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Voltage Response of Three-dimensional RC-medium to Prolonged Step Voltage Change

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Introduction

Many living tissues are formed of separate cells connected in between by junctions capable of conducting the electric current. The properties of plasmic (electrogenic) membrane and intercellular contacts are important in studying the functioning mechanisms of tissues. The plasmic (electrogenic) membrane of excitable tissues cells is responsible for generation of ionic currents, which propagate through tissue via intercellular contacts. The purpose of intercellular contacts depending on tissue may be different. For example, the destination of contacts in myocardium is synchronization of contraction process. In non-excitable tissues the intercellular contacts give an opportunity for contiguous cells to interchange by various molecules. Therefore investigations of intercellular contacts permeability and electrogenic membrane ionic currents are actual in many branches of medicine. One of methods to investigate the electric properties of intercellular contacts is through estimation of the distribution of electrotonic potential in the tissue, close to the current electrode, by using a microelectrode, and through further theoretical analysis of anisotropic ohmic media [1–2]. Early modeling of electrotonic potential distribution in two-dimensional and three-dimensional syncytial tissue (RC-medium) for rectangular current pulse was performed when the current electrode is point-shaped, disk-shaped or spherical-shaped [3-6]. In solving these simplified cases, we obtained one of the features of RC-media: the time $t_{1/2}$, in which the electrotonic potential reaches half the steady amplitude, depends linearly on the distance r between the point-shaped current source and the point where the electrotonic potential is measured.

However in some cases of physiological interest, it is more appropriate to obtain the response to a step voltage pulse than to a step current pulse. The application of a voltage step to a cell cluster has become possible through the development of voltage-clamp techniques using microelectrodes (point-clamp). Application of whole-cell patch or other point voltage-clamp techniques risk subtle but significant error when measuring active ionic current properties in poorly space-clamped cells. A voltage-clamp experiment was simulated in a long one-dimensional cable of neuron and the simple numerical algorithm that corrects the distortions of incomplete space clamp was presented [7]. However the distribution of voltage step in three-dimensional tissue has not yet investigated.

The purpose of this work is theoretical investigation of electrotonic potential V_m distribution in three-dimensional (x, y, z) syncytial tissue modeling it as an isotropic continuous resistive-capacitive (RC) medium, when the voltage electrode is point-shaped or spherical.

Distribution of electrotonic potential in a three-dimensional RC medium when a spherical voltage electrode is used

The distribution of transmembrane electrotonic potential $V_m = V_m(x, y, z, t)$ in three–dimensional isotropic RC medium is described by equation [6]

$$\lambda^2 \nabla^2 V_m - V_m - \frac{\partial V_m}{\partial T} = 0, \qquad (1)$$

where ∇ - Hamilton operator (in Decart system of coordinates $\nabla \equiv \frac{\partial}{\partial x}\boldsymbol{i} + \frac{\partial}{\partial y}\boldsymbol{j} + \frac{\partial}{\partial z}\boldsymbol{k}$), $\lambda = \sqrt{R_m / \beta \rho_i}$ – medium space constant of electrotonic decay, ρ_i – resistivity of intracellular medium, β – ratio of the cell plasmatic membrane area to the cell volume, T is a normalized time ($T = t/\tau_m$, $\tau_m = R_m C_m$, τ_m – time constant of plasmatic membrane, R_m – resistivity of plasmatic membrane, C_m – is the specific capacitance of the plasmatic membrane).

Laplace transform of equation (1) yield:

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

where $\overline{V}_m = \overline{V}_m(X, Y, Z, s)$ – Laplace transform of function $V_m = V_m(X, Y, Z, T)$, ($X = x/\lambda$, $Y = y/\lambda$, $Z = z/\lambda$).

The general solution of equation (2) is

$$\overline{V}_m(R,s)=\frac{1}{R}\left\{A(s)\exp\left(-R\sqrt{1+s}\right)+B(s)\exp\left(R\sqrt{1+s}\right)\right\} \quad (3)$$

where $A(s)$ and $B(s)$ are indices that depend on boundary and initial conditions, and $R=\sqrt{x^2+y^2+z^2}/\lambda$. When $R\to\infty$, $V_m(R,T)\to 0$ (a case of infinite medium), therefore $\overline{V}_m(R,s)\to 0$ when $R\to\infty$. This condition is satisfied when $B(s)=0$. We obtain that

