Simulation of Cardiac Action Potential Propagation Using Hybrid Models

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Abstract

This paper investigates hybrid computational models as an approach to efficient simulation of electrical activity in cardiac tissue. In the hybrid approach, computational requirements are reduced by modelling only a local region using a detailed model, and embedding this within a simpler model of a larger tissue. We argue that the validity of this approach is dependent upon the method used to couple the different component models. We develop a simple coupling method for creating hybrid models in which the ionic Luo-Rudy phase 1 model is embedded within a tissue that uses the 3-variable Fenton-Karma model. The hybrid models are shown to preserve depolarisation fronts propagating through tissue as well as accurate action potential behaviour within embedded regions.

1. Introduction

Mathematical models of the cardiac action potential include complex biophysically-derived ionic models, simpler generic ionic models, and phenomenologically-derived models that caricature the action potential and its propagation. Complex models are computationally demanding, often prohibitively so depending on the space and time scales that need to be simulated. To investigate many spatio-temporal behaviours (e.g. reentrant arrhythmias), simpler models are often more computationally effective. These include reduced variable continuous models or completely discrete models such as cellular automata. However, these models are often insufficiently rich to represent many dynamics and pathological states of interest.

Hybrid, or multi-level, models have been proposed as a way of gaining many of the benefits of detailed ionic models but with significantly reduced computational costs [1, 2]. In the hybrid approach, regions (or single cells) of tissue modelled at a biophysically-detailed level are embedded within a larger tissue that employs a simpler action potential model. Thus points or regions of specific interest (e.g. tissue affected by ischemia, or an area around the tip of a spiral wave) can be realistically modelled, but with computational requirements greatly reduced for the surrounding tissue.

The validity of the hybrid approach requires that action potentials propagate from one region to another without significant changes in velocity, and with correct morphology; in particular, the shape (and duration) of action potentials within an ionic model-based embedded cell or region should not be adversely affected by the different action potential shape of a simpler model in the surrounding space. Construction of hybrid models requires that computational elements from the component models are coupled at the interface between the regions, and it is this coupling that determines the influence of one model on another.

Where both models are continuous, an obvious approach to inter-model coupling is to allow element-element diffusion to apply unaltered across the interface. In [1] it is shown that, using this diffusive method of coupling, the velocity of depolarisation wavefronts can be preserved across models, but the action potentials within the embedded region can take an incorrect shape, influenced by those of the other model.

In this paper, we consider hybrid simulations which use two well-known action potential models, the ionic Luo-Rudy phase 1 model [3] and the simplified Fenton-Karma model [4]. We demonstrate shortcomings of the diffusive coupling method when used with these component models. We then present an alternative method in which inter-model coupling is dependent upon the phases of the action potential at the interface of the two regions. Our method is shown to perform well in simulations of propagation in 1D and 2D hybrid models.

2. Methods

Our method of coupling applies to component computational models which have a regular spatial structure and share the following property: the state (i.e. variables) of each computational element i at time $t + \Delta t$ is dependent upon the element's voltage v_i^t and its other variables (e.g. gating variables) at time t, and on a diffusion term d_i^t. This diffusion term involves voltages of neighbouring elements at time t; for example, for a 1D finite difference model, $d_i^t = D(v_{i-1}^t + v_{i+1}^t - 2v_i^t)/\Delta x^2$, where D is a diffusion coefficient and Δx the numerical space-step between elements. Commonly, the model we wish to embed will have

a finer spatial and temporal structure and each element will contain a greater number of variables; it will be (possibly vastly) more computationally intensive. The two models may also be of different mathematical type (e.g. numerical approximation to a continuous model versus cellular automaton). For simplicity, in this paper we consider two specific continuous models, and assume that the computational implementations share both space-step and time-step. Specifically, we embed elements or regions of tissue modelled with the 8-variable ionic Luo-Rudy I cell dynamics (LR) within a larger space which utilises the computationally less demanding 3-variable Fenton-Karma (FK) model. Figure 1 gives the structure of such hybrid models.

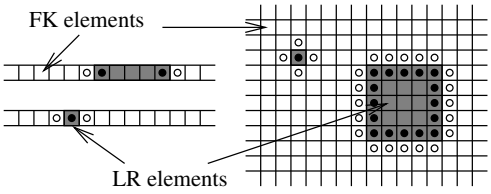

Figure 1. Structure of 1D and 2D FK/LR hybrid models. Single elements or regions of the LR model (shaded) are embedded within a tissue composed of FK elements. Interface elements are denoted by • (LR) and ○ (FK).

