Computational Biology and Chemistry 68 (2017) 245–259

Contents lists available at ScienceDirect

Computational Biology and Chemistry

journal homepage: www.elsevier.com/locate/compbiolchem

Research Article

Cell-to-cell modeling of the interface between atrial and sinoatrial anisotropic heterogeneous nets

Gabriel López Garza[a,*], Norma P. Castellanos[b], Rafael Godínez[b]

[a] Mathematics Department, Universidad Autónoma Metropolitana, M. City, Mexico
[b] Electric Engineering Department, Universidad Autónoma Metropolitana, M. City, Mexico

ARTICLE INFO

Article history:
Received 21 October 2016
Accepted 17 April 2017
Available online 21 April 2017

Keywords:
SA node
Synchrony
Bifurcations
Interdigitations
Liminal length

ABSTRACT

The transition between sinoatrial cells and atrial cells in the heart is not fully understood. Here we focus on cell-to-cell mathematical models involving typical sinoatrial cells and atrial cells connected with experimentally observed conductance values. We are interested mainly in the geometry of the microstructure of the conduction paths in the sinoatrial node. We show with some models that appropriate source-sink relationships between atrial and sinoatrial cells may occur according to certain geometric arrangements.

1. Introduction

It has been observed in different species that going from the center of the sinoatrial node (SAN) in the heart toward the atrium, there is a transitional zone of cells having morphological and electrophysiological properties between that of typical sinoatrial (SA) and atrial (A) cells (Masson-Pévet et al., 1984). The transitional cells have an aspect intermediate between that of typical nodal cells and that of the common atrial cells. Typical nodal cells have poor development of the contractile system and they do not contract, but they possess automaticity in firing their action potential. Besides, the existence of connexin43 is undetectable in the SA node center (see Coppen et al., 1999 and references therein). On the contrary, atrial cells do contract themselves, but they require a stimulus in order to contract, and they contain mainly connexin-43. These characteristics are included in the cells models used in this paper. A whole range of intermediate cells have been reported, but more important to the models in this paper, cells with one end connected to SA cells and the other end with A cells have been found (Masson-Pévet et al., 1984). The basic structure conforming the cytoarchitecture of these groups of cells consists of interdigitations of nodal and atrial bundles forming histological connections between nodal and atrial myocytes at regular distances (Oosthoek et al., 1993). These interdigitations were observed and studied in papers such as (Csepe et al., 2016). In Winslow and Jongsma (1995), the authors, introduce a model of strands of atrial cells penetrating the SA node observed in the Pig. The model was constructed with 101×101 atrial and SA cells modeled with Oxsoft HEART V4.5. The lattice so constructed has a center of SA cells forming a circle of 30 cells of radius with twelve atrial interdigitations positioned at 30° intervals. In that paper, interdigitations are defined as sets of atrial cells at least ten cells distant from the node centre, which are subtended by an angle of 15°.

With respect to the action potential model's shapes, years ago, Joyner and van Capelle (1986) noticed that the presence of electrical coupling among cells create transitional action potential shapes in cells near the border zone between two distinct cell types. According to the authors, the electrotonic influences make it very difficult to prove that cells in a particular region are truly transitional in terms of their intrinsic membrane properties. In our models, action potential shapes behave in a kind of transitional manner which may provide some coincidence with the behavior of transitional cells observed in vivo. We achieve these "transitional cells" through the cytoarchitecture keeping the conductance as mentioned above, i.e., without any gradient between cells.

