Generating Correlatively Constrained Populations of Cell Models for Tissue Scale Simulations

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Abstract

Introduction: *Cardiac electrophysiology and intracellular calcium (Ca^{2+}) handling vary between cells, shaping action potential dynamics, arrhythmia susceptibility, and drug response. Tissue-scale population modelling remains difficult because ionic parameters must vary spatially without losing physiological behaviour and parameter correlations. We develop a novel framework generating heterogeneous populations of models for tissue simulations.*

Methods: *Model derivation was performed using 2D simulations where each cell was randomly assigned an average Ca^{2+} target and parameters iteratively updated until the target was met for each cell. Correlations between Ca^{2+} target and model parameters then inform generator functions to produce parameter combinations for a given input. Two models were considered, one where all parameters were perfectly correlated with each-other, and another that assumed no correlation of input.*

Results: *I_{CaL} scaling factor was linearly related to the Ca^{2+} target and other parameters derived from this, dependent on which of the two approaches were used. The generator functions were able to produce parameter combinations that were valid for the original derivation population.*

Conclusions: *Calcium-targeted feedback provides a simple and robust approach for generating heterogeneous cell and tissue populations from a single control parameter while preserving physiological variability.*

1. Introduction

Cardiomyocytes exhibit substantial intercellular variability in their electrophysiological properties. Underpinned by variation in the expression and balance of ion channels, transporters, exchangers, and Ca^{2+} handling proteins, these intercellular differences manifest as measurable heterogeneity in action potential properties and homeostasis and may influence arrhythmia susceptibility, dynamics, and the response to intervention [1,2].

These observations have motivated the development of computational models that incorporate populations of cells, wherein the parameters describing the main features of the primary ion currents and Ca^{2+} handling proteins are varied between individual myocytes [2]. Such models have indicated that cell-to-cell variability can influence repolarisation patterns even in the presence of the strong electrotonic coupling associated with intact cardiac tissue [3]; intercellular heterogeneity may therefore strongly influence vulnerability to arrhythmia and the safety and efficacy of pharmacological intervention.

Populations of models have proved very successful in implementations of *in silico* pharmacology, helping to improve the predictive accuracy. Despite these successes, there remain areas that need to be further developed to fully deliver on the promise that these approaches present. Firstly, models commonly vary each parameter randomly and then filter out the resultant population to exclude unrealistic or unphysiological properties [4]; correlations between the various parameters have not been systematically explored, and it is not clear that the exclusion of "unphysiological" cells in *isolation* genuinely correspond to electrophysiological parameter combinations that are not allowed *in situ*. Secondly, applications of the models are generally performed in single cell rather than in tissue and it is not obvious how to distribute parameter variability in tissue models in a controlled and reproducible manner. Thus, it would be highly valuable to develop an approach that derives the population in the context of electrotonically coupled tissue, intrinsically accounts for correlations between parameters, is fully reproducible, and contains an easy mechanism to distribute the population in tissue models.

In a previous study, Moise *et al* [5] developed a long-term model of atrial fibrillation induced remodelling that was based on a highly simplified developmental biology concept: that cardiomyocytes aim to regulate and maintain their average intracellular Ca^{2+} concentration through feedback between Ca^{2+} and ion current expression. One feature of this approach was that at each time point, or after each intervention, a population of cell model parameters was produced, representing the *in situ* requirements for

each cell to maintain its own Ca^{2+} target. Thus, the model contains a single controlling parameter (the Ca^{2+} target), is built on correlations between different channels, and is derived in the context of electrotonically coupled tissue with no arbitrary exclusion filters.

In this study, we explore the possibility of developing a "population of models" generator based on this underlying concept of local Ca^{2+} target driving heterogeneity in model parameters.