We divide the original LR model time constants τ_{d} and τ_{f} in [3] by two in order to give speeded up calcium kinetics. We use the parameter values given in [4] for the FK model to approximate the restitution properties of the modified LR model. Thus, the models' (i) action potential duration versus diastolic interval (DI) behaviour, and (ii) conduction velocity versus DI behaviour, both match approximately. This is clearly an important prerequisite for a hybrid model to demonstrate valid behaviour. Figure 2 shows action potentials of each of the LR and FK models at a point on a 1D tissue strand.

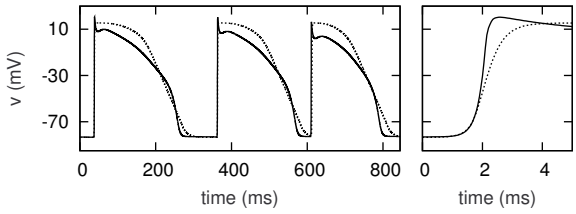

Figure 2. Left: Action potentials generated by three stimuli at one end of a 1D cable for the LR model (solid line) and the fitted FK model (dotted line). Right: Upstrokes of LR and FK action potentials.

We now consider how to couple elements at an FK/LR interface; i.e., what the diffusion terms d should be at interface elements (those that include one or more elements from the other component model within their neighbourhood). The simplest approach, taken in [1, 2], is to use a diffusion term equivalent to that used for all other non-boundary elements. This method has been shown to adequately preserve depolarisation fronts passing through the interface regions. However, as demonstrated in Figure 3, action potentials within embedded LR region(s) are affected by the different morphology of those in the surrounding FK space. There are two problems. Firstly, the plateau and recovery phases at LR interface elements tend to take the shape of an FK action potential, with this effect only slowly diminishing as we move towards the centre of an embedded region (experiments suggest that an LR 'buffer' region of approx. 5mm is needed for the shape and duration to closely approximate those of the LR-only model). Second, an LR interface element fails to depolarise correctly to peak voltage because the upstroke of its neighbouring FK elements are not sufficiently steep (variations of the effect illustrated occur for left and right interface elements of a larger embedded LR region).

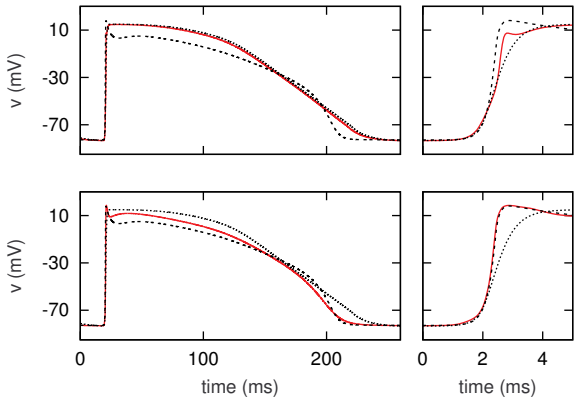

Figure 3. Top: Action potential and upstroke (red) for a single LR element embedded within a 1D FK model using diffusive coupling, shown with normal LR (dashed) and FK (dotted) action potentials. Bottom: Action potential at the centre of a 1.1mm embedded LR region.

The new coupling method aims to address both problems, but particularly the former since valid and accurate behaviour within an embedded region is what motivates the use of hybrid models. The poor LR upstroke at the interface appears not to affect LR elements further away, and so this issue needs to be resolved mainly if we wish to use very small (or single element) embedded regions.

For a typical action potential model the diffusion term d is significant only during and just after depolarisation. Figure 4 shows, for the LR model, that d returns rapidly towards zero immediately after depolarisation, and remains insignificantly small for the remainder of the action potential. At the interface elements of Figure 3, it is a significant

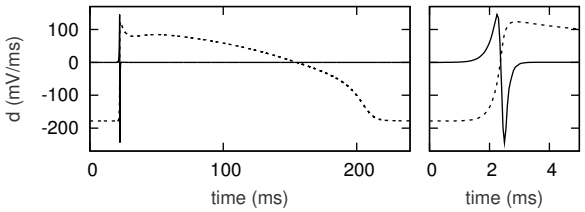

Figure 4. Diffusion term d (solid) shown alongside an action potential (dashed) for an LR element on a 1D strand.

value of d that leads to an incorrect action potential shape.

