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Modeling of Electric Stimulation in a Three-Dimensional Isotropic Bidomain RC-Medium: a Rectangular Current Stimulus Case

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Abstract. Laplace equations were used for modeling of electrotonic potential in three-dimensional isotropic double-space RC medium. Solutions of Laplace equations for the case of rectangular current pulse stimulation using spherical electrode we obtain using Laplace transforms in imaginary space. Solutions in original space we got using numerical invert Laplace transform. It showed that the rising front of the transmembrane potential becomes less steep in regard to rising radius of the stimulating electrode and asymptotically reaches single-dimensional cable case (evenly distributed RC-circuit). The steady state value of transmembrane potential decreases with the increasing distance from stimulating electrode. It remains always positive when stimulus current is negative.

Key words: RC-model, electrical stimulation, transmembrane potential, Laplace equations, passive electrical properties of the tissue.

1. Introduction

Some cardiac arrhythmia do not respond to pharmaceutical treatment and implantation of a cardiac pacemaker remains the only possibility to rescue the patient. It has been experimentally established that the parameters of cardiac pacing (the threshold current, potential, power) depend on the size and shape of the electrode, the shape and duration of the pulse (Bredikis *et al.*, 1978; Irnich, 1975). There are some published results of modeling of the excitation spread in myocardial tissue during anode or cathode stimulating pulses in single-dimensional case (Krassowska *et al.*, 1992), two-dimensional case (Sepulveda *et al.*, 1989), and three-dimensional case (Roth and Wikswo, 1994). However in these publications there are no data about influence of electrode size or stimulating pulse length on threshold stimulating parameters for typical myocardial tissue. Such data could be very important for optimization of stimulating mode.

2. The Mathematical Model of the Cardiac Tissue

The cardiac tissue consists of two conductive spaces: the intracellular and the extracellular, separated by the plasmic membrane from each other. The intracellular space consists of the cells coupled via low resistance intercellular junctions. Let assume that the resistance of contacts is evenly distributed over the whole volume of the cell. Each point of the double-space medium, r, at the time moment t is characterized by the intracellular potential V_i, and the density of intracellular current $\mathbf{j_i}$, as well as by extracellular potential V_e and extracellular current density $\mathbf{j_e}$.

Let consider a homogeneous infinite three-dimensional double-space medium in which the specific resistance of the intracellular continuum is ρ_i, and the specific resistance of the extracellular space is ρ_e. The equation of the electric field (Peskoff, 1979) is applicable for the both: intracellular and extracellular areas:

$$\rho_i \mathbf{j_i} = -\nabla V_i, \tag{1a}$$

$$\rho_e \mathbf{j_e} = -\nabla V_e. \tag{1b}$$

The law of charge conservation looks following:

$$\nabla \cdot \mathbf{j_i} = -\frac{\partial q_i}{\partial t}, \tag{2a}$$

$$\nabla \cdot \mathbf{j_e} = -\frac{\partial q_e}{\partial t}, \tag{2b}$$

where q_i, q_e are the charge densities in the intracellular and extracellular areas, respectively. Let assume the source of current is placed in the extracellular area and ∇ is the Hamilton operator ($\nabla \equiv \frac{\partial}{\partial x}\mathbf{i} + \frac{\partial}{\partial y}\mathbf{j} + \frac{\partial}{\partial z}\mathbf{k}$ in Decart coordinate system). So far the difference of intracellular charge density is opposite to extracellular one ($\Delta q_i = -\Delta q_e$) and $\frac{\partial q_i}{\partial t} = j_m/b$ (Bukauskas *et al.*, 1975), we obtain:

$$\nabla \cdot \mathbf{j_i} = -j_m/b, \tag{3a}$$

$$\nabla \cdot \mathbf{j_e} = j_m/b, \tag{3b}$$

where j_m – the density of transmembrane current oriented from the intracellular to the extracellular area (the hyperpolarizing current is positive). j_m is described by the equation:

$$j_m = \frac{1}{R_m}(V_i - V_e) + C_m \frac{\partial}{\partial t}(V_i - V_e), \tag{4}$$

where R_m is the specific resistance of the electrogenic membrane, C_m is the specific capacitance. Assume that R_m is not dependent upon the time and potential. Substitution of (3a), (3b) and (4) in Eqs. 1a and 1b yields:

$$\nabla^2 V_i - \frac{\rho_i}{R_m b}(V_i - V_e) - \frac{C_m \rho_i}{b}\frac{\partial}{\partial t}(V_i - V_e) = 0, \tag{5}$$

$$\nabla^2 V_e + \frac{\rho_e}{R_m b}(V_i - V_e) + \frac{C_m \rho_e}{b}\frac{\partial}{\partial t}(V_i - V_e) = 0. \tag{6}$$

