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Tissue-Based Optimization of a Sino-Atrial Node Disc Model

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***Abstract*— A cardiac sino-atrial tissue model based on a simplified 2D disc geometry and a generic ionic model is described and optimized to fit intact-tissue microelectrode experimental recordings. Concentric regions were defined representing the central and peripheral sino-atrial node and the atrium, each with a unique set of ionic model parameters. Intracellular action potentials were recorded from the respective myocytes in an intact rabbit *in vitro* sino-atrial tissue preparation. The 2D disc geometry was described numerically using a modified version of the cable equation of electrical propagation. The cell-specific model parameters at three nodes representing each region of the disc geometry were optimized, using a curvilinear gradient optimization algorithm, to generate action potentials waveforms that fitted the experimentally recorded waveforms. The optimized model was able to reproduce spontaneous sino-atrial node activation and atrial excitation and propagation. It offers an improved representation of the electrotonic interactions between heterogenous cell types and is able to reproduce the transition in action potential morphology between different regions. This tissue based optimization approach is a contribution to the development of realistic electro-anatomical cardiac models based on experimental data.**

I. Introduction

The growth of the Physiome project [1] and the need for multiscale models of cardiac electrical activity which incorporate a pacemaker region able to excite the surrounding atrium, requires greater understanding of the electrical interaction between regions of the myocardium with different electrophysiological properties.

A number of approaches have have been utilized to bridge the gap between experimental and computational studies in this area. Algorithms have been developed to synchronize electroanatomical data to a bi-domain atrial model [2]. In addition, rather than relying on the traditional approach of manually adjusting a few ionic model parameters to replicate intracellularly recorded action potential (AP) waveforms, various parameter optimization procedures have been employed to accurately fit cardiac ionic models to experimentally recorded APs.

Parameter optimisation can be based on nonlinear least square methods (e.g. curvilinear gradient [3]), particle swarm [4] or genetic algorithms [5]. In each of these studies, AP waveforms generated by each single cell ionic model was optimized to fit experimentally recorded APs.

Syed argued that the use of a more realistic pulse to stimulate the cell ionic model produced better optimization results compared to the conventional approach of employing a rectangular suprathreshold pulse [5]. In particular, the use of the second derivative of the AP as a stimulus pulse produced a more accurate fit of the AP upstroke and peak compared to a standard rectangular suprathreshold stimulus pulse [5].

This idea was further improved by optimizing a single node representing a cell in a 1D ring model of electric propagation, as such a model is better able to simulate intracellular coupling and propagation [6]. However in this study only the optimized and original parameter values were reported and compared, rather than illustrating how accurate the AP waveform fits were. In another study, a generic cardiac cell ionic model was developed and fitted to intracellular APs recorded from central sino-atrial node (cSAN), peripheral sino-atrial node (pSAN) and right atrial (RA) myocytes from intact rabbit sino-atrial tissue preparations [7]. The electrotonic interactions between different cell types were modelled by introducing a coupling current in addition to two time-dependent currents and one leakage current. The ionic models, with cell-specific parameters, were incorporated into a realistic 3D atrial geometry, reconstructed from the male Visible Human Dataset and used to simulate spontaneous sino-atrial excitation and electric propagation in the atria [8].

In the present study, a more realistic approach of modelling electrotonic interactions in a heterogenous tissue model is formulated. The cable equation of electric propagation was modified to represent a 2D disc geometry and the generic cardiac ionic model [8] was used to describe the electrical activity at each node. The 2D disc consisted of cSAN, pSAN and atrial regions, and parameters specific to each region were optimized to fit intracellular APs recorded from the respective myocyte type in an intact sino-atrial *in vitro* tissue preparation.

II. Methods

A. In vitro Action Potential Recordings

Spontaneous APs were recorded from cSAN, pSAN and RA myocytes in a rabbit *in vitro* sino-atrial intact tissue preparation using glass microelectrodes. More details on the experimental methods are given in Abed et al. [8].

