

Re-entry in the Luo-Rudy Ventricular Tissue Model with Different Models of Ca^{2+} Dynamics

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Abstract

Based on the Luo-Rudy equations for a single ventricular cell, we develop a family of computational models for 2D excitable media consisting of such cells – i.e., construct virtual ventricular tissues. The models comprised virtual epicardial and endocardial tissues with either standard or buffered intracellular Ca^{2+} handling. Re-entry, manifested as rotating spiral waves, was found to be stable in each model. We characterized re-entry by measuring spatial extent of tip meander R and rotation time period T of the spiral waves. For the standard epi- and endo- tissues we measured $T = 90$ ms and $R = 0.5$ mm, and $T = 110$ ms and $R = 0.7$ mm, respectively. For epi- and endo-tissues with buffered Ca^{2+} we obtained $T = 90$ ms and $R = 0.4$ mm, and $T = 100$ ms and $R = 0.5$ mm, respectively. We conclude that simplified Ca^{2+} handling introduces only small differences in simulation of re-entrant phenomena.

1. Introduction

Re-entry is an important arrhythmia mechanism, currently attracting great interest in cardiology [1,2]. During re-entry, the same wave-front repeatedly re-excites a site of cardiac tissue after propagation around an anatomical or functional block. Re-entrant waves have been optically mapped on the surface of cardiac ventricles [3,4] and are believed to underlie ventricular tachycardia and fibrillation.

A spiral wave in a two-dimensional homogeneous excitable medium formed by electrically coupled cardiac cells provides a model for re-entry. Spiral waves emerge from breaks of plane wave-fronts, and rotate around a central core, periodically re-exciting the medium. Motion of such a wave can be characterized by the period of its rotation and trajectory of its tip, reflecting shape of the core [5,6].

Thus, a convenient method for studying the re-entrant phenomena is using the current generation of cardiac cell models, allowing idealization of the cardiac tissue as an excitable medium supporting rotation of spiral waves.

The aim of this study was to develop a family of computational models for excitable media representing

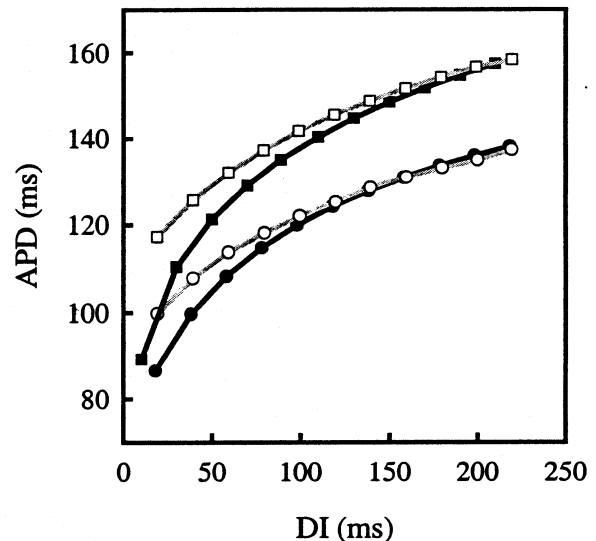
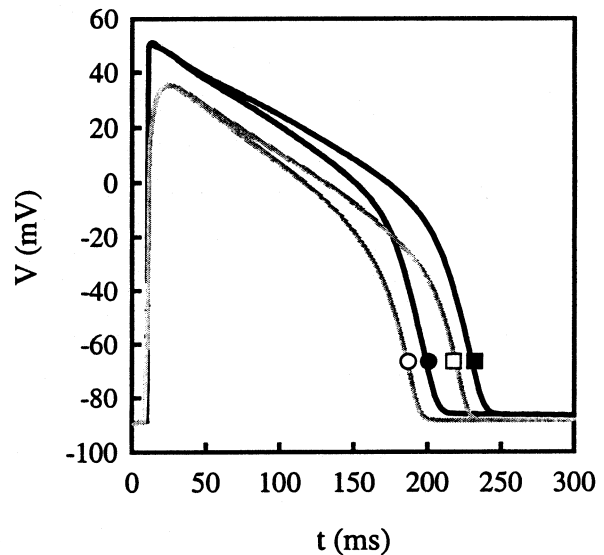


Figure 1. Cellular properties in the Luo-Rudy family models. Action potentials (top panel) and restitution curves (bottom panel) are presented for epicardial cell with standard $[\text{Ca}^{2+}]_i$ handling (filled circles), endocardial cell with standard $[\text{Ca}^{2+}]_i$ handling (filled squares), epicardial cell with buffered $[\text{Ca}^{2+}]_i$ (open circles) and endocardial cell with buffered $[\text{Ca}^{2+}]_i$ (open squares).

ventricular tissue - *virtual ventricular tissues* - and measure basic characteristics of re-entry (spiral wave rotation period and pattern traced out by the tip) in each one. In particular, we compared LRd-type models [7] with standard and simplified dynamics of intracellular Ca^{2+} to study the influence of calcium handling upon re-entry.

