INTRACELLULAR BIOPOTENTIALS DURING STATIC EXTRACELLULAR STIMULATION

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ABSTRACT Two properties of the intracellular potentials and electric fields resulting from static extracellular stimulation are obtained for arbitrarily shaped cells. First, the values of intracellular potential are shown to be bounded by the maximum and minimum values of extracellular potential on the surface of the cell. Second, the volume average of the magnitude of intracellular electric field is shown to have an upper bound given by the ratio of the magnitude of the largest extracellular potential difference on the surface of the cell to a generalized length constant $\lambda = [\sigma_{\text{intra}} V_{\text{cell}}/(\sigma_{\text{memb}} A_{\text{cell}})]^{1/2}$, where V_{cell} and A_{cell} are the volume and surface area of the cell, σ_{intra} is the intracellular conductivity (reciprocal ohms per centimeter), and σ_{memb} is the membrane conductivity (reciprocal ohms per square centimeter). The use of the upper bound on the volume average of the magnitude of intracellular electric field as an estimate for intracellular isopotentiality is discussed and the use of the generalized length constant for electrically describing arbitrary cells is illustrated for cylindrical- and spheroidal-shaped cells.

INTRODUCTION

Biological cells are subjected to extracellular stimulation both by experimentally applied currents and by the electrical activity of other cells. In this paper, we examine the intracellular potentials and electric fields generated within arbitrarily shaped cells by such extracellular stimulation. Two properties of these potentials and fields for static conditions are obtained. First, the values of intracellular potential are shown to be bounded by the maximum and minimum values of extracellular potential on the surface of the cell. Second, the volume average of the magnitude of intracellular electric field is shown to have an upper bound given by the ratio of the magnitude of the largest extracellular potential difference on the surface of the cell to a generalized length constant λ:

$$\lambda = \left(\frac{\sigma_{\text{intra}} V_{\text{cell}}}{\sigma_{\text{memb}} A_{\text{cell}}}\right)^{1/2}, \qquad (1)$$

where V_{cell} and A_{cell} are the volume and surface area of the cell, σ_{intra} is the intracellular conductivity (reciprocal ohms per centimeter), and σ_{memb} is the membrane conductivity (reciprocal ohms per square centimeter).

These results are obtained in the following manner: first, the appropriate differential equations and boundary conditions for the intra- and extracellular biopotentials are given; next, using these governing equations the bounds on intracellular potentials are derived; finally, the upper bound on the average magnitude of intracellular electric field is obtained using Green's first identity, the divergence theorem, and the bounds on intracellular potentials.

Throughout the paper the effects of the normal resting potential are excluded. All potentials and fields are thus induced potentials and fields resulting from the extracellular stimulation.

Governing Equations

The governing equations for the intra- and extracellular biopotentials during extracellular stimulation are Laplace's and Poisson's equations, respectively (Plonsey and Heppner, 1967):

$$\nabla^2 \Phi_{\text{intra}} = 0, \tag{2}$$

and

$$\nabla^2 \Phi_{\text{extra}} = -I_{\text{applied}}/\sigma_{\text{extra}} \, ,$$

where Φ_{intra} and Φ_{extra} are the intra- and extracellular deviations from resting conditions caused by the applied volume source density I_{applied} (amperes per cubic centimeter), and σ_{extra} is the extracellular conductivity (reciprocal ohms per centimeter). Φ_{intra} and Φ_{extra} are assumed to be continuous in their respective domains up to the surface of the cell.

