

Parameter Sensitivity Analysis of a Human Atrial Cell Model using Multivariate Regression

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Abstract

Atrial cell models form the building blocks of complex multicellular models and contain many input parameters within a large parameter space. A rapid systematic way of quantifying changes in model outputs due to input parameter variability would enhance mechanistic understanding. A parameter sensitivity study on input model conductances within the Courtemanche-Ramirez-Nattel (CRN) human atrial cell model was performed. Input maximal ionic conductances were varied by randomly scaling baseline model values, and used in single cell action potential (AP) simulations. Multivariable regression was performed to find regression matrix B which minimised differences between output Y and predicted $Y^ = XB$. Regression values were mean-centred and normalized to SD, such that a $+0.5$ value implied parameter input 1SD above mean increased output by $0.5SD$. AP determinants were compared ($n = 100$). dV/dt_{max} and V_{amp} showed strong sensitivity only to maximal sodium conductance G_{Na} , whilst APD and t_{peak} were weakly sensitive to multiple conductances. Predicted outputs showed strong correlation to measured values: $0.880 \leq R^2 \leq 0.998$ for measured AP determinants. Multivariable regression is a novel tool for examining parameter sensitivity of the CRN AP model and offers rapid insight to the relative importance of input parameters to specific outputs.*

1. Introduction

Mechanisms of atrial fibrillation (AF) initiation and maintenance are poorly understood and may be addressed by computational models which capture electrical behaviour of atrial cells and tissue. Models of atrial cells are coupled to complex multicellular tissue models to simulate AF initiation and maintenance in the atrium. Biophysically detailed atrial cell models contain many input parameters within a large parameter space (e.g. Courtemanche-Ramirez-Nattel (CRN) [1]).

Parameters are typically taken directly from published lit-

erature in model simulations; however there is increasing interest in understanding the sensitivity of the model to variation in model input parameters to explore the effects of natural variability, disease or pharmacological intervention. Existing methods to carry out parameter sensitivity analysis in cell models of AF are based on investigating single parameter changes systematically; this can be time and cost-consuming and non-exhaustive considering the size of the parameter space and the possibility of parameters co-varying [2]. Thus, a rapid yet systematic method to characterise changes in model outputs due to input variability in atrial cell models would be a novel and useful tool to enhance mechanistic understanding of AF.

2. Methods

A parameter sensitivity study on input model conductances within the CRN human atrial cell model was performed, following the regression analysis performed by Sobie et al on ventricular cells [3].

Briefly, input maximal ionic conductances were varied by randomly scaling baseline model values to a normal or log-normal distribution, generating parameter sets. Each parameter set was used as inputs in single cell action potential (AP) simulations, generating time series data from which model outputs were calculated and extracted. For consistency with the cardiac electrophysiology modelling community, the CRN model code used in the simulations was the downloadable version from the CellML repository. The AP model was simulated with a pacing rate of $1Hz$ over multiple beats, and the final AP was analysed to obtain model outputs. AP activation time was defined as the time at which the membrane potential exceeded $-60mV$. Simulations were performed in Matlab (Mathworks).

$p = 13$ model inputs were chosen, and n runs were simulated. From the input value matrix X ($p \times n$), $m = 10$ model outputs per simulation were extracted to output matrix Y ($n \times m$), and multivariable regression was performed using the NIPALS algorithm [4,5], to find a $m \times p$ regression matrix B which minimised differences between output Y and predicted output $Y^* = XB$.

The structure of these matrices are shown in Figure 1. Re-

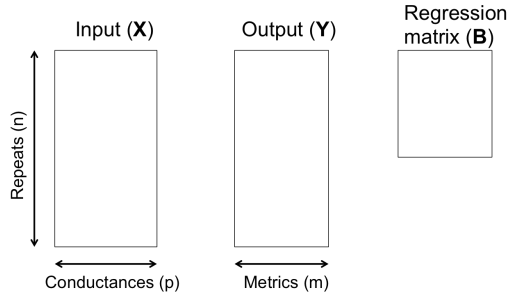


Figure 1. Schematic of input, output and regression matrix structures. The input matrix is of size $n \times p$, the output is of size $p \times m$ and the regression matrix is $p \times m$.

gression values were mean-centred and normalized to standard deviation (SD). A +0.5 value implies that a parameter input 1SD above mean increases the output by 0.5SD.

