INTEGRAL EQUATION SOLUTION FOR BIOPOTENTIALS OF SINGLE CELLS

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ABSTRACT A Fredholm integral equation of the second type is developed for the biopotentials of single cells. Two singularities arise in the numerical solution of this integral equation and methods for handling them are presented. The problem of a spherical cell in an applied uniform field is used to illustrate the technique.

INTRODUCTION

The biopotentials within and surrounding a passive cell in an applied field, having equal intra- and extracellular conductivities, can be found by numerically solving an inhomogeneous Fredholm integral equation of the second kind. The integral equation is obtained by a three-step process. First, the total field at any point is written as the superposition of the applied field (Φ_a) and an induced field due to the transmembrane potentials (V_m) generated on the cell surface by the applied field (Plonsey, 1969, p. 273) (see Fig. 1 for geometry and nomenclature):

$$\Phi(p') = \Phi_a(p') - \frac{1}{4\pi}\int_{S_m} V_m \frac{\partial[1/r(p', p)]}{\partial n}\, dS. \tag{1}$$

Then, the value of the normal current density at the membrane surface is obtained by differentiating equation 1 with respect to the normal n':

$$J_m(n') = -\sigma \frac{\partial\Phi(p')}{\partial n'} = -\sigma \frac{\partial\Phi_a(p')}{\partial n'} + \frac{\sigma}{4\pi}\frac{\partial}{\partial n'}\int_{S_m} V_m \frac{\partial[1/r(p', p)]}{\partial n}\, dS.$$

Finally, the desired Fredholm integral equation is obtained by equating this normal current density to the product of transmembrane potential and membrane admittance, Y_m (reciprocal ohms per square centimeter):

$$Y_m V_m(n') = -\sigma \frac{\partial\Phi_a(p')}{\partial n'} + \frac{\sigma}{4\pi}\frac{\partial}{\partial n'}\int_{S_m} V_m \frac{\partial[1/r(p', p)]}{\partial n}\, dS. \tag{2}$$

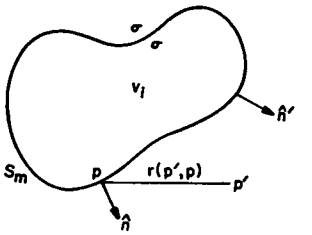

FIGURE. 1 Cell geometry and nomenclature: field points are primed (p') and those which lie on the membrane surface (S_m) are associated with primed unit outward normals ($\hat{n}'$); source points are unprimed (p) and are associated with unprimed normals ($\hat{n}$); $r(p', p)$ is the distance from the field point (p') to the source point (p); σ is the conductivity of both the intra- and extracellular media (reciprocal ohms per centimeter); v_i is the intracellular volume.

This equation is solved numerically for V_m and the resulting values substituted into equation 1 to find the potentials within and surrounding the cell.

To solve equation 2 for V_m, one interchanges the order of integration and differentiation, discretizes the surface of the membrane into n pieces, approximates the integral by a finite sum over the n pieces, and evaluates the expression at each piece, obtaining n equations of the form:

$$Y_m V_m(i) = -\sigma \frac{\partial \Phi_a}{\partial n_i} + \frac{\sigma}{4\pi} \sum_{j=1}^{n} V_m(j) \frac{\partial^2 (1/r_{ij})}{\partial n_i \, \partial n_j} \Delta S_j ,$$

or, in matrix notation with combined physical parameters:

$$\bar{A} \cdot \vec{V}_m = \vec{f}, \tag{3}$$

where

$$a_{ij} = (Y_m/\sigma)\delta_{ij} - \frac{1}{4\pi} \frac{\partial^2 (1/r_{ij})}{\partial n_i \, \partial n_j} \Delta S_j ,$$

$$f_i = -\frac{\partial \Phi_a}{\partial n_i} ,$$

and δ_{ij} is the Kronecker delta. This set of n simultaneous equations in the n unknowns $V_m(i)$ is then solved by standard numerical techniques such as gaussian elimination.

SINGULARITIES

Two singularities arise in this numerical procedure: first, as $Y_m/\sigma \to 0$ the matrix $\bar{A}$ becomes singular ("matrix singularity"); secondly, when $i = j$ (the "self-term"), the expression $\partial^2 (1/r_{ij})/\partial n_i \partial n_j$ is singular ("self-term singularity").

