# Parameter sensitivity from Single Atrial Cell to Tissue: How much does it matter? A Simulation and Multivariate Regression Study

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## Abstract

*We previously performed parameter sensitivity analysis in the Courtemanche-Ramirez-Nattel (CRN) human atrial cell model, and sought to extend this to address sensitivities across spatial scales. Thus, we investigated how input variability and uncertainty at cellular level propagates through to affect tissue level dynamics.*

*We simulated action potential (AP) propagation in a strip of cardiac tissue, using the monodomain and CRN tissue/cell models. Input maximal conductances (p=12) within the CRN model were varied within 1/3 of baseline, and points in parameter space selected by Latin hypercube sampling. The tissue was paced for twenty beats at 1Hz (S1), and 6 metrics of AP shape were derived for the final beat (max dV/dt, max voltage, resting voltage, action potential duration to 90% repolarisation (APD90), resting voltage and APD to 50% repolarisation (APD50)). S1 pacing was followed by a single ectopic beat (S2) at different intervals, at one end and the midpoint of the tissue. Additional tissue metrics were calculated, including conduction velocity (CV), CV and APD restitution curves and the size of the tissue vulnerable window. Subsequently, parameter sensitivity on both tissue and cell level outputs was performed using Partial Least Squares regression. Simulations and postprocessing were performed in Nektar++ and Matlab (Mathworks).*

*Regression values were smaller in tissue compared to cell (APD90/max dV/dt R2=0.43/0.27 in tissue vs R2=0.92/0.97 in cells). AP metrics exhibited stronger sensitivities to maximal ionic conductances in single cell compared to tissue simulations (sensitivity indices 0.98/0.99 for max dVdt/max voltage to $G_{Na}$ in cell vs 0.48/0.59 in tissue) while CV was sensitive to $G_{Na}$ (0.61) and VW to $G_{Na}$ (-0.58) and $G_{K1}$ (-0.61). Further analysis of functional metrics in tissue will determine sensitivity of tissue to cellular changes.*

## 1. Introduction

Atrial arrhythmias has a prevalence of $1-2\%$ in the UK and significantly increases risk of stroke. Despite advances in clinical and experimental studies, the initiation and maintenance of atrial arrhythmias remain poorly understood. Theoretical investigation using computational models have become increasingly useful in developing a quantitative understanding of cellular and multicellular electrical activity, by coupling detailed biophysics and their interactions at different spatial scales. Such models continue to grow in complexity, incorporating an ever-expanding set of parameters; a detailed study of how changes in these parameters affect model outputs (sensitivity analysis) is an important research question.

We previously performed a parameter sensitivity analysis in an isolated Courtemanche-Ramirez-Nattel (CRN) human atrial cell model [1, 2] using partial least squares (PLS) regression, and wished to extend these analyses in a multicellular environment. In this study we investigated how input variability and uncertainty in a cellular model propagates through to cellular outputs when coupled to other cells in an idealised tissue, and how this variability affects outputs at tissue level.

## 2. Methods

We simulated action potential (AP) propagation in a thin 2D strip of cardiac tissue (50×0.5mm), using a monodomain representation of the tissue, coupled to the CRN atrial cell model. To investigated the sensitivity of the simulation outputs to inputs, we computed 100 sets of simulations each with a different set of input parameters. Input maximal conductances (p=12) within the CRN model were varied within 1/3 of the baseline (default) value and normalised to the range 0 to 1 (0.5 being the baseline value), using Latin hypercube sampling to sample the parameter space. A spatial resolution of $0.25$mm in the tissue was used, which represented the length of a single cardiac myocyte. The tissue was pre-paced for twenty beats at 1Hz

(S1), and 6 metrics of AP shape were derived for the final S1 beat (max dV/dt, max voltage, resting voltage, action potential duration to 90% repolarization (APD90), resting voltage and APD to 50% repolarization (APD50)).