The boundary conditions which these potentials must satisfy at biological membranes under static conditions are (Plonsey, 1969, Eqs. 5.160 and 5.161):

$$-\sigma_{\text{extra}} \frac{\partial \Phi_{\text{extra}}}{\partial n} \bigg|_{S_{\text{cell}}} = -\sigma_{\text{intra}} \frac{\partial \Phi_{\text{intra}}}{\partial n} \bigg|_{S_{\text{cell}}} ,$$

and

$$\sigma_{\text{memb}} (\Phi_{\text{intra}} - \Phi_{\text{extra}}) \bigg|_{S_{\text{cell}}} = -\sigma_{\text{intra}} \frac{\partial \Phi_{\text{intra}}}{\partial n} \bigg|_{S_{\text{cell}}} , \tag{3}$$

where n is the outward normal at the cell's surface S_{cell}. The first of these equations expresses the requirement that the normal current density be continuous across the thin cell membrane while the second equation relates this current density to the resulting transmembrane potential produced by the conductance of the assumed passive membrane.

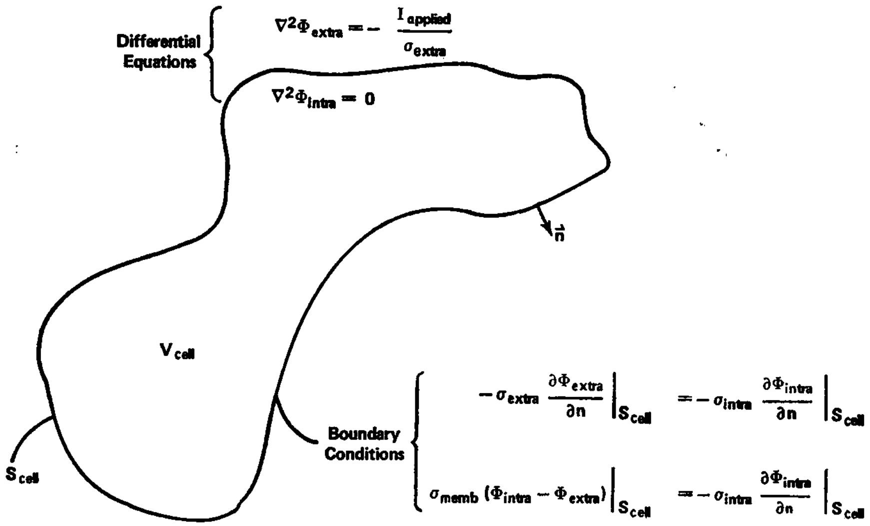

FIGURE 1 Governing equations and cell shape. S_{cell} is a smooth cell surface bounding a closed cell volume V_{cell}; n is the outward normal to S_{cell}; Φ_{intra} and Φ_{extra} are the intra- and extracellular deviations from resting conditions caused by the applied volume source density $I_{applied}$ (amperes per cubic centimeter); σ_{intra} and σ_{extra} are the intra- and extracellular conductivities (reciprocal ohms per centimeter); σ_{memb} is the membrane conductivity (reciprocal ohms per square centimeter).

These governing equations are shown in Fig. 1 for a smooth cell surface bounding a closed cell volume which will be the only restrictions placed upon the shape of the biological cell.

Using these equations we next obtain bounds on the intracellular biopotentials during static extracellular stimulation.

DERIVATIONS

Bounds on Intracellular Potentials

Beginning with the maximum-minimum properties of the solutions to Laplace's equation (Morse and Feshbach, 1953, p. 7) and using the boundary conditions at biological membranes, the following inequality will be proved:

$$\min\left[\Phi_{extra}\,|_{S_{cell}}\right] \leq \Phi_{intra} \leq \max\left[\Phi_{extra}\,|_{S_{cell}}\right]. \qquad (4)$$

Proof: Since Laplace's equation (Eq. 2) holds in the interior of the cell, the harmonic function Φ_{intra} cannot have a maximum or minimum value within the cell unless, of course, Φ_{intra} is a constant (Morse and Feshbach, 1953, p. 7). In either case it then follows that Φ_{intra} attains its maximum and minimum values on the interior surface of the cell membrane. Designating by $P_{intramax}$ ($P_{intramin}$) any one of the possible locations on the membrane surface of the maximum (minimum) value of intracellular potential, we can write the following inequalities for the normal derivatives at these points:

$$\left.\frac{\partial \Phi_{\text{intra}}}{\partial n}\right|_{P_{\text{intramax}}} \geq 0$$

(*n* is the outward normal)·

$$\left.\frac{\partial \Phi_{\text{intra}}}{\partial n}\right|_{P_{\text{intramin}}} \leq 0$$

These inequalities follow directly from the behavior of the potential near a maximum or minimum of potential; the potential must be increasing or constant as one approaches a maximum and decreasing or constant as one approaches a minimum.

