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Theoretical Evaluation of Space Constants of Electrotronic Decay in Resistive Anisotropic Media: Common Equation

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Introduction

Various physiological and pathological effects may evoke changes in the electric excitation wave of the heart that can lead to disorders in the mechanical activities of the heart. It is known that the intercellular electrical communication in the working myocardium deteriorates under some pathological conditions or factors. However, due to complexity of the myocardium structure, direct measurement of the degree of deterioration of intercellular electrical coupling is not possible.

Lately, intensive works have been pursued in modeling ECG [1], cardiac pacing [2-5], excitation wave spread in the myocardium tissue under normal and pathological conditions [6-8], repolarization processes [9]. In these tasks myocardium is treated as two-dimensional or three-dimensional resistive-capacitive medium [10-11], electrotonic anisotropy being characteristic of the intracellular and intercellular areas. To solve the tasks, different experimentally obtained values of the parameters of the passive electric properties of myocardium are used (such as specific resistances of the intracellular medium, plasmic (electrogenic) membrane, membrane of intercellular contacts, space constants of electrotonic decay, time constants of the plasmic membrane). However, modeling makes sense only provided the used values of parameters are most precise. One of possibilities to find the parameters is by measuring experimental space constants of electrotonic decay ($\lambda_{xe}, \lambda_{ye}, \lambda_e$,) (i.e. the distance at which the amplitude of potential decreases by 2.71 times) and the distribution of electrotonic potential in the cardiac tissue close to the current delivering electrode, with further analysis of data by mathematical models of resistive (R) and resistive-capacitive (RC) media. Such media are described by differential equations of second order with partial derivatives, and the analytical solutions may only be obtained in the presence of either spherical or cylindrical symmetry (for a point-shaped source of current) [12-15]. As myocardium is a complex anisotropic structure and the current is delivered to the intracellular medium by circle-shaped suction-electrodes (i.e. there is no spherical or cylindrical symmetry in a normalized system of coordinates), it is impossible to obtain analytical expressions that would describe the distribution of electrotonic potential in the anisotropic medium. Therefore, the analysis of experimental data is made basing on models of isotropic medium and theoretical conclusions derived on such basis [16-18].

In the present study common equations describing distribution of electrotonic potential in three-dimensional anisotropic bidomain RC medium are derived and the solutions for two-dimensional and three-dimensional resistive media are obtained, when a current electrode shape do not satisfy cylindrical or spherical symmetry case.

Common equations for electrotonic potential distribution in the three-dimensional anisotropic bidomain RC medium

The derivation of common equations for electrotonic potential distribution in isotropic three-dimensional bidomain RC medium was presented in earlier article [19]. There the theory for anisotropic case will be developed.

The cardiac tissue consists of two conductive areas - intracellular and extracellular, that occupies the same space, are separated from each other by plasmic (electrogenic) membrane, and both areas have properties of electrotonic anisotropy. The intracellular area is formed of cells connected by low-resistance cell-to-cell junctions. Assume that the resistance of intracellular area consists of the myoplasm resistance and the resistance of junctions evenly distributed over the whole volume of cells, and that the resistance of extracellular area consists of the resistance of intercellular gaps evenly distributed over the whole tissue volume. Each point of the bidomain medium (x, y, z) at time moment t is characterized by intracellular potential V_i and intracellular current density $\boldsymbol{j}_i$ as well as by extracellular potential V_e and extracellular current density $\boldsymbol{j}_e$.

Consider a continuous anisotropic three-dimensional bidomain medium in which the tensor of specific resistance of the intracellular area is $\overline{\rho}_i$, and the tensor of specific resistance of extracellular area is $\overline{\rho}_e$.

The equation of electrical field is valid both for the intracellular and extracellular areas:

$$\overline{\rho}_i \boldsymbol{j_i} = -\nabla V_i , \qquad (1a)$$

$$\overline{\rho}_e \boldsymbol{j_e} = -\nabla V_e . \qquad (1b)$$

The charge conservation law is applicable, too:

$$\nabla \cdot \boldsymbol{j_i} = -\frac{\partial q_i}{\partial t} , \qquad (2a)$$

$$\nabla \cdot \boldsymbol{j_e} = -\frac{\partial q_e}{\partial t} , \qquad (2b)$$

