Control theory inspired considerations of the mathematical models of defibrillation

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Abstract—One efficient approximate solution of the bidomain equations, which are used as a mathematical model of the heart tissue electrical properties, has been described. Moreover, the selected algorithm for discretization of partial differential equations, consisting of the method of separation of variables and modal analysis technique, results in the state-space representation of cardiac electrical activities, which makes the model suitable for applications of modern control theory. Also, the finite-dimensional model reveals the connection to the older models of defibrillation - simple circuit equivalents. Finally, an optimal controller designed for the generalized version of a simple parallel resistor-capacitor circuit has been applied to one- and three-mode expansions of the bidomain model.

I. INTRODUCTION

There is more than one reason why ventricular fibrillation has been recognized as a very challenging problem for both experimental and theoretical research: 1) It represents the most dangerous and life-threatening form of all cardiac arrhythmias 2) The process is not spontaneously reversible 3) In order to avoid sudden cardiac death, it is essential to proceed with an immediate application of an electric countershock therapy known as defibrillation. The extensive work in the field of defibrillation over the past two decades has been published in many studies and research articles, as listed in [1]. From there it becomes clear that all scientific efforts have been and still are oriented towards better understanding of electrical activities in the cardiac tissue in the presence of strong electric fields, with the main purpose of improving defibrillation therapies and increasing levels of their efficiency and safety.

The first mathematical models used to study defibrillation were simple electrical circuit equivalents ([2]), with a parallel resistor capacitor (RC) circuit as the most important one. They resulted from the endeavor to model the transmembrane voltage time course caused by different defibrillation waveforms. The models were used by the researchers to study the efficacy of different defibrillating pulses, and despite their simplicity, in several cases, predictions based on calculations with simple electrical circuit equivalents have been confirmed experimentally [3]. However, the advancements in the equipment and methods for obtaining measurements in the clinical and laboratory settings gave a clear indication that defibrillation and reentry are affected not by cell channel effects only, but by the cardiac tissue structure as well. The need to create a model capable of predicting regions of alternating transmembrane potential (virtual electrodes) throughout the heart has resulted in so-called bidomain models ([4],[5]) currently considered as the most complete description of cardiac electrical activities.

So far different variations of the bidomain model have been considered in numerous studies, but no analytical solutions for any realistic conditions have been reported. The applied approximate methods are usually finite difference ([5], [6]), finite element techniques [4], or just in some cases spectral methods (most often the finite Fourier transform, as in [7]). Regardless of the type and capacity of hardware resources used, the large amount of computer time needed to complete bidomain simulations has been reported, with the exception of spectral methods applications [7]. In this article, the method of eigenfunction expansion will be used for discretization of the bidomain equations. This method is fundamentally identical to the finite transform methods, since in both cases the system response is represented as series of suitable eigenfunctions. However, it will be shown that the method of eigenfunction expansion allows for computing the eigenfunctions, while the finite transform methods must start with an assumed set of eigenfunctions, as presented in [7]. The method of separation of variables, as a general technique which leads to a particular eigenfunction expansion or transform, will be incorporated as well. In addition, it will be possible to get the model of the system in the state-space form (as in [8]), which is well known as the most suitable for control applications.

Once the state-space version of the bidomain model was derived, it became clear that the bidomain model can be interpreted as a circuit consisting of an infinite number of simple parallel RC models, connected through the same input. This finding might be the missing link between two seemingly completely different classes of mathematical models of defibrillation. Also, it is obvious that the so far unexplained success of simple RC circuit models can be better understood.

The complexity of cardiac activities in myocardium during fibrillation and defibrillation has certainly been one of the main causes for the apparent delay in development of control applications for defibrillation. In this article, the advantage has been taken of the already mentioned connection between the finite dimensional bidomain model and the parallel RC circuit equivalent. First, the framework for a new model for optimal cardiac defibrillation based on simultaneous minimization of energy consumption and defibrillation time.
requirements, has been introduced. Finally, the necessary modifications have been done so that the same controller can be applied to the one mode expansion as the simplest form of the bidomain model.