S1 pre-pacing was followed by delivering a single ectopic beat (S2) at varying time intervals, using two separate protocols: one S2 beat delivered at one end of the tissue and one at the midpoint. Tissue metrics were measured, including conduction velocity (CV) between two points distal from the tissue edge and the size of the tissue vulnerable window, defined as the time window during which a single beat delivered in the middle of the tissue resulted in unidirectional conduction block. Parameter sensitivity on both tissue and cell level outputs was performed using partial least squares regression following Sobie (2009). Parameter generation and postprocessing was completed in Matlab (Mathworks) and tissue simulations were performed in Nektar++ (http://www.nektar.info).

## 3. Results and Discussion

Figure 1 shows sample action potentials from 25 of these parameter sets, from single cell simulations versus corresponding AP traces using the same parameters coupled to tissue. We noticed that in general, the AP shapes were altered when the cell was coupled in tissue with more significant changes in the max voltage and max dV/dt, and this had an effect on reducing the sensitivity of the AP outputs to the input parameters (maximal ionic conductances) which we comment on below. This result is perhaps expected knowing that electrotonic coupling alters AP shape. We also noticed that varying the input maximum conductances altered the conduction velocity (CV) and vulnerable window (VW) in the tissue.

A result we wish to highlight was that, despite all 100 parameter sets produced analysable AP data in single cell simulations, a small sample of the parameter sets (n=5) produced outlying or unphysiological results when coupled to tissue, and these were excluded from further analysis. These include one AP which had different repolarisation shape and resting potential within the tissue, an AP which did not exhibit a spike and dome morphology and APs which exhibited significantly long vulnerable windows. The results from these AP runs were excluded from further analysis.

The goodness of fit results from PLS regression is shown in Figure 2. This showed that regression values were smaller when computed in tissue outputs compared to cell (APD90/max dV/dt $R^2 = 0.43/0.27$ in tissue vs $R^2 = 0.92/0.97$ in cells). This highlights that the quality of the PLS regression fitting is sensitive to the goodness of the correlation between inputs and model outputs, and so such techniques need to be applied with care.

Nonetheless, we used the PLS regression technique to generate a heatmap of sensitivity indices shown in Figure 3, which showed, for variation in input parameters, the relative effect it had on changes in outputs. We found that AP metrics exhibited stronger sensitivities to maximal ionic conductances in single cell compared to tissue simulations (sensitivity indices 0.98/0.99 for max dVdt/max voltage to $G_{Na}$ in cell vs 0.48/0.59 in tissue). At tissue level, CV showed sensitivity to $G_{Na}$ (0.61) and VW to $G_{Na}$ (-0.58) and $G_{K1}$ (-0.61). A +0.5 value indicates that a parameter input of 1 SD greater than the mean will increase the output by half an SD.

## 4. Conclusions

We found, in general, that simulated behaviour of action potentials are different in isolated cells versus tissue, and importantly, that parameter sets that produce physiological action potentials in single tissue may not necessarily propagate to be meaningful at tissue scale, both physiologicaly and numerically. Tissue parameters such as conduction velocity and vulnerable window were affected by certain cell-level parameters. Sensitivity analysis tools such as PLS regression are less effective when considering uncertainty propagation across scales and thus results from single cell simulations should be applied with care when extrapolating to more complex multi-scale systems. Further work should be undertaken to analyse restitution properties or consider tissue heterogeneities.

## Acknowledgements

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## References

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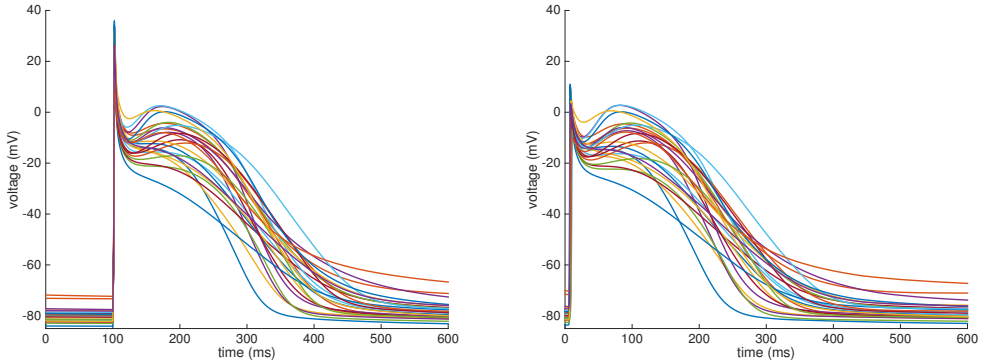