To study these singularities we solved for the transmembrane potentials of a spherical cell in an applied uniform field. A closed form analytic solution is available

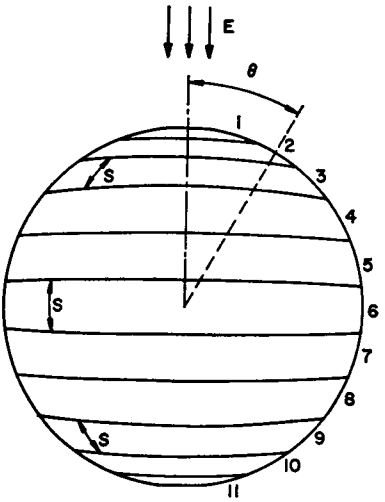

FIGURE 2

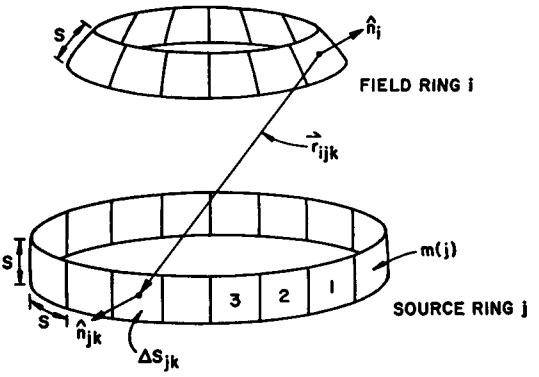

FIGURE 3

FIGURE 2 Discretation of a spherical cell. Rings are used since both the applied uniform field E and the spherical cell are axially symmetric. All rings have equal polar arc length s.
FIGURE 3 Discretation of an individual ring for calculation of coupling coefficients. $\hat{n}_i$ and $\hat{n}_{jk}$ are the unit normals to field ring i and piece k of source ring j, respectively; $\vec{r}_{ijk}$ is the vector from field ring i to piece k of source ring j; $m(j)$ is the number of pieces in source ring j adjusted so that all ΔS_{jk} are squares of approximately equal area (s^2).

for this problem (Klee and Plonsey, 1972) and thus a comparison was easily made between the numerical and analytic results. The applied field was assumed to be DC ($Y_m = \sigma_m$) and to have a magnitude of 10 v/cm, the Y_m/σ ratio[1] was set at 1×10^{-7} cm^{-1}, and the cell radius was chosen to be 15 μ. Gaussian elimination was used to invert the coefficient matrix.

The discretation of the cell surface employed is shown in Fig. 2 where advantage has been taken of the axial symmetry of the biological cell and the applied field to reduce the size of the coefficient matrix. To calculate the expression $\partial^2(1/r_{ij})/\partial n_i \partial n_j \Delta S_j$ (the "coupling coefficient") a further discretation of each ring was made, as shown in Fig. 3, giving the following for the coupling coefficient between source ring j and field ring i (Pilkington et al., 1968, equation 4):

$$\frac{\partial^2(1/r_{ij})}{\partial n_i\, \partial n_j}\,\Delta S_j = \sum_{k=1}^{m(j)} \frac{1}{r_{ijk}^3}\,(\hat{n}_i \cdot \hat{n}_{jk} - 3\hat{n}_{jk} \cdot \hat{r}_{ijk}\,\hat{n}_i \cdot \hat{r}_{ijk})\Delta S_{jk}, \qquad [k \neq m(j) \text{ for } i = j], \quad (4)$$

where $\hat{r}_{ijk}$ is a unit vector from field ring i to piece k of source ring j and $m(j)$ is the number of pieces in source ring j adjusted so that all ΔS_{jk} are squares of approximately equal area.

[1] Physiological values of this ratio are around 10^{-2} cm^{-1}; the value of 10^{-7} cm^{-1} was chosen since it provides a more severe test of the numerical technique.

In the following discussions of each of the two singularities it is assumed that the correct technique for handling the other singularity is employed.

Matrix Singularity

The first singularity results from the boundary conditions at the cell surface becoming equivalent to Neumann boundary conditions as Y_m/σ becomes small, thus giving the characteristic Neumann singularity. In theory, a unique solution for the $V_m(i)$ should be obtainable for $Y_m/\sigma > 0$, but, in practice as $Y_m/\sigma \to 0$ the matrix $\bar{A}$ becomes ill conditioned and an arbitrary constant (C) appears in the solution for the $V_m(i)$: $V_m(i) = V_m^*(i) + C$. This behavior is illustrated in column 2 of Table I for a spherical cell in an applied uniform field. The arbitrary constant in this case was approximately 252 mv.