II. BIDOMAIN MODELS

The full version of the bidomain model consists of two coupled, second order nonlinear partial differential equations, governing the electrical potentials induced in the intracellular and extracellular domains of the myocardium. Intracellular and extracellular domains refer to the space inside and outside the cells. In the most general form, the multi-dimensional bidomain model is given by the following set of equations:

\[ \nabla (G_i \nabla \Phi_i) = \beta I_m - I_i^{ext}; \nabla (G_e \nabla \Phi_e) = -\beta I_m - I_e^{ext} \] (1)

\[ I_m = C_m \frac{d\Phi_m}{dt} + I_{ion}(\Phi_m, t); \Phi_m = \Phi_i - \Phi_e \] (2)

In these equations, the subscripts \( i, e \) refer to the intracellular and extracellular domains, respectively. The parameters used in (1)-(2) are: electric potentials \( \Phi [V] \), specific conductivity tensors in the myocardium per unit length \( G [S/m] \), transmembrane current density per unit area \( I_m [A/m^2] \), membrane surface-to-volume ratio \( \beta [m^{-1}] \), the membrane capacitance per unit area \( C_m [F/m^2] \), the volume density of the externally applied current to the system \( I^{ext} [A/m^3] \), the ionic current density per unit area \( I_{ion} [A/m^2] \), and the transmembrane potential \( \Phi_m [V] \).

The ionic current term in excitable tissue deserves special attention, because once the voltage increases to a certain threshold value, an active tissue response will be initiated. In that case, \( I_{ion}(\Phi_m, t) \) in (2) must be replaced by an appropriate nonlinear model. When the passive tissue response is observed, the membrane can be represented as a linear resistor-capacitor circuit, since \( I_{ion} = G_m \Phi_m \), where \( G_m [S/m^2] \) represents the specific membrane conductance in the passive tissue.

The passive version of the bidomain model lacks the ability to predict the postshock response. According to [9], the approximation of the full bidomain model by its passive form is justified by the fact that the initial phase of the cardiac response to external stimuli is predominantly the period of virtual electrodes formation. This situation has also been explored in a particular experimental setting. Based on these considerations, the passive bidomain model of a three-dimensional volume of the myocardium, with the assumption of uniform fiber direction aligned with the z axis (in this case, the conductivity tensors are diagonal, with the elements denoted by \( g_T \) and \( g_L \), both in [S/m], representing specific macroscopic electrical conductivities of the myocardium perpendicular to and parallel to fiber axis, respectively), could be adopted as a very good basis for initial further analysis:

\[ \beta_2 \left( \frac{\partial^2 \Phi_m}{\partial x^2} + \frac{\partial^2 \Phi_m}{\partial y^2} + \frac{\partial^2 \Phi_m}{\partial z^2} \right) - \frac{\partial \Phi_m}{\partial t} = -\beta_1 \frac{\partial \Psi}{\partial z^2} + \kappa_1 \gamma_e - \kappa_3 \gamma_i \] (3)

\[ \beta_2 \left( \frac{\partial^2 \Psi}{\partial x^2} + \frac{\partial^2 \Psi}{\partial y^2} + \frac{\partial^2 \Psi}{\partial z^2} \right) = \beta_4 \left( \frac{\partial^2 \Phi_m}{\partial x^2} + \frac{\partial^2 \Phi_m}{\partial y^2} \right) - \kappa_2 \gamma_e - \kappa_2 \gamma_i \] (4)

It should be emphasized that the model (3)-(4) has been obtained from the passive form of the bidomain model given by (1) and (2) by means of scaling and linear transformations [10]. One of the variables in the new model is the transmembrane potential \( \Phi_m \), introduced earlier in (2), and the other one an auxiliary potential \( \Psi \) with no simple physical interpretation: \( \Psi = \Phi_i + (g_{cL}/g_{IL}) \Phi_e \).

When an isolated piece of tissue is observed, meaning that the tissue is surrounded by air (non-conductor), simple no-flux boundary conditions are usually applied at the tissue-air borders. For models in Cartesian coordinate system, the natural way to proceed is to assume a two- or three-dimensional slice of tissue, with \( a, b, \) and \( c \) as its dimensions in the \( x, y, \) and \( z \) directions, respectively.

