From Microscopic Calcium Sparks to the ECG: Model Reduction Approaches for Multi-scale Cardiac Simulation

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Abstract

Malfunctions in the intracellular calcium handling system are being increasingly linked to multiple cardiac arrhythmias. Feedback mechanisms in spatio-temporal sub-cellular calcium dynamics are critical for the development of spontaneous calcium waves which may underlie ectopic focal activity. However, computational models which account for such processes are unsuitable for incorporation into organ-scale simulations, thus limiting the ability of multi-scale modeling approaches to explain and dissect the role of spatio-temporal calcium handling in organ-level arrhythmogenesis.

In this study we demonstrate two methods to increase the computational efficiency of models which account for spatio-temporal calcium dynamics, thus facilitating true multi-scale modeling approaches. One method is guided by empirical analysis of the microscopic model; the second method takes advantage of mesoscopic physics approaches to naturally capture critical stochastic behaviour.

Both methods successfully reproduced the macroscopic consequences of spatio-temporal calcium dynamics in efficient single cell models. This allowed integration into a whole-organ model of the ventricle and simulation of the ECG.

1. Introduction

Intracellular calcium handling dynamics plays a critical role in cardiac function in normal conditions; malfunctions of the calcium handling system have been increasingly linked to cardiac arrhythmogenesis [1,2]. During the cardiac cycle, 'calcium-induced-calcium-release' is largely responsible for cellular contraction. This refers to the mechanism by which calcium influx through the membrane calcium channels binds with the ryanodine receptors (RyR), triggering a significant release of calcium into the cytosolic space from an intracellular store. This occurs in restricted volumes of the cytosol called dyads, which are spatially distributed throughout the cell.

It is this feedback mechanism, and the coupling of the intracellular calcium transient to membrane currents, which is conjectured to play a role in arrhythmogenesis: spontaneous calcium waves activate the sodium-calcium exchanger causing a membrane depolarisation which may result in a full, spontaneous action potential. This can lead to ectopic activity in tissue, interrupting sinus rhythm and mediating the development of self-perpetuating re-entrant excitation.

The spatial nature of the cardiomyocyte and the microscopic structure of the dyad are both critical in the generation of spontaneous calcium waves. A random transition of a few RyRs within a single dyad can result in a calcium release sufficient to trigger opening of further receptors within the dyad. This released calcium can then propagate into neighbouring dyads, thus triggering a calcium spark mediated chain-reaction. Under the right conditions (such as an increase in RyR sensitivity to calcium associated with β-stimulation, heart failure and atrial fibrillation [2]), this can propagate throughout the cell as an intracellular calcium wave. Thus, microscopic fluctuations can manifest in whole-cell and even whole-organ dynamics and altered electrocardiograms (ECG).

Dissecting these mechanisms and their role in cardiac disease therefore requires true multi-scale approaches. Computational modelling provides a powerful tool for such multi-scale investigation of cardiac dynamics. In the last decade or so, a multitude of multi-scale cardiac models have been developed which can simultaneously account for detailed single cell electrophysiology and both small- and large-scale anatomical structure [3]. These multi-scale models require computationally efficient descriptions of the single cell, traditionally achieved using non-spatial, or 0D, cell models. Whereas this type of model has been successfully applied to a variety of cardiac behaviour, it cannot capture the critical mechanisms dependent on microscopic stochastic processes and intracellular structure.

Recently, more detailed single cell models have been developed to explicitly model spatio-temporal calcium dynamics [1]. These models consider individual dyads and the dynamics of individual RyRs contained within them, preserving stochastic processes in spontaneous release mechanisms and spatial calcium diffusion.

However, this comes at a significant computational cost: single cell models which account for spatio-temporal calcium dynamics in three-dimensions can be individually equally computationally intensive as whole-organ models employing millions of 0D single cell descriptions.

In this study we develop two different model reduction methods to model stochastic processes at the organ scale, by accounting for stochastic intracellular dynamics in computationally efficient, 0D cell models. As a proof-of-concept, the approaches are applied to demonstrate the impact of sub-cellular calcium dynamics under increased RyR sensitivity on whole-organ excitation and the ECG.