As suggested by Forsythe and Wasow (1960, section 25.9), this constant can be removed from the numerical solution by applying a physical constraint. We will require that the net current passing through the cell membrane be equal to the total current applied intracellularly and will use this constraint to evaluate the constant C. We write:

$$\int_{v_i} I_a \, dV = \int_{S_m} J_m \, dS = \sum_{i=1}^{n} Y_m V_m^*(i) \Delta S_i = \sum_{i=1}^{n} Y_m [V_m(i) - C] \Delta S_i ,$$

from which

$$C = \frac{\sum_{i=1}^{n} Y_m V_m(i) \Delta S_i - \int_{v_i} I_a \, dV}{\sum_{i=1}^{n} Y_m \Delta S_i} , \tag{5}$$

TABLE I

MATRIX SINGULARITY

θ	Transmembrane potentials		
	$V_m(i)$	$V_m^*(i) = V_m(i) - C$	Analytic solution
degrees	*mv*	*mv*	*mv*
15	229.05	−23.15	−21.73
30	231.39	−20.80	−19.49
45	235.20	−17.00	−15.91
60	240.17	−12.03	−11.25
75	245.96	−6.23	−5.82
90	252.19	0.00	0.00
105	258.43	6.23	5.82
120	264.22	12.03	11.25
135	269.19	17.00	15.91
150	273.00	20.80	19.49
165	275.34	23.15	21.73

where $V_m(i)$ is the numerical solution to matrix equation 3, I_a is the known applied volume source density (amperes per cubic centimeter), and v_i is the intracellular volume. The results of using equation 5 for the uniform field stimulation of a spherical cell ($\int_{v_i} I_a \, dV = 0$) are shown in column 3 of Table I. The adjusted numerical solution $V_m^*(i)$ closely agrees with the analytic solution.

Self-Term Singularity

The second singularity requires finding an appropriate expression for the self-term. One possible, but unsuccessful, approach involves not interchanging the order of integration and differentiation in equation 2 but rather first doing the surface integral over a small patch of membrane and then taking the normal derivative at the patch (Pikington et al., 1968). Using this method for a circular piece of membrane of radius R gives (Pilkington et al., 1968):

$$\frac{\partial}{\partial n_i} \int_{s_i} \frac{\partial (1/r)}{\partial n_i} \, dS = -\frac{2\pi}{R}, \tag{6}$$

while for a square piece of side (s) one obtains:

$$\frac{\partial}{\partial n_i} \int_{s_i} \frac{\partial (1/r)}{\partial n_i} \, dS = -\frac{8\sqrt{2}}{s}. \tag{7}$$

The results of calculating the transmembrane potentials on a sphere in an applied uniform field with this approach are shown in column 2 of Table II. The large errors result from the fact that equation 7 is an inappropriate evaluation of the singular self-term.

TABLE II
SELF-TERM SINGULARITY

θ	Transmembrane potentials		
	Equation 7	Equation 10	Analytic solution
degrees	*mv*	*mv*	*mv*
15	−10.30	−23.15	−21.73
30	−9.67	−20.80	−19.49
45	−7.98	−17.00	−15.91
60	−5.66	−12.03	−11.25
75	−2.93	−6.23	−5.82
90	0.00	0.00	0.00
105	2.93	6.23	5.82
120	5.66	12.03	11.25
135	7.98	17.00	15.91
150	9.67	20.80	19.49
165	10.30	23.15	21.73