$$\overline{V}_m(R,s)=\frac{A(s)}{R}\exp\left(-R\sqrt{1+s}\right). \quad (4)$$

Let assume the initial conditions. We will consider that before a beginning of rectangular voltage pulse the electrogenic membrane was at the resting state, i.e. $V_m(R,0)=0$. Let assume that the center of spherical intracellular voltage electrode of radius r_o is in point $x=y=z=0$, and the pulse of voltage is set as: $V=0$, when $T<0$ and $V=V_o$, when $T>0$. Laplace transform of the voltage pulse is:

$$\overline{V}=\frac{V_o\left[1-\exp\left(-sT_{st}\right)\right]}{s}, \quad (5)$$

where T_{st} is a normalized duration of rectangular voltage pulse ($T_{st}=t_{st}/\tau_m$, where t_{st} – duration of pulse, τ_m – time constant of electrogenic membrane). Next to spherical voltage electrode at point R_o ($R_o=r_o/\lambda$) the potential value in the imaginary space is:

$$\overline{V}_m(R_o,s)=\frac{A(s)\exp\left(-R_o\sqrt{1+s}\right)}{R_o}=\frac{V_o\left[1-\exp\left(-sT_{st}\right)\right]}{s}. \quad (6)$$

From (6) we obtain the expression of $A(s)$:

$$A(s)=\frac{V_oR_o\left[1-\exp\left(-sT_{st}\right)\right]}{s\exp\left(-R_o\sqrt{s+1}\right)}. \quad (7)$$

We substitute the expression of $A(s)$ into equation (4) and obtain final expression of solution of equation (1), when $R\geq R_o$:

$$\overline{V}_m(R,s)=\frac{V_oR_o\left[1-\exp\left(-sT_{st}\right)\right]}{Rs\exp\left[-\left(R_o-R\right)\sqrt{s+1}\right]}. \quad (8)$$

The solution (8) is valid in imaginary space. To obtain the actual values of potentials $V_m(R,T)$, inverse Laplace transform must be performed:

$$V_m(R,T)=\frac{1}{2\pi i}\int_{\gamma-i\infty}^{\gamma+i\infty}\frac{V_oR_o\left[1-\exp\left(-sT_{st}\right)\right]}{\exp[-(R_o-R)\sqrt{s+1}]Rs}\exp(Ts)ds. \quad (10)$$

As the voltage pulse is of finite duration T_{st} and finite amplitude V_o, the integral (10) converges:

$$\int_0^{\infty}\left|V_m(R,T)\right|dT<\infty. \quad (11)$$

Therefore according to [8], the inverse Laplace transform can be substituted by the inverse Furje transform using $s=i\omega$:

$$V_m(R,T)=\frac{1}{2\pi}\int_{-\infty}^{\infty}\frac{V_oR_o\left[1-\exp\left(-i\omega T_{st}\right)\right]\exp\left(iT\omega\right)}{R\omega i\exp\left[-\left(R_o-R\right)\sqrt{i\omega+1}\right]}d\omega, \quad (12)$$

where i – imaginary unit. When $T\to\infty$ and $T_{st}\to\infty$ we obtain the stationary solution (for resistive medium):

$$V_m(R,\infty)=\frac{V_oR_o\exp\left(R_o-R\right)}{R}. \quad (13)$$

Normalized electrotonic potential $V(R,T)$ is defined:

$$V(R,T)=\frac{V_m(R,T)}{V_m(R,\infty)}. \quad (14)$$

When $T\to\infty$, $V(R,\infty)\to 1$. After substitution of equation (12) and (13) into equation (14) we obtain, that

$$V(R,T)=\frac{1}{2\pi i}\int_{-\infty}^{\infty}\frac{\left[1-\exp\left(-i\omega T_{st}\right)\right]\exp\left(iT\omega\right)}{\omega\exp\left[-\left(R_o-R\right)\left(1-\sqrt{\omega i+1}\right)\right]}d\omega. \quad (15)$$

Dependence of electrotonic potential half-time on distance and on the voltage electrode size

As the normalized potential value is equal to 0,5, when $T=T_{1/2}$, the equation (15) can be transcribed as follows:

$$V\left(R,T_{1/2}\right)=\frac{1}{2\pi i}\int_{-\infty}^{\infty}\frac{\left[1-\exp\left(-i\omega T_{st}\right)\right]\exp\left(iT_{1/2}\omega\right)}{\omega\exp\left[-\left(R_o-R\right)\left(1-\sqrt{\omega i+1}\right)\right]}d\omega=0{,}5. \quad (16)$$