Figure 1: Sample action potential traces from single cell simulations (left) vs corresponding traces in tissue (right) highlighting differences between single cell and tissue simulations, particularly in the height of the AP upstroke and the max dV/dt. .

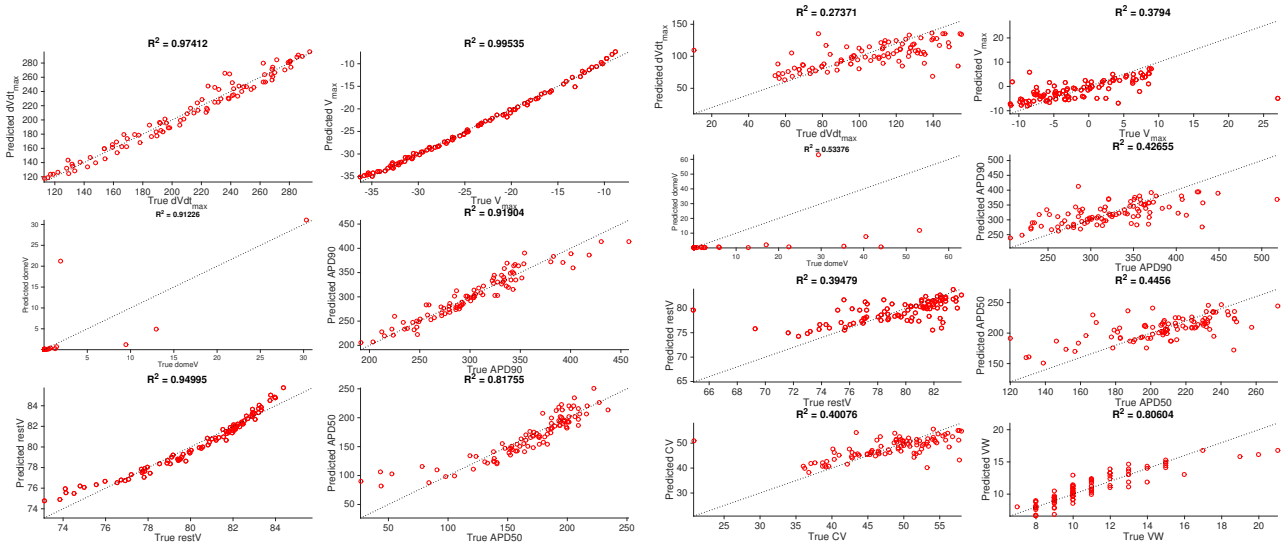


Figure 2: Predictions of the PLS regression model compared against simulated AP and tissue outputs for cell and tissue simulations. Scatterplots of six AP outputs: dV/dtmax (top left), Vmax (top right), dome V (middle left), APD90 (middle right), restV (below left) and APD 50 (below right). In the tissue outputs, there is additionally conduction velocity (CV) (bottom left) and vulnerable window (VW) (bottom right). A larger R2 value is indicative of a close match between computed outputs Y and the predicted outputs Y*. .