Combining these inequalities with the boundary conditions at a biological membrane (Eq. 3) we have:

$$\sigma_{\text{memb}}\left.(\Phi_{\text{intra}} - \Phi_{\text{extra}})\right|_{P_{\text{intramax}}} = -\sigma_{\text{intra}}\left.\frac{\partial \Phi_{\text{intra}}}{\partial n}\right|_{P_{\text{intramax}}} \leq 0,$$

and

$$\sigma_{\text{memb}}\left.(\Phi_{\text{intra}} - \Phi_{\text{extra}})\right|_{P_{\text{intramin}}} = -\sigma_{\text{intra}}\left.\frac{\partial \Phi_{\text{intra}}}{\partial n}\right|_{P_{\text{intramin}}} \geq 0,$$

from which we immediately obtain ($\sigma_{\text{memb}} > 0$):

$$\Phi_{\text{intra}}\,|_{P_{\text{intramax}}} \leq \Phi_{\text{extra}}\,|_{P_{\text{intramax}}},$$

and

$$\Phi_{\text{intra}}\,|_{P_{\text{intramin}}} \geq \Phi_{\text{extra}}\,|_{P_{\text{intramin}}}.$$

Since

$$\Phi_{\text{extra}}\,|_{P_{\text{intramax}}} \quad \text{and} \quad \Phi_{\text{extra}}\,|_{P_{\text{intramin}}}$$

are bounded by the maximum and minimum values of extracellular potential on the surface of the cell and since Φ_{intra} is bounded by

$$\Phi_{\text{intra}}\,|_{P_{\text{intramax}}} \quad \text{and} \quad \Phi_{\text{intra}}\,|_{P_{\text{intramin}}},$$

it follows that:

$$\min\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}] \leq \Phi_{\text{intra}} \leq \max\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}]. \tag{4}$$

Thus, the values of intracellular potential are bounded by the maximum and minimum values of extracellular potential along the surface of the cell. The maximum magnitude of potential deviation from resting conditions within the cell is never greater than the maximum magnitude of potential deviation from resting conditions on the exterior surface of the cell membrane.[1]

Using these bounds on the intracellular potentials, we next obtain an upper bound on the volume average of the magnitude of intracellular electric field.

Bound on Intracellular Electric Field

Beginning with Green's first identity and using the divergence theorem and the bounds on intracellular potentials, the following inequality will be proved:

$$\text{ave}\,|\mathbf{E}_{\text{intra}}| \le \frac{\max\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}] - \min\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}]}{\lambda}, \qquad (5)$$

where ave $|\mathbf{E}_{\text{intra}}|$ is the volume average of the magnitude of intracellular electric field defined by:

$$\text{ave}\,|\mathbf{E}_{\text{intra}}| = \left(\frac{\int_{V_{\text{cell}}} \mathbf{E}_{\text{intra}}\cdot\mathbf{E}_{\text{intra}}\,dv}{V_{\text{cell}}}\right)^{1/2}. \qquad (6)$$

Proof: Green's first identity relates the behavior of functions on the boundary of a region to their behavior within the region. Specifically, if S is a regular surface bounding a closed region of space V, if n is the outward normal to this surface, and if ψ and ϕ are two scalar functions defined in V which are continuous and have continuous first and second partial derivatives throughout V and on the surface S,