The dependence of the half-time on distance $T_{1/2}(R)$ is an implicit function. To find the derivative of this function in respect to distance, one should introduce a new function $F\left(R,T_{1/2}\right)$:

$$F\left(X,T_{1/2}\right)=V\left(X,T_{1/2}\right)-0{,}5. \quad (17)$$

Since the three-dimensional RC-medium under consideration is continuous, the function $F\left(X,T_{1/2}\right)$ outside of the voltage electrode zone has continuous partial derivatives in respect to R and $T_{1/2}$, which are not equal to zero. We can state that

$$F\left[R,T_{1/2}(R)\right]=V\left[R,T_{1/2}(R)\right]-0{,}5=0 \quad (18)$$

and then in accordance to [9]

$$\frac{dT_{1/2}}{dR}=-\frac{F'_R\left(R,T_{1/2}\right)}{F'_{T_{1/2}}\left(R,T_{1/2}\right)}=-\frac{V'_R\left(R,T_{1/2}\right)}{V'_{T_{1/2}}\left(R,T_{1/2}\right)}. \quad (19)$$

We will find the potential (16) partial derivatives in respect to R and $T_{1/2}$:

$$\frac{\partial V\left(R,T_{1/2}\right)}{\partial R}=$$

$$=\frac{1}{2\pi}\int_{-\infty}^{\infty}\overline{V}(R,i\omega)\cdot\left(1-\sqrt{\omega i+1}\right)\exp\left(i\omega T_{1/2}\right)d\omega, \quad (20)$$

$$\frac{\partial V(R,T_{1/2})}{\partial T_{1/2}} = \frac{1}{2\pi}\int_{-\infty}^{\infty}\overline{V}(R,i\omega)\exp(i\omega T_{1/2})i\omega d\omega . \quad (21)$$

Put formulas (20) and (21) into (19) and obtain a half-time derivative in respect to distance for a infinite three-dimensional RC-medium when a voltage electrode is spherical:

$$\frac{\partial T_{1/2}}{\partial R} = \frac{\int_{-\infty}^{\infty}\overline{V}(R,i\omega)\cdot\left(1-\sqrt{\omega i+1}\right)\exp(i\omega T_{1/2})d\omega}{\int_{-\infty}^{\infty}\overline{V}(R,i\omega)\exp(i\omega T_{1/2})i\omega d\omega}, \quad (22)$$

where

$$\overline{V}(R,i\omega) = \frac{[1-\exp(-i\omega T_{st})]\exp\left[(R_o - R)\sqrt{i\omega+1}\right]}{i\omega\exp(R_o - R)}. \quad (23)$$

The computer programs were created and the calculations were carried out. The speed of alteration of the anterior frontier of V depends on the distance between the center of the electrode R and the recording point V. For a fixed voltage electrode radius R_o with increase of R the rising front of transmembrane potential flattens (Fig.1), i.e. time $T_{1/2}$ in which V reaches half the stationary amplitude increases.

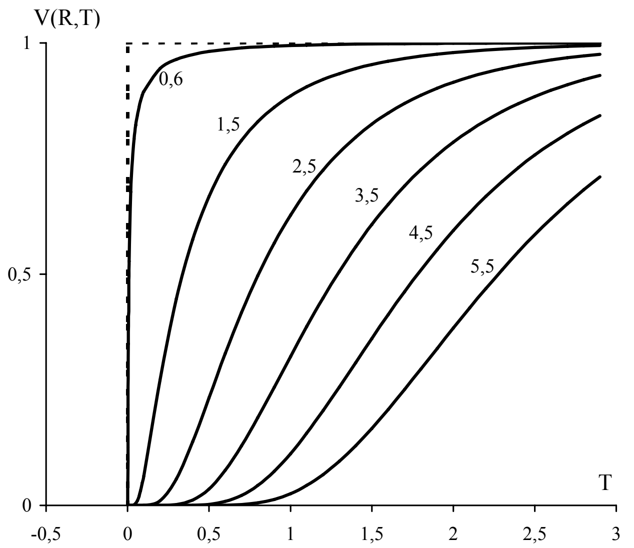

Fig. 1. Dependency of the alteration of the normalized transmembrane potential V on normalized time in case of stimulation of intracellular rectangular voltage pulse. The numbers next to curves are the distance R from the center of spherical electrode of radius $R_o = 0{,}5$. The curves were obtained with aid of formula (15)

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.

