Matemática Contemporânea, Vol. 10, 75–87
http://doi.org/10.21711/231766361996/rmc103
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EVOLUTIONARY BIDOMAIN MODEL OF THE CONTINUOUS EXCITABLE MEDIUM

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Abstract

We outline a first step in our current research program to build a deductive theory of wave propagation in cardiac tissue. We describe a new evolutionary model of the excitable medium, which extends the existing static bidomain models of cardiomagnetism and Hodgkin-Huxley type reaction-diffusion partial differential equations. The model separates intra- and extracellular currents and allows a more accurate computation of the magnetic field using the Biot-Savart Law. Numerical examples of spiral waves and of the magnetic fields they generate are discussed.

Resumo

Delineamos o primeiro passo de nosso atual projeto de pesquisa, visando a elaboração de uma teoria dedutiva sobre propagação de ondas em tecido cardíaco. Descrevemos um novo modelo de evolução em meio excitável, que estende os modelos de bidomínio estáticos para cardiomagnetismo e para equações diferenciais parciais de Hodgkin-Huxley do tipo reação-difusão. O modelo trata em separado correntes intra e extracelulares e permite um cálculo mais preciso do campo magnético, usando a Lei de Biot-Savart. Exemplos numéricos de ondas espirais e dos campos magnéticos por elas gerados são estudados.

1. Introduction

A major problem in cardiophysiology is understanding the electrical activity of the heart. Advances in clarification of its electrodynamics have many clinical applications [1-3].

In the last two decades, dramatic advances were made in biomagnetism and cardiomagnetism, because of the development of sensitive quantum magnetometers, which may be employed within shielding environment to allow the

measurement of extremely weak magnetic fields [4-6]. The main advantages of the usage of such magnetic measurements lie in their non-invasive nature and in the possibility of source localization for cases where electrocardiography is not applicable, either due to electrical insulation of the sources from the body surface, such as in the case of the brain in the skull, or to masking by a stronger signal, such as in the case of the fetus in the amniotic fluid. The next frontier in cardiomagnetism is the development of clinically viable procedures. In this article, we describe our current work towards this goal – the direct modeling of electrochemical waves for the normal or arrhythmic heart. In contrast to other more mature areas of continuum mechanics and applied mathematics, there are still many open basic questions related to the modeling of excitable media.

In this paper, we outline a first step in our modeling program. Our objective is to build a deductive theory in order to model wave propagation in cardiac tissue based on first principles such as conservation of number of ions, the first and the second Kirchhoff laws, supplemented by constitutive equations. The approach is standard in continuum mechanics and electromagnetism for fluids, gases, elastic media, and plasma [7]. It is different from the parameter fitting approach to empirical models often used in economics and sociology, as well as in Hodgkin-Huxley type heuristic modeling in excitable media [8].

The current theory of electrodynamics of cardiac tissue is based on the partial differential equations of reaction-diffusion type proposed for a single nerve cell by Hodgkin-Huxley in 1952 and on its asymptotic reduction by FitzHugh-Nagumo in 1961-2 [8]. Some of the qualitative predictions of these models were recently verified experimentally, but quantitative predictions are usually only approximations of the order of magnitude of the event [1]. The equations for computing the magnetic field are based on the Biot-Savart law involving the intra- and extracellular currents only. The transmembrane currents have a negligible contribution to cardiomagnetic fields due to the thinness of the membrane and radial symmetry [4], [9]. As a result, the classical theory that focuses on transmembrane currents has to be modified in order to model cardiomagnetic fields.

In this article, we develop a new evolutionary model of the excitable medium, that extends the existing static bidomain models of cardiomagnetism and of Hodgkin-Huxley type reaction-diffusion partial differential equations [8], [11]. The model separates intra- and extracellular currents; it should allow a more accurate computation of the magnetic field using the Biot-Savart law.

The derivation of the new time-dependent model is based on the assumption of static bidomain theory: to each point of the medium we associate two state variables, one representing the intracellular variable, and the other representing the extracellular variable [11]. For example, if one thinks of the inner-membrane space as the space between two coaxial cylinders, then the standard modeling is based on the assumption that each point in the medium lies between the cylinders (the membrane), while in our bidomain model, at each point we represent quantities associated to the space outside the outer cylinder (extracellular space) as well as quantities associated to the space inside the inner cylinder (intracellular space), at the same time, ignoring quantities between the two cylinders. Under the above assumption, we write two coupled equations, one for the intracellular current and another for the extracellular current, respectively, at each point of space.