3. Results and Discussion

Sample voltage-time plots of five simulated CRN action potentials are shown in Figure 2, based on one baseline (blue dashed line) and four randomly varied maximal input conductance sets (parameter variation shown in right inset, normalised and mean-centred to baseline). The top and bottom insets show expanded views of variation in peak AP and in AP resting potential.

Ten model outputs were calculated from post processing

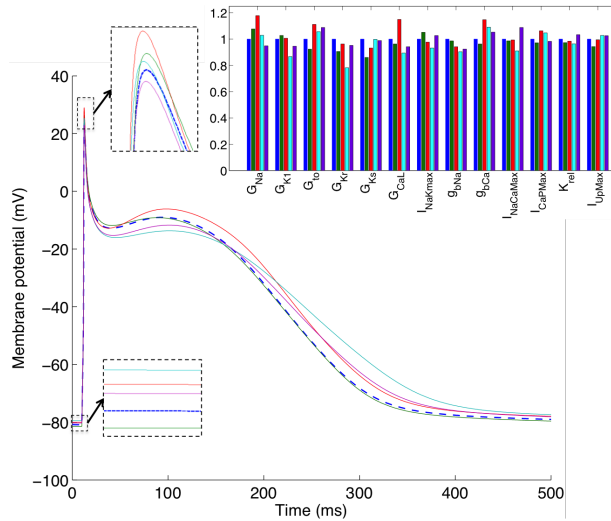


Figure 2. Change in AP morphology relative to baseline (blue dashed line), produced by randomly varying maximal input conductances in CRN model2. Right inset: Coloured bar graph shows conductances normalised to baseline (blue). Top/bottom insets: expanded views of AP peak and AP resting potential.

the simulated CRN model, including outputs determining the shape of the resultant AP and also for the intracellular calcium concentration (Ca_i). Within this study, we focussed on regression analysis of the AP outputs, and in particular to the four AP outputs most commonly considered in the literature: action potential duration (APD), amplitude of AP (V_{amp}), time from AP activation to peak voltage (t_{peak}), and max AP upstroke velocity dV/dt_{max} .

3.1. Regression analysis for true vs predicted outputs from regression model

Based on simulations from generated datasets of randomly varied maximal ionic conductances ($n = 100$), regression matrix B was determined, and used to calculate predicted output matrix Y^* using reverse regression. A regression analysis for true (Y) versus predicted (Y^*) output values was performed, and the results for four of these outputs, APD , V_{amp} , t_{peak} and dV/dt_{max} are shown as scatterplots in Figure 3.

Predicted outputs showed strong correlation to simulated values, with R^2 values as follows: APD : 0.966, V_{amp} : 0.998, t_{peak} : 0.880, dV/dt_{max} : 0.961. This indicates a high predictive power of the regression model in estimating the effects of input parameter variability in the absence of a detailed computer model, and may have further application in using predicted parameter sensitivities in guiding development of new models, or in predicting the effect of small natural variabilities on atrial AP morphologies between individuals with different gene expressions.

However, as highlighted by Sobie in [3], the regression model assumes a linear approximation between inputs and outputs, and cannot predict whether this approximation will hold true for a wider range of parameter values that may still be within physiological range. Thus the regression model would need to be complemented by further empirical study to determine the confidence levels of the model in specific circumstances.

3.2. Parameter sensitivity analysis

Of the ten extracted model outputs, four outputs of action potential duration (APD), AP amplitude (V_{amp}), time from activation to peak (t_{peak}) and max AP upstroke velocity dV/dt_{max} were compared to determine the relative sensitivity of the outputs to variation in maximal input conductance ($n = 100$). These results are displayed in Figure 4.

dV/dt_{max} and V_{amp} showed strong sensitivity only to maximal sodium conductance G_{Na} (0.98 and 0.94 respectively), whilst APD and t_{peak} were weakly sensitive to multiple conductances: G_{K1} (-0.35), G_{to} (0.49), G_{Kr} (-0.56), G_{bCa} (0.32) for APD , and G_{K1} (0.63), I_{NaKmax} (0.33), G_{bCa} (-0.53) for t_{peak} .