B. Generic Cardiac Cell Ionic Model

A generic cardiac ionic model for single cells was given by:

$$\frac{dE_m}{dt} = -\frac{1}{C_m}(I_L + \sum_{j=1}^{N} I_j) \quad (1)$$

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where E_m (mV) and C_m ($\mu F.cm^{-2}$) are the membrane potential and capacitance per unit area respectively. C_m was set to 1 ($\mu F.cm^{-2}$) for all models. The time-independent leakage current (I_L) was described by

$$I_L = \overline{g}_L(E_m - E_{rev,L}) \quad (2)$$

and each generic time-dependent current (I_j) by

$$I_j = \overline{g}_j p_j q_j (E_m - E_{rev,j}) \quad (3)$$

with

$$\frac{dp_j}{dt} = \alpha_{pj}(1-p) - \beta_{pj} p \quad (4)$$

$$\frac{dq_j}{dt} = \alpha_{qj}(1-q) - \beta_{qj} q \quad (5)$$

where $\overline{g}_j$ (μS.cm^{-2}) is the maximum conductance, E_{rev} (mV) the reversal potential, and p_j and q_j are gating variables for the j^{th} active ionic conductance. The total number of ionic currents (N) is user-defined. In this study, two active currents were used (a general inward and a general outward). α and β are rates (with units of s^{-1}) controlling each gating variable determined by

$$\alpha = \frac{k_\alpha}{1 + e^{s_\alpha(E_m - E_{50})}} \quad (6)$$

$$\beta = \frac{k_\beta}{1 + e^{s_\beta(E_m - E_{50})}} \quad (7)$$

where k_α, k_β (s^{-1}), E_{50} (mV), and s_α and s_β (mV^{-1}) are rate-specific variables for each gate (p_j, q_j) of I_j.

III. Ionic Model Parameter Optimisation

All the model parameters except, for C_m, were optimized and this process consisted of two stages

1) A single cell ionic model was initially optimised to fit a series of AP waveforms experimentally recorded from each intact myocyte type. Three models with different parameters representing single cSAN, pSAN and ATR cells were optimized seperately. As a result there was no electrotonic interaction between the different single cell models.
2) The unique set of cSAN, pSAN, ATR single cell ionic model parameters generated by step one were used as initial values to optimize AP waveforms generated by a sino-atrial node disc model to fit to the experimentally recorded AP traces. The disc consisted of a central cSAN region surrounded by a pSAN region which in turn was surrounded by a larger atrial region. Similarly to step 1 all model parameters, except for C_m were optimised. Each ionic model describing each region was optimised in the presence of electrotonic currents contributed by the other regions while keeping the parameters of those region's ionic models fixed. This procedure was repeated for all regions and several iterations were required to simultaneously fit all three AP waveform types to experimentally recorded APs.

Numerically, electric excitation and propagation in the disc was modelled using a modified version of the 1D cable equation of electric propagation [9]:

$$\begin{aligned} \frac{\partial}{\partial r}\left(\frac{r\sigma b}{2}\frac{\partial E_m}{\partial r}\right) &= -rI_m \\ &= -r\left(C_m\frac{\partial E_m}{\partial r} + I_L + \sum_{j=1}^{N} I_j\right) \end{aligned} \quad (8)$$

where r (cm) is the distance from the center of the disc and b (2x10^{-3} cm) the thickness of the disc, assuming it is one cell layer thick. I_m is the total membrane current (nA.cm^{-2}) and σ (μ.cm^{-1}) is the tissue conductivity. σ was set to 50 μ.cm^{-1} and 10^3 μ.cm^{-1} in the SAN and atrial regions respectively, in order to approximately match experimentally recorded conduction velocities.

The cable was 4 cm in length, with cSAN, pSAN and atrial sections measuring 0.2, 0.6 and 3.2 cm in length respectively. It was constructed by connecting a number of nodes each representing a single cell described by a generic cardiac ionic model (internodal distance = 2 mm). The three sections on the cable represent numerically three concentric regions. AP waveforms generated at selected nodes on the cable, representing the cSAN, pSAN and the atrium, were optimized to fit experimental data, using a curvilinear gradient optimization method [10] implemented in Matlab (Mathworks, USA). The cable equation was solved by finite differences using the method of lines in Matlab. All optimization procedures were performed on a standard desktop computer and a typical simulation using the 2D cSAN-pSAN-ATR disc took 2.4 s to solve.

