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Variance Based Sensitivity Analysis of I_{Kr} in a Model of the Human Atrial Action Potential using Gaussian Process Emulators

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Abstract. Cardiac cell models have become valuable research tools, but biophysically detailed models embed large numbers of parameters, which must be fitted from experimental data. The provenance of these parameters can be difficult to establish, and so it is important to understand how parameter values influence model behaviour. In this study we examined how model parameters influence the repolarising current I_{Kr} in the Courtemenache-Ramirez-Nattel model of the human atrial action potential. We used a statistical approach in which Gaussian processes (GP) are used to emulate the model outputs. A GP emulator can treat model inputs and outputs as uncertain, and so can be used to directly calculate sensitivity indices. We found that 3 of the 10 parameters influencing I_{Kr} had a strong influence on APD_{70}, APD_{90}, and Dome V_m. These three parameters scale the magnitude of the I_{Kr} gating variable time constant and the voltage dependence of the steady state activation curve, and these mechanisms act to modify the amplitude of I_{Kr} during repolarisation. This study highlights the potential value of statistical approaches for investigating cardiac models, and that uncertainties or errors in parameters resulting from attempts to fit experimental data during model development can ultimately affect model behaviour.

1 Introduction

Since the introduction of the first model of cardiac cellular electrophysiology over 50 years ago [12], models of electrical activation and recovery in cardiac cells have become important research tools. The present generation of cardiac cell models

represent not only changes in transmembrane potential resulting from movement of ions through the cell membrane, but also the diffusion, storage, release, and uptake of Ca^{2+} within the cell [5]. Typically, cardiac cell models are a stiff, non-linear system of coupled ordinary differential equations, and are solved using a numerical scheme to obtain time series of membrane voltage, intracellular Ca^{2+} concentration, and other quantities of interest.

Each of the equations involve parameters; for equations describing transmembrane current flow through ion channels, pumps, and exchangers these parameters typically include a maximum current density per unit membrane area, and other parameters that regulate the dynamic behaviour of the current. The parameters are fitted from experimental data often following the approach pioneered by Hodgkin and Huxley [6]. Many models take a modular approach to building the full suite of equations representing transmembrane current flow, with re-use of parameters from older models and experiments. The provenance of these parameters is not always easy to establish [11], yet the influence of uncertain parameters on model behaviour is difficult to assess because of model complexity.

Recent studies have begun to address this problem by examining the sensitivity of model outputs such as action potential duration (APD) to variable model parameters [2,16]. These studies have concentrated on maximum conductances of ion channels, but even with this subset the potential parameter space to explore is vast. Although cardiac cell models are relatively cheap to compute, a comprehensive exploration of very high dimensional parameter space remains computationally demanding.

An alternative approach is to build a statistical model (an *emulator* or meta-model), which acts as a fast running surrogate for the original model or *simulator*. This approach has been used to examine models of systems including atmospheric pollution [8] and galaxy formation [17], where the emulator is a Gaussian process (GP) [13]. A particular advantage of a GP emulator is that the simulator parameters, or *inputs*, can be treated as uncertain so that they are represented by a distribution rather than a fixed value. Using Gaussian (normal) distributions allows direct calculation of expected mean and variance of an output given uncertainty in the inputs. The proportion of output variance that is accounted for by variance in each input is then a first order sensitivity index [13]. Furthermore, the main effect of model inputs can be directly calculated, showing how a single input affects an output given specified distributions on the other inputs. This approach has been used to examine cardiac cell models, where inputs were ion channel maximum conductances and outputs were features of the action potential [3,7].

The rapidly inactivating K^+ current I_{Kr} regulates repolarisation in cardiac myocytes, and is an important pharmaceutical target. The aim of the present study was therfore to undertake sensitivity analysis of the I_{Kr} channel in the Courtemanche-Ramirez-Nattel (CRN) model of the human atrial action potential [4].