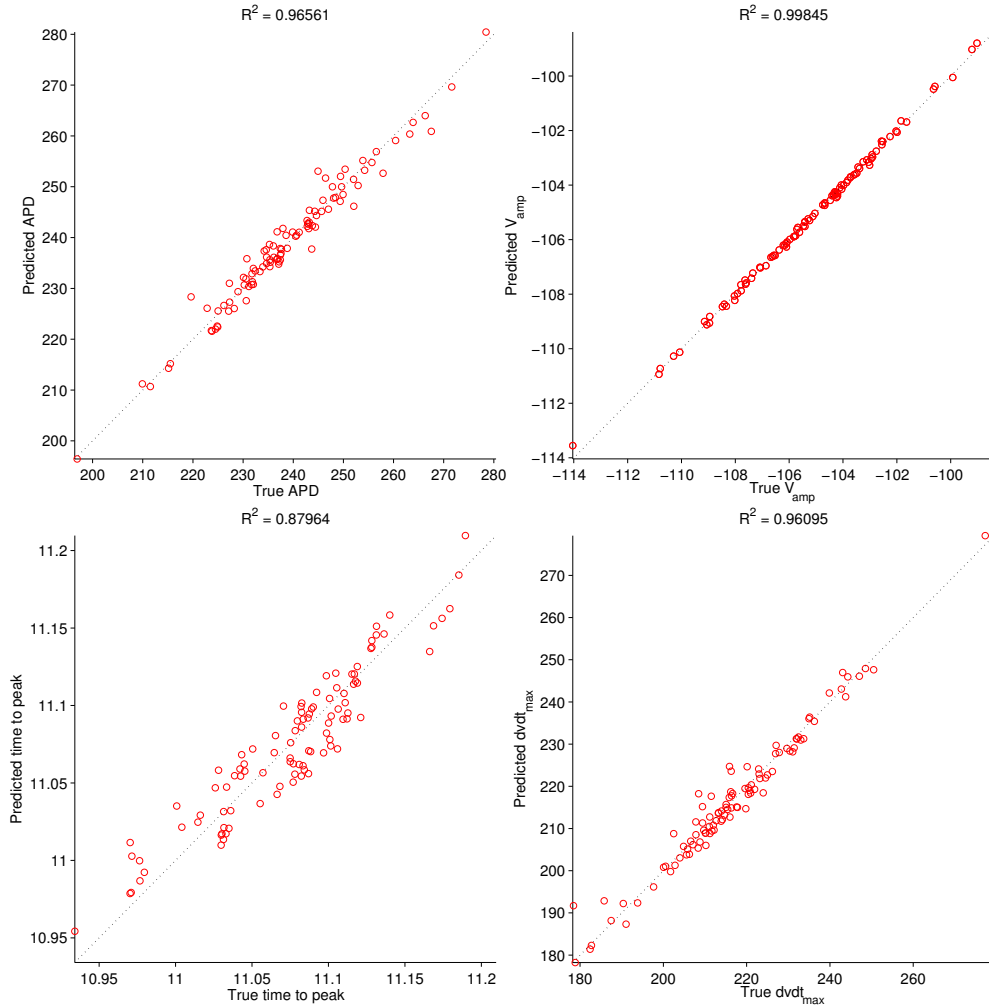


Figure 3. Predictions of the regression model against simulated outputs. Four computed outputs from simulations of the CRN single cell model, against predicted values generated by reverse regression. A larger R^2 value is indicative of a close match between computed outputs Y and the predicted outputs Y^* based on the regression matrix B .

Several of these results, namely the sensitivities of V_{amp} and dV/dt_{max} to G_{Na} confirm the strong relationship between sodium channels and AP activation that is well known in the scientific community, thus serving to sanity-check the predictive power of the model. Other more subtle results highlight the multi-parametric sensitivity of given outputs to different input ionic conductances, which may inform mechanistic understanding of AF initiation and maintenance, and guide future pharmacological interventions to target specific AP outputs. These results are based on local neighbourhood sensitivity analyses of the input parameters, and further work to explore the effect of larger parameter variability on outputs would improve the model. The regression model technique may also be useful in comparing and revealing subtle variations, between different published models of an atrial AP or between the

model and experimental data allowing researchers to select or modify the chosen model for future simulation studies.