2. Methods

We constructed an excitable medium for ventricular tissue by incorporating ordinary differential equations for ventricular cell excitability into a partial differential equation model for two-dimensional ventricular tissue [6]. For the single-cell kinetics we used the Luo-Rudy model for a guinea pig ventricular cell [7], downloaded from the web-site:

<http://www.cwru.edu/med/CDRTC/LRdOnline>.

We then modified this model to describe four variants of ventricular cells:

- epicardial cells (standard LRd model)
- endocardial cells (65% I_{Ks} , see [8])
- epicardial cells with intracellular Ca^{2+} buffering
- endocardial cells with intracellular Ca^{2+} buffering

The two latter variants were a replacement of the complicated (and in part non-physiological, see Discussion) description for $[\text{Ca}^{2+}]_i$ dynamics in the Luo-Rudy phase II model [7] by a single equation proposed earlier [9] to describe intracellular calcium buffering to a certain level $[\overline{\text{Ca}^{2+}}]_i$:

$$\frac{d[\text{Ca}^{2+}]_i}{dt} = -[\text{Ca}^{2+}]_i I_{\text{Ca,tot}} + 0.07([\overline{\text{Ca}^{2+}}]_i - [\text{Ca}^{2+}]_i)$$

Each variant has been validated to the available experimental data to reproduce restitution curves for a single ventricular cells (Figure 1), and we set the diffusion coefficient $D = 0.6 \text{ cm}^2\text{s}^{-1}$ to provide feasible values for the plane wave propagation velocity, $v = 0.45 \text{ ms}^{-1}$.

We solved the resulting equations numerically using an explicit scheme in $8 \times 8 \text{ cm}^2$ square medium, with time step of $50 \mu\text{s}$ and space step of 0.2 mm . Re-entry was initiated by the phase distribution method [6], and position of the spiral wave tip was identified from the intersection of isolines of the membrane voltage V ($V_{\text{iso}} = -40 \text{ mV}$) and gating variable f ($f_{\text{iso}} = 0.5$). We measured characteristics of the spiral waves: rotation time period T and spatial extent of their meander R – radius of a circle comprising the tip trajectory. Note that the accuracy of each value corresponds to the time and space steps of simulation output, which was 5 ms and 0.2 mm , respectively.

3. Results

Our simulations showed that in all the four variants mentioned above re-entry corresponds to stable

rotation of a spiral wave with no break-up (Figure 2). The rotation was rigid (i.e., the tip trajectory is a circle) for standard epicardial tissue, as well as for endocardial tissue with either standard or buffered Ca^{2+} handling, but bi-periodic for epicardial tissue with buffered Ca^{2+} .

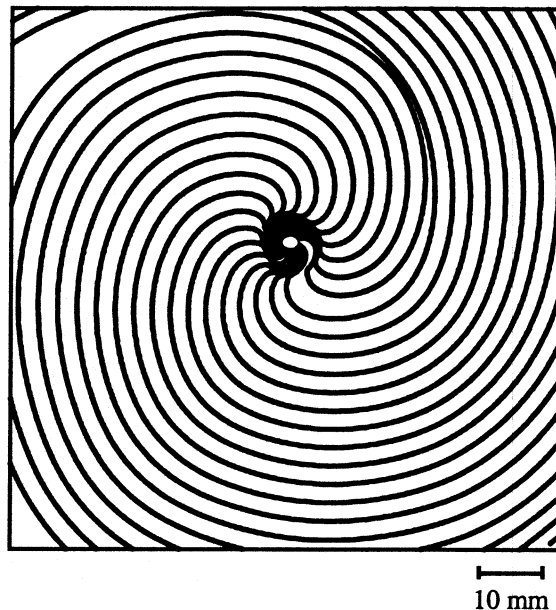


Figure 2. Spiral wave rotation in virtual epicardial tissue. Membrane voltage isochrones at 5 ms intervals during one rotation period (300-390 ms after initiation of re-entry) are shown. The isochrones are defined as loci of $V = -40 \text{ mV}$ and $f > 0.5$. Scale below bar indicates a spatial scale in the 2D tissue.