2 Methods

2.1 CRN Model Inputs and Outputs

The equations describing the I_{Kr} current in the CRN model [4] are given below. The current density I_{Kr} is given by

$$I_{Kr} = \frac{g_{Kr} x_r \left(V_m - E_K\right)}{1.0 + \exp\left[\dfrac{V_m + Kr_1}{Kr_2}\right]} \quad . \tag{1}$$

Where the gating variable x_r varies between 0 and 1, and is given by

$$\frac{\mathrm{d}x_r}{\mathrm{d}t} = \frac{x_{r\infty} - x_r}{\tau_{xr}} \quad ; \tag{2}$$

where the gating variable time constant τ_{xr} and steady state activation $x_{r\infty}$ depend on transition rates α_{xr} and β_{xr};

$$\alpha_{xr} = Kr_3 \frac{V_m + Kr_4}{1.0 - \exp\left[-\dfrac{V_m + Kr_4}{Kr_5}\right]} \quad , \tag{3}$$

$$\beta_{xr} = Kr_6 \frac{V_m - Kr_7}{\exp\left[\dfrac{V_m - Kr_7}{Kr_8}\right] - 1.0} \quad , \tag{4}$$

$$\tau_{xr} = \frac{1.0}{\alpha_{xr} + \beta_{xr}}, \tag{5}$$

$$x_{r\infty} = \left[1.0 + \exp\left(-\frac{V_m + Kr_9}{Kr_{10}}\right)\right]^{-1} \quad . \tag{6}$$

Each of the 10 parameters labelled Kr_1 to Kr_{10} appear as numbers without units in the original formulation, and in this study we examined variation in the range 0.5× to 1.5× these values as shown in shown in Table 1. The maximum conductance g_{Kr} was set to a baseline value of 0.0294 nS/pF and E_K was set to -86.7653 mV for fixed intracellular K^+ concentration, as described below.

We identified seven outputs that describe features or biomarkers of the action potential, based on previous work [2,3], and these are illustrated in Fig 1.

2.2 Implementation of CRN Model

The CRN model equations were implemented in Matlab (Mathworks, CA), using code automatically generated from the CellML repository (`http://cellml.org`). The cell models were solved using the Matlab `ode15s` time adaptive solver for stiff systems of ODEs, with tolerances set to 10^{-6}. The CRN model does not properly balance intracellular ion concentrations [18], so we fixed $[Na^+]_i$ and $[K^+]_i$ at baseline values of 11.1 mM and 139.0 mM respectively.

Table 1. Baseline values for each input, and range over which each input was varied for design data.

Parameter	Baseline	range
Kr_1	15.0	(7.5 - 22.5)
Kr_2	22.4	(11.2 - 33.6)
Kr_3	3.0 $\times 10^{-4}$	(1.5 - 4.5) $\times 10^{-4}$
Kr_4	14.1	(7.05 - 21.15)
Kr_5	5.0	(2.5 - 3.75)
Kr_6	7.3898 $\times 10^{-5}$	(3.6949 - 11.0847) $\times 10^{-5}$
Kr_7	3.3328	(1.6664 - 4.9992)
Kr_8	5.1237	(2.5619 - 7.6856)
Kr_9	14.1	(7.05 - 21.15)
Kr_{10}	6.5	(3.25 - 9.75)

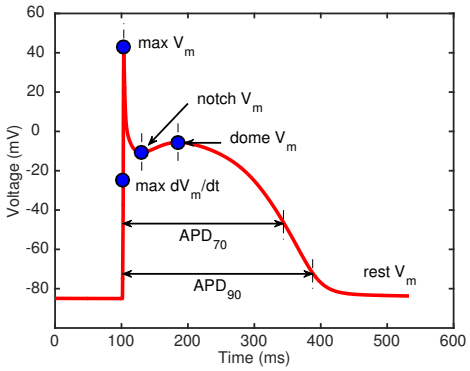

Fig. 1. Action potential features

2.3 Emulator Design Data

For fitting and evaluating the GP emulators, we obtained design data comprising a set of 500 simulator runs. For each run, a value for each input was selected from the range shown in Table 1, using Latin hypercube sampling to ensure an even distribution of points in the input space. To achieve a stable action potential duration, each simulator run included 40 stimuli of strength -2.0 nA and duration 2 ms delivered at a 1000 ms cycle length to represent a resting human heart rate. The final action potential in this sequence was used to obtain the outputs. The distribution of action potentials and I_{Kr} gating dynamics are shown in Fig 2, where the influence of uncertain inputs on repolarisation is clearly visible.