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[1] It has been pointed out to the author by Dr. John Z. Hearon that inequalities 4 can also be obtained if the intracellular conductivity is not a constant. In this case, instead of Laplace's equation (Eq. 2) we have

$$\nabla\cdot(\sigma_{\text{intra}}\,\nabla\Phi_{\text{intra}}) = 0$$

or

$$\sigma_{\text{intra}}\,\nabla^2\Phi_{\text{intra}} + \nabla\sigma_{\text{intra}}\cdot\nabla\Phi_{\text{intra}} = 0$$

or

$$\nabla^2\Phi_{\text{intra}} + \nabla\ln\sigma_{\text{intra}}\cdot\nabla\Phi_{\text{intra}} = 0, \qquad \sigma_{\text{intra}} > 0.$$

For σ_{intra} finite, this equation satisfies the requirements of the generalized maximum-minimum theorem for elliptic operators (Protter and Weinberger, 1967, chapter 2, section 3) allowing us to conclude, as with continuous functions satisfying Laplace's equation, that Φ_{intra} attains its maximum and minimum values on the interior surface of the cell membrane. The remainder of the proof is identical with that presented above.

we can write Green's first identity as (Stratton, 1941, p. 165):

$$\int_V \nabla\psi\cdot\nabla\phi \, \mathrm{d}\,v + \int_V \psi\nabla^2\phi \, \mathrm{d}\,v = \int_S \psi(\partial\phi/\partial n)\, \mathrm{d}a.$$

Choosing $\psi = \phi = \Phi_{\text{intra}}$ and S and V to be the surface and volume of the cell, this identity becomes:

$$\int_{V_{\text{cell}}} \nabla\Phi_{\text{intra}}\cdot\nabla\Phi_{\text{intra}}\, \mathrm{d}v + \int_{V_{\text{cell}}} \Phi_{\text{intra}}\, \nabla^2\Phi_{\text{intra}}\, \mathrm{d}v = \int_{S_{\text{cell}}} \Phi_{\text{intra}}\, (\partial\Phi_{\text{intra}}/\partial n)\, \mathrm{d}a.$$

Substituting $\mathbf{E}_{\text{intra}} = -\nabla\Phi_{\text{intra}}$, Laplace's equation (Eq. 2), and the boundary conditions at biological membranes (Eq. 3), we have the intermediate result:

$$\int_{V_{\text{cell}}} \mathbf{E}_{\text{intra}}\cdot\mathbf{E}_{\text{intra}}\, \mathrm{d}v = (-\sigma_{\text{memb}}/\sigma_{\text{intra}}) \int_{S_{\text{cell}}} \Phi_{\text{intra}}\, (\Phi_{\text{intra}} - \Phi_{\text{extra}})\, \mathrm{d}a. \quad (7)$$

To transform this equation into a useful upper bound, we first apply the divergence theorem ($\int_V \nabla\cdot\mathbf{A}\, \mathrm{d}v = \int_S \mathbf{A}\cdot\mathbf{n}\, \mathrm{d}a$) to the vector $\nabla\Phi_{\text{intra}}$ obtaining:

$$\int_{V_{\text{cell}}} \nabla^2\Phi_{\text{intra}}\, \mathrm{d}v = \int_{S_{\text{cell}}} (\partial\Phi_{\text{intra}}/\partial n)\, \mathrm{d}a,$$

or from Eqs. 2 and 3:

$$0 = (-\sigma_{\text{memb}}/\sigma_{\text{intra}}) \int_{S_{\text{cell}}} (\Phi_{\text{intra}} - \Phi_{\text{extra}})\, \mathrm{d}a. \quad (8)$$