IV. Results

As illustrated in Fig. 1A, there was a transition in AP morphology recorded from central to peripheral to atrial intact myocytes. In particular, SAN APs exhibited a slow pacemaker depolarization which is absent in atrial APs.

A generic ionic model with two time-dependent (inward and outward) and one leakage current was used for all cell types for both single cell and disc models.

The root mean square error (RMSE) between experiment and model generated AP waveforms was 1.08 mV, 2.50 mV and 3.73 mV for cSAN, pSAN and RA intact myocytes respectively when the individual single cell models were optimized (data not shown, refer to a previous study by Guo et al. for examples of optimized cSAN, pSAN and atrial AP waveforms [7]).

Fig. 1 illustrates the optimized model and experimental AP waveforms for cSAN, pSAN and RA intact myocytes in the sino-atrial node disc model. The RMSE between experiment and model generated AP waveforms was 1.27 mV, 0.84 mV and 2.06 mV for cSAN, pSAN and RA myocytes respectively. There was a transition in the reconstructed currents from cSAN to RA models. The peak magnitude of each time-dependent current increased from cSAN to pSAN to RA models (Fig. 1B).

Using the parameters obtained by optimizing the disc model, good AP waveform fits, SAN activation, frequency

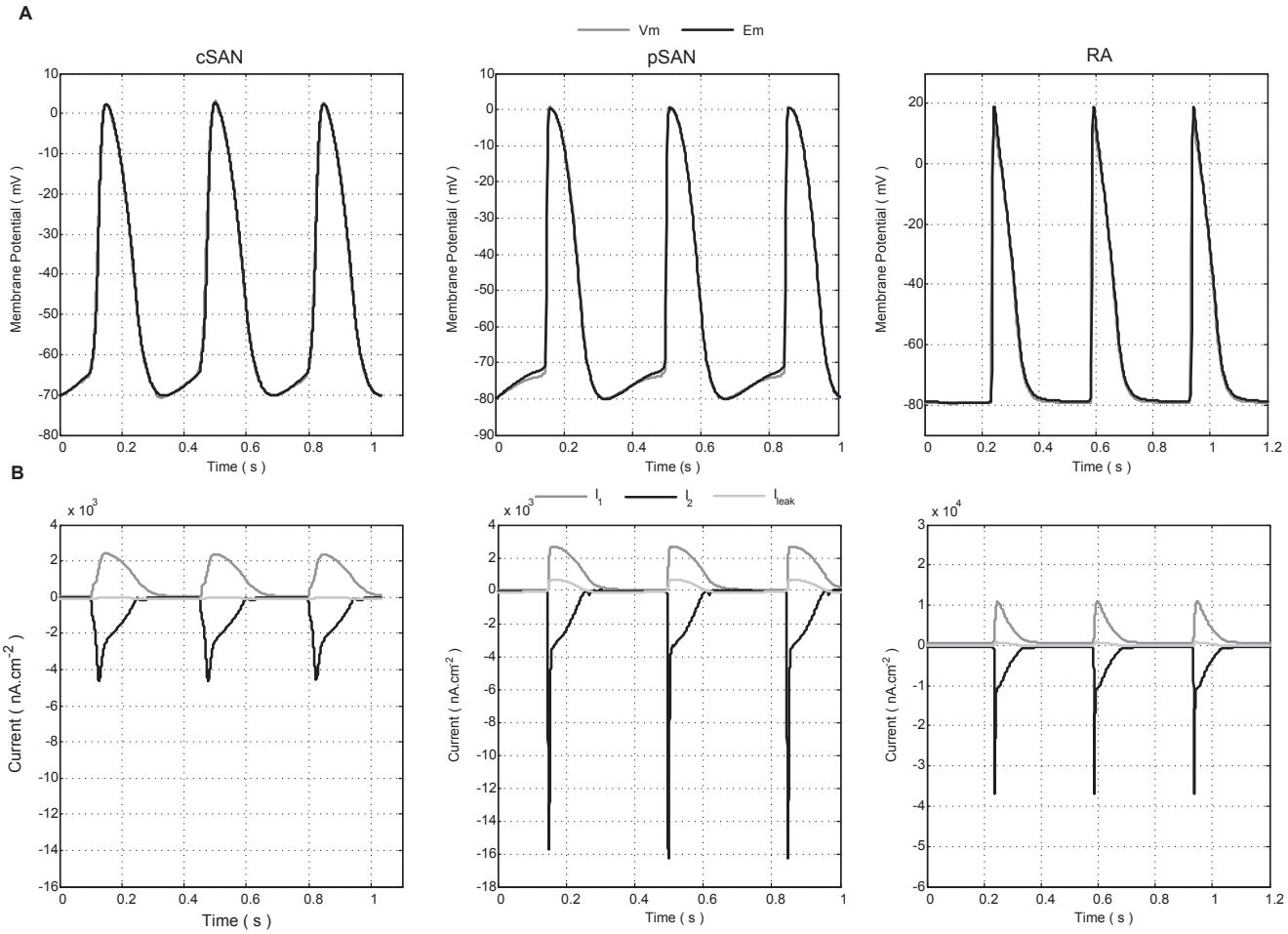

Fig. 1. Optimized cSAN, pSAN and RA models for the sino-atrial disc tissue model. (A) The optimized cSAN, pSAN and RA AP waveforms (E_m) are overlaid on top of AP traces recorded experimentally (V_m) from cSAN, pSAN and RA myocytes respectively in an intact *in vitro* rabbit sino-atrial tissue preparation. (B) Inward, outward and leakage ionic currents reconstructed from the optimized cSAN, pSAN and RA models respectively.

entrainment of and propagation into the RA could be obtained. As illustrated in figure 2A, there was a smooth transition in AP morphology from SAN to atrial types.