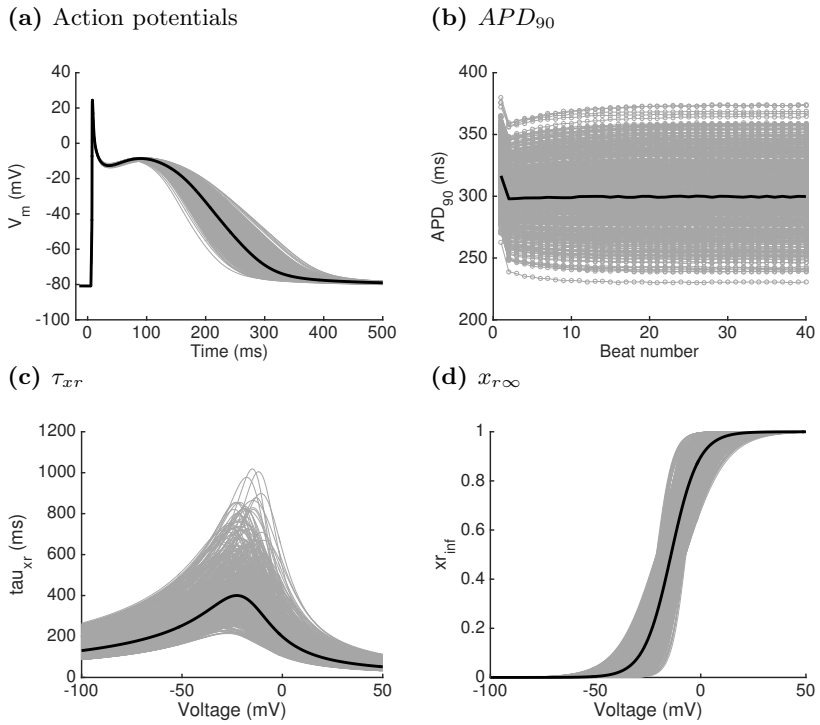

Fig. 2. Design data showing (a) final action potential out of a sequence of 40; (b) stabilisation of APD_{90} during the 40 beat sequence; (c) and (d) voltage dependence of steady state activation $x_{r\infty}$ and gating variable time constant τ_{xr} for each set of inputs. Bold lines indicate the model behaviour for baseline values of the inputs, grey lines show design data.

2.4 Sensitivity Analysis

First order sensitivity indices produced from a GP emulator represent the proportion of total output variance that is accounted for by variance in each input [13]. We assumed that inputs and outputs could be described by a normal distribution, with the mean of each input set to the baseline value and variance set to 0.01 of the range shown in Table 1.

3 Results

3.1 Emulator Fitting and Evaluation

We fitted and evaluated a separate GP emulator for each of the 7 outputs, using an open source Python implementation; details including the URL have

been withheld to ensure anonymity of the authors.`GP_emu_UQSA` (available from `http://doi.org/10.5281/zenodo.215521`). For each output, the 500 design data were separated into a training set of 450 simulator runs and a test set of 50 simulator runs. Emulator hyperparameters were fitted to the training set with a maximum likelihood approach described previously [3], using the `fmin_l_bfgs_b` optimisation function available in the Python SciPy package. Fitting was repeated five times to ensure that local maxima were avoided, and the fit with greatest likelihood was selected. The test set was then used to compare outputs predicted by the emulator against those produced by the simulator for the same set of inputs. The difference between emulator and simulator outputs was summarised using the Mahanalobis distance, which for a test set of 50 runs has a reference distribution with mean 50 and standard deviation 10.5 [1].

Table 2. Fit and evaluation of emulator for each output.