Eqs. 5 and 6 are coupled partial differential equations. They may be decoupled in the following way: we subtract the Eq. 6 from the Eq. 5 and obtain:

$$\nabla^2 (V_i - V_e) - \frac{\rho_i + \rho_e}{b}\left(\frac{1}{R_m}(V_i - V_e) + C_m \frac{\partial}{\partial t}(V_i - V_e)\right) = 0. \tag{7}$$

Multiplication of Eq. 5 by ρ_e/ρ_i and term by term addition to the Eq. 6 yields

$$\nabla^2 \left(\frac{\rho_e}{\rho_i} V_i + V_e\right) = 0. \tag{8}$$

The equations (7) and (8) make the system of coupled differential equations. By setting

$$V_i - V_e = V_m, \tag{9}$$

$$V_i \frac{\rho_e}{\rho_i} + V_e = \Psi, \tag{10}$$

$$R_m b/(\rho_i + \rho_e) = \lambda^2, \tag{11}$$

$$\tau_m = R_m C_m, \tag{12}$$

where V_m = transmembrane potential, Ψ – we introduce this variable to convert the differential equation into the form of Laplace equation (see below (14)), λ – constant of electrotonic decay, τ_m – time constant of the electrogenic membrane. In normed coordinate system (R, T) where $R = r/\lambda$, and $T = t/\tau_m$, we obtain:

$$\nabla^2 V_m - V_m - \frac{\partial V_m}{\partial T} = 0, \tag{13}$$

$$\nabla^2 \Psi = 0. \tag{14}$$

Laplace transforms of Eqs. 13 and 14 yield

$$\nabla^2 \overline{V}_m - (1 + s)\overline{V}_m = 0, \tag{15}$$

$$\nabla^2 \overline{\Psi} = 0, \tag{16}$$

where $\overline{V}_m = \overline{V}_m(R, s)$ and $\overline{\Psi} = \overline{\Psi}(R, s)$ are Laplace transforms of functions $V_m = V_m(R, T)$ and $\Psi = \Psi(R, t)$. The general solution of Eq. 15 is

$$\overline{V}_m = \frac{1}{R}\left\{A(s)\exp(-R\sqrt{1+s}) + B(s)\exp(R + \sqrt{1+s})\right\}, \tag{17}$$

where $A(s)$ and $B(s)$ are indices that depend on boundary conditions. $V_m(R, T) \to 0$ when $R \to \infty$, therefore $\overline{V}_m(R, s) \to 0$ when $R \to \infty$. This condition is satisfied when $B(s) = 0$. We obtain that

$$\overline{V}_m = \frac{A(s)}{R}\exp(-R\sqrt{1+s}). \tag{18}$$

The general solution of Eq. 16 is:

$$\overline{\Psi} = C(s)\frac{1}{R}. \tag{19}$$

The values of indices $A(s),\ B(s),\ C(s)$ depend on the initial and boundary conditions. Assume that before the stimulation moment the electrogenic membrane was in the state of rest, i.e.

$$V_i(R,0) = V_e(R,0) = 0.$$

3. Stimulation Using Rectangular Pulse

Let assume that r_o is the radius of the extracellular spherical pacing electrode in the metric system of axes, and the pulse of current is set as: $I = I_o$, when $T_{st} \geqslant T > 0$ and $I = 0$, when $T < 0$ and $T > T_{st}$. Laplace transform of the pulse of current is:

$$\overline{I} = \frac{I_0\left[1 - \exp(-sT_{st})\right]}{s}. \tag{20}$$

The change in extracellular potential ΔV_e on the spherical layer, with thickness Δr, of the extracellular space next to the electrode is equal to:

$$\Delta V_e \cong -\frac{I_0\rho_e}{4\pi r_0^2}\Delta r. \tag{21}$$

As $r = R\lambda$, and $r_o = R_o\lambda$, we obtain that

$$\left(\frac{\partial V_e}{\partial R}\right)_{R=R_0} = -\frac{I_0\rho_e}{4\pi R_0^2\lambda} \tag{22}$$