The evolutionary model. The derivation of the evolutionary model proceeds from the first Kirchhoff law of conservation of currents, expressed as a conservation equation for each ionic species. The system has to be closed by realistic phenomenological constitutive relations. Currently, we have implemented only the first part of the proposed program – the separation of intra- and extracellular spaces. One of the future tasks is the validation of the new model. It requires setting up the physically measurable electrophysiological constitutive equations of state for the cardiac tissue. It is of special importance to study planar traveling waves, target and spiral waves, and the magnetic field generated by such wave patterns. There is already a body of mathematical literature on such interesting waves, based on simplified reaction-diffusion equations [8]. Extending this mathematical analysis to more realistic models should be a chal-

lenging problem.

The conservation of current at each point of the medium can be written as

$$\sum_i J_i = 0,$$

where J_i's represent ionic transmembrane currents, ohmic currents flowing near the surface of the membrane, capacitance currents across the membrane, and other currents present.

Identifying various currents results in models of various degrees of sophistication. For example, a single cable equation is recovered if we identify the ohmic current as $\nabla(\sigma\nabla u)$, the nonlinear current through the membrane as $f(u)$ for suitable f, and the current resulting from the capacitance of the membrane as $-C\partial u/\partial t$. Substituting these into Kirchhoff's law gives

$$C\frac{\partial u}{\partial t} = f(u) + \nabla.(\sigma\nabla u),$$

where u is a single variable describing the transmembrane potential, σ describes the conductivity of the medium, and C is the capacitance of the cell membrane [8].

Notice that in standard models, for electrophysiological activity of excitable media, it is tacitly assumed that all points in the medium lie within the inner cell membrane [8]. The main effort in standard modeling of the excitable medium is the identification and description of the various membrane ionic currents. For example, the model of DiFrancesco-Noble identifies fifteen different ionic currents [10], while the above cable equation assumes a single transmembrane ionic current, $f(u)$.

The derivation of the new time-dependent model is based on the assumption that each point of the medium has two state variables, one representing the intracellular variable, and the other representing the extracellular variable [11].

In our model, we do not focus on the transmembrane current because the currents through the membrane, no matter how complicated they might be, do

not contribute directly to the generation of the magnetic field, due to radial symmetry and to the thinness of the membrane. This fact is well known in biomagnetism [4], [9]. In addition, it is known that in certain situations the extracellular current also has negligible contribution to the generation of the magnetic field [4], [9].

For example:

a) the bidomain analogue of the above single cable will be

$$C_i \frac{\partial u_i}{\partial t} = f(u) + \nabla \cdot (\sigma_i \nabla u_i),$$
$$C_o \frac{\partial u_o}{\partial t} = -f(u) + \nabla \cdot (\sigma_o \nabla u_o),$$

where the indices i and o stand for the inner and outer spaces respectively, and $u = u_i - u_o$ is a transmembrane potential;

b) the standard FitzHugh-Nagumo model,

$$C \frac{\partial u}{\partial t} = J_i + J_o + \nabla \cdot (\sigma \nabla u),$$
$$\frac{\partial v}{\partial t} = u - v.$$

where $J_i = f(u)$ and $J_o = -v$ represent the inner and outer going currents, respectively, has the following bidomain generalization:

$$C_i \frac{\partial u_i}{\partial t} = J_i + J_o + \nabla \cdot (\sigma_i \nabla u_i),$$
$$C_o \frac{\partial u_o}{\partial t} = -J_i - J_o + \nabla \cdot (\sigma_o \nabla u_o), \tag{1}$$
$$\frac{\partial v}{\partial t} = u - v,$$

where v is thought of as a lumped variable representing currents evolving on a slower time scale, e.g., potassium.

The first equation in FitzHugh-Nagumo and other multi-current models is the first Kirchhoff law, while the other equations are heuristic closures of the

first Kirchhoff law. In our modeling approach, we would like to replace the heuristic closures by the equations of state of the myocardium, based on the experimental data. This should be done by means of observable quantities such as extracellular potentials, concentrations and permeabilities of various ions, and magnetic fields associated with various waves propagating in a tissue.

Numerical examples. In this section we describe and explore some numerical solutions of the new model (1) under two different closures for $f(u,v) = J_i + J_o$. The first closure is analogous to the model used in [12],

$$\begin{aligned} C_i \frac{\partial u_i}{\partial t} &= f_a(u,v) + \nabla \cdot (\sigma_i \nabla u_i), \\ C_o \frac{\partial u_o}{\partial t} &= -f_a(u,v) + \nabla \cdot (\sigma_o \nabla u_o), \\ \frac{\partial v}{\partial t} &= u - v, \end{aligned} \tag{A}$$

with $f_a(u,v) = u(1-u)(u-(v+b)/a)/\epsilon$. The second closure is analogous to the model in [13],

$$\begin{aligned} C_i \frac{\partial u_i}{\partial t} &= f_b(u,v) + \nabla \cdot (\sigma_i \nabla u_i), \\ C_o \frac{\partial u_o}{\partial t} &= -f_b(u,v) + \nabla \cdot (\sigma_o \nabla u_o), \\ \frac{\partial v}{\partial t} &= -\epsilon(\gamma u + v), \end{aligned} \tag{B}$$

with

$$f_b(u,v) = v - h(u), \qquad h(u) = \begin{cases} \lambda_1 u + e_1, & \text{if} \quad u \geq u_1; \\ \lambda_2 u + e_2, & \text{if} \quad u \leq u_0; \\ \lambda_3 u + e_3, & \text{otherwise}, \end{cases}$$