4. Conclusion

Multivariable regression is a novel and rapid tool for examining multiple input parameter sensitivities within the CRN AP model, and can offer detailed insight to the relative importance of chosen input parameters on specific model outputs, with promising applications in improving mechanistic understanding of AF and guiding future experimental design. However, the technique is based on linear input-output regression in a local neighbourhood of parameter space, and further work is required to fully explore parameter sensitivities of atrial cells, in single cells and in multicellular tissue.

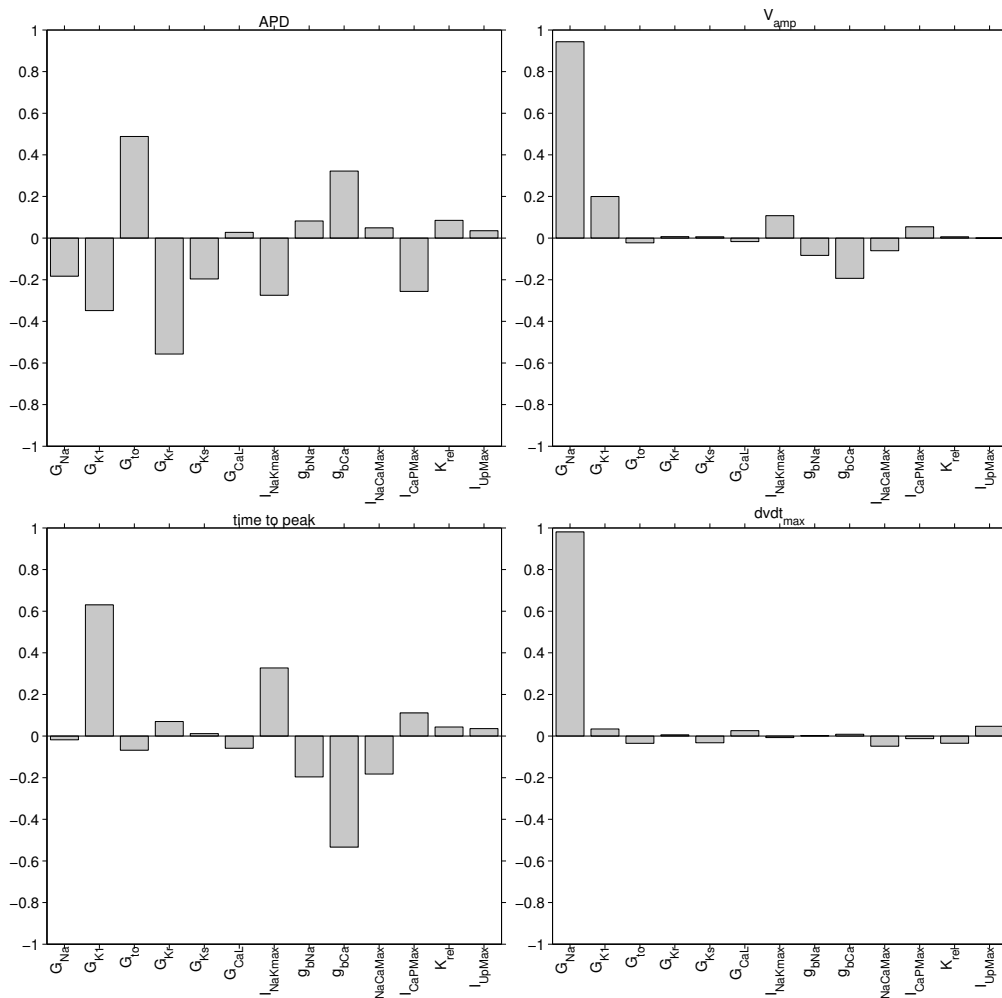


Figure 4. Results of parameter sensitivity analysis for APD , V_{amp} , t_{peak} and dV/dt_{max} . In each plot, a single column of regression coefficients in the matrix B is plotted, indicating how relative changes in input parameters lead to variation in a particular output. Values are mean-centred and normalised to SD. A value of +0.5 indicates that a parameter input of 1 SD greater than the mean will increase the output by half an SD.

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