An understanding of the source of this error along with an appropriate expression for the self-term results from calculating zero for the normal electric field at an infinite plane of membrane having a constant transmembrane potential. For the discretation shown in Fig. 4, this problem allows the numerical process to be simulated analytically. We write (see Fig. 4 and equation 1):

$$\Phi(p') = -\frac{1}{4\pi}\int_{S_m} V_m \frac{\partial[1/r(p', p)]}{\partial n}\, dS = -\frac{V_m}{4\pi}\int_{S_m} \frac{\partial[1/r(p', p)]}{\partial n}\, dS,$$

from which

$$-\frac{\partial\Phi(p')}{\partial n'}\bigg|_0 = +\frac{V_m}{4\pi}\frac{\partial}{\partial n'}\int_{S_m}\frac{\partial[1/r(p', p)]}{\partial n}\, dS\bigg|_0$$

$$= \frac{V_m}{4\pi}\frac{\partial}{\partial n_0}\int_{S_0}\frac{\partial(1/r)}{\partial n_0}\, dS + \frac{V_m}{4\pi}\sum_{j=1}^{\infty}\frac{\partial^2(1/r_{0j})}{\partial n_0\, \partial n_j}\,\Delta S_j. \tag{8}$$

Using equation 6 to evaluate the self-term and equation 4, without the k summation, to evaluate the coupling coefficients, we now have for the normal electric field

$$E_n = -\frac{V_m}{4\pi}\frac{2\pi}{(\delta/2)} + \frac{V_m}{4\pi}\sum_{j=1}^{\infty}\frac{1}{r_{0j}^{\delta}}(2\pi r_{0j}\,\delta),$$

where $r_{0j} = j\delta$ (Fig. 4), and thus

$$E_n = -\frac{V_m}{\delta} + \frac{V_m}{2\delta}\sum_{j=1}^{\infty}\frac{1}{j^2}.$$

The value of the infinite sum is known to be $\pi^2/6$, (Gradshteyn and Ryzhik, 1965, p. 7 No. 0.233, 3), giving us the exact numerical solution:

$$E_n = -\frac{V_m}{\delta} + \frac{\pi^2}{12}\frac{V_m}{\delta}. \tag{9}$$

This solution, since it does not equal zero, is in error for any finite δ. As shown in equation 9, the final result was obtained by subtracting two infinite quantities ($\delta \to 0$). These two quantities were evaluated by different expressions: equation 6

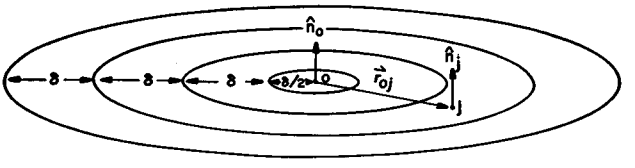

FIGURE 4 Discretation of infinite plane. $\hat{n}_0$ and $\hat{n}_j$ are the unit normals to membrane pieces 0 and j, respectively; $\vec{r}_{0j}$ is the vector from field piece 0 to source piece j; $|\vec{r}_{0j}| = j\delta$.

for the singular self-term and equation 4 for the singular coupling coefficients. It is this use of two different expressions to evaluate the same singularity that leads to the error.

With this understanding of the origin of the error, we can now write an appro priate expression for the self-term. We will use only the coupling coefficients to evaluate the singularity and, as suggested by equation 8, will set the self-term equal to minus the sum of the coupling coefficients between all other membrane pieces and the self-piece:

$$\frac{\partial}{\partial n_i}\int_{S_i}\frac{\partial(1/r)}{\partial n_i}\,dS = -\sum_{\substack{j=1\\ j\neq i}}^{n}\frac{\partial^2(1/r_{ij})}{\partial n_i\,\partial n_j}\,\Delta S_j, \tag{10}$$

or, in matrix notation:

$$a_{ii} = Y_m/\sigma - \sum_{\substack{j=1\\ j\neq i}}^{n} a_{ij}.$$

This definition automatically gives the correct answer for the infinite plane problem and, in general, guarantees that the numerical process will calculate zero for the electric field generated by a constant transmembrane potential on a closed surface.

The results of using equation 10 to calculate the transmembrane potentials on a spherical cell in an applied uniform field are shown in column 3 of Table II. The marked improvement between equation 10 and equation 7 is clear.

Mesh Size

The effect of varying the mesh used to discretize the membrane surface is shown in Table III. The transmembrane potentials of a spherical cell stimulated by a uniform field were calculated with 11, 23, and 47 rings (see Fig. 2) and as shown in Table III increasingly good agreement between the numerical and analytic solutions resulted as the mesh was made finer.

Complex Membrane Admittance

For a complex membrane admittance,[2] the matrix $\bar{A}$ and the vectors $\vec{V}_m$ and $\vec{f}$ in matrix equation 3 are treated as complex quantities. The methods for handling the matrix and self-term singularities are unchanged except for the fact that the arbitrary constant C (equation 5) is now a complex number.