where q_i, q_e - charge density of intracellular and extracellular area, ∇ - Hamilton operator (in Cartesian coordinates system $\nabla \equiv \frac{\partial}{\partial x}\boldsymbol{i} + \frac{\partial}{\partial y}\boldsymbol{j} + \frac{\partial}{\partial z}\boldsymbol{k}$). Assume there is a source of current in the medium. As with increase of q_i, q_e decreases by the same extent ($\Delta q_i = -\Delta q_e$) and $\frac{\partial q_i}{\partial t} = j_m \beta$ [19] (β - ratio between the area of plasmic membrane and the medium volume):

$$\nabla \cdot \boldsymbol{j_i} = -j_m \beta , \qquad (3a)$$

$$\nabla \cdot \boldsymbol{j_e} = j_m \beta , \qquad (3b)$$

where j_m – transmembrane current density, and the direction is from the intracellular to the extracellular area (the hyperpolarizing current is positive). When the electrogenic membrane is electrically passive, j_m is described by the equation:

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

where R_m – specific resistance of the electrogenic/plasmic membrane, and C_m - specific capacitance. Assume that R_m does not depend on time and potential. We introduce equations 3a, 3b and 4 into 1a, 1b and obtain:

$$\nabla^2 V_i - \frac{\beta \overline{\rho}_i}{R_m}(V_i - V_e) - C_m \beta \overline{\rho}_i \frac{\partial}{\partial t}(V_i - V_e) = 0 , \qquad (5)$$

$$\nabla^2 V_e + \frac{\beta \overline{\rho}_e}{R_m}(V_i - V_e) + C_m \beta \overline{\rho}_e \frac{\partial}{\partial t}(V_i - V_e) = 0 . \qquad (6)$$

By subtracting equation (6) from equation (5), we obtain:

$$\frac{R_m}{\beta(\overline{\rho}_i + \overline{\rho}_e)} \nabla^2 (V_i - V_e) - (V_i - V_e) - \tau_m \frac{\partial}{\partial t}(V_i - V_e) = 0 , \qquad (7)$$

where τ_m - time constant of plasmic membrane. By designating

$$V_i - V_e = V_m , \qquad (8)$$

$$T = t / \tau_m , \qquad (9)$$

where V_m is transmembrane potential and T -normalized time, we obtain:

$$\frac{R_m}{\beta(\overline{\rho}_i + \overline{\rho}_e)} \nabla^2 V_m - V_m - \frac{\partial V_m}{\partial T} = 0 . \qquad (10)$$

The analytical solution of equation (10) may only be obtained in the presence of spherical or cylindrical symmetry. Assume that the major axes of tensors $\overline{\rho}_i$ and $\overline{\rho}_e$ coincide and are x, y, z. We designate the specific resistances of intracellular and extracellular media along the major tensor axes as ρ_{ix}, ρ_{iy}, ρ_{iz}, ρ_{ex}, ρ_{ey}, ρ_{ez}. With regard to the magnitude of resistances, their interrelations and the values of normalized time T, equation (10) can be simplified. Below the analysis of some simplified cases is presented.

Distribution of electrotonic potential in a two-dimensional anisotropic resistive medium when the source of current is point-shaped

When $\rho_{ex} = \rho_{ey} = \rho_{ez} = 0$, $\rho_{iz} \to \infty$ and $T \to \infty$ the three-dimensional medium turns into a flat cell in which the distribution of electrotonic potential is expressed by the equation:

$$\lambda_x^2 \frac{\partial^2 V_m}{\partial x^2} + \lambda_y^2 \frac{\partial^2 V_m}{\partial y^2} = V_m , \qquad (11)$$

where $\lambda_x = (R_m h_c / 2\rho_{ix})^{1/2}$, $\lambda_y = (R_m h_c / 2\rho_{iy})^{1/2}$ (λ_x, λ_y – space constants of electrotonic decay, h_c – the cell thickness of the flat cell).

Assume that in point ($x = y = 0$) there is a point-shaped rectangular current source of amplitude I_o. According to [14] in the normalized system of coordinates X, Y ($X = x/\lambda_x, Y = y/\lambda_y$) the solution of equation (11) is as follows:

$$V_m(R_2) = \frac{\tilde{\rho}_2 I_o}{2\pi h_c} K_o(R_2) , \qquad (12)$$

where $K_o(R_2)$ - McDonald's function, $\tilde{\rho}_2 = \sqrt{\rho_{ix} \cdot \rho_{iy}}$, and $R_2 = \sqrt{X^2 + Y^2}$.