Emulator	Expectation of Mean	Expectation of variance	Mahanalobis distance
$dV_m/dtMax.(mV/ms)$	218.13	0.007	63.85
$V_mMax.(mV)$	24.47	5.62×10^{-6}	9.43
$NotchV_m(mV)$	-12.64	0.02	41.92
$DomeV_m(mV)$	-8.62	0.015	43.29
$APD_{70}(ms)$	233.04	59.26	49.99
$APD_{90}(ms)$	300.14	89.69	51.19
$RestingV_m(mV)$	-80.81	0.001	38.12

We considered a Mahanalobis distance between 30 and 70 (*i.e.* $\pm$ 2 SD) to indicate a well fitted emulator, and the only emulator that did not meet this criterion was $V_mMax.$. The was not surprising, since I_{Kr} predominantly influences repolarisation, and inspection of the design data showed a change of only $\pm 0.06mV$ in $V_mMax.$ arising from inputs varied across the full range.

3.2 Sensitivity Indices

The first order sensitivity indices were obtained using `GP_emu_UQSA` and are shown in Fig 3. Each row shows the relative contribution of each input, and the sum of these contributions is shown in the column to the right of the main figure. For six of the emulators, the sum of sensitivity indices was close to 1.0, indicating that interaction effects are negligible. The sum of sensitivity indices for the $V_mMax.$ emulator was lower, indicating additional variance arising from either the relatively poor fit or possible interactions.

Three of the inputs had the greatest effect on the outputs: $Kr9$ influenced all outputs except for Dome V_m, $Kr3$ had a strong effect on Dome V_m, and $Kr4$ had an intermediate effect on all outputs. In Fig 4 we have plotted the main effect (obtained using `GP_emu_UQSA`) of these three inputs on APD_{70}, APD_{90}, and

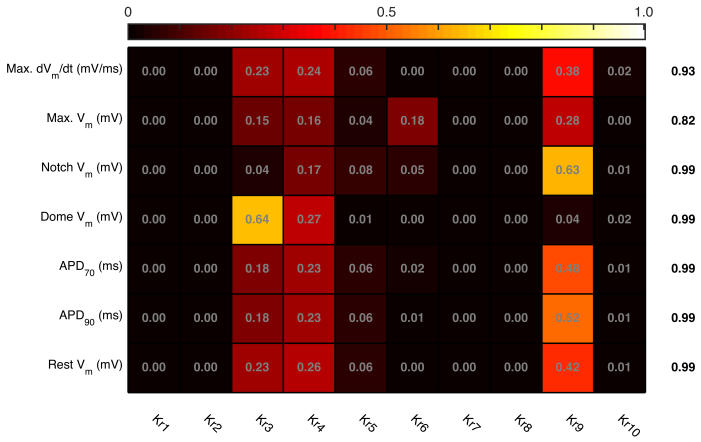

Fig. 3. Sensitivity indices for each combination of input and output. The column to the right is the sum of sensitivity indices for each output. Inputs Kr3 and Kr4 scale the magnitude and voltage dependence of gate activation (equation 3), and input Kr9 scales the voltage dependence of steady state activation (equation 6).

Dome V_m. The main effect is the change in the expected mean of the emulator output as one input changes while all others are assigned a fixed distribution with mean 0.5 and variance 0.01 (in normalised units). These plots show that increasing all three inputs acts to decrease APD.

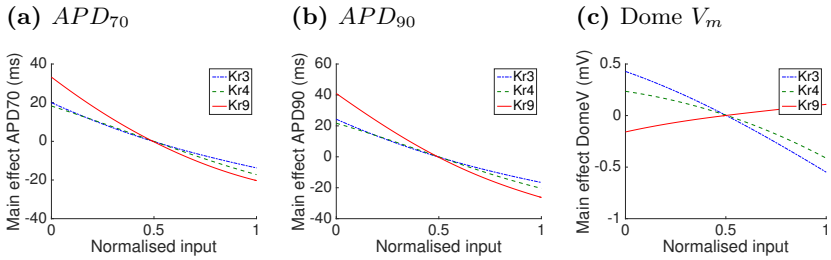

Fig. 4. Main effects of inputs $Kr3$, $Kr4$, and $Kr9$ on (a) APD_{70}, (b) APD_{90}, and (c) dome V_m. Each input is plotted on a normalised scale corresponding to the range in Table 1.

