The third-order action potential model for computer simulation of electrical wave propagation in cardiac tissue
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Abstract

Computer simulation of heart arrhythmia and fibrillation in 2D and 3D cardiac tissue requires adequate mathematical models. The models based on the latest physiological data are very complicated even for modern supercomputers. The widely used second-order simplified models give only qualitative results and do not reproduce properly the cell recovery processes, which affect the appearance of spiral waves, the character of their propagation and possible breakup of the wavefront. In order to overcome the limitations of second-order simplified models third-order models are introduced. The synthesis of these models is based on up-to-date physiological data and includes the effect of the gate variable \( j \) on a fast inward current and the total effect of a time-independent outward current and time-dependent slow inward current on the shape of action potential (AP). The reduction of the eighth-order Luo and Rudy (LR) model to the third-order simplified model is used to illustrate the proposed approach. The third-order simplified model retains all the major characteristics and parameters of AP of the original model including the shape of AP, AP duration (APD) and \( (dE/dt)_{\text{max}} \) restitution.

1 Introduction

Progress in cell membrane theory and clamp experiment techniques achieved in the past two decades has led to sophisticated mathematical models of cardiac cells. These models describe the electrophysiological processes in isolated cardiac cells with comparatively high accuracy and in great detail.
They are very useful for the simulation of the intimate cell mechanisms, but appear to be too complicated for the simulation of AP propagation in 2D and 3D cardiac tissue. Even modern super- and massively-parallel computers are not fast enough to permit interactive computer experiments.

Therefore, it seems reasonable to separate the whole problem into two subproblems: study the cellular processes of AP generation using detailed mathematical models, and investigate the AP propagation along the heart tissue using appropriate simplified models. In the latter case, the simplified model has to reproduce correctly the global characteristics of AP (maximum rate of depolarization \((dE/dt)_{\text{max}}\), APD, maximum value of AP \(E_{\text{max}}\)) and the cell recovery processes inherent in the detailed model.

A number of successful attempts were made to provide simplified models. The widely used FitzHugh-Nagumo model [1] and its numerous modifications [2, 3, 4] represent one group of simplified models. These models are not ionic models in the common sense of the term and solely give rough quantitative results. The other group of simplified models (Van Capelle and Durrer [5], Karma [6, 7]) was obtained as a result of reducing the ionic Noble model (1962) of the Purkinje fiber [8] to two first-order nonlinear ordinary differential equations.

The comparative analysis of both groups of simplified models [9] shows that all of them, in spite of superficial dissimilarities, are based on the same assumptions and old physiological data used in the Noble model. They produce decreased maximal rate of depolarization and do not reproduce properly the cell recovery processes and the shape of AP. Some attempts were made to implement the experimental APD restitution data onto the FH-N model [4] and to adjust artificially the desired steepness of the APD restitution curve and dispersion characteristics in the Karma models [10]. Both improvements do not solve the global problem of creating the simplified model based on modern physiological data nor are they capable of reproducing correctly the recovery processes.

This paper is focused on the synthesis of the simplified model which would reproduce correctly the global characteristics of AP and the cell recovery processes important for computer simulation of AP propagation in the heart muscle tissue. The model is based on modern data used in the sophisticated physiological models proposed by Luo and Rudy [11].

2 The analysis of Luo and Rudy model

General considerations

For any cell membrane we have:

\[-C \frac{dE}{dt} = I_{\text{total}}\]  \hspace{1cm} (1)

where \(C\) – membrane capacitance, \(E\) – transmembrane potential, \(I_{\text{total}}\) – total current through the membrane.
The total current can be divided into three components: general inward ionic current $I_{inw}(E, t)$, general outward ionic current $I_{outw}(E, t)$, and external current produced by a stimulus and neighboring cells $I_{ext} = I_{stim} + I_n$. The current from the neighboring cells, when heart muscle tissue is considered as a syncytium, is determined by the Laplacian of the appropriate dimension. Thus, the equation for AP generation and propagation takes the general form

$$-C \frac{\partial E}{\partial t} = I_{inw} + I_{outw} + I_{stim} + \alpha_x \left( \frac{\partial^2 E}{\partial x^2} + A_1 \frac{\partial^2 E}{\partial y^2} + A_2 \frac{\partial^2 E}{\partial z^2} \right)$$

Here $\alpha_x$ represents intracellular conductivity in the fiber longitudinal direction, $A_1, A_2$ determine anisotropy ratios of the tissue.