In the preceding equations, \( \beta_1 \div \beta_4, \) and \( \kappa_1 \div \kappa_3 \) are all constants, and \( \gamma_i \) and \( \gamma_e \) represent scaled source terms, defined as \( \gamma_i = I_i^{ext}/(\beta G_m) \) and \( \gamma_e = I_e^{ext}/(\beta G_m) \).

III. EIGENFUNCTION SELECTION FOR THE BIDOMAIN MODEL

The modified version of the bidomain model defined by (3)-(4), and non-flux boundary conditions for \( \Phi_m \) and \( \Psi \), adopted earlier for the purpose of analysis and simulations in this paper, is linear, with homogeneous boundary conditions. Therefore, to make the separation of variables possible, the only needed modification is to temporarily take out the input terms from the partial differential equations. Also, it is apparent that the solution to the eigenvalue problem will be valid for nonlinear bidomain model as well.

In order to make the separation of variables procedure succeed, it may be reasonable to seek solutions of the partial differential equations in the following form:

\[ \Phi_m(x, y, z, t) = X(x)Y(y)Z(z)T(t) \] (5)

\[ \Psi(x, y, z, t) = X(x)Y(y)Z(z)W(t) \] (6)

Two expressions (5) and (6) impose a constraint on the result such that both \( \Phi_m \) and \( \Psi \) must be expressed in terms of the same eigenfunctions (or spatially dependent mode shapes) \( X(x), Y(y), \) and \( Z(z) \), whereas their time dependent parts (modes), \( T(t) \) and \( W(t) \) are different functions in general. However, it will be shown that in the zero input case, the modes are proportional and that implies their identity for the purpose of separation of variables. The main results of solving the bidomain model under consideration via modal analysis can be stated as follows:

Theorem 3.1: The Bidomain system of equations (3)-(4), accompanied by Neumann boundary conditions for both variables \( \Phi_m \) and \( \Psi \), admits a solution in the following form:

\[ \Phi_m(x, y, z, t) = \sum_{p,q,r=0}^{\infty} X_p(x)Y_q(y)Z_r(z)T_{pqr}(t) \] (7)

\[ \Psi(x, y, z, t) = \sum_{p,q,r=0}^{\infty} X_p(x)Y_q(y)Z_r(z)W_{pqr}(t) \] (8)

7417
where \( T_{pqr}(t) \) and \( W_{pqr}(t) \) satisfy the differential-algebraic system of equations given by:

\[
T_{pqr} = -\left( \frac{p^2\pi^2}{a^2} + \frac{q^2\pi^2}{b^2} + \frac{r^2\pi^2}{c^2} + 1 \right) T_{pqr} - \beta_1 \frac{r^2\pi^2}{c^2} W_{pqr} = \frac{8}{abc\kappa_3} \int_0^{a,b,c} \gamma_d(x,y,z,t)X_p(x)Y_q(y)Z_r(z)dx dy dz + \frac{8}{abc\kappa_3} \int_0^{a,b,c} \gamma_d(x,y,z,t)X_p(x)Y_q(y)Z_r(z)dx dy dz \tag{9}
\]

and \( X_p(x) \), \( Y_q(y) \), and \( Z_r(z) \) are eigenfunctions given by:

\[
X_p(x) = A_p \cos(\sqrt{\lambda}x); \quad \lambda = \frac{p^2\pi^2}{a^2}; \quad p = 0, 1, \ldots, \infty \tag{11}
\]

\[
Y_q(y) = A_q \cos(\sqrt{\mu}y); \quad \mu = \frac{q^2\pi^2}{b^2}; \quad q = 0, 1, \ldots, \infty \tag{12}
\]

\[
Z_r(z) = A_r \cos(\sqrt{\nu(1+\frac{1}{z})}); \quad \nu = \frac{r^2\pi^2}{c^2} - 1; \quad r = 0, 1, \ldots, \infty \tag{13}
\]

In (11)-(13), \( \lambda \), \( \mu \) and \( \nu \) denote eigenvalues, and \( A_p \), \( A_q \), and \( A_r \) are constants.

Proof: Consider the bidomain model given by (3)-(4) with Neumann boundary conditions for both \( \Phi_m \) and \( \Psi \). The selected approach for obtaining its state-space representation consists of two main steps:

1) Eigenfunction computation via the method of separation of variables.