More recently in Csepe et al. (2016), Csepe et al. study the functional-structural connection of the SAN and the atria. Their studies suggest that the microstructure of the connection paths between A and SA cells plays a crucial role in human SAN conduction and contributes to normal SAN pacemaking. Our paper may be considered as a local approach to the complexity of the specialized branching myofiber tracts comprising the SA connection

* Corresponding author.
E-mail address: gabl@xanum.uam.mx (G. López Garza).

http://dx.doi.org/10.1016/j.compbiolchem.2017.04.008
1476-9271/

paths described by Csepe et al. As an antecedent, we mention Benson et al. paper (Benson et al., 2006), where the authors study a finite, one-dimensional strand of cells with conduction patterns similar qualitatively to the model studied in the present paper. In their simulations a length step of $\Delta x = 0.2$ mm was taken. This length corresponds to two cells of the size that we are considering, and consequently, a bigger approximation error in the numerical approximation, in comparison to the cell-to-cell model that we introduce in our example.

This paper is divided as follows: (a) In Section 4 we make a mathematical analysis of how it is possible to compare cell-to-cell models with partial differential equations (PDE) models. We reformulate the concept of liminal length in the context of cell-to-cell models, and establish that our approach is not opposite to Ruston's liminar length concept for the cable equation, but in some sense complementary. (b) In Section 5 we state in Lemma 1, that the multidimensional parameter $\alpha = (g_{12}, \ldots, g_{ij}, \ldots, g_{nm})$ is a bifurcation parameter of a net of cells composed with n SA cells and m A cells coupled with conductance values g_{ij}, $i \neq j$, $1 \leq i \leq n$, $1 \leq j \leq m$. We show that the sum $\sum_{ij} g_{ij}$ influences the behavior of the entire net in such a way that introducing conductance values as free parameters should lead to misleading conduction patterns in modeling nets. We give an elementary analytical proof of Lemma 1. We provide some arguments that prove that the geometry of a net is expressed implicitly by the non-zero conductance values and that they determine the change of qualitative behavior of the entire net. (c) In Section 6, we provide examples of nets formed with sound SA and A cell models for which we construct different geometric arrangements. These structures resemble, locally, interdigitations in the interface zone. (d) In Appendix A by using the piece-wise FitzHugh-Nagumo model we introduce elementary examples that illustrate the phenomenon stated in (a) and in (b).

2. General materials and methods

To fulfill point (d) in the introduction, we use the Lugo et al. (LC), (Lugo et al., 2014) (Human) model which is a refinement of Nygren et al. (N), (Nygren et al., 1998) (Human) model and, basically, modifies the dynamics of the RyR2 and CA++ release of the sarcoplasmic reticulum (SR) in order to model the effect of SR release refractoriness in appearance of electromechanical alternants. The N model reconstructs action potential data that are representative of recordings from human cells. In the N model the sustained outward K^+ current determines the duration of the AP. On the other hand, the AP shape during the peak and plateau phases is determined primarily by transient outward K^+ current, I_{sus}, and L-type Ca^2 current. For the L model we use the equations in Appendix A of the corresponding paper. A code provided by Lugo can be found at http://calugo.github.io/blog/2014/10/14/models-of-calcium-release-in-the-human-atria, but it is based on Nygren et al. model, whose code can be found at the repository CellML.

For SA cells, in our net models, we use the Severi et al. model (S), (Severi et al., 2012) (Rabbit). This model based on up-to-date experimental data, generates Action Potential (AP) waveforms typical of rabbit SAN cells whose parameters fall within experimental ranges: 352 ms cycle length, 89 mV AP amplitude, −58 mV maximum diastolic potential, 108 ms Action Potential Duration at its half amplitude (APD_{50}), and 7.1 V/s maximum upstroke velocity; and, more interestingly, describes satisfactorily experimental data concerning autonomic stimulation, funny-channel blockade and inhibition of the Ca^{2+}-related system by BAPTA. The Severi et al. code we is at the repository at https://models.cellml.org. For both models (S) and (LC) there are no bugs reported.