Distribution of electrotonic potential in the three-dimensional anisotropic RC medium for a point-shaped source of current

As the electrotonic potential is measured on the surface of myocardium tissue, when a piece of tissue is perfused by low-resistance Tyrode solution, it may be assumed that $\overline{\rho}_e = 0$. When $T \to \infty$, the equation (10) becomes:

$$\lambda_x^2 \frac{\partial^2 V_m}{\partial x^2} + \lambda_y^2 \frac{\partial^2 V_m}{\partial y^2} + \lambda_z \frac{\partial V_m}{\partial z^2} = V_m , \qquad (13)$$

where λ_x, λ_y, λ_z - space constants of electrotonic decay along axes *x, y, z; (* $\lambda_x = \sqrt{R_m / \beta\rho_{ix}}$, $\lambda_y = \sqrt{R_m / \beta\rho_{iy}}$, $\lambda_z = \sqrt{R_m / \beta\rho_{iz}}$). The solution of equation (13) for a rectangular jump of current I_o is:

$$V_m(R_3) = \frac{I_o \sqrt[3]{\rho_{ix}\rho_{iy}\rho_{iz}}}{4\pi R_3 \sqrt[3]{\lambda_x \lambda_y \lambda_z}} \frac{\exp(-R_3)}{R_3}, \qquad (14)$$

where $R_3 = \sqrt{x^2/\lambda_x^2 + y^2/\lambda_y^2 + z^2/\lambda_z^2}$ - is a normalized distance between the point-shaped current source and the recording point.

Mathematical modeling of electrotonic potential distribution in an anisotropic resistive medium when the source of current is disc-shaped or cylinder-shaped

In the two-dimensional anisotropic medium the expression of electrotonic potential derived for a point-shaped current source (12) can also be applied in the case of an elliptic source of current the half-axes of which x_o and y_o are respectively proportional to λ_x and λ_y (i.e. $x_o / y_o = \lambda_x / \lambda_y$):

$$V_m(R_2) = V_m(R_o) \frac{K_o(R_2)}{K_o(R_o)}, \qquad (15)$$

where $V_m(R_o)$ – a potential of elliptic electrode with half-axes $x_o = R_o \lambda_x$, $y_o = R_o \lambda_y$, and $R_2 = \sqrt{(x/\lambda_x)^2 + (y/\lambda_y)^2}$, $R_o = \sqrt{(x_o/\lambda_x)^2 + (y_o/\lambda_y)^2}$.

In the three-dimensional anisotropic medium the expression of electrotonic potential derived for a point shaped current source case (14) is applicable for an ellipsoid-shaped current source, the half-axes of which (x_o, y_o, z_o) are proportional to λ_x, λ_y and λ_z (i.e. $x_o/\lambda_x = y_o/\lambda_y = z_o/\lambda_z = R_o$). In this case the electrotonic potential expression is:

$$V_m(R_3) = \frac{I_o \sqrt[3]{\rho_{ix}\rho_{iy}\rho_{iz}}}{4\pi \sqrt[3]{\lambda_x \lambda_y \lambda_z}(1+R_o)} \frac{\exp(R_o - R_3)}{R_3} . \qquad (16)$$

In fact, the correct choice of the elliptic- or ellipsoid-shaped electrodes for experimental use in a two-dimensional or a three-dimensional cardiac tissue with initially unknown properties is impossible in practice, because its dimensions must fulfill these conditions: for two-dimensional case $x_o/\lambda_x = y_o/\lambda_y$, for three-dimensional case $x_o/\lambda_x = y_o/\lambda_y = z_o/\lambda_z$, and the direction of largest half-axis of current electrode (x_o) must coincide with direction of the major axis *x* of tensor $\overline{\rho}_i$. When microelectrode as the current electrode is applied, the amplitude of the electrotonic potential with increasing of distance abruptly decreases, and in such experimental conditions it is impossible to measure precisely the electrotonic potential amplitude.

Therefore during the electrophysiological experiments the current is delivered to the intracellular medium of the cardiac tissue by circle-shaped suction electrode. Assume that in the metric system of coordinates (x, y) the radius of the current source is r_o and its center is at the origin of coordinates. In two-dimensional normalized system of coordinates (X, Y) the current electrode is ellipse-shaped, the shortest half-axis X_o is equal to r_o/λ_x and the longest half-axis Y_o is equal to r_o/λ_y . In three-dimensional system of coordinates (X, Y, Z) the ellipse-shaped electrode coincide with XY plane and is perpendicular to Z axis.