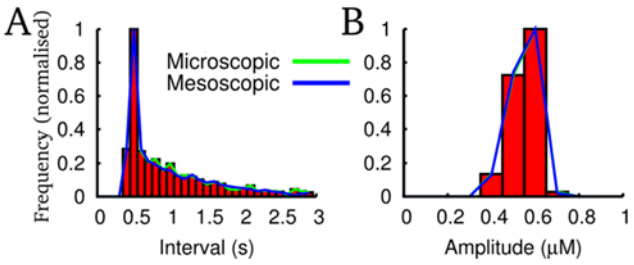

Figure. 1: Incidence and magnitude of spontaneous calcium sparks over 1000 simulations. Histogram plots of time to first spontaneous spark (A) and magnitude of whole-cell transient (B). The bars and green lines represent the microscopic case; the fit achieved by model reduction method 1 is represented by the blue line.

2. Methods

2.1. Cell and tissue models

The Gaur-Rudy model describing the Guinea-pig ventricular cell is selected for demonstration of the model-reduction approaches [1]. The model accounts explicitly for 100 dyads in an idealised 1D transverse-tubule, each containing multiple RyRs modelled stochastically (Nryr = 100 per dyad for control). We then derive two further models: a 3D model of the whole single cell (containing 10 000 dyads and a semi-idealised structure) and a 0D deterministic model which will form the basis for the '0D mesoscopic cell model' - i.e. the 0D model which incorporates stochastic spatio-temporal calcium dynamics.

To demonstrate suitability for the investigation of multi-scale arrhythmogenesis, the sensitivity of the RyR to calcium is increased (mimicking the type of effect heart failure and β-stimulation have on calcium dynamics) and the membrane dynamics are slightly adjusted to promote spontaneous action potentials resulting from delayed-after-depolarisations (DADs). The 0D mesoscopic model is then mapped onto a reconstruction of ventricular anatomy and the mono-domain equation is solved to describe electrical activity in tissue. ECGs are computed using a boundary element method on an idealised torso mesh [4].

2.2. Model reduction method 1: Modeling calcium waves based on empirical analysis of the microscopic model

The first method focuses on a simple way to account for the macroscopic effect of sub-cellular spatio-temporal calcium dynamics in the 0D cell model. This is achieved through inducing state-transitions of the whole-cell, deterministic RyR model guided by empirical analysis of the microscopic, stochastic cell model.

Multiple simulations of the microscopic model are performed to determine the incidence and magnitude of whole-cell calcium waves (Figure 1). Simple functions are then derived from these distributions, one describing the incidence of calcium waves (dependent on time since last RyR opening) and the other describing the magnitude. The incidence function is then combined with a random number to determine the initiation of a calcium wave. Once this has been determined, the effective calcium 'seen' by the deterministic RyR model is then adjusted based on a second random number and the magnitude function, mimicking the effect of a sub-cellular calcium wave on whole-cell RyR dynamics. Thus, opening of the deterministic RyR is achieved in-line with the behaviour observed in the microscopic cell model, with only the inclusion of a few extra equations.

2.3. Model reduction method 2: The large-N approximation

The second method is based on mathematical analysis of the system, taking advantage of mesoscopic physics approaches; namely, through the application of the large-N approximation [5]. This provides the opportunity to capture the critical feedback mechanisms resulting from microscopic fluctuations without explicitly modelling individual RyRs, and thus at a reduced computational cost.

To describe the method, we must first consider the microscopic, master equation which describes the probability of the system (in this case, the RyR) of being in a state n at a time t:

$$\frac{dP_{\boldsymbol{n}}(t)}{dt} = \sum_{\boldsymbol{m}\neq\boldsymbol{n}} [T(\boldsymbol{n}|\boldsymbol{m})P_{\boldsymbol{m}}(t) - T(\boldsymbol{m}|\boldsymbol{n})P_{\boldsymbol{n}}(t)] \qquad (1)$$

For large values of N, the system can be described by the Fokker-Planck, mesoscopic equation [5] which describes the ensemble behaviour of the fraction $\mathbf{x}=\mathbf{n}/N$ of RyRs in each state. It is more useful to express this equation in its equivalent form, in terms of the state-

evolution, rather than the probability density function:

$$\frac{dx_i}{d\tau} = A_i(\boldsymbol{x}) + \frac{1}{\sqrt{N}}\eta_i(\tau) \qquad (2)$$

Where the deterministic description, $A_i(\boldsymbol{x})$, is modified by a Gaussian-noise term, $\eta_i(\tau)$, $\tau=t/N$. And thus we have a mesoscopic description of the state-evolution of a collection of RyRs which captures noise-induced state-transitions. It is important to note that for mathematical and physiological accuracy, the noise-term must be based on the system itself, and not introduced arbitrarily; the information is contained in the variance of the noise, derived from the microscopic equation, and is state-dependent.