3.1. Standard epi- and endo- tissues

For the standard epi- and endocardial tissues we measured $T = 90 \text{ ms}$ and $R = 0.5 \text{ mm}$, and $T = 110 \text{ ms}$ and $R = 0.7 \text{ mm}$, respectively. Thus, re-entry in endocardial tissue was characterized by increased rotation period and tip meander in comparison to epicardial tissue (Figure 3). This is not surprising, since single endo- cells are characterized by a longer action potential duration than epi- cells (Figure 1).

3.2. Tissues with buffered Ca^{2+}

For epi- and endocardial tissues with Ca^{2+} buffered to a steady state concentration of 0.0001 mM we obtained $T = 90 \text{ ms}$ and $R = 0.4 \text{ mm}$, and $T = 100 \text{ ms}$ and $R = 0.5 \text{ mm}$, respectively. Thus, endocardial tissue has a larger rotation period and larger tip meander than epicardial tissue for both standard and buffered Ca^{2+} dynamics. However, the pattern of meander in the epi-tissue with Ca^{2+} buffering was different from that in standard epi- tissue (Figure 3). In addition, tissues with buffered Ca^{2+} were characterized by decreased rotation period and spatial extent of tip meander in comparison to the standard tissues.

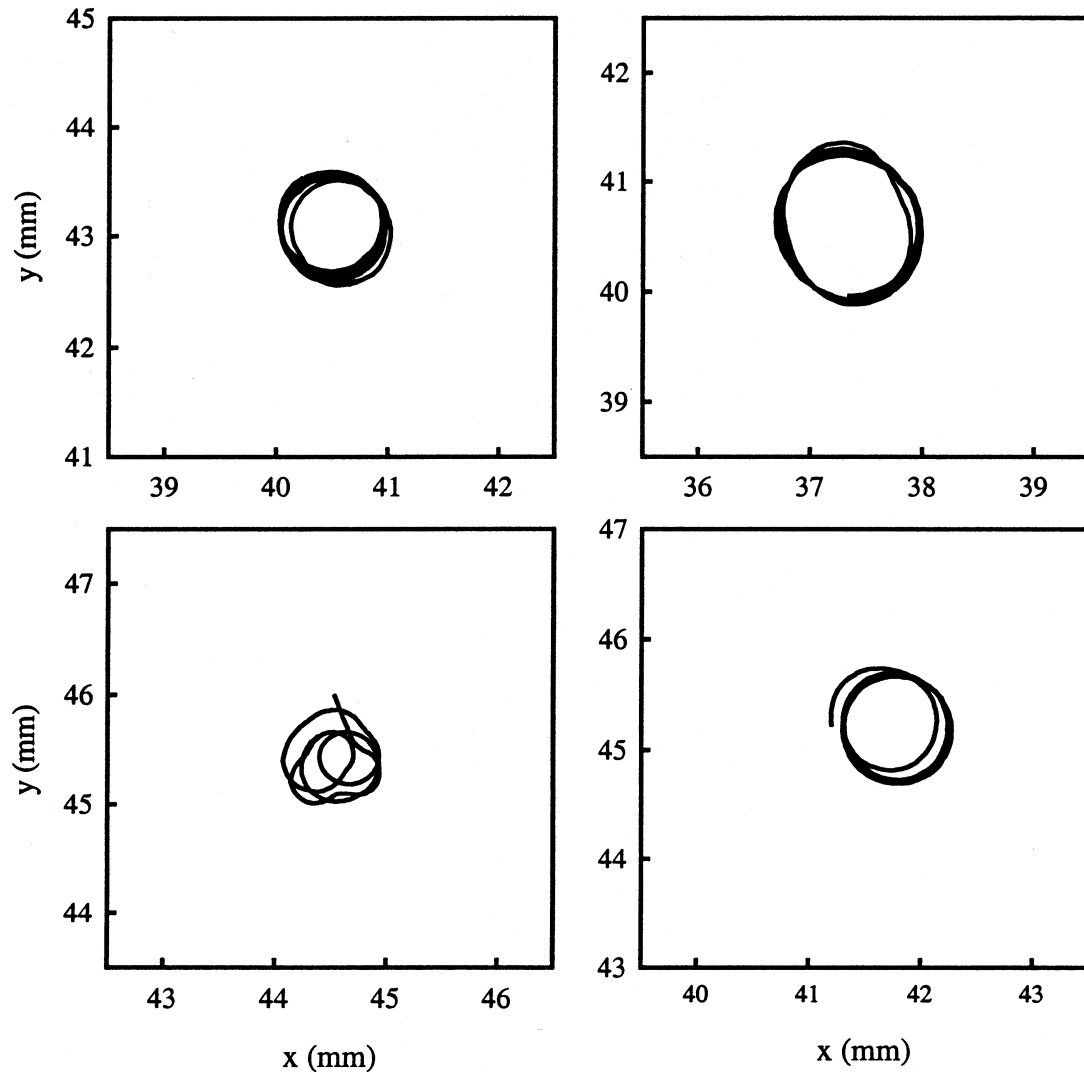


Figure 3. Tip trajectories of spiral waves in the LRd family models. The trajectories are presented for central regions of virtual epicardial tissue with standard $[Ca^{2+}]_i$ handling (top left panel), endocardial tissue with standard $[Ca^{2+}]_i$ handling (top right), epicardial tissue with buffered $[Ca^{2+}]_i$ (bottom left) and endocardial tissue with buffered $[Ca^{2+}]_i$ (bottom right).

3.3. Differential calcium buffering

To compare two different levels of calcium buffering, we also simulated re-entry in epicardial tissue with intracellular Ca^{2+} buffered to a lower steady state concentration of 0.00006 mM, resulting in the values $T = 90$ ms and $R = 0.4$ mm. Thus, decreasing the calcium buffering level about twice does not change the rotation period and tip meander within the accuracy of our computations.

4. Discussion

In this paper we have constructed and simulated several computational models of 2D ventricular tissue, namely, epi- and endocardial tissues with two types of Ca^{2+} dynamics: standard LRd and simplified LRd with buffered intracellular calcium.

For both standard and buffered Ca^{2+} dynamics,