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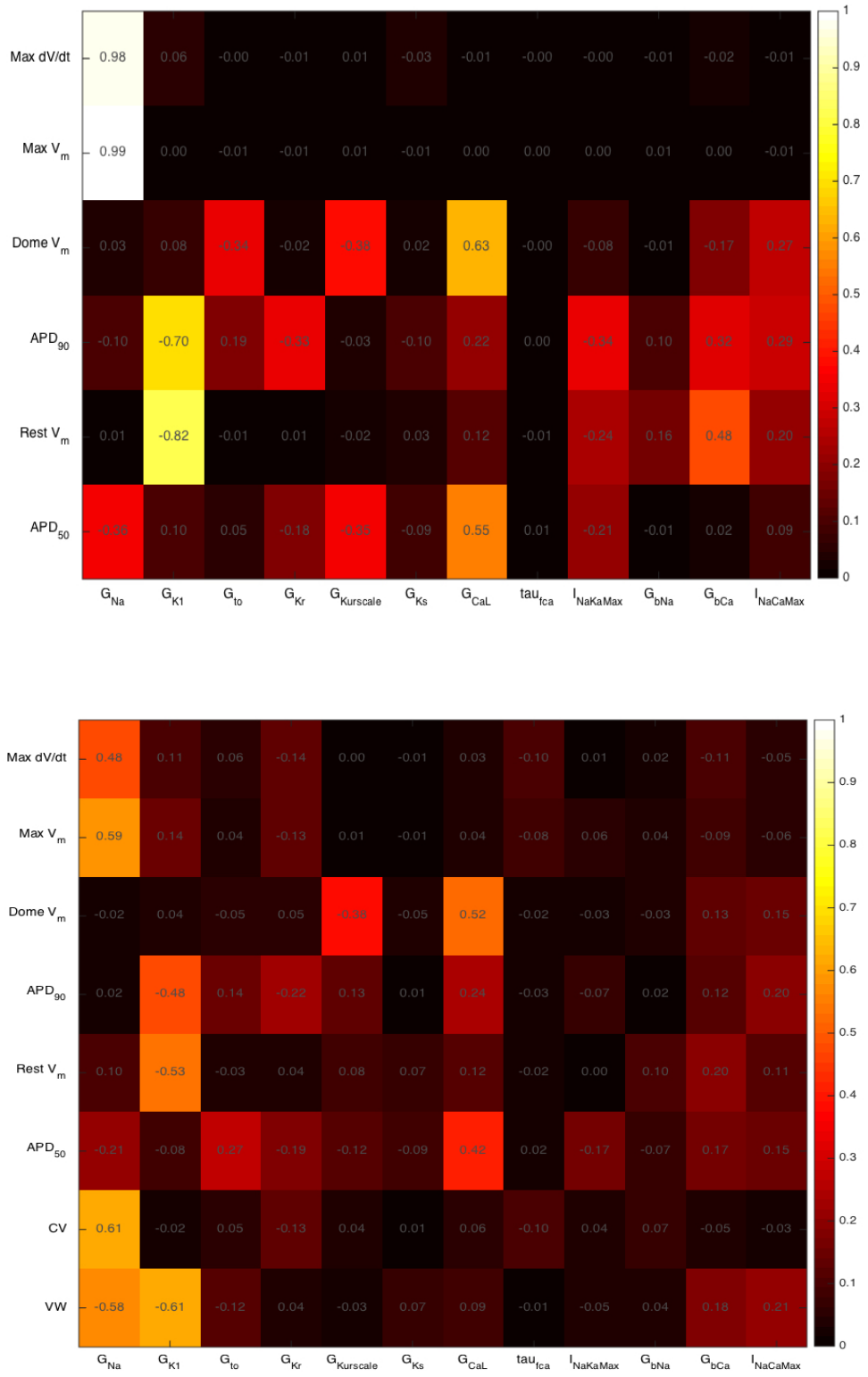


Figure 3: Heatmap of sensitivity indices generated using PLS regression, for single cell (top) and tissue simulations (bottom). In each graph, each row indicates how changes in input parameters lead to changes in outputs for the output corresponding to the row. Each column reflects the effects of the input on all outputs.Values are mean-centred and normalised to SD. A +0.5 value indicates that a parameter input of 1 SD greater than the mean will increase the output by half an SD.