Following the Hodgkin - Huxley formalism, different and increasingly complicated analytical expressions for inward and outward currents of heart cells were proposed. For example, the LR model of ventricular cardiac action potential, introduced in 1991 [11], gives a more detailed description of the inward and outward currents, including the effects of $[Ca]_i$ and $[K]_o$ changes:

$$I_{inw}(t, E) = I_{Na} + I_{si}$$
$$I_{Na}(t, E) = 23m^3hj(E - E_{Na})$$
$$I_{si}(t, E) = 0.09df(E - E_{si})$$
$$E_{si} = 7.7 - 13.0287ln([Ca]_i)$$
$$\frac{d[Ca]_i}{dt} = -10^{-4}I_{si} + 0.07(10^{-4} - [Ca]_i)$$
$$I_{outw}(t, E) = I_K + I_{K_i(T)} = g_K X(E, t)X_i(E)(E - E_K) + I_{K_i(T)}(E)$$

Here $m, h, j, d, f, X$ are the gate variables determined by

$$\tau_y(E) \frac{dy}{dt} = y_\infty(E) - y; \quad y = m, h, j, d, f, X$$

Details of the LR model can be found in their original publication [11].

Computer simulation of the LR model shows that under normal conditions the global characteristics of the generated AP are: APD at the level of 90% $E_{max}$ is 384 msec, $(dE/dt)_{max} = 344 V/sec$, $E_{max} = 110 mV$, $E_{rest} = -84.2 mV$. The recovery processes are characterized by the time behavior of the gate variables $j, f$, and $X$ after the completion of the AP repolarization phase (see Fig. 1). The residual part of gate variable $j$ is responsible for $(dE/dt)_{max}$ restitution, while gate variables $X$ and $f$ are responsible for APD restitution. The residual $j$ and $f$ variables are pronounced during the first $75 - 100$ msec, the residual gate variable $X$ is present during most of the diastolic interval.

The AP depolarization phase is fully determined by the variation of sodium current (4), while the repolarization phase is determined by the summary effect of all other currents (5-8).
3 Synthesis of cardiac cell simplified mathematical model

The following considerations were used in our approach for developing the simplified cardiac cell model:

1. The detailed description of all ionic current components and corresponding membrane gate variables is not necessary for the adequate simulation of AP propagation. It is necessary to reproduce exactly only the AP characteristics which affect the speed of propagation ($\frac{dE}{dt}_{\text{max}}$, $E_{\text{max}}$, $D$) and the variables which characterize the cell recovery processes (APD restitution and $\frac{dE}{dt}_{\text{max}}$ restitution). The latter plays an important role when the cell is excited repeatedly.

2. The model must be based on the up-to-date physiological experimental data. Our model is based on the data used in the sophisticated LR cardiac cell model and, therefore, can be considered as a LR model simplified for the computer simulation of AP propagation.

3. In our model all ionic currents are combined into two groups: the currents participating in membrane depolarization and the currents involved in membrane repolarization.

4. In our model only the gate variables $j$ and $X$ are expressed explicitly as a solution of the corresponding ordinary differential equations. The effect of gate variable $f$ on recovery processes is taken into account by adjustment of $\tau X(E)$ when $dX/dt < 0$.

With these considerations and for $\alpha_x = 0$ we obtain:

\begin{align*}
-C \frac{dE}{dt} &= I_{\text{dep}}(E,t) + I_{\text{rep}}(E,t) + I_{\text{stim}} \quad (10) \\
I_{\text{dep}}(E,t) &= j(E,t)f_1(E) \quad (11) \\
I_{\text{rep}}(E,t) &= f_2(E) + X(E,t)f_3(E) \quad (12)
\end{align*}
Figure 2: The shape of AP for the LR model (1) and for the third order simplified model (2).

\[
\begin{align*}
\tau_j(E) \frac{dj}{dt} &= j_\infty(E) - j \\
\tau_X(E) \frac{dX}{dt} &= X_\infty(E) - X
\end{align*}
\]  