2. Methods

2.1. Overview of approach

We develop two approaches to derive a population generator: a fully correlated model that follows the same fundamental process as introduced in Moise *et al* [5], and an uncorrelated model that does not assume correlations between any parameters. The process of model derivation is the same for each approach: each node of a 2D tissue model was assigned a local Ca^{2+} target sampled from a normal distribution with a given mean and standard deviation and according to a spatial random field with a given length-scale. The model was then paced at a cycle length of 1000 ms (1 Hz) to steady state and the difference between the average Ca^{2+} over the final two beats of each node and its assigned Ca^{2+} target was calculated. This difference informs the iterative update of either all parameters (correlated model) or solely the conductance of I_{CaL} (uncorrelated model) in an attempt to match the cell's average Ca^{2+} with its assigned target. The process was repeated such that all nodes have sufficient time to reach their assigned Ca^{2+} target, and only those that successfully met this target were retained. The parameters of the ion currents and Ca^{2+} handling channels were then correlated with the given Ca^{2+} target to derive equations that generate parameter combinations from an input Ca^{2+} target – the "population generator". This enables the population to be described by one primary parameter, the Ca^{2+} target, thusly providing a convenient mechanism to control the way heterogeneity is distributed in tissue models.

In this model development, the Courtemanche–Ramirez–Nattel (CRN) human atrial cell model was used [6]. Models were derived in both coupled tissue and uncoupled, single cell conditions to explore the influence of electrotonic coupling on the generated populations. Generated populations could then be simulated also in either single cell or coupled tissue conditions to assess how the parameter combinations manifest as action potential heterogeneity.

2.2. Fully correlated model

The fully correlated model follows the same process outlined in the previous study. Each node was initially assigned the default set of parameters (corresponding to all scaling factors being set to exactly 1.0). The difference between the average Ca^{2+} at each node and its assigned Ca^{2+} target informed a linear iterative update of each current to match the target. The process was repeated until all targets were either met or deemed unattainable. Each current was assigned a weighting factor to represent the strength of its influence on Ca^{2+} homeostasis.

It was determined that in the CRN cell model, I_{to} had very little direct impact on the Ca^{2+} transient and was hence treated as an independent parameter to introduce further (and random) variability; for each node, the scale factor for I_{to} was randomly sampled from a normal distribution, truncated between 0.3 and 1.7 at 0.1% to 0.99% of the population.

The scale factor for I_{CaL} was then fit against the Ca^{2+} target, which was conveniently linearly related. Thus:

$$G_{CaL} = f(Ca^{2+}) \qquad (1)$$

Where f is a simple linear function with parameters derived from the data and G_{CaL} is the derived scale factor for I_{CaL}. The scale factor for all other currents was then derived from the I_{CaL} scale factor by adjusting for the assigned weight of that parameter:

$$G_i = 1 + w_i(G_{\mathrm{CaL}} - 1). \qquad (2)$$

where G_i is the scale factor for each given current, and w_i is the weighting factor assigned to that current, which is negative if it changes opposite to I_{CaL}.

2.3. Uncorrelated model

Whereas the fully correlated model offers simplicity and convenience, its underlying assumption that all currents vary between cells in a correlated manner is not physiological. We therefore attempt to overcome this limitation through the derivation of an uncorrelated model. In this instance, each node is randomly assigned the scale factors for all relevant parameters from truncated normal distributions in the same way as I_{to} in the correlated model. Only I_{CaL} was iteratively updated during the derivation process. The correlations between parameters of the successfully fit cells were then explored at various Ca^{2+} targets to derive a model that relates to all parameters. To facilitate this, discretized Ca^{2+} target maps were used to provide 10 Ca^{2+} target "bins" within which the correlations between parameters can be explored.