In order to apply the separation of variables method, the inputs in (3)-(4) must be set to zero \((\gamma_c = \gamma_i = 0)\). Two cases will be considered while substituting (5),(6) into (3)-(4) with zero inputs:

- Case 1: \( W(t) = T(t) \)

Since both partial differential equations in the model with no inputs contain the same term \( \partial^2 \Psi / \partial z^2 \), it is possible to incorporate the steady-state part of the model into the equation containing the time derivative of the transmembrane potential. Next, replacing variables \( \Phi_m \) and \( \Psi \) with their corresponding eigenfunction expansions yields the eigenvalue problem, with the solution for eigenfunctions given by (11)-(13).

- Case 2: \( W(t) \neq T(t) \)

In order to make the method of separation of variables succeed, it must be assumed that \( W(t) = c_1 T(t) \), where \( c_1 \) denotes a constant. Also, for the purpose of computing the eigenfunctions, the coefficient \( c_1 \) is not important, and the usual procedure is to make it equal to 1. That would reduce the analysis to Case 1, and all previously derived results apply.

2) Obtaining the differential-algebraic system of equations for computing the system states \( T(t) \) and \( W(t) \).

The next step requires that the computed eigenfunctions (11)-(13) get substituted into the equations defining the infinite mode expansion (7) and (8). Then, the infinite mode expansion (7)-(8) is introduced back into the partial differential equations describing the bidomain cardiac representation (3), and (4). In the next three consecutive steps, each of the newly formed equations should be multiplied by the eigenfunctions \( X_i, Y_j, Z_k \) and integrated over the domains \([0,a],[0,b],[0,c]\), respectively. The system of one ordinary differential equation and one algebraic equation will be obtained for each \( i,j,k \), or equivalently \( pqr \) (in the already used notation) mode. These equations are given in the statement of the Theorem as (9) and (10).

In the most general case, the input source signals \( \gamma_c \) and \( \gamma_i \) are functions of \( x, y, z, \) and \( t \). Therefore, they can be expanded as follows:

\[
\gamma_{c,i}(x, y, z, t) = X_{c,i}(x)Y_{c,i}(y)Z_{c,i}(z)T_{c,i}(t) \tag{14}
\]

Taking into account the expansions described by (14), the differential (9) and (10) part of the solution for \( pqr \) mode can be written as:

\[
\dot{T}_{pqr} = a_{pqr11}T_{pqr} + a_{pqr12}W_{pqr} + b_{pqr11}I_c + b_{pqr12}I_i \tag{15}
\]

\[
0 = a_{pqr21}T_{pqr} + a_{pqr22}W_{pqr} + b_{pqr21}I_c + b_{pqr22}I_i \tag{16}
\]

where coefficients \( a_{pqr11} \div a_{pqr12} \), and \( b_{pqr11} \div b_{pqr12} \) are introduced as the short notation for the coefficients in (9) and (10).

As in the first step, two different cases will be considered:

- Case 1: \( W(t) = T(t) \)

Under the assumption that this equality holds, the solution for the mode \( pqr \) defined by (15), (16) becomes a system of two equations containing one unknown only, and the only possible result is the trivial solution: \( T_{pqr}(t) = W_{pqr}(t) = 0 \). Therefore, this case will be taken out from any further analysis.

- Case 2: \( W(t) \neq T(t) \)

In this case, (15) and (16) apply, and it is possible to find the unique solution. In the zero input case \( I_i = I_c = 0 \), the following relation between \( W_{pqr} \) and \( T_{pqr} \) follows readily from (16):

\[
W_{pqr} = -a_{pqr21}/a_{pqr22}T_{pqr} = c_1T_{pqr}, \quad \text{where} \ c_1 \text{ is a constant, which means that the result is identical with the one obtained in the first step.}
\]

The final set of completely uncoupled ordinary differential equations is obtained by expressing \( W_{pqr}(t) \) in (16) as a function of \( T_{pqr}(t) \) and applied inputs and substituting the new expression into (15). It should be pointed out that for
any practical implementation, the number of modes in (7)-(8) has to be changed from an infinite to some finite number $N$. The final result will be a finite-dimensional state-space representation of defibrillation, which is needed as a basis for any application of modern control methods.