In point $R = R_o$ the whole stimulating current flows to the extracellular space, therefore

$$V_i(R_0,T) = 0, \tag{23}$$

$$V_m(R_0,T) = -V_e(r_0,T). \tag{24}$$

Making the Laplace transform of the Eq. 22 and taking into account (24), we obtain

$$\left(\frac{d\overline{V}_m}{dR}\right)_{R=R_0} = \frac{I_0\left[1 - \exp(-sT_{st})\right]\rho_e}{4\pi R_0^2\lambda s}. \tag{25}$$

We substitute the value (18) of $\overline{V}_m$ in Eq. 25 and obtain:

$$A(s) = -\frac{I_0\rho_e\left[1 - \exp(-sT_{st})\right]\exp(R_0\sqrt{s+1})}{4\pi\lambda s(R_0\sqrt{s+1}+1)}. \tag{26}$$

The final expression of the solution when $R \geqslant R_o$, is following:

$$\overline{V}_m = -\frac{I_0 \rho_e \left[1 - \exp(-sT_{st})\right] \exp\left[(R_0 - R)\sqrt{s+1}\right]}{4\pi R \lambda s (R_0 \sqrt{s+1} + 1)}. \tag{27}$$

For a point-type source of current ($R_o = 0$), when $T_{st} \to \infty$, Eq. 27 is analogous to the expression of intracellular potential ((Jack *et al.*, 1975), equation 5.34). From Eqs. 10, 19, 23 and 24 we obtain

$$C(s) = -R_0 \overline{V}_m(R_0, s). \tag{28}$$

From Eq. 27 we derive the expression $\overline{V}_m(R_0, s)$ and make the substitution in equation (28):

$$C(s) = \frac{I_0 \rho_e \left[1 - \exp(-sT_{st})\right]}{4\pi \lambda s (R_0 \sqrt{s+1} + 1)}. \tag{29}$$

Substitution of $C(s)$ with (29) in Eq. 19 and the Laplace transform of $\overline{\Psi}(R, s)$ expression (10) yield:

$$\frac{\rho_e}{\rho_i} \overline{V}_i + \overline{V}_e = \frac{I_0 \rho_e \left[1 - \exp(-sT_{st})\right]}{4\pi \lambda s R (R_0 \sqrt{s+1} + 1)}. \tag{30}$$

From Eqs. 9, 27 and 30 we derive the values of intracellular and extracellular potentials in the imaginary space:

$$\overline{V}_i = \frac{\rho_i \rho_e}{\rho_i + \rho_e} \cdot \frac{I_0 \left[1 - \exp(-sT_{st})\right]}{4\pi R \lambda s (R_0 \sqrt{s+1} + 1)} \left\{1 - \exp\left[(R_0 - R)\sqrt{s+1}\right]\right\}, \tag{31}$$

$$\overline{V}_e = \frac{\rho_i \rho_e}{\rho_i + \rho_e} \cdot \frac{I_0 \left[1 - \exp(-sT_{st})\right]}{4\pi R \lambda s (R_0 \sqrt{s+1} + 1)} \left\{1 + \frac{\rho_e}{\rho_i} \exp\left[(R_0 - R)\sqrt{s+1}\right]\right\}. \tag{32}$$

Solutions (27), (31), (32) remain valid for the imaginary space. To receive the actual values of potentials, inverse Laplace transform must be made.

$$V_m(R, T) = \frac{1}{2\pi j} \int_{\gamma - j\infty}^{\gamma + j\infty} \overline{V}_m(R, s) \exp(Ts)\, ds. \tag{33}$$

As the stimulating current is of finite magnitude, the integral (34) converges:

$$\int_0^\infty |V_m(R, T)|\, dT < \infty. \tag{34}$$

According (Aramanovich *et al.*, 1968), the inverse Laplace transform can be substituted by the inverse Fourier transform using $s = j\omega$:

$$V_m(R, T) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \overline{V}_m(R, j\omega) \exp(j\omega T)\, d\omega. \tag{35}$$