endocardial tissue showed increased period of re-entrant spiral waves and spatial extent of tip meander in comparison to epicardial. The difference in rotation period between epi- and endo- tissues is ~ 10 ms, which would lead a de-synchronization of 50 ms during five rotations of a spiral wave. Taking the average rotation period of 100 ms, this gives a 180° twist between spiral waves in two layers considered separately from each other. It is possible that twist induced by regional differences in rotation period could be a mechanism for the breakup of transmural re-entrant waves. The question whether such a twist can be actually generated in the entire ventricular wall, where epi- and endocardial layers are coupled in parallel electrotonically, is a matter for further study involving a bi-layer or 3D model of ventricular tissue.

Note that meander of spiral waves was not rigid for all the virtual tissues considered: it was bi-periodic for the case of epicardial tissue with buffered Ca^{2+} . However, we found that the pattern of meander in the

LRd model was highly dependent on the method of tip identification (which is not the case for earlier models, such as the LR phase I model [9]). For example, if we trace the tip trajectory by another method, looking at intersection of the voltage isoline $V_{iso} = -60$ mV and the line $dV/dt=0$, than the meander pattern is rigid for all four tissues. Finding out reasons for such a method-dependence of the tip meander pattern is also a matter for separate study.

Another aspect of our simulations is considering the possibility of alternative description for the calcium dynamics in ventricular tissues. Part of the LRd model for intracellular Ca^{2+} handling uses a mathematical procedure which is not based on any physiological assumptions – namely, a 2 ms delay between the maximum rate of voltage upstroke and Ca^{2+} -induced Ca^{2+} release [7]. Two attempts to replace this procedure were undertaken [10,11], introducing a detailed set of ordinary differential equations for calcium handling. Such quantitative description is essential in some cases, e.g., when oscillations of the intracellular Ca^{2+} concentration lead to break-up of spiral waves [11].

Ultimately, the validity of these different approaches to modelling Ca^{2+} handling will depend on the availability of experimental data. In the interim, when considering some basic mechanisms of re-entry (e.g., stably rotating spiral waves), a reasonable and at the same time simple description of Ca^{2+} dynamics is useful. We have presented such a description for LRd model, shown that simplified Ca^{2+} handling allows simulation of re-entrant phenomena, and estimated the accuracy of such representation.

Acknowledgements

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