This approximation can be applied to single dyads, wherein the dynamics of the dyad are now described by a single set of stochastic mesoscopic equations, rather than considering each RyR separately. Such an approach can be used to reduce the computational load of spatial cell models in any dimension, producing '1D or 3D mesoscopic models', for example.

The method can also be expanded to describe the whole cell, used to produce a mesoscopic 0D cell model. However, model reduction to this level is non-trivial and must preserve the nature of a single dyad and calcium propagation. We overcome this problem using a compartmentalisation approach and an algorithm which models both a single dyad and the whole-cell behaviour, applied to the idealised 1D cell model.

We did not attempt to reduce the 3D single cell model which accounts for semi-realistic intracellular structure to a 0D cell model. This presents new challenges beyond the scope of the study, such as accounting for non-uniform dyad distribution and variable transverse-tubule or sarcoplasmic reticulum density and organization.

3. Results

3.1. Model reduction approaches

Both methods were capable of reproducing the macroscopic consequences of spatio-temporal calcium cycling at a significantly reduced computational cost.

The mesoscopic 0D cell model produced by the empirically-guided *method 1* successfully reproduced whole-cell calcium wave incidence and magnitude observed in the 1D stochastic cell model (Figure 1) at only ~1% of the computational cost (comparable to the efficiency of the deterministic 0D cell model).

Application of the large-N approximation to individual dyads in *method 2* reproduces single dyad and whole-cell calcium dynamics under calcium clamp, cardiac-excitation and quiescent conditions (Figure 2).

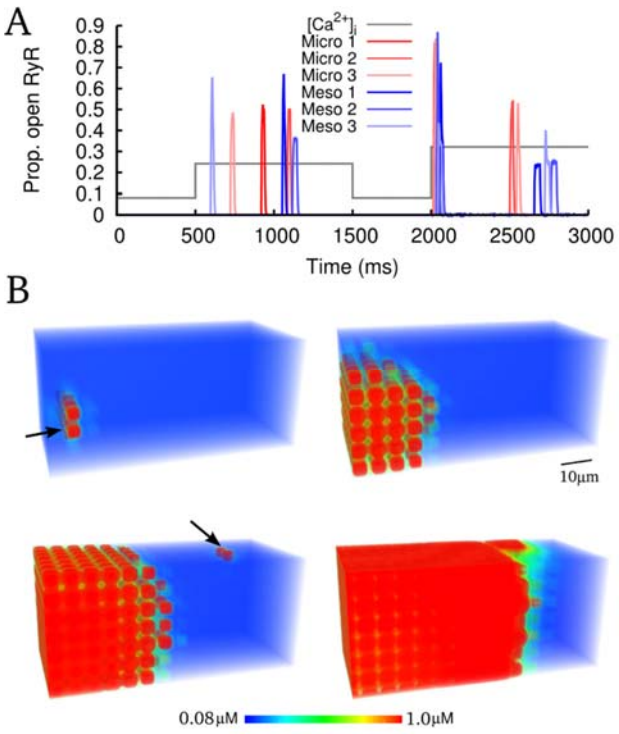

Figure 2. A – Demonstration of RyR dynamics under calcium clamp (grey line) conditions in the microscopic (red lines) and mesoscopic (blue lines) descriptions. B – Spontaneous calcium sparks and calcium waves in the 3D single cell model under quiescent conditions, using the mesoscopic descriptions for single dyads. Arrows indicate spontaneous calcium sparks.

The 1D mesoscopic model had a computational gain of a factor of 20 compared to the 1D microscopic model; gain in efficiency in the 3D mesoscopic model (compared to the 3D microscopic model) is less significant due to the computational load of solving the reaction-diffusion equation in 3D.