In models (A) and (B), a, b, γ, ϵ, the λ_i's, and the e_i's are given parameters. Both closures can be written in similar form if v is changed to $-v$ and other variables are rescaled. The model has two time scales, of order 1 and ϵ. In all our computations we set $\epsilon = 0.006$, $a = 0.3$, $b = 0.01$, $C_i = 1.0$, $C_o = 4.0$, and

$\gamma = 8.0$; the conductivity matrix σ is assumed to be diagonal with diagonal elements $\sigma_{ox} = 1.0$, $\sigma_{ix} = 0.2$, $\sigma_{oy} = 0.2$, and $\sigma_{iy} = 1.0$, respectively.

In the following figures, we show the results obtained by applying model (1) to several initial conditions. We consider one- and two-dimensional traveling waves, and the interaction between them. In addition, the magnetic field of some spiral waves was computed.

Fig. 1. Dependence of the one-dimensional traveling wave profiles for the closure (B) on the parameters: (a) $\epsilon = 0.01$, $\lambda_1 = \lambda_2 = 2.0$, $e_1 = e_2 = 1.6$, $e_3 = 8.0$, $u_0 = u_1 = 0.05$; (b) $\epsilon = 0.006$, the rest of the parameters as in (a); (c) $\epsilon = 0.06$, $\lambda_1 = 1.0$, $e_1 = 4.0$, $\lambda_2 = 20.$, $e_2 = 22.4$, $u_0 = -0.8$, $u_1 = -0.42$, and the rest as in (a); (d) traveling wave profiles for the closure (A) with $\epsilon = 0.006$, $a = 0.3$, and $b = 0.01$.

In Figure 1, we show one-dimensional profiles of traveling wave solutions

moving to the left, under various closures. Under the two time-scale dynamics, the front and back of the waves are always sharp. We have experimented with various forms of the piecewise linear function $h(u)$. In figure 1(a), $h(u)$ is a discontinous sawtooth function, that makes the back as large as a front. In figure 1(b) smaller ϵ makes the pulse more narrow. Figure 1(c) shows the possibility of cutting off the tail of the pulse by making the slope (λ_2) large. The choice in figure 1(d) shows a pulse having step function form.

All the profiles are different from the experimental data for atrial tissue [9], where the u-profile has a triangular shape – a sharp increase in the front of the pulse and an almost straight sloping line on the back of the pulse.

Fig. 2. Traveling wave profiles and magnetic field for the closure (B), left (right) columns show the u and current profiles, contour and surface plots, respectively.

Fig. 3. Traveling wave profiles and magnetic field for the closure (A): u and v profiles, respectively; (c) current profile; (d) contour plot of the z-component of the magnetic field.

Fig. 4. A two-dimensional anisotropic spiral wave for the closure (A).

In Figures 2 and 3, we illustrate the dipolar type magnetic field generated by the above profiles rotating uniformly on a circle at a fixed moment in time. We show the u and the magnetic field generated at a plane above the circle, at a fixed moment in time. We have used the Biot-Savart taking into account only the inner source current, J_i.

Figure 4 shows a two-dimensional spiral wave admitted by the new model for the closure A, at a fixed moment of time.

Fig. 5. Interaction of the five periodic point sources with the spiral wave, closure (A), at four equal time intervals.

Finally, the interaction of periodic point sources, placed at different locations of the domain and firing with the same frequency, with the spiral of Figure 4 wave is shown in Figure 5 at four equal time intervals.

Conclusion. In this paper we have introduced a time-dependent model of excitable media. The model is a continuum extension of the standard electrophysiological models to situations where it is important to take into account both intra- and extracellular currents for accurate simulation. The new model

is suitable for biomagnetic simulations. In particular, it allows to study the magnetic field generated by various waves and by their interaction. It can also be used to understand the effect of injected currents. The model may be applied to the inverse problem of source localization, to the determination of the inner conductivity from the measured outer conductivities, and to the reconstruction of the current fluxes based on experimental or synthetic data.

Acknowledgements. We would like to thank P. Costa Ribeiro, E. Costa Monteiro, A. C. Bruno, and their students at the Department of Physics of PUC-Rio for introducing us to the field of Biomagnetism and for numerous helpful discussions. The work of M. B. was partially supported by CNPq under Grant 30.0659/94-6, while on sabbatical leave from the University of Arizona. The work of D. M. was partially supported by CNPq under Grant DMS-9011548.

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Received January 19, 1996
Revised April 24, 1996