3.3 Insight into model mechanism

The mechanisms by which $Kr3$, $Kr4$, and $Kr9$ act to modify the action potential shape and duration are shown in Fig 5 and Fig 6. In Fig 5 the effect of multiplying

$Kr3$, $Kr4$, and $Kr9$ by 0.5 and 1.5 on the voltage dependence of τ_{xr}, xr_∞, and steady state I_{Kr} is shown. An increased $Kr3$ and $Kr4$ resulted in a shorter activation gate time constant, while an increased $Kr9$ resulted in a leftward shift in the voltage dependence of xr_∞, and consequently an increased I_{Kr} at voltages close to 0 mV.

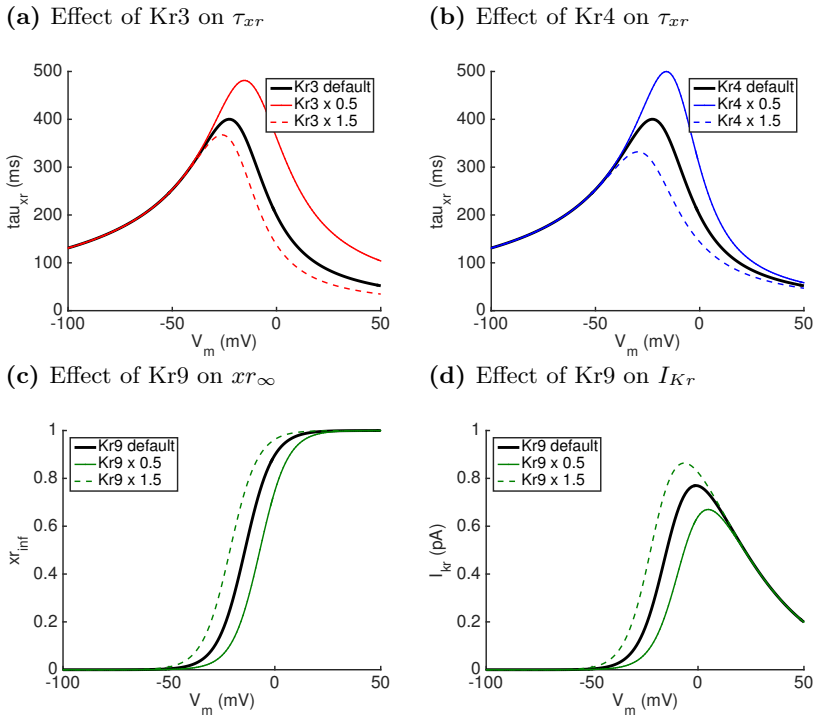

Fig. 5. Effect of multiplying inputs (a) $Kr3$ and (b) $Kr4$ by 0.5 and 1.5 on voltage dependence of τ_{xr}, and effect of multiplying $Kr9$ by 0.5 and 1.5 on (c) xr_∞, and (d) I_{Kr} calculated using steady state values of x_r, xr_∞. Bold lines show baseline model output.

The effects of changes in the gating parameters on I_{Kr}, I_{Ks}, and the action potential are shown in Fig 6. Increased $Kr3$, $Kr4$, and $Kr9$ all acted to increase the magnitude of I_{Kr}, resulting in more outward current during the plateau phase of the action potential and a shorter APD. The increased outward current led to a more rapid repolarisation, which in turn acted to reduce magnitude of I_{Ks}. The change in I_{Ks} compensated for increased I_{Kr}, but not enough to offset the increase in outward current. The magnitude of other currents was not changed (data not shown).