In experimental conditions, the internal electric structure of stimulating suction-electrode is very complex: a part of current from the suction-electrode flows into intracellular medium, the rest part flows into intercellular clefts. For increasing of intracellular current portion, the suction-electrodes with internal perfusion of isotonic KCl solution are used [20]. According to [21] an equivalent current source is cylinder-shaped, and its altitude h depends on internal radius of suction electrode (r_o) and negative pressure applied for suction. According to these authors the value of h could be in range $0 \div 2r_o$.

In two-dimensional medium case on basis of some theoretical assumptions [22] by using the principle of superposition accepted in electrostatics, we divide the source of current into elementary point-shaped sources by modes:

Mode 1: a) in the metric system of coordinates (x, y) we evenly position the point-shaped sources on the circle of radius r_o (Fig.1a); b) in the normalized system of coordinates (X, Y) the circle transforms into an ellipse, the half-axes of which are equal to r_o/λ_x and r_o/λ_y; and the point-shaped sources are more dense in the direction of y axis (Fig. 1b).

Mode 2: a) we pass from the (x, y) system of coordinates to (X, Y) coordinates system, and the circle becomes an ellipse with half-axes equal to r_o/λ_x and r_o/λ_y; b) we evenly position the point-shaped sources on the perimeter of the ellipse (Fig. 1c); the point-shaped sources are more dense in the direction of x axis (in metric x, y coordinate system).

Mode 3: the current electrode (circular disk) is divided into point-shaped sources symmetrically to x and y -axis by square lattice mean (Fig 1d).