The I_{CaL} scale factor was correlated with the Ca^{2+} target to provide a mean (expected value) fit and a measure of the variability in allowed I_{CaL} at each target. As with the correlated model, the mean I_{CaL} was linearly related to the Ca^{2+} target (equation 1). The approach to relating all other parameters can be summarized as: calculate the residual G_{CaL} for each node (difference between G_{CaL} and the mean

expected at that Ca^{2+} target) and then determine which parameter most strongly correlates with this residual. In this implementation, this was found to be G_{NCX}: the expected value for G_{NCX} correlated with the G_{CaL} residual. The G_{NCX} residual was then calculated and the parameter that most strongly determines this was found (in this case, it was the sum of I_{Kr}, I_{Ks}, I_{Kur}, I_{K1} and I_{NaK}). This process was continued, sequentially determining which next parameter most strongly correlates with the residual of the previous parameter until all parameters were related.

The generator was then based on these correlations and involves the following process: 1. Randomly sample Ca^{2+} target. 2. Calculate mean expected G_{CaL} and the variation of G_{CaL} based on this target. 3. Randomly sample the G_{CaL} residual based on this, which gives the final value for G_{CaL}. 4. Calculate the mean expected G_{NCX} and the variation of G_{NCX} based on this residual. 5. Randomly sample the G_{NCX} residual, which gives the final value of G_{NCX}. 6. Derive the next parameter from the G_{NCX} residual, and so on until all parameters are defined. Thus, this approach involves a given number of *independent* random inputs to determine the sampling to generate *interdependent* parameter values.

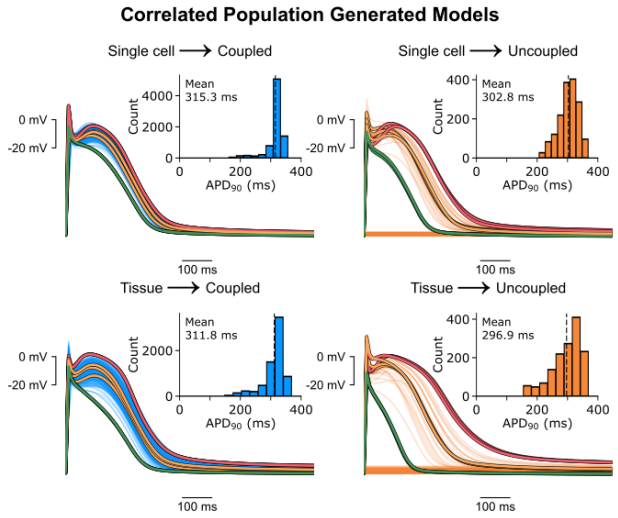

Figure 1. Action potential properties arising from the generated population based on the fully correlated model. Figure illustrates the generated population that resulted from the derivation in single cell (upper) or tissue (lower) and then simulated in tissue (left) or as isolated cells (right).

3. Results

3.1. Generated populations

Both models generated populations with variation in action potential morphology and duration that were correlated with variation in the underlying Ca^{2+} transient (**Figs. 1-2**). Deriving the population in tissue led to a larger variability of parameters and action potential features than in single cell across both models, as the electrotonic smoothing enables a wider range of parameters to result in the same average Ca^{2+}. Similarly, the generated populations resulted in a greater degree of action potential heterogeneity simulated as isolated cells than in coupled tissue. The largest variabilities were therefore observed for the models derived in coupled tissue with the generated population simulated in isolated cells, which most directly reproduces the context of myocyte isolation to perform single cell experiments such as patch clamp.

3.2. Generation of "unviable" cells

In the uncorrelated model, wherein the range of values for currents such as I_{K1} vary substantially more and unrelated to other parameters, isolated cells exhibited the most substantial variability, with some demonstrating unrobust action potentials or spontaneous activity that is never observed in coupled tissue (**Fig. 2**). This is analogous to isolated cell experiments where many cells may be discarded as being "unviable". Whereas some of this is likely due to cell damage during the isolation process, it is highly likely that it also represents a physiologically meaningful range of cell behaviors, given that these cells behave entirely reasonably in tissue and hence there would be no reason for biology to disallow them. It may indeed be that these extreme cases have a large impact on the overall tissue response to intervention and thus we argue it is imperative to retain them in the population.