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[2] $Y_m = \sigma_m + j\omega C_m$; σ_m is the membrane conductivity (reciprocal ohms per square centimeter), $j = \sqrt{-1}$, ω is the angular frequency (radians per second), and C_m is the membrane capacitance (farads per square centimeter). For a discussion of the use of complex phasor notation to handle time varying signals see Klee and Plonsey (1972, p. 1661).

TABLE III

MESH SIZE

θ	Transmembrane potentials			
	11 rings	23 rings	47 rings	Analytic solution
degrees	*mv*	*mv*	*mv*	*mv*
3.75			−22.82	−22.45
7.50		−23.03	−22.67	−22.31
11.25			−22.43	−22.07
15.00	−23.15	−22.45	−22.09	−21.73
18.75			−21.66	−21.31
22.50		−21.48	−21.13	−20.79
26.25			−20.51	−20.18
30.00	−20.80	−20.14	−19.81	−19.49
33.75			−19.02	−18.71
37.50		−18.45	−18.15	−17.85
41.25			−17.20	−16.92
45.00	−17.00	−16.45	−16.17	−15.91
48.75			−15.08	−14.84
52.50		−14.16	−13.92	−13.70
56.25			−12.71	−12.50
60.00	−12.03	−11.63	−11.44	−11.25
63.75			−10.12	−9.95
67.50		−8.90	−8.75	−8.61
71.25			−7.35	−7.23
75.00	−6.23	−6.02	−5.92	−5.82
78.75			−4.46	−4.39
82.50		−3.04	−2.99	−2.94
86.25			−1.50	−1.47
90.00	0.00	0.00	0.00	0.00
93.75			1.50	1.47
97.50		3.04	2.99	2.94
101.25			4.46	4.39
105.00	6.23	6.02	5.92	5.82
108.75			7.35	7.23
112.50		8.90	8.75	8.61
116.25			10.12	9.95
120.00	12.03	11.63	11.44	11.25
123.75			12.71	12.50
127.50		14.16	13.92	13.70
131.25			15.08	14.84
135.00	17.00	16.45	16.17	15.91
138.75			17.20	16.92
142.50		18.45	18.15	17.85
146.25			19.02	18.71
150.00	20.80	20.14	19.81	19.49
153.75			20.51	20.18
157.50		21.48	21.13	20.79
161.25			21.66	21.31
165.00	23.15	22.45	22.09	21.73
168.75			22.43	22.07
172.50		23.03	22.67	22.31
176.25			22.82	22.45

TABLE IV

COMPLEX MEMBRANE ADMITTANCE

$Y_m/\sigma = 1 \times 10^{-7} e^{45°j}$ cm^{-1}

θ	Transmembrane potentials			
	Numerical solution		Analytic solution	
	Magnitude	Phase	Magnitude	Phase
degrees	*mv*	*rad*	*mv*	*rad*
15	23.15	3.14	21.73	3.14
30	20.80	3.14	19.49	3.14
45	17.00	3.14	15.91	3.14
60	12.03	3.14	11.25	3.14
75	6.23	3.14	5.82	3.14
90	0.00	—	0.00	—
105	6.23	0.00	5.82	0.00
120	12.03	0.00	11.25	0.00
135	17.00	0.00	15.91	0.00
150	20.80	0.00	19.49	0.00
165	23.15	0.00	21.73	0.00

The transmembrane potentials produced by an applied uniform field on a spherical cell having a complex membrane admittance are shown in Table IV. For this computation the Y_m/σ ratio was changed to $1 \times 10^{-7} e^{45°j}$ cm^{-1}. The numerical solution closely agrees with the analytic solution in both magnitude and phase.

SUMMARY AND DISCUSSION

In this paper, a Fredholm integral equation of the second kind has been developed for the biopotentials of a single cell. Two singularities arise in the numerical solution of this equation and methods for handling them have been presented. The problem of a spherical cell in an applied uniform field served to illustrate the technique.

This integral equation approach will be useful in solving problems not compatible with the preceding finite difference solution for the biopotentials of axially symmetric cells (Klee and Plonsey, 1972). Specifically, the computer storage requirements for the integral equation solution are less than those of the finite difference approach (two-dimensional surfaces vs. three-dimensional volumes) and thus nonaxially symmetric cells and groups of cells can now be studied.

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