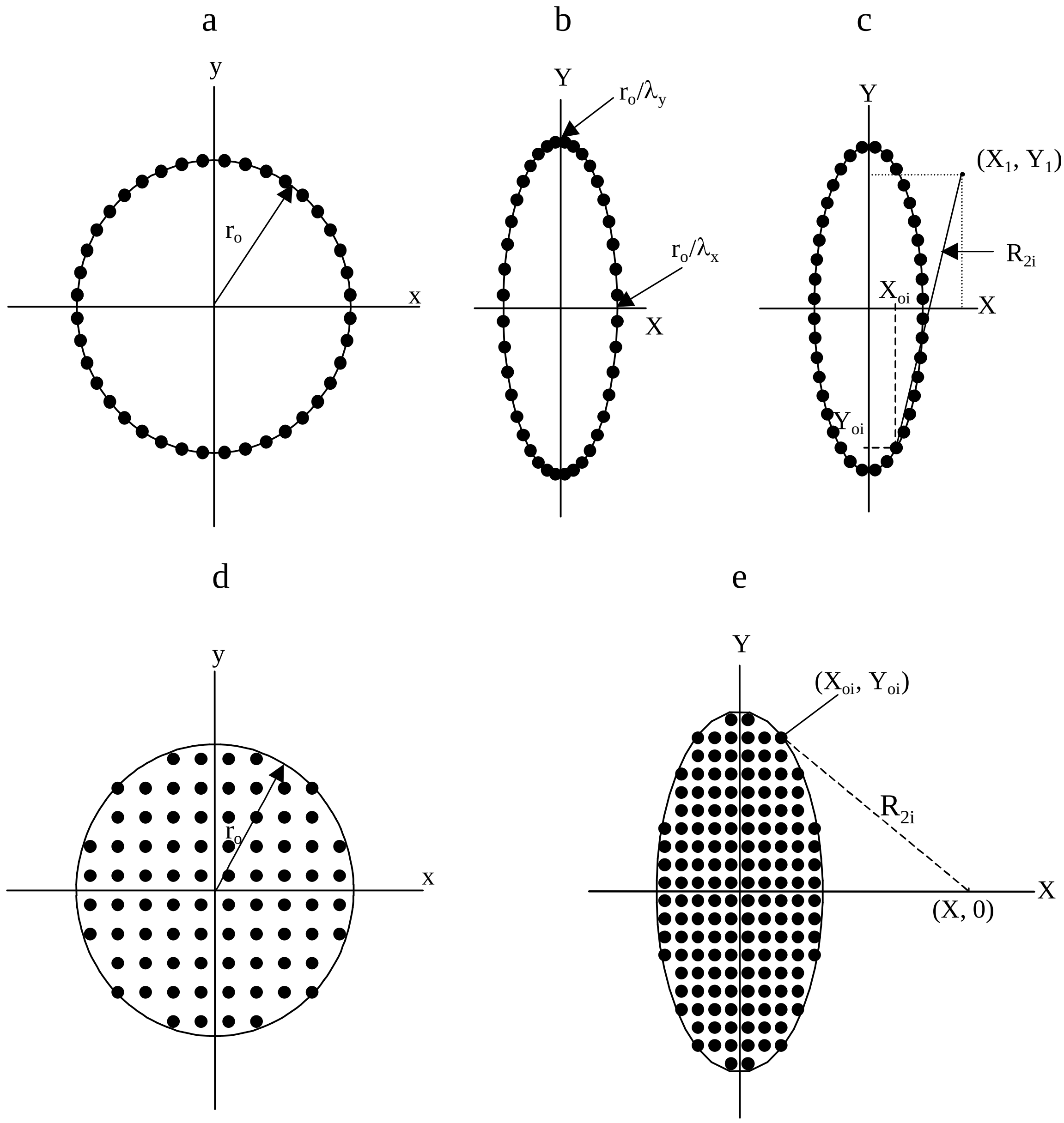

Fig. 1. Modes of division of intracellular current electrodes into point-shaped sources. **a:** even division of circle electrode perimeter into point-shaped sources (in metric coordinate system *x,y*); **b:** a view of division (**a**) in a normalized coordinate system (*X,Y*); **c:** even division of circle perimeter into point-shaped sources in normalized coordinate system; **d:** division of circular disk electrode into point-shaped sources in metric coordinate system; **e:** division of circular disk electrode into point-shaped sources in normalized coordinate system

In the two-dimensional medium in accordance with the principle of superposition, potential V_m in point X_1,Y_1 is equal to

$$V_m(X_1,Y_1) = \sum_{i=1}^{M} B_i K_o(R_{2i}), \quad (17)$$

where M - number of point-shaped sources, B_i - coefficient proportional to the intracellular current generated by the point source ($B_i = \tilde{\rho}_2 I_{oi} / 2\pi h_c$, where I_{oi} - current of the *i*-th point-shaped source), and $R_{2i} = \sqrt{(X_i - X_{oi})^2 + (Y_i - Y_{oi})^2}$. As in the electrically passive resistive medium the values of parameters λ_{xe}, λ_{ye}, λ_x, λ_y do not depend on the amplitude of current delivered through the electrode, for convenience we assume that $B_1 = 1$, i.e. all point-shaped sources are equal.

In three-dimensional anisotropic medium of finite thickness d the suction electrode will be described as disk/cylinder-shaped current electrode which radius in (x,y,z) coordinate system is r_o and altitude – h ($h \le d$). In a normalized system of coordinates (X,Y,Z) a current electrode will transform to elliptic cylinder which altitude $H = h/\lambda_z$ and half-axes $X_o = r_o/\lambda_x$, $Y_o = r_o/\lambda_y$ (Fig.2).

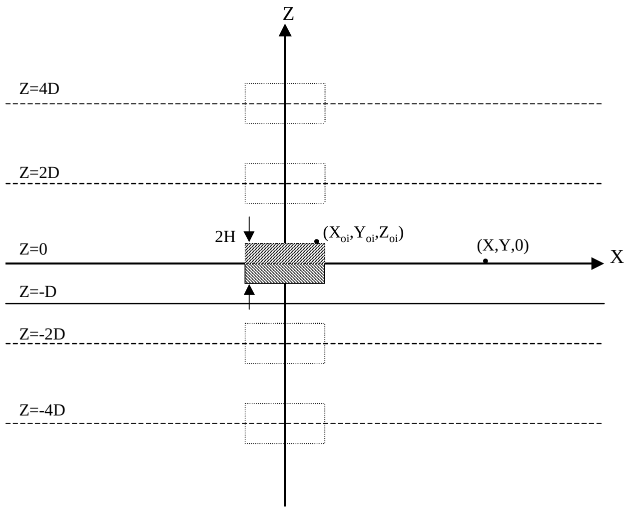

Fig. 2. Arrangement of cylinder-shaped current electrodes in the model of three-dimensional resistive medium of finite thickness, restricted by parallel planes *Z*=0 and *Z*= –*D*. *Y*-axis is perpendicular to plane *XZ*