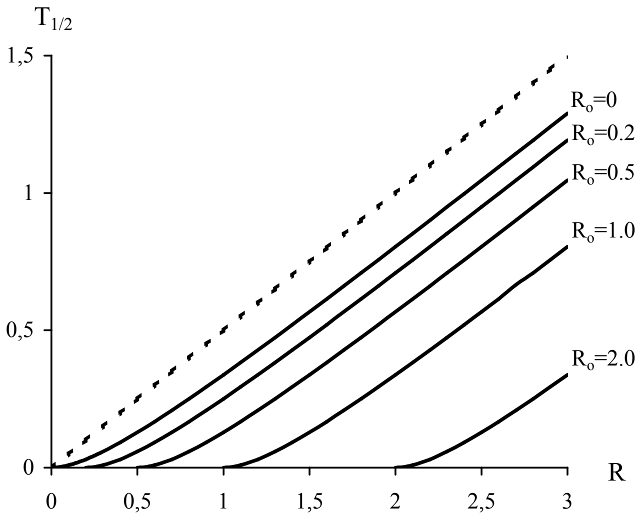

Fig. 2. The dependence of half-time $T_{1/2}$ on voltage electrode radius (R_o) for various fixed distances between a potential recording site and electrode center (R). The dotted line represents the linear dependency $R = T_{1/2}/2$

As we can see the value of $T_{1/2}$ calculated on the surface of electrode ($R = R_o$) for all electrodes is equal to 0, i.e. the alteration of electrotonic potential next to electrode is as a rectangular step. In close proximity of electrode the dependency $T_{1/2} = f(R)$ is not linear.

When in voltage clamp experiments a spherical electrode of finite dimensions is used the potential is clamped only in close vicinity of electrode surface. Away from the surface of electrode a stationary value of potential decreases according to formula (13), i.e. abruptly. Due to capacitive properties of biological tissues instantaneous value of electrotonic potential decreases more quickly: away from the surface of electrode the derivative of half-time of anterior frontier of voltage stimulus increases (Fig. 3).

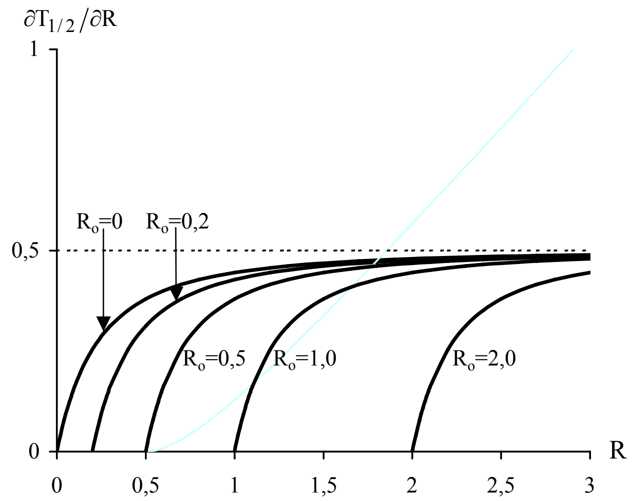

Fig. 3. Dependence of half-time derivative in respect to a distance R between an electrode center and a potential recording site for various values of R_o – a voltage electrode radius. The curves were obtained with aid of formulae (20-23)

The greater a voltage electrode radius R_o, the less a half-time $T_{1/2}$ derivative in respect to distance ($\partial T_{1/2}/\partial R$). Besides, when a distance R increases, a derivative $\partial T_{1/2}/\partial R$ asymptotically approaches to 0,5.

Discussion

We obtained that the character of variations of electrotonic potential half time ($T_{1/2}$) and derivative ($\partial T_{1/2}/\partial R$) in three-dimensional infinite medium for a voltage electrode is the same as in case of current electrode sources [3–6]: the time $T_{1/2}$ during which the electrotonic potential reaches a half of its stationary amplitude, asymptotic linearly depend on the distance R between the voltage electrode and the electrotonic potential measurement site: $T_{1/2} \cong 0{,}5R + const$. So, in biomedical experiments with patch-clamp or space-clamp the errors in cause of poor spatial control by point voltage clamp could arise.