When the disc model was solved using parameters obtained by optimizing the cSAN, pSAN and RA experimental AP waveforms using three individual single cell models, only spontaneous activation of the cSAN and entrainment of the pSAN region was achieved. Although passive propagation into the atrial region did occur, it was insufficient to excite the atrium and generate a propagating atrial AP (Fig. 2B).

V. Discussion

A process was developed that allows cardiac ionic models to be optimized to fit experimental AP waveforms recorded from intact tissue preparations. A generic cardiac ionic model was described which consists of a user-defined number of active time-dependent currents, and a single leakage current. A standard set of equations were formulated to describe each active current using two gating variables (p and q) each controlled by two rate variables (α and β). A number of parameters were defined for each ionic current and by optimizing these parameters, a variety of ionic currents could be reconstructed to produce morphologically distinct AP waveforms. A curvilinear gradient optimization algorithm was used to fit the model to heterogenous spontaneous APs recorded from different myocyte types in an intact rabbit sino-atrial tissue preparation.

Since the experimental APs were recorded from an intact *in vitro* tissue preparation in the presence of electrotonic coupling from neighboring cells, a tissue disc, rather than single cell models, incorporating the cSAN, pSAN, and atrial regions was optimized. This approach represents a move from single cell model optimization to that of tissue-based optimization, in an attempt to bridge the gap between cellular, tissue, and whole-organ based models to develop multiscale cardiac models. The use of a 1D cable representation of a 2D disc geometry significantly reduces the time required to solve the model and therefore makes the optimisation process computationally efficient. Although this study was based on modelling sino-atrial node APs, the optimization methodology developed can be applied to incorporate any experimental or clinically recorded cardiac AP into 3D realistic models of the heart.