Next we multiply Eq. 8 by

$$-\min\, [\Phi_{\text{extra}}\, |_{S_{\text{cell}}}]$$

and add the result to Eq. 7:

$$\int_{V_{\text{cell}}} \mathbf{E}_{\text{intra}}\cdot\mathbf{E}_{\text{intra}}\, \mathrm{d}v = -\frac{\sigma_{\text{memb}}}{\sigma_{\text{intra}}} \int_{S_{\text{cell}}} (\Phi_{\text{intra}} - \min\, [\Phi_{\text{extra}}\, |_{S_{\text{cell}}}])(\Phi_{\text{intra}} - \Phi_{\text{extra}})\, \mathrm{d}a.$$

Taking absolute values gives:

$$\int_{V_{\text{cell}}} \mathbf{E}_{\text{intra}}\cdot\mathbf{E}_{\text{intra}}\, \mathrm{d}v \leq \frac{\sigma_{\text{memb}}}{\sigma_{\text{intra}}} \int_{S_{\text{cell}}} |\Phi_{\text{intra}} - \min\, [\Phi_{\text{extra}}\, |_{S_{\text{cell}}}]\, |\, |\Phi_{\text{intra}} - \Phi_{\text{extra}}|\, \mathrm{d}a. \quad (9)$$

We now use the bounds on intracellular potentials (Eq. 4) to write:

$$|\Phi_{\text{intra}} - \min[\Phi_{\text{extra}}|_{S_{\text{cell}}}]|\Big|_{S_{\text{cell}}} \leq \max[\Phi_{\text{extra}}|_{S_{\text{cell}}}] - \min[\Phi_{\text{extra}}|_{S_{\text{cell}}}],$$

and

$$|\Phi_{\text{intra}} - \Phi_{\text{extra}}|\Big|_{S_{\text{cell}}} \leq \max[\Phi_{\text{extra}}|_{S_{\text{cell}}}] - \min[\Phi_{\text{extra}}|_{S_{\text{cell}}}],$$

so that Eq. 9 becomes:

$$\int_{V_{\text{cell}}} \mathbf{E}_{\text{intra}}\cdot\mathbf{E}_{\text{intra}}\,dv \leq \frac{\sigma_{\text{memb}}}{\sigma_{\text{intra}}}(\max[\Phi_{\text{extra}}|_{S_{\text{cell}}}] - \min[\Phi_{\text{extra}}|_{S_{\text{cell}}}])^2 \int_{S_{\text{cell}}} da. \quad (10)$$

Dividing by the intracellular volume, taking the square root, and substituting the definitions of ave $|\mathbf{E}_{\text{intra}}|$ (Eq. 6) and λ (Eq. 1), we finally obtain:

$$\text{ave}\,|\mathbf{E}_{\text{intra}}| \leq \frac{\max[\Phi_{\text{extra}}|_{S_{\text{cell}}}] - \min[\Phi_{\text{extra}}|_{S_{\text{cell}}}]}{\lambda}.$$

Thus, if we know, or can estimate, the largest extracellular potential difference on the surface of the cell we can calculate an upper bound for the volume average of the magnitude of intracellular electric field by dividing this difference by the generalized length constant λ.

DISCUSSION

Intracellular Isopotentiality

The upper bound on the volume average of the magnitude of intracellular electric field can be used as an estimate, in the sense of an average, for the departure from intracellular isopotentiality. When the expression

$$(\max[\Phi_{\text{extra}}|_{S_{\text{cell}}}] - \min[\Phi_{\text{extra}}|_{S_{\text{cell}}}])/\lambda$$

is small, the volume average of the absolute value of the function $\nabla\Phi_{\text{intra}}$ must be small, leading to the conclusion that Φ_{intra} must be almost constant. We cannot conclude that the intracellular medium is close to being isopotential everywhere but we can conclude in the sense of an average that the intracellular medium is close to being isopotential.