In our coupling method, the diffusion term at an interface element is only used at certain phases of its action potential; at other times diffusion is ignored (i.e. assumed to be 0). To determine whether the diffusion term is used, each interface element is assigned a discrete 'coupling variable' which at any time is in exactly one of five possible states, as illustrated in Figure 5. An element's coupling variable changes to a new state only when the element's voltage v and diffusion term d satisfy the condition given on the corresponding transition. For example, if an element is in the 'Stimulated' state, and its voltage becomes greater than a threshold v_{th}, then its coupling variable changes to the 'Upstroke' state.

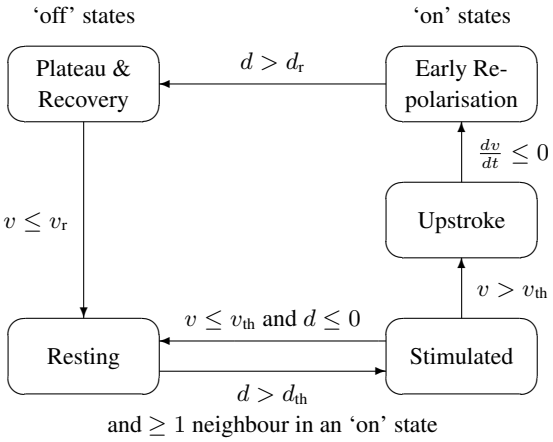

Figure 5. States and transitions for interface elements.

The three states on the right-hand side of Figure 5 are denoted 'on' states—in these states the diffusion term is used normally. For the 'off' states on the left-hand side, the diffusion term is ignored. Note that for the transition from 'Resting' to 'Stimulated', not only does diffusion need to exceed a threshold d_{th}, but at least one neighbouring element must be in an 'on' state. This prevents an element from becoming prematurely stimulated by a recovering neighbouring element of the other component model which has a higher voltage (e.g. due to differences in action potential shape or restitution). Because of this, all non-interface neighbours of interface elements also need to include a coupling variable, although the diffusion terms for such elements are always used normally. For our FK/LR coupling, we use the following parameter values: $v_{\text{th}} = -60$, $v_{\text{r}} = -70$; for LR elements, $d_{\text{th}} = 1.5$, $d_{\text{r}} = -70$; for FK elements, $d_{\text{th}} = 0.01$, $d_{\text{r}} = -2.5$.

To improve upon the upstroke behaviour illustrated in Figure 3, an LR interface element requires that neighbouring FK elements give a better approximation to an LR upstroke. To achieve this, we transform each FK element's voltage before it is used in the LR element's diffusion term.

We note the following from Figure 2: (i) the initial phase of the models' upstrokes (upto approx. -60mV) is similar; (ii) after this, the LR upstroke is steeper; (iii) the LR upstroke takes a more complex form (with peak); (iv) the height of the LR upstroke is dependent on the diastolic interval. We introduce a simple piecewise linear map ϕ to convert FK voltages, by increasing upstroke steepness:

$$\phi(v) = \begin{cases} v & \text{if } v \leq -60 \\ 1.54(v+60) - 60 & \text{if } v > -60. \end{cases}$$

We do not attempt to reproduce the DI-dependent peak and early-repolarisation of the LR model when converting an FK voltage. Rather, the current diastolic interval of each LR interface element is recorded and used to determine an upper limit for ϕ-converted FK voltages used in its diffusion term. We use a pre-computed lookup table to store these limits, which range from 9mV for DI $<$ 36ms, upto 21mV for DI $>$ 150ms. Thus, the upstrokes of neighbouring FK elements appear to an LR interface element quite similar to those of square waves of variable amplitude.

To convert a neighbouring LR voltage for an FK interface element, we take an even simpler approach. Voltages upto -60mV are left unaltered, as for ϕ. Above -60mV we use a lookup table to trace a generic FK action potential independently of the LR element's voltage.

3. Results

Computer simulations were performed for isotropic 1D and 2D tissues, with diffusion coefficient $D = 0.1\text{mm}^2/\text{ms}$, using a finite difference method with time-step $\Delta t = 0.01$ms and space-step $\Delta x = 0.1$mm. Diastolic intervals were determined using a threshold of -60mV.