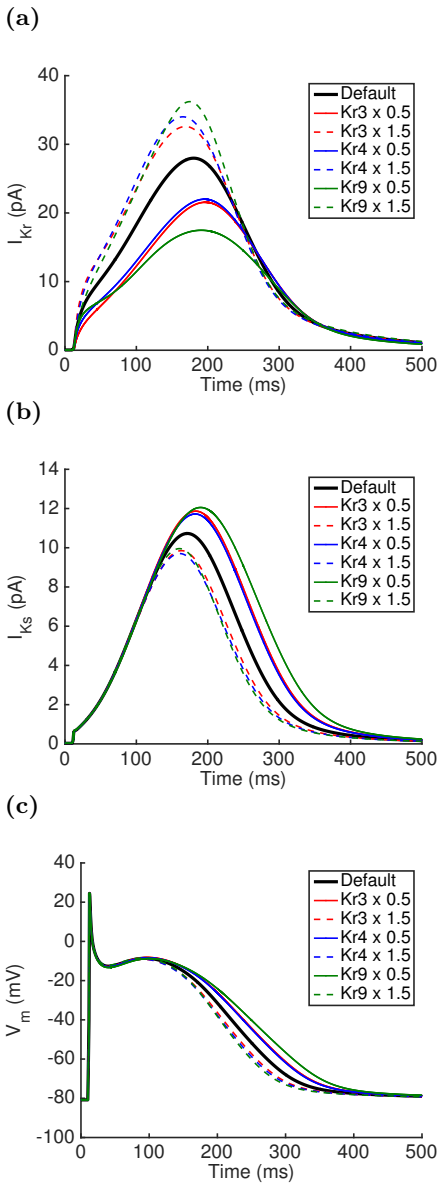

Fig. 6. Effect of multiplying inputs $Kr3$, $Kr4$, and $Kr9$ by 0.5 and 1.5 on the time course of (a) I_{Kr}, (b) I_{Ks}, and (c) V_m. Each plot shows the final action potential of a 40 beat sequence with a cycle length of 1000 ms, and the bold lines show model output for baseline parameter settings.

4 Discussion and Conclusions

In this study we have focussed on how the dynamical behaviour of a single ion channel depends on parameters (or inputs) that are fitted from experimental data. We have used GP emulators to calculate sensitivity indices, and have identified three inputs that have the greatest influence on model outputs. This study builds on previous work that has studied how maximum ion channel conductance influence model outputs [2,3,15,16], and another study that has investigated how the dynamics of I_{Na} influence model behaviour [14]. Taken together, these studies show that tools developed for other modelling communities can be valuable for examining computationally intensive cardiac models, and that uncertainty or errors in fitting cardiac cell model parameters may have an important influence on model behaviour. The present study highlights a number of directions for future research, and these are discussed below.

Several different approaches have been adopted for sensitivity analysis of cardiac models, and these include partial least squares regression [9,16] and a population of models [15]. In this study we chose to construct GP emulators to examine the properties of the I_{Kr} formulation in the Courtemanche model because this approach has already shown promise for analysis of complete cardiac cell models [3,7]. One advantage of GP emulators over other techniques is that the emulator can treat model inputs and outputs as uncertain quantities. Under the assumption that inputs and outputs have a normal distribution then is it possible to directly calculate an output distribution given distributions on model inputs, and this approach is computationally very efficient compared to a more standard Monte Carlo method [3]. Another benefit from a fast-running surrogate of a computationally demanding model is that a large number of model runs can be used to identify sets of model parameters that are consistent with experimental observations, a technique called history matching [17].

To fit the GP emulators, we generated design data by varying each of the inputs $Kr1$ to $Kr10$ in the range $0.5\times$ to $1.5\times$ their baseline value. The baseline values of these inputs are subject to constraints; for example $Kr2$, $Kr3$, $Kr5$, $Kr6$, and $Kr10$ should be positive and non-zero. The range of model inputs over which we trained the emulators was selected so that we could undertake sensitivity analysis without breaking the model. However, it is possible that sensitivities are different outside this range. We also note that the effect of varying input $Kr9$ on the voltage dependence of steady state I_{Kr} shown in Fig 5(d) results in a curve that no longer fits the experimental data shown in Figure 3 of [4]. History matching of the I_{Kr} formulation to new experimental data, given our finding that $Kr3$, $Kr4$, and $Kr9$ have a strong influence on model behaviour, would be an interesting future direction and may be more computationally efficient than other approaches [10].

We have only examined the dynamics of I_{Kr} at a single cycle length corresponding to a resting human heart rate, and it is possible that different inputs begin exert a stronger influence at shorter cycle lengths. Recent studies of cycle length dependent sensitivity analysis have concentrated on the effect of inputs that control the maximum flow of current through ion channels, pumps and ex-

changers [9]. A useful extension of this approach and the present study would be to combine analysis of maximum conductances with model inputs that control ion channel dynamics.

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