IV. COMPUTER IMPLEMENTATION OF THE BIDOMAIN MODEL AND SIMULATION RESULTS

The state-space form of the bidomain model can be easily generated from the equations for computing the modes $T_{pq}$ and $W_{pq}$ of the transmembrane potential $\Phi_{m}$ and the auxiliary potential $\Psi$, respectively, which have been derived earlier. Apparently, $T_{pq}$ and $W_{pq}$ in this context are state variables and components of the state vectors $T$ and $W$. One way to compute the state vectors, is to form the state-space representation of defibrillation, which is needed as a basis for any application of modern control methods.

Once the system modes are known, the distribution of the transmembrane potential within the cardiac tissue can be computed by using the expression for the eigenfunction expansion (7). The results computed with the steady-state values of the system modes are presented on Fig. 1 and 2 as isopotential lines in $x - y$, $y - z$, and $x - z$ planes, at heights $z = 0$, $x = 0$, respectively. The pattern of the spatial distribution of the transmembrane potential is obtained by using the Matlab command CONTOUR, with automatically selected absolute values of the isopotentials to be displayed. As seen from the figures, the tissue with unequal anisotropy responds to point stimulation by producing adjacent regions of depolarization and repolarization. Further away from the stimulating electrodes are regions of hyperpolarization associated with the cathode and regions of depolarization associated with the anode. Also, the analysis of the pattern of the transmembrane potential indicates that stimulation along and across the fibers differs significantly. It can be shown that the position of the bipole across fibers results in larger number of zones of alternating membrane polarity.

V. CONNECTION BETWEEN THE BIDOMAIN MODEL AND SIMPLE RC CIRCUIT EQUIVALENTS OF DEFIBRILLATION

Even though simplified, lumped equivalents of the heart tissue in the presence of strong electric fields appear in the literature in a variety of combinations of resistors and capacitors, and sometimes inductors, a simple parallel RC circuit can be adopted as a representative of this class of models [11]. The principal characteristic of these models is that they are described by first order ordinary differential equations, and as such are very convenient for building different algorithms for computations. The second class of models are newer, so-called bidomain models, more exact and more difficult to deal with from the mathematical point

![Fig. 1. Computed values of the steady-state values of the transmembrane potential $\Phi_{m}$ in $x - y$ plane at $z = 0$ cm](image-url)
of view. Despite the current tendency of scientists to use bidomain models exclusively in studying defibrillation, so far all the research efforts have been concentrated on finding the most efficient numerical method for solving partial differential equations and, more importantly, no applicable results have been reported. The obvious consequence is that only the knowledge gained through the work with seemingly completely different and perhaps unacceptably simple [12] RC circuit models has been used in practice.

As a mathematical model of a simple parallel resistor-capacitor circuit, Fig.3 contains the schematic representation of the connection between the bidomain model in the \( n \)-dimensional state-space and the final output of the bidomain model, the transmembrane potential \( \Phi_m \). The key detail is that each state (mode) \( T_i \) of the bidomain model, can be computed from one parallel RC circuit.

This finding might be the missing link between the two of models for defibrillation and clarify the so far unexplained success of simple RC models in predicting the outcome of defibrillating shocks.

VI. FINITE DIMENSIONAL BIDOMAIN MODEL AND A TIME-ENERGY OPTIMAL CONTROLLER FOR A GENERALIZED RC CIRCUIT MODEL

Next, the results of the application of an algorithm developed for the optimal defibrillating pulse synthesis based on mathematically strict optimization will be presented. All the results of this theoretical study have been obtained for the proposed model, under the assumption that cardiac tissue can be represented by a linear, time-invariant, first-order differential equation:

\[
\frac{dV_m(t)}{dt} + a_0V_m(t) = b_1 \frac{dV_s(t)}{dt} + b_0V_s(t),
\]

where the system input and output signals \( V_s(t) \) and \( V_m(t) \) are generic, that is, they could each be a voltage or a current. Parameters \( a_0, b_0, b_1 \) are constants. In particular, setting \( b_1 = 0 \) reduces this model to the simple parallel resistor-capacitor circuit used to study defibrillation. The objective is to design the control function \( V_s(t) \) based on the measured output \( V_m(t) \) to steer the internal state of the system (19) (or the output \( V_m(t) \)) from an arbitrary initial to a specified final value in finite time \( t_f \), while minimizing a weighted balance between \( t_f \) and a measure of the energy spent. The proposed cost criterion given by:

\[
J = \int_0^{t_f} \left[ \rho + u^2(t) \right] dt
\]

is more general than the one proposed in [11], which is based on minimization of energy only. The interpretation of the parameter \( \rho > 0 \) is that it penalizes the elapsed time. The limiting cases of \( \rho \to 0 \) (time is cheap) and \( \rho \to \infty \) correspond to minimum-effort and minimum time problems, respectively. Also, \( u(t) \) in the cost function is the dimensionless control variable defined as: \( u(t) = V_s(t)/V_{s_{max}} \Rightarrow |u(t)| \leq 1.0 \), since the constraint expressed as \( |V_s(t)| \leq V_{s_{max}} \) has been imposed on the input \( V_s(t) \).

Detailed report on the derivation of the optimal solution via Hamiltonian approach is given in [13], and simulation results for the case \( b_1 = 0 \) are presented in [14].

It is well known that most control designs for distributed parameter models such as bidomain model, must be performed on some lower order models. With the established connection with the simple parallel RC circuit, it was natural to assume that the feedback design should start from there. With the reference to Fig.3, it is clear that the one mode expansion will be identical to one RC circuit model. The only difference is that the one mode expansion originates from a distributed parameter model, which implies that the transmembrane potential \( \Phi_m \) will be a function of spatial coordinates as well.

For a collocated one point sensor-actuator case and the input signal delivered via extracellular space, the same optimal time-energy controller designed for a parallel RC circuit model has been synthesized for one mode expansion (mode \( T_{111} \)) of the bidomain model. As expected, the controller will take \( T_{111} \) from the initial value (0) to the specified value \( T_f \). All the plots have the same shape as the ones in the
lumped parameter case [13], [14]. Here, only the plots of normalized curves of $V_s(t)$ and $T_{111}(t)$ are shown in Fig.4 and 5, respectively. In addition, Fig.5 also contains the result of application of the same optimal controller (designed for one mode expansion case) to two more modes $T_{112}$ and $T_{121}$. In the end of the period with the controller on, $T_{111}$ reaches $T_f$ as expected, and $T_{112}$ and $T_{121}$ get to 97 and 99.4 percent of $T_f$, which means that the error produced in the case of a higher dimensional model is acceptable. It should be emphasized that the selection of modes as representatives for one- and three-mode expansions has been arbitrary and not based on any assessment of their relative importance for the overall system response.

VII. CONCLUSIONS

In order to improve the efficiency and safety of currently used defibrillators, the application of control techniques to the existing mathematical models of cardiac tissue exposed to strong electric fields is proposed.

To this end, the passive bidomain model for a three-dimensional slice of myocardium has been discretized and the tool used for that purpose is the classical method of separation of variables. The preference for this particular method originated in the fact that this technique is less expensive than others from the computational point of view. More importantly, it was possible to get the model of the system in the state-space form, which is known as the most suitable for control applications. Also, the solutions for eigenfunctions apply to the bidomain nonlinear model as well. The results of the computation in the state space form have been used for finding the distribution of the transmembrane potential within a three dimensional slice of myocardium. The presence of virtual electrodes is evident in the plots obtained during simulations, and the pattern of the transmembrane potential distribution is in very good agreement with the results reported in the reviewed literature.

A missing link has been established between bidomain models, and much simpler lumped parameter equivalents of the heart in the presence of strong electric fields. Then, as a feedback control application, the defibrillating waveform, simultaneously optimal with respect to time and energy, has been derived. All the results have been obtained for a general first order model that, as a special case, reduces to the simple parallel RC circuit. Also, it was outlined that with minimal changes, the optimal controller design can be used in the case of one mode expansion of the distributed parameter model. Finally, exactly that controller has been applied to the three-dimensional mode expansion. In this work, the control of the distributed parameter model has been realized by means of one point sensor-actuator. One possible direction in future research is to test different aspect of multi-input and spatially distributed control on a high-dimensional model.

REFERENCES