Although only two time-dependent currents were used,

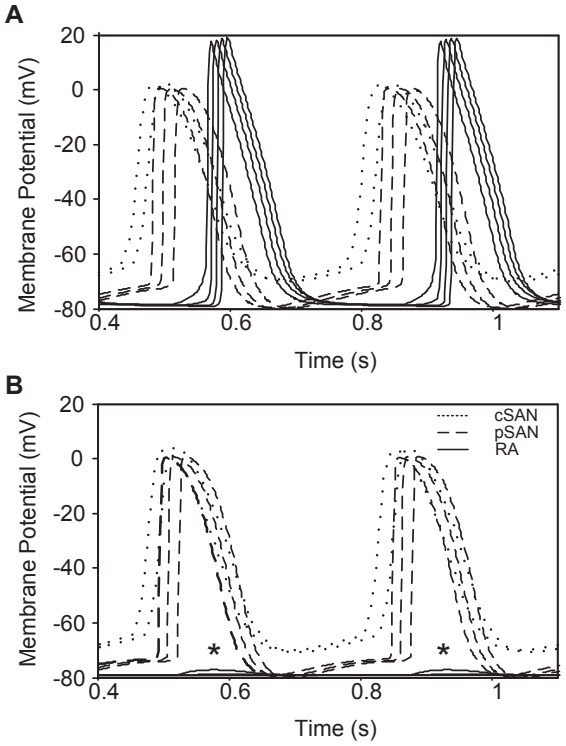

Fig. 2. The transition in action potential waveform morphologies in a cSAN-pSAN-RA disc model using parameters obtained by optimising (A) a sino-atrial disc model, or (B) individual cSAN, pSAN and atrial single cell models. * Note failure of propagation into the atrium.

tissue-based model optimization was able to produce a transition in reconstructed ionic currents underlying the transition in AP morphology from the SAN to the right atrium. Tissue disc simulations using parameters obtained by optimizing the single cell models individually were able to reproduce spontaneous SAN pacemaking activity. However, these models failed to produce atrial excitation and propagation (Fig. 2B).

The results from this study are consistent with the proposal by Syed et al. [5] that the use of more physiologically realistic stimulus currents to evoke APs during optimization will result in improved AP morphologies and fits to experimental AP waveforms. This study is an advance on their approach, as they used the second derivative of the experimental AP waveform as an estimate of the stimulus current. In our study however, the tissue disc model, by incorporating three electrophysiologically distinct regions, is better able to reproduce the electrotonic interactions between these regions. Moreover, the membrane current generated in the SAN region due to its spontaneous pacemaking ability provides a more physiologically realistic coupling current into the atrial region and thus is better able to represent the increase in the membrane potential of atrial cells to the threshold required to generate an AP.

One limitation of the disc model is that the internode interval in the 1D cable approximation of a 2D disc geometry was 2 mm. The choice of this value was a tradeoff between computational efficiency of the optimization procedure and the accuracy in solving the electric propagation model. Further analysis is required to assess the influence of the internode interval on the model solution. However this limitation was compensated for by utilizing the interplay between internodal distance and the value of tissue conductivity needed to achieve a certain conduction velocity. An appropriate tissue conductivity value (σ_{ATR} = 10^3 μ.cm^{-1}) was set to produce the desired physiological conduction velocity ($\sim$ 80 cm.s^{-1}) in the disc model.

VI. Conclusion and future work

A computationally efficient approach is presented to optimize APs generated by a simplified heterogenous sino-atrial tissue model to fit intracellular AP waveforms recorded from myocytes in an intact rabbit sino-atrial node tissue preparation. The model was able to produce spontaneous sino-atrial node activation and atrial excitation, as well as the transition of AP morphology between different regions.

The approach outlined in this study is a step towards the ultimate aim of directly coupling experimental data into 3D electro-anatomically accurate cardiac models.

The generic ionic model was implemented and optimized in a simplified 2D disc geometry. The next step in validating this tissue-based optimization approach is to implement these parameters in an atrial propagation model based on an anatomically realistic 3D geometry, to ascertain the extent to which the optimized parameters are also able to generate spontaneous sino-atrial node activation, atrial excitation and propagation. To improve parameter identifiability, optimisation of APs recorded under experimental different conditions and a parameter sensitivity analysis is required.

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