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A SINGULAR PERTURBATION ANALYSIS OF INDUCED ELECTRIC FIELDS IN NERVE CELLS*

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Abstract. The electric field induced by a microelectrode inserted in a nerve cell is investigated in order to interpret the results obtained by the single and double probe techniques. The solution is obtained by means of a singular perturbation expansion in terms of the ratio of the membrane conductance to the cell conductivity. Both finite and infinite cells are considered and special attention is devoted to the spherical and cylindrical geometries.

1. Introduction. Nerve cells, like other cells which make up the tissues of animals, consist of material suspended in a salt solution surrounded by a thin membrane, typically 10^{-6} cm thick. The primary function of the membrane is to maintain a constant chemical and physical environment within the cell by isolating the cell interior from its surroundings. Thus, cell membranes are invariably quite impermeable to the movement of the solute molecules commonly found in biological systems. In particular, the membranes have low permeability to ions, and thus can be described electrically as having very small specific conductivity (typically, 3×10^{-10} ohm^{-1} cm^{-1}). However, the thinness of the membrane implies that the conductance of one square centimeter of membrane, called the membrane conductance G_m in the physiological literature (the reciprocal being the membrane resistance R_m), is small but not negligible, namely some 3×10^{-4} ohm^{-1} cm^{-2}. Similarly, the thinness of the membrane means that the capacitance of the membrane (usually about 1μF/cm^2) is appreciable. Thus, small but significant amounts of current, either ionic (that is, resistive) or capacitive, can cross the membrane.

The flow of these currents within cells and from cell to cell is of great importance for the function of many living systems:

(i) The signal which initiates muscular contraction is electrical [17].

(ii) Embryonic cells and the epithelial cells which make up most secretory organs have specialized regions of membrane which allow current to flow from one cell to another. The significance of this electrical coupling is not well known [13], but is likely to be important.

(iii) Sensory systems, such as the eye, ear, taste cells, pressure sensitive cells, etc. are transducers which convert the appropriate natural stimuli into electrical signals [9], [4].

(iv) Signaling and information processing in the nervous system are essentially electrical in nature [11], [12].

Thus, the study of the electrical properties of cells is of considerable biological significance.

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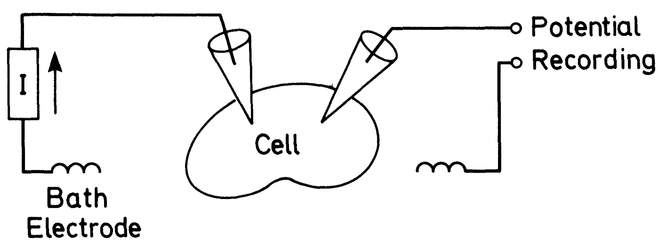
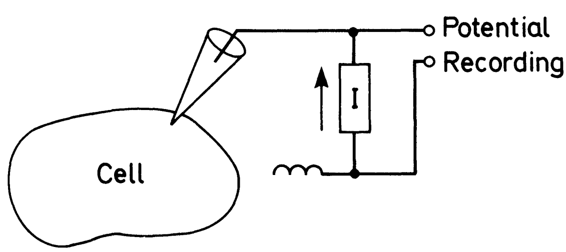
Experimental procedures which record the natural electrical activity of cells must preserve the integrity of the cell, that is to say, the procedures must not destroy the isolation of the cell interior from the outside world. Thus, the probes which record this activity must be so small that they do not damage the membrane. Wherever possible, this activity is measured by inserting into the cell a small diameter (less than 10^{-4} cm) glass pipette filled with an electrically conducting salt solution, and then measuring the electrical potential in the solution filling the pipette. With care and luck this can be done without significant damage to the cell.

Measurements of the electrical parameters of the cell, as opposed to simple recordings of natural electrical activity, face further difficulties since the experiment must be arranged so that current flows through the structures of interest. Since the membrane, which has the highest impedance of any of the cellular structures, is most important in determining the electrical properties of the cell, the current is usually applied across the membrane. This is often done by inserting a second micropipette into the cell and passing current between it and an "indifferent" electrode in the external solution, meanwhile recording potential with the first pipette (the "two probe technique" shown in Fig. 1(a)). In many cases however, it is possible to insert only one probe into the cell: then the one probe technique (Fig. 1(b)) must be used. In either case, measurements are made of the change in potential produced by the flow of current.