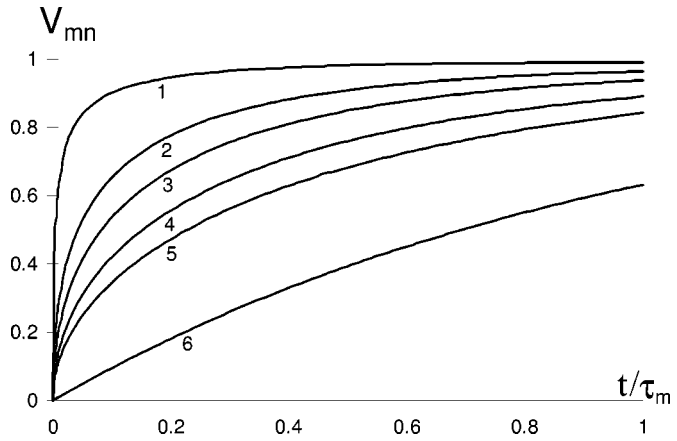

Fig. 1. Dependency of the alteration of the normalized transmembrane potential V_{mn} on normalized time in case of stimulation by a rectangular current pulse. Curves 1–4 are obtained in a three-dimensional medium in which V_m was calculated in point R_o(R_o – radius of the electrode). Curve 1: $R_o = 0.1$; curve 2: $R_o = 0.5$; curve 3: $R_o = 1.0$; curve 4: $R_o = 3.0$. Curve 5 reflects the alteration of V_m in a single-dimensional infinite cable when the points of pacing and recording coincide. Curve 6 – dependency $V_{mn} = 1 - exp(-t/\tau_m)$ (case of point membrane).

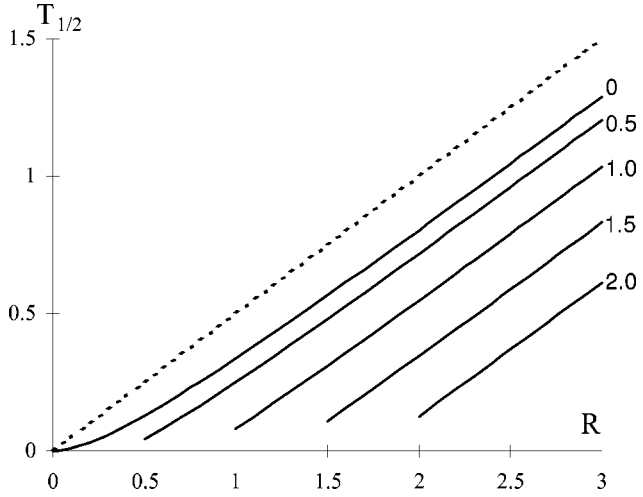

Fig. 2. Dependency of half-time $T_{1/2}$ on the distance between the center of the pacing electrode and the potential of the recording point R, for different radius of the pacing electrode. The dotted line shows the dependency $T_{1/2} = R/2$, and the figures near the curves indicate R_o, the radius of the pacing electrode.

Analogous expressions can be derived for the intracellular and extracellular potential.

The inverse Fourier transform was performed in a numerical way using the Fillon method (Hamming, 1962). We found that the speed of alteration of the anterior frontier of V_m depends on radius R_o of the stimulating electrode and the distance between the center of the electrode and the recording point R. With increase of R_o, when the point of record-

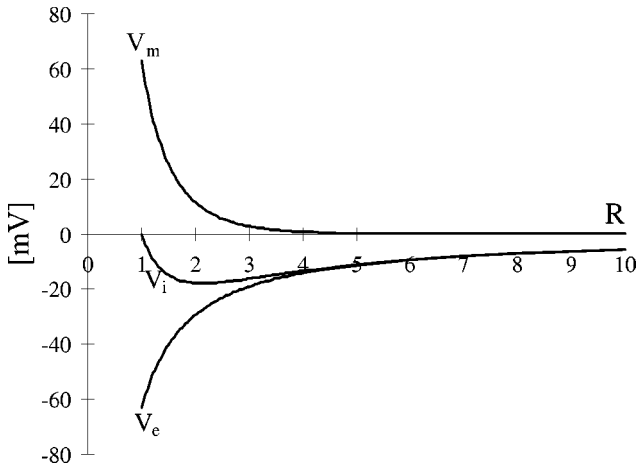

Fig. 3. Steady state values of V_m, V_i, V_e in regard to the distance from pacing electrode of radius $R_o = 1.0$. For further details, see the text.