(13)  

(14)

Here the time independent \( \tau_1, \tau_2 \) and \( \tau_3 \) correspond to the following currents in the LR model during the AP obtained for the normal conditions:

\[
\begin{align*}
f_1(E) &\rightarrow I_{Na}(t, E) \\
f_2(E) &\rightarrow I_{si}(t, E) + I_{K1}(E) \\
f_3(E) &\rightarrow \bar{g}_K X_i(E)(E - E_K)
\end{align*}
\]  

(15)  

(16)  

(17)

Functions \( \tau_j(E), j_\infty(E) \) and \( X_\infty(E) \) are the same as in the LR model. In order to take into consideration the effect of gate variable \( f \) on APD restitution, the function \( \tau_X \) is modified as follows:

\[
\tau_X = \begin{cases} 
1.0 & \text{if } dX/dt \geq 0 \\
0.002 & \text{if } dX/dt < 0, X \geq 0.23 \\
0.85 & \text{otherwise}
\end{cases}
\]  

(18)

Thus, we reduce the original eighth - order LR model, with fifteen nonlinear functions, to a third - order model, with seven nonlinear functions. The functions \( f_1 \) and \( f_2 \) in our model are piece-wise approximated in six intervals by second - order polynomials with a maximal relative error not exceeding 3.2 %. The remaining five functions are calculated using analytical
Figure 3: The restitution curves in normalized form obtained for the LR model (1,3) and for the third order simplified model (2,4). 1,2 – APD restitution curves; 3,4 – \( (dE/dt)_{\text{max}} \) restitution curves.

expressions provided by Luo and Rudy. The relative errors in reproducing the global characteristics of AP by our model with respect to the LR model are: error in APD is 0.3 %, error in \( (dE/dt)_{\text{max}} \) is 2.2 %, error in \( E_{\text{max}} \) is negligible. To reduce the computation time we tabulated all seven functions with the uniform steps of \( E \) equal to 1 mV. In this case the errors were: 1.1 % for APD, 0.6 % for \( (dE/dt)_{\text{max}} \) and 0.7 % for \( E_{\text{max}} \). The time required for simulation of one AP in comparison with the original LR model was: 4.5 times less for the case of \( f_1 \) and \( f_2 \) piece-wise quadratic approximations, 19 times less for the case of tabulated functions. The shapes of the AP reproduced by the third - order simplified model and the LR model are shown in Fig. 2. The AP restitution and \( (dE/dt)_{\text{max}} \) restitution curves are shown in Fig. 3 together with those of the LR model. The APD restitution curves are in good agreement and both have the slope not exceeding 1 for all realistic diastolic intervals.

The simplified model described above was used in computer simulation of AP propagation along one-dimensional ring of cardiac cells. The ring is formed by the line of cell models interconnected by diffusion (2). Some time after the stimulus is applied to one of the ends of the line, both ends are connected numerically into a ring in the usual manner [12]. There exists a critical length of the ring for which the AP propagation becomes impossible. When the slope of APD restitution curve is smaller than 1, for our model \( L_{cr} = 10.76 \text{ cm} \). When the slope of APD restitution is greater
than 1 for some diastolic interval, there exists a range of ring lengths (in our case $12.9 \text{ cm} < L < 13.9 \text{ cm}$) where propagation of AP is unstable. For greater ring lengths the AP circulating in the ring reaches its steady state duration and velocity of circulation. The lower limit of the range of instability corresponds to the critical ring length when AP no longer can propagate. This coincides with theoretical results and computer studies done for the Beeler – Reuter mathematical model [7, 12].

4 Conclusion

- The proposed simplified third - order model in contrast to the existing second - order models is based on the modern physiological data; it correctly reproduces the cell recovery processes (including $(dE/dt)_{max}$ restitution) and the shape of AP.

- In the generation of one AP the use of this model with tabulated functions gives a 95 % decrease of computation time in comparison with the LR model, and about 35 % decrease in comparison with the Van Capelle and Durrer second - order model.

- The application of the proposed simplified model to AP propagation in the ring of cells shows good agreement with the same study but with the full mathematical cell model.

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References