(a)



(b)

FIG. 1. *Two setups for recording the current–voltage relations of cells. Part* (a) *shows the two probe technique. Two probes* (*microelectrodes*), *here shown as cones, are inserted into the cell: one probe passes current to a bath electrode located in the solution outside the cell; the other records potential with respect to another bath electrode.*

Part (b) *shows the one probe technique. Current is passed from a microelectrode to a bath electrode outside the cell and voltage is recorded between these two electrodes.*

In this paper we are concerned with the interpretation of changes in potential recorded by the two probe method and the determination of the electrical properties of individual parts of the cell (the cell membrane or cell interior) from these measurements. The one probe method will be considered in another paper. The properties we shall be concerned with are the so-called linear properties of the cell, that is to say, the responses of cells to small current. The nonlinear processes, for example those processes which actually produce and amplify the signals in the nervous system (see [10] for a discussion of these), are not susceptible to an analysis of this kind. Moreover, we shall be primarily concerned with the steady state.

The essential problem which faces us then is to analyze the flow of current within cells so as to predict the change in potential produced by the application of current. This problem has been considered in some detail by many physiologists over the last century (see [16] for references); our contribution will be to analyze the flow of current with as few assumptions about the nature of the electric field as possible. In particular we shall not follow the usual practice of assuming that the field can be described by a differential equation with only one spatial coordinate. Falk and Fatt [8] were the first to analyze this problem without such an assumption; Eisenberg and Johnson [6] have discussed in detail the practical implications of this theoretical work and have extended the analysis to different cell geometries. Adrian, Costantin and Peachy [1] have computed the solution for a cylinder; Eisenberg and Engel [5] have treated the spherical cell in some detail. In this previous work, expansions in the eigenfunctions which describe the potential in cells of various shapes were used; they gave rise to expressions which have little physical meaning and which require extensive numerical computations. By using a singular perturbation expansion based upon the small dimensionless value of the membrane conductance, we are able to derive equivalent but simpler expressions and to interpret physically the meaning of the various terms of the solution. Furthermore, in the case of the spherical cell, we can simplify the expressions involved to the point where subsequent treatment of the single probe method becomes practicable.

2. Formulation. Denoting by $\mathbf{j}'$, $\mathbf{E}'$ and G_i the current density, electric field and conductivity of the material within the cell, we can write Ohm's law and the continuity equation thus:

$$\mathbf{j}' = G_i \mathbf{E}', \tag{1}$$

$$\nabla' \cdot \mathbf{j}' = Q, \tag{2}$$

where Q is the source distribution. Introducing the potential V' defined by

$$\mathbf{E}' = -\nabla' V', \tag{3}$$

we can express the continuity of current at the membrane as follows:

$$-G_i \mathbf{n} \cdot \nabla' V' = G_m V', \tag{4}$$

where $\mathbf{n}$ is the unit outward normal and G_m is the conductance of one cm^2 of the membrane. The membrane is treated here as a zero thickness structure providing a contact resistance between the internal and external solutions. We have also assumed that the potential outside the cell is constant, equal to zero; the validity of this assumption is discussed by Rall [14], [15].

Throughout this paper we shall restrict our attention to a point source of current which, in addition to providing a good approximation for the micropipette, yields the Green's function for this class of problems.

Let us introduce dimensionless variables (unprimed) in an obvious way associated with the apparent orders of magnitude inside the cell,

$$\mathbf{E} = \frac{G_i}{lq}\mathbf{E}', \qquad V = \frac{G_i}{l^2 q}V', \qquad \mathbf{j} = \frac{1}{ql}\mathbf{j}',$$

where l is a typical cross-sectional length (in m) and q a measure of the strength of the current distribution (in amp/m^3). As a result, the problem becomes

$$\begin{aligned} \nabla^2 V &= -\,\delta(\mathbf{r} - \mathbf{R}) \quad \text{in } D, \\ \partial V/\partial n + \varepsilon V &= 0 \quad \text{on } \Gamma, \end{aligned} \tag{5}$$

where $\delta(\cdot)$ is the Dirac delta function, $\mathbf{r}$ the position vector, $\mathbf{R}$ the position of the current source, D the volume of the cell and Γ its membrane. The dimensionless number ε is defined as follows:

$$\varepsilon = lG_m/G_i. \tag{6}$$

For situations of physiological interest, ε is of the order 10^{-3}.

