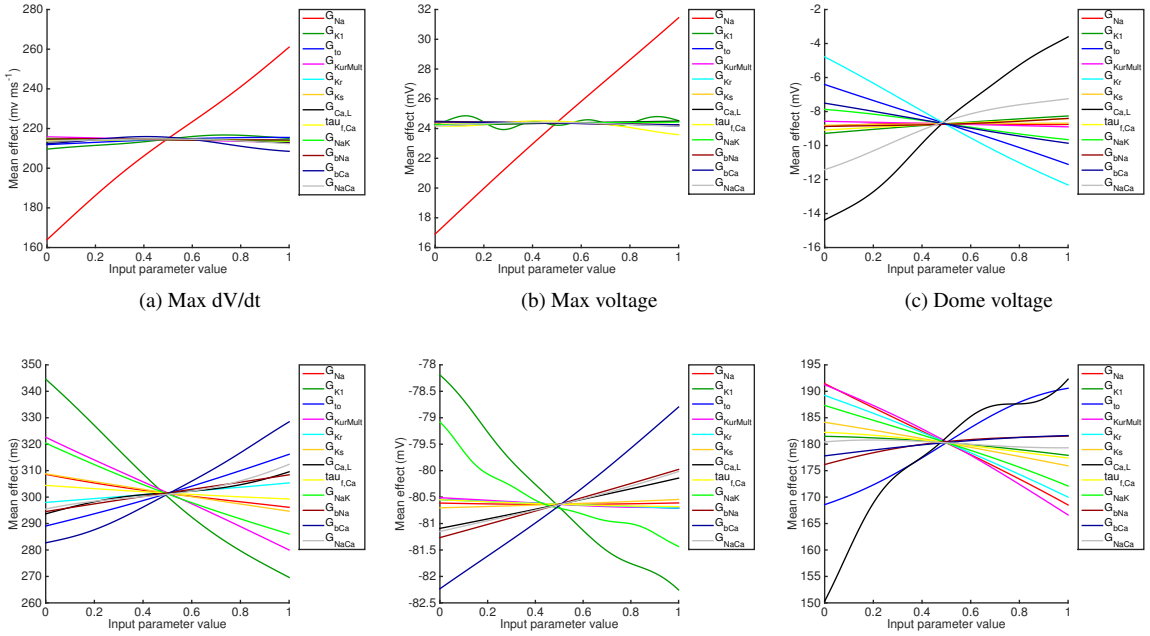

(a) Max dV/dt (b) Max voltage (c) Dome voltage

(d) APD90 (e) Resting voltage (f) APD50

Figure 2: Mean effects plots from the emulator, visualising how varying each input conductance between 0 and 1 influences the expectation of the resultant emulator output, when the other input conductances are held at 0.5 (the default value) with a variance of 0.4.

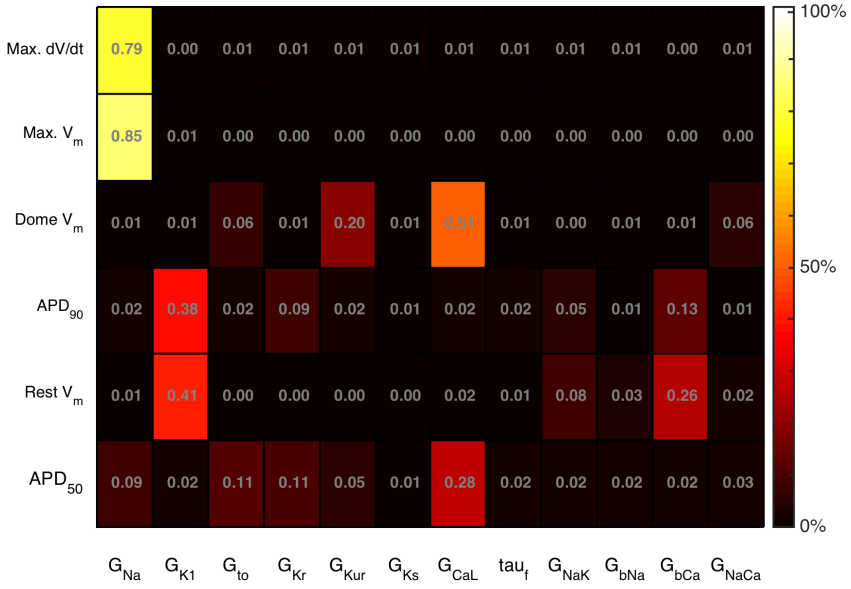

Figure 3: Sensitivity indices calculated for the CRN model based on 150 design data points, showing the relative contribution of variance from each input (column) towards the variance of a given output (row). Max dV/dt and max V_m show strong sensitivities to G_{Na} only whilst other outputs are weakly sensitive to a combination of input maximal conductances..