The 0D mesoscopic model produced through *method 2* is more computationally intensive than the model produced by *method 1* but is still significantly more efficient than the 1D stochastic model, and thus suitable for large-scale tissue simulation.

3.2. Ability to reproduce changes in dynamics and cell structure

An important property of model reduction approaches is the ability to reproduce a range of conditions such as cellular remodeling or autonomic regulation, which may alter intracellular kinetics or structure. We test our approaches by modifying multiple parameters (*Nryr*, the gating kinetics of the RyR, dyadic cleft volume and strength of inter-dyad coupling) in the 1D cell model.

The empirical nature of *method 1* means that the

functions describing the incidence and magnitude of intracellular calcium waves must be re-derived for each condition which elicits a macroscopic change in behavior which is not reproduced in the 0D cell model, thus requiring analysis of the microscopic model in each condition. However, once this has been performed, the model successfully reproduces the behavior observed in each condition; multiple simulations in tissue may then be performed without the need to update the model further.

Because the approximation derived in *method 2* is based on the microscopic description and preserves the schematic structure of individual dyads, it naturally accounts for alterations to gating kinetics, *Nryr* and dyadic cleft volume. Changes to cell structure (i.e. inter-dyad coupling) are also naturally incorporated into the spatial mesoscopic models. Furthermore, it is possible incorporate changes to inter-dyad coupling into the 0D mesoscopic model through the coupling between single dyad and whole-cell compartments.

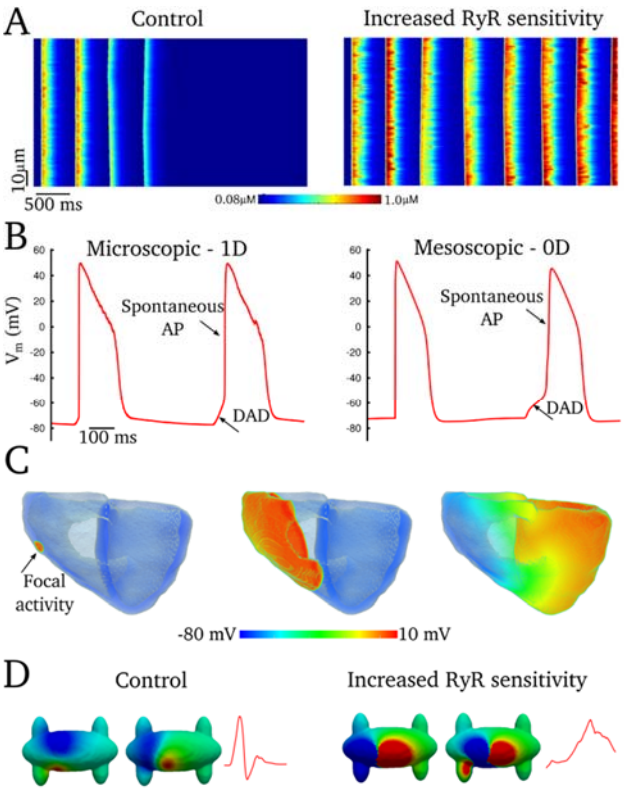

Figure 3: From microscopic calcium sparks to the ECG. A – Spontaneous calcium sparks in the microscopic model in control and increased sensitivity conditions. B – Triggered activity in the microscopic and mesoscopic models following DADs. C – Incorporation of the mesoscopic model into an anatomical model produces focal beats associated with increased RyR sensitivity. D - Body-surface potential snapshots and lead II ECGs in both conditions.

The increase to RyR sensitivity promotes significant spontaneous calcium sparks and waves (Figure 3A) which manifests as triggered activity in the single cell, reproduced by the mesoscopic 0D model (Figure 3B). In the 3D tissue model, this led to natural focal activity and alterations to the ECG QRS-complex (Figure 3C,D).

4. Conclusion

We have demonstrated two different methods to reproduce the macroscopic consequences of microscopic spatio-temporal calcium dynamics in computationally efficient, 0D cell models. This will allow detailed multi-scale investigation into the interaction of sub-cellular calcium waves with complex tissue-level excitation dynamics, and their markers in the ECG.

The empirically-guided method is simple to implement but is not as powerful as the method based on mesoscopic physics approaches, which naturally accounts for modifications to gating kinetics and schematic dyad structure.

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