It should be noted that

$$(\max[\Phi_{\text{extra}}|_{S_{\text{cell}}}] - \min[\Phi_{\text{extra}}|_{S_{\text{cell}}}])/\lambda$$

being small is not a necessary condition for intracellular isopotentiality. The conservative steps between Eqs. 7 and 10 have led to a high upper bound for the average magnitude of intracellular electric field.[2] The right-hand side of inequality 5 can be large and the intracellular medium may still be virtually isopotential.

Generalized Length Constant

The generalized length constant $\lambda = [\sigma_{\text{intra}} V_{\text{cell}}/(\sigma_{\text{memb}} A_{\text{cell}})]^{1/2}$ arose naturally in the development of an upper bound for the volume average of the magnitude of intracellular electric field during extracellular stimulation. More generally, this constant should serve as a convenient parameter for electrically describing arbitrary cells.

With this application in mind, we now separate λ into two parts. Using the generalized space constant Λ (Eisenberg and Engel, 1970) for the ratio of σ_{intra} to σ_{memb} we write:

$$\lambda = (\Lambda)^{1/2}(V_{\text{cell}}/A_{\text{cell}})^{1/2}.$$

In this form, we can distinguish between the contributions to the generalized length constant of electrical parameters and of cell shape.

As examples, we have listed in Table I the expressions for the generalized length constants of cylindrical- and spheroidal-shaped cells. These expressions grow as the square root of the size of the cell which generalizes to the statement that, for similarly shaped cells with similar electrical parameters (Λ's), smaller cells will have smaller length constants.

To isolate the shape-dependent part of λ, we have plotted, in Fig. 2, $\lambda/(\Lambda A)^{1/2}$

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[2] For example, by using the analytic solution for the biopotentials of a spherical cell in an applied uniform electric field (Klee and Plonsey, 1972, p. 1670), we can write for the intracellular electric field

$$\mathbf{E}_{\text{intra}} \simeq 1.5\,(A\sigma_{\text{memb}}/\sigma_{\text{intra}})\mathbf{E}_{\text{applied}} \tag{11}$$

and for the maximum extracellular potential difference

$$\max\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}] - \min\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}] \simeq 3A\,|\,\mathbf{E}_{\text{applied}}\,|$$

where A is the radius of the cell and $\mathbf{E}_{\text{applied}}$ is the applied uniform field. λ for a spherical cell is given by

$$\lambda = (\sigma_{\text{intra}}/\sigma_{\text{memb}})^{1/2}(A/3)^{1/2}$$

so that inequality 5 becomes

$$\text{ave}\,|\,\mathbf{E}_{\text{intra}}\,| \leq \frac{3A\,|\,\mathbf{E}_{\text{applied}}\,|}{(\sigma_{\text{intra}}/\sigma_{\text{memb}})^{1/2}(A/3)^{1/2}} = 3(3)^{1/2}(A\sigma_{\text{memb}}/\sigma_{\text{intra}})^{1/2}\,|\,\mathbf{E}_{\text{applied}}\,|. \tag{12}$$

Since for physiological situations ($A\,\sigma_{\text{memb}}/\sigma_{\text{intra}}$) is of the order 10^{-3}, we see that the upper bound of Eq. 12 is approximately two orders of magnitude larger than the actual intracellular electric field of Eq. 11 ($1.6 \times 10^{-1}\,|\,\mathbf{E}_{\text{applied}}\,|$ vs. $1.5 \times 10^{-3}\,|\,\mathbf{E}_{\text{applied}}\,|$).