For the 1D simulations, we used two cables of length 45mm, one using the LR model, and one using the FK model with a single LR element embedded at 30mm. The first 1mm of each cable was stimulated at different rates to generate action potentials along the strands. Figure 6 compares the action potentials of the LR model with the hybrid FK/LR model at 30mm for different diastolic intervals. The upper graph shows that the correct LR action potential shape and duration is preserved in the hybrid model

across a wide range of DI values (compare with Figure 3). The lower graphs compare upstrokes of the two models at the same LR element location for each of the three DI values. The LR upstroke has been approximated well throughout most of its height, although the peak is delayed slightly (compare with Figure 3). Different peak voltages (for different DIs), are also preserved accurately.

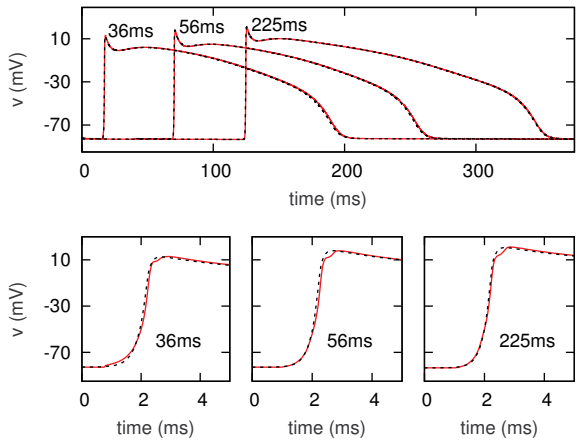

Figure 6. Top: Action potentials for a single LR element embedded within a 1D FK model (red) shown with those from the LR-only model (dashed), for three different DIs. Bottom: Upstrokes of these three action potentials.

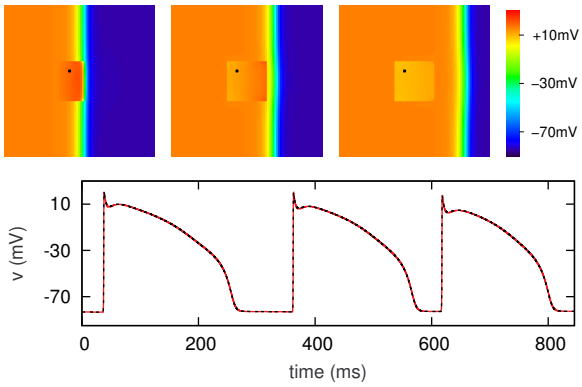

Figure 7. A 2mm LR region embedded within a 8mm square FK model. Top: Snapshots (with interval 1ms) of a wavefront passing through the LR region. Bottom: Action potentials generated by three stimuli at the left edge of the 2D hybrid model (red) at the point marked by •, and for a 8mm square LR-only model (dashed).

Figure 7 shows a 2D hybrid model which comprises an 8mm square isotropic tissue using the FK model, with a 2mm square LR region embedded at the centre. The tissue was stimulated along the left-hand edge to give planar waves travelling through the FK and LR regions. The snapshots show a single depolarisation front moving from left to right through the tissue. The LR region can easily be identified due to the differences in membrane potential at the top of the upstroke and plateau phase (as illustrated in Figure 2). The snapshots demonstrate that the LR region has little effect on the FK depolarisation front; the near vertical wavefront shows only a slight deformation. The lower graph compares the hybrid model with an 8mm square LR-only model. Three stimuli were applied at the left edge of each model to produce three propagating action potentials with different DIs. The membrane potential of the element identified by • in the snapshots is shown against that of the corresponding element in the LR model. The correct action potential shape of the LR model is faithfully preserved within the embedded LR region.

For 1s of this 2D simulation, the hybrid model, and an FK-only model, take 16.8% and 13.6% of the runtime of the LR-only model, respectively. The computational overhead for coupling is less than 10% of the total runtime.

4. Discussion and conclusions

Hybrid models of cardiac tissue can provide a computationally-realistic approach to the simulation of action potential propagation. We have demonstrated the importance of coupling at the interface for the hybrid approach to be useful, and developed a coupling method for tissues employing the LR and FK action potential models. This method is shown to successfully preserve the shape and basic properties of the action potential within an embedded LR region. Whilst being specific to these two component models, the method appears sufficiently simple to allow it to be adapted for use with other models.

References

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