References

1. **Veteikis R., Grigaliunas A. and Muckus K.** Comparative study of the space constants of electrotonic decay in the endocardium and epicardium of the right atrium of the rabbit heart // Biophysics. – 2001. – Vol. 46, No. 2. – P. 305–309.
2. **Grigaliūnas A., Veteikis R.** Investigation of passive electrical properties in the right atrium // Series on Biophysics and Biocybernetics. Chaos And Noise In Biology And Medicine. ISBN 981-02-3600-X // World Scientific, Singapore, New Jersey, London, Hon Kong / Edited by Michele Barbi & Santi Chillemi (Istituto di Biofisica, Pisa, Italy). – 1998. – Vol. 7. – P. 271–274.
3. **Veteikis R.** Modelling the distribution of the electrotonic potential in two-dimensional anisotropic resistive-capacitive media // Biophysics. – 1997. – Vol. 42, No. 6. – P. 1319–1325.
4. **Grigaliūnas A., Veteikis R.** Mathematical modeling of the Distribution of Electrotonic Potential in three-dimensional Anisotropic RC Media // Electronics and Electrical Engineering. – 2000. – No. 1(24). – P. 41–45.
5. **Veteikis R.** The calculation of electrotonic potential half-time and its derivative in respect to distance in one- and two-dimensional RC media // Informatica. – 2000. – Vol. 11, No. 4. – P. 479–494.
6. **Veteikis R.** Theoretical aspects of evaluation of the plasma membrane time constant in myocardial tissue using a model of three-dimensional RC-medium of finite thickness // Biophysics. – 2005. – Vol. 50, No. 4. – P.719–725.
7. **Schaefer A. T., Helmstaedter M., Sakmann B., Korngreen A.** Correction of conductance measurements in non-space-clamped structures: 1. Voltage-gated K+ channels // Biophys J. – 2003. – Vol. 84, No. 6. – P. 3508–3528.
8. **Араманович И. Г., Лунц Г. Л., Эльсгольц Л. Э.** Функции комплексного переменного. Операционное исчисление. Теория устойчивости. – Москва: Наука, 1968.
9. **Выгодский М. Я.** Дифференциальное исчисление. – Москва: Наука, 1965.

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R. Veteikis. Voltage Response of Three-dimensional RC-medium to Prolonged Step Voltage Change // Electronics and Electrical Engineering. – Kaunas: Technologija, 2006. – No. 7(79). – P. 49–52.

The analytical expressions of electrotonic potential distribution in three-dimensional ohmic-capacitive medium, when long square voltage pulses are applied, were derived. The expression of half-time ($T_{1/2}$) derivative in respect to distance ($\partial T_{1/2}/\partial R$) was obtained. The dependencies of $T_{1/2}$ and $\partial T_{1/2}/\partial R$ on the voltage electrode dimensions and the distance between the voltage electrode and the potential measurement place were calculated. The calculations demonstrate that the slope of the function $T_{1/2}=f(R)$ depends both on the distance between the potential measurement site and the voltage electrode, as well as the voltage electrode dimensions. Close to the voltage source, the dependence of $T_{1/2}$ on distance deviates from linear. Ill. 3, bibl. 9 (in English; summaries in English, Russian and Lithuanian).

Р. Ветейкис. Электротоническое распределение прямоугольного скачка потенциала в трехмерной резистивно-емкостной среде // Электроника и электротехника. – Каунас: Технология, 2006. – № 7(79). – С. 49–52.

Получены аналитические выражения распределения электротонического потенциала в трехмерной RC-среде при стимулировании длинным скачкообразным импульсом напряжения. Определена зависимость времени ($T_{1/2}$), за которое электротонический потенциал достигает половины стационарной амплитуды, и производной $\partial T_{1/2}/\partial R$ от расстояния между точкой регистрации и электродом R. При помощи компьютерного моделирования показано, что наклон функции $T_{1/2} = f(R)$ зависит от расстояния между электродом и точкой измерения, а также от размеров электрода. Вблизи электрода зависимость $T_{1/2} = f(R)$ отклоняется от линейной. Ил. 3, библ. 9 (на английском языке; рефераты на английском, русском и литовском яз.).

R. Veteikis. Elektrotoninis stačiakampio įtampos šuoliuko pasiskirstymas trimatėje ominėje-talpinėje terpėje // Elektronika ir elektrotechnika. – Kaunas: Technologija, 2006. – Nr. 7(79). – P. 49–52.

Gautos elektrotoninio potencialo pasiskirstymo trimatėje ominėje-talpinėje terpėje analitinės išraiškos, kada stimuliuojama ilgos trukmės stačiakampiu įtampos šuoliuku. Nustatyta laiko, per kurį terpės elektrotoninis potencialas pasiekia pusę stacionarios amplitudės ($T_{1/2}$), išvestinės ($\partial T_{1/2}/\partial R$) priklausomybė nuo atstumo tarp elektrodo ir matavimo taško (R), kada terpė stimuliuojama stačiakampiu įtampos impulsu. Modeliuojant kompiuteriu nustatyta, kad funkcijos $T_{1/2}=f(R)$ polinkis priklauso nuo atstumo R bei nuo stimuliuojančio elektrodo dydžio. Arti elektrodo priklausomybė $T_{1/2} = f(R)$ nėra tiesinė. Il. 3, bibl. 9 (anglų kalba; santraukos anglų, rusų ir lietuvių k.).