The prevalence of one SA model over any other is nowadays still under debate. The cell's distribution of the I_f channels activated by hyperpolarization is not yet known. These channels have been considered as the main cause of automaticity in SA cells. This last hypothesis is still subject to discussion. In a recent paper of Sirenko et al. (2016) the authors claim that automaticity is due mainly to electrochemical gradients of Na and Ca ions, channels allegedly distributed along the entire cell. So, the models that we have chosen should be considered as instances, not as prototypes, but also as current actual sound models. The equations used in this paper are of the form

$$\frac{dV}{dt} = I(V) + (g_1 M_1 + g_2 M_2 + g_3 M_3 + g_4 M_4)V \tag{1}$$

$$V|_{t=0} = V_0,$$

where the transposed vector $V^t = (V_{A1}, \ldots, V_{An}, V_{SA1}, \ldots, V_{SAm})$ corresponds to the Voltage (mV) of the A ($A1$ to An) and SA ($SA1$ to SAm) cells, with n, m values varying in different models, $I(V)^t = (I(V_{A1}), \ldots, I(V_{SAm}))$, is a vector representing the currents (mV/ms) of A and SA cells, $M1$ is a connection matrix between A cells, $M2$ is a connection matrix between A and SA cells, $M3$ gives the connections between SA and A cells, and M_4 is the connection matrix between SA cells; the constants $g_1 = g_{A-A}/C_{mA}, g_2 = g_{A-SA}/C_{mA}, g_3 = g_{SA-A}/C_{mSA}$, $g_4 = g_{SA-SA}$. Here $CmSA = .000032\,\mu$F; $CmA = .00005$ μF, and g_{SA-A}, g_{A-SA}, g_{A-A} are the conductance values between corresponding cells which values are specified in each model. The vector $V|_{t=0} = V_0$, i. e. V at time $t = 0$, takes values which vary randomly with normal distributions, accordingly: for Atrial cells, mean −74.2525 mV, and for SA cells, mean −58 mV, with standard variation.1 mV in both cells types. All the initial conditions in our models were taken from their respective papers, supplements, and codes provided by the authors when available. In tree models we keep $g_{SA-A} = g_{A-SA} \approx .6$ nS, with the precise value given in the corresponding model. We explore in Section 6.2 the possibility of $g_{SA-A} \neq g_{A-SA}$, which cannot be excluded a priori due to the possibility of existence of different kind of connexin types in the cell-to-cell connections through the transitional zone. Note that the FitzHugh-Nagumo equations in Appendix A of the paper are adimensional.

We assume in our models that SA cells are synchronized in phase, as theoretically predicted in the well-known paper of Torre Torre (1976). In fact, for the Severi et al. model, varying randomly V_0 in each simulation (up to 20 simulations), we obtained synchronization in phase of up to 100 SA cells, even before the first cycle ended with conductance g_{SA-SA} as low as.6 nS. For the numerical simulations of the synchronization of SA cells we considered different geometric arrangements: in series, forming an anullus, and even with a random matrix of connections (which is histologically improbable). To model connections between 100 SA cells we take in (1) $M_1 = M_2 = M_3 = \mathbf{0}_{100\times100}$ where $\mathbf{0}_{100\times100}$ is the zero matrix of size 100×100, and $g_4 = .6\text{nS}/CmSA$.

The cell-to-cell approach requires: (a) individual cell dynamics, modeled by Hodgking-Huxley type equations. For SA node cells, we use the model of Severi et al. (2012), described in Section 2.1, and Lugo et al. model (Lugo et al., 2014) for atrial cells; (b) For the SA cytoarchitecture, we assume that the SA cells ran parallel and meet mostly end to end (Shimada et al., 2004), and that each cell is connected via intercalated disks with approximately 9.1±2.2 other cells (Hoyt et al., 1989). A model of idealized two-dimensional arrangements of cells using a similar structure can be found in Spach and Heidlage (1995); (c) In order to implement better models, an approximate number of cells in SA node is required. This number may be estimated to be in the order of million, and we give an estimation in Section 8. Our approach to the transitional zone is local and the number of cells considered, varies between 30 and 78, which is enough to approximate some source-sink relations between A and SA cells in this specific part of the SAN.