TABLE I

GENERALIZED LENGTH CONSTANTS FOR CYLINDRICAL- AND SPHEROIDAL-SHAPED CELLS

	$\lambda = (\Lambda)^{1/2}(V_{\text{cell}}/A_{\text{cell}})^{1/2}$ $\Lambda = \sigma_{\text{intra}}/\sigma_{\text{memb}}$	
Infinite cylinder	$\lambda = (\Lambda)^{1/2}(A/2)^{1/2}$	A = radius[3]
Finite cylinder	$\lambda = (\Lambda)^{1/2}\left(\dfrac{A}{2 + (A/B)}\right)^{1/2}$	A = radius B = half length
Sphere	$\lambda = (\Lambda)^{1/2}(A/3)^{1/2}$	A = radius
Prolate spheroid	$\lambda = (\Lambda)^{1/2}\left(\dfrac{2/3\,A}{\dfrac{A}{B} + \dfrac{\sin^{-1}\epsilon}{\epsilon}}\right)^{1/2}$	A = minor semiaxis B = major semiaxis $\epsilon = (1 - A^2/B^2)^{1/2}$
Oblate spheroid	$\lambda = (\Lambda)^{1/2}\left(\dfrac{2/3\,A}{\dfrac{A}{B} + \dfrac{B}{2A\epsilon}\ln\dfrac{1+\epsilon}{1-\epsilon}}\right)^{1/2}$	A = major semiaxis B = minor semiaxis $\epsilon = (1 - B^2/A^2)^{1/2}$

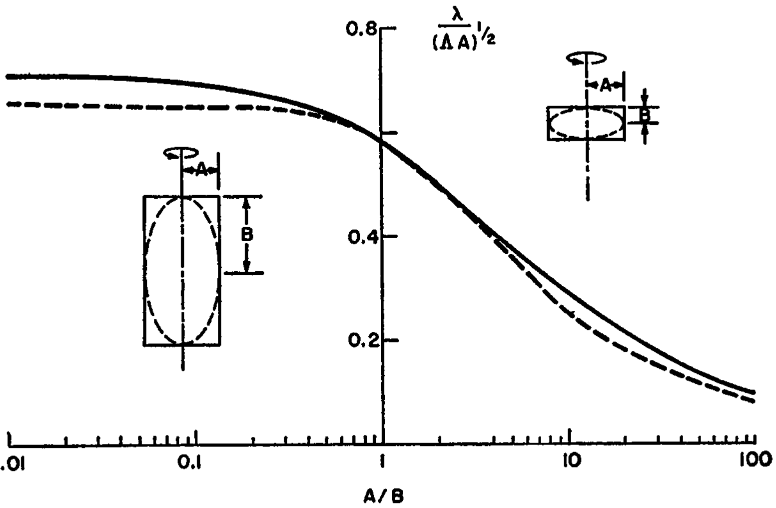

Figure 2 Dependence of λ upon cell shape. Solid line represents finite cylinders; dashed line represents prolate spheroids ($A/B \leq 1$) or oblate spheroids ($A/B \geq 1$); see Table I for expressions used to calculate $\lambda/(\Lambda A)^{1/2}$.

for cylindrical- and spheroidal-shaped cells having different aspect ratios A/B.[3] For cells having the same generalized space constant Λ and dimension A, we see from this figure that the largest λ occurs for the infinite cylinder ($A/B \rightarrow 0$), that spheroidal cells have smaller λ's than comparable cylindrical cells, and that squat cells have smaller λ's than long cells.

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[3] See Fig. 2 for pictorial definitions of A and B.

SUMMARY

In this paper, we have established the following inequalities for the intracellular biopotentials and intracellular electric fields resulting from static extracellular stimulation:

$$\min\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}] \leq \Phi_{\text{intra}} \leq \max\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}],$$

and

$$\text{ave}\,|\mathbf{E}_{\text{intra}}| \leq \frac{\max\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}] - \min\,[\Phi_{\text{extra}}\,|_{S_{\text{cell}}}]}{\lambda},$$

where λ is a generalized length constant given by:

$$\lambda = [\sigma_{\text{intra}} V_{\text{cell}}/(\sigma_{\text{memb}} A_{\text{cell}})]^{1/2}.$$

The use of the upper bound on the average magnitude of intracellular electric field as an estimate for intracellular isopotentiality was discussed and the use of the generalized length constant for electrically describing arbitrary cells was illustrated for cylindrical- and spheroidal-shaped cells.

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