Let's extend the medium by its mirror reflection (for details see [23]) in direction of axis Z. We obtain a number of virtual sources on Z-axis (see Fig.2). The altitude of these virtual sources is equal to $2H$, and the distance between centers of cylinders – $2D$ (the twofold altitude of a virtual cylinder-shaped current electrode is obtained in cause of mirror reflection of real current source in plane $Z = 0$). Let's divide uniformly the surface of the virtual current source into M point-shaped sources with coordinates of *i-th* source X_{oi}, Y_{oi}, Z_{oi}. After extending a medium by its mirror reflection the coordinates X_{oi} and Y_{oi} will not change but the coordinate with respect to Z-axis will be $Z_{oi} + 2Dj$, where j is the number of reflection. Applying the superposition principle and expression of electrotonic potential for point-shaped current source (14) will obtain that

$$V_m(X,Y,0) = \sum_{j=-\infty}^{\infty} \sum_{i=1}^{M} \frac{I_{oi}\sqrt[3]{\rho_{ix}\rho_{iy}\rho_{iz}}}{4\pi\sqrt[3]{\lambda_x\lambda_y\lambda_z}} \cdot \frac{\exp(-R_{3ij})}{R_{3ij}}, \quad (18)$$

where $R_{3ij} = \sqrt{(X - X_{oi})^2 + (Y - Y_{oi})^2 + (Z_{oi} + 2Dj)^2}$, D – a normalized thickness of medium ($D = d/\lambda_z$), M – a number of point-shaped current sources, I_{oi} - a current generated by *i-th* point-shaped source.

Discussion

It should be noted that this model is only applicable to myocardial tissue on condition that electrogenic (plasmic) membrane resistance R_m is independent of the electrotonic potential. In the experiment, this condition is observed through stimulating the myocardial intracellular medium with subthreshold negative pulses of small amplitude. Violation of this condition may cause R_m to change and lead to the propagation of nonlinear subthreshold pulses in myocardium, when application of this model is erroneous.

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A mathematical model of the electrotonic potential distribution in a three-dimensional bidomain anisotropic resistive-capacitive medium (myocardium) is devised for the case when the source of current is point-, circle- disc- or cylinder-shaped. Using the superposition principle, the current electrode is approximated by point sources, arranging them on the perimeter of the circle-shaped electrode in two ways such that: a) the distances between them are identical in the metric system of coordinates; b) the distances between the point sources are identical in a normalized system of coordinates. The disk-shaped and cylinder-shaped current sources are approximated by point sources, evenly arranging them on the surface. Ill. 2, bibl. 23 (in English; summaries in English, Russian and Lithuanian).

Р. Ветейкис. Теоретическая оценка постоянных длины электротонического затухания в омических анизотропных средах: общее уравнение // Электроника и электротехника. – Каунас: Технология, 2008. – № 8(88). – С. 37–42.

Разработана математическая модель распределения электротонического потенциала в трехмерной двухкомпонентной анизотропной проводящей среде с распределенной емкостью (миокардиальной ткани), когда источник тока имеет форму точки, окружности, диска или цилиндра. С использованием принципа суперпозиции источник тока аппроксимировали точечными источниками, располагая их на периметре окружности двумя способами: 1) так, чтобы расстояния между ними были одинаковыми в метрической системе координат; 2) так, чтобы расстояния между точечными источниками были одинаковыми в нормализованной системе координат. Дискообразный и цилиндрический источник тока аппроксимировали точечными источниками, равномерно располагая их на поверхности. Ил. 2. библ. 23 (на английском языке; рефераты на английском, русском и литовском яз.).

R. Veteikis. Elektrotoninio gesimo konstantų teorinis įvertinimas ominėse–talpinėse anizotropinėse terpėse: bendroji lygtis // Elektronika ir elektrotechnika. – Kaunas: Technologija, 2008. – Nr. 8(88). – P. 37–42.

Pateiktas elektrotoninio potencialo pasiskirstymo trimatėje dvisritėje anizotropinėje RC terpėje (miokarde) matematinis modelis, kai srovės šaltinis yra taško, apskritimo, disko ir cilindro formos. Naudojant superpozicijos principą srovės elektrodas yra aproksimuotas taškiniais šaltiniais, išdėstytais ant apskritimo formos elektrodo perimetro dviem būdais, taip, kad a) atstumai tarp taškinių šaltinių yra vienodi metrinėje koordinačių sistemoje; b) atstumai tarp taškinių šaltinių yra vienodi normalizuotoje koordinačių sistemoje. Disko ir cilindro formos srovės elektrodai yra aproksimuoti taškiniais šaltiniais, tolygiai išdėstytais jų paviršiuje. Il. 2, bibl. 23 (anglų kalba; santraukos anglų, rusų ir lietuvių k.).