ing $R = R_o$, the rising front of transmembrane potential flattens and asymptotically approaches that in a single-dimensional cable, when the points of stimulation and recording coincide (Fig. 1). Away from the surface of the stimulating electrode ($R_o = \text{const.}$), the rising front of V_m also flattens, i.e. time $T_{1/2}$ in which V_m reaches half the stationary amplitude increases. Fig. 2 provides the dependency of $T_{1/2}$ on R for different values of R_o: with increase of R, the functional dependency $T_{1/2} = f(R)$ asymptotically reaches the straight line whose tangent of the sloping angle is equal to 0.5.

To calculate the absolute values of $V_m,\ V_i,\ V_e$ for a stationary case, with $T \to \infty$, the values of parameters ρ_i, ρ_e, R_m, C_m, b must be known. As our model is concerned with an isotropic case whereas the cardiac tissue is anisotropic, we take the specific resistance of intracellular and extracellular spaces in the $x,\ y,\ z$ axis directions from reference (Plonsey and Barr, 1982), and in accordance with (Bukauskas *et al.*, 1975) we assume that, $\rho_i = \sqrt[3]{\rho_{ix}\rho_{iy}\rho_{iz}}$, $\rho_e = \sqrt[3]{\rho_{ex}\rho_{ey}\rho_{ez}}$, where $\rho_{ix},\ \rho_{iy},\ \rho_{iz}$ are the specific resistance of the intracellular space of the cardiac tissue, $\rho_{ex},\ \rho_{ey},\ \rho_{ez}$ are the specific resistance of the extracellular space of the cardiac tissue taken from reference (Plonsey and Barr, 1982). We take $R_m = 2000\Omega\cdot$ cm^2 (Sepulveda *et al.*, 1989), $C_m = 1\mu$F/cm^2 (Barr and Plonsey, 1984), $b = 5\cdot 10^{-4}$cm (Sepulveda *et al.*, 1989), $\rho_i = 2500\Omega\cdot$cm, $\rho_e = 300\Omega\cdot$cm, $I_o = -0.1$ mA and find that close to the spherical stimulating electrode with radius equal to 1λ, the transmembrane potential is equal to 63 mV. The steady state value of transmembrane potential decreases with the distance from the surface of the pacing electrode. At the same time the transmembrane potential always remains positive when the pacing current is negative (Fig. 3).

The elaborated the mathematical model of electrical stimulation which could allow to find a stimulation mode with minimal energy resources. Such stimulating mode could be very useful for maximizing of life time of the power source of a cardiac pacemaker. On the other hand minimal stimulating energy will reduce the inescapable injury of the cardiac tissue during stimulation.

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Elektrinės stimuliacijos modeliavimas trimatėje izotropinėje dvisritėje ominėje – talpuminėje terpėje: stimuliavimas stačiakampiu srovės šuoliuku

R. Veteikis, A. Kriščiukaitis

Elektrotoninio potencialo pasiskirstymas dvisritėje trimatėje RC-terpėje yra aprašomas Laplaso lygtimis. Atlikus Laplaso transformaciją vaizdų erdvėje yra gauti šių lygčių sprendiniai, kai stimuliuojama stačiakampiu srovės impulsu ekstraląsteliniu sferiniu elektrodu. Sprendiniai originalų erdvėje yra gauti skaitmeniniu būdu atlikus atvirkštinę Laplaso transformaciją. Gauta, kad transmembraninio potencialo priekinio fronto kitimo greitis, didėjant elektrodo spinduliui, mažėja ir asimptotiškai artėja prie vienmačio kabelio atvejo. Stacionari transmembraninio, intraląstelinio ir ekstraląstelinio potencialo reikšmė tolstant nuo elektrodo paviršiaus mažėja, tačiau transmembraninis potencialas visada išlieka teigiamas, kai stimuliuojanti srovė yra neigiama.