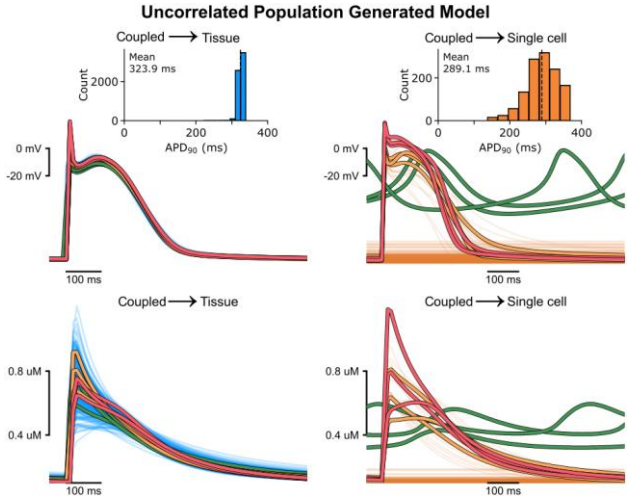

Figure 2. Action potential and Ca^{2+} transient properties arising from the generated population based on the uncorrelated model. All panels show the model derived in coupled tissue and then simulated in tissue (left) or single cells (right).

3.3. Validation of generated populations

For the fully correlated model it follows trivially that each member of the generated population corresponds to a valid member of the original population on which the generator was derived. However, this is far less trivial for the uncorrelated model. It needs to be determined that the correlations between different parameters and residuals are correct and that the generator does not produce parameter combinations which would not have been produced in the original derivation simulations.

Validity was assessed through applying a sequence of filters to the original population used for model derivation based on a given set of generated parameters. Within a set tolerance (± 15%) the original dataset was first filtered to include only those that were within this tolerance for G_{CaL}. The resulting population was then further filtered by G_{NCX} and so on for all parameters. The proportion of parameter combinations that fail at each filter was then recorded. If the model is valid, then very few or ideally no failures should occur for the first few filters. However, because we are combining many filters to a finite population, it becomes statistically less likely that members of the original dataset happen to exist at each specific parameter combination as the number of filters increases. Thus, we also estimate the expected failure rate at each filter.

From this initial implementation, approximately 70% of generated parameter combinations passed all of the filters in sequence, with only negligible numbers failing during the first few filters (**Fig. 3**). The actual failure rate was comparable to the expected failure rate, giving confidence that the correlations between these parameters were correctly captured and that the generator does not produce combinations that would not have been allowed in the original dataset.

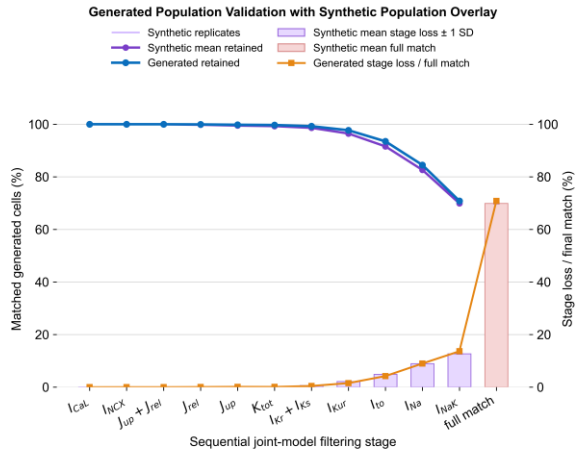

Figure 3. Validation of the generated population against the reference population and expected failure rate.

4. Conclusion

We have demonstrated the viability of developing a "population of models" generator that produces valid correlations of model parameters associated with a given input Ca^{2+} target. The approach enables robust and reproducible implementation of intercellular heterogeneity in tissue models and highlights the importance of deriving model parameters in an electrotonically coupled context.

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