In the present paper we propose to develop a procedure for solving (5) for rather general cell geometries, based on the smallness of ε. It should be noted that a regular perturbation expansion is not possible. Indeed, if such an expansion existed, its first term, say v, would have to be a solution of the following problem:

$$\begin{aligned} \nabla^2 v &= \delta(\mathbf{r} - \mathbf{R}) \quad \text{in } D, \\ \partial v/\partial n &= 0 \quad \text{on } \Gamma. \end{aligned} \tag{7}$$

But the above problem has no solution: it is physically impossible to have a source of current within the cell and no flow of current across the membrane!

3. Finite cells. It seems evident that the difficulty with the previous expansion is that the estimate of the order of magnitude of V is incorrect; in order to drive a current across a highly resistive membrane a large potential must build up inside the cell. The following form of expansion leads to a consistent set of approximations:

$$V = \frac{1}{\varepsilon}V^{(0)} + V^{(1)} + \varepsilon V^{(2)} + \cdots, \tag{8}$$

where $V^{(0)}, V^{(1)}, \cdots$ are independent of ε. Substituting (8) into (5) and equating powers of ε we deduce a sequence of problems for the various terms. In particular, the boundary value problem for $V^{(0)}$ is

$$\begin{aligned} \nabla^2 V^{(0)} &= 0 \quad \text{in } D, \\ \partial V^{(0)}/\partial n &= 0 \quad \text{on } \Gamma. \end{aligned} \tag{9}$$

The most general solution is

$$V^{(0)} = C, \tag{10}$$

where C is a constant. Similarly the problem for $V^{(1)}$ is

$$\begin{aligned} \nabla^2 V^{(1)} &= -\delta(\mathbf{r} - \mathbf{R}) \quad \text{in } D, \\ \partial V^{(1)}/\partial n &= -C \quad \text{on } \Gamma. \end{aligned} \tag{11}$$

Integrating the equation for $V^{(1)}$ over the domain D and making use of the divergence theorem we get

$$\iint_\Gamma \frac{\partial V^{(1)}}{\partial n} dS = -1. \tag{12}$$

From the boundary condition for $V^{(1)}$ we therefore deduce that

$$C = 1/A, \tag{13}$$

where A is the area of the membrane. It should be noted at this stage that (11) specifies $V^{(1)}$ only to within an arbitrary constant. Just as for $V^{(0)}$, the indeterminacy in $V^{(1)}$ is removed by considering the next order field. Indeed, the boundary value problem for $V^{(2)}$, viz.

$$\begin{aligned} \nabla^2 V^{(2)} &= 0 \quad \text{in } D, \\ \partial V^{(2)}/\partial n &= -V^{(1)} \quad \text{on } \Gamma, \end{aligned} \tag{14}$$

implies that

$$\iint_\Gamma V^{(1)} dS = 0. \tag{15}$$

We can now rewrite the problem for $V^{(1)}$ thus:

$$\begin{aligned} \nabla^2 V^{(1)} &= -\delta(\mathbf{r} - \mathbf{R}) \quad \text{in } D, \\ \partial V^{(1)}/\partial n &= -1/A \quad \text{on } \Gamma, \\ \iint_\Gamma V^{(1)} dS &= 0. \end{aligned} \tag{16}$$

Similarly, the problem for the higher order terms is

$$\begin{aligned} \nabla^2 V^{(n)} &= 0 \quad \text{in } D, \\ \partial V^{(n)}/\partial n &= -V^{(n-1)} \quad \text{on } \Gamma, \\ \iint_\Gamma V^{(n)} dS &= 0 \end{aligned} \tag{17}$$

for $n = 2, 3, \cdots$.

The above sequence of problems enables us to give a simple physical interpretation of the various contributions to the potential. $V^{(0)}$ represents a constant potential independent of position. $V^{(1)}$ represents the field produced by a point source of current within a cell surrounded by a membrane which allows *all* the current to flow uniformly across its *entire* surface. This problem introduces the singularity in potential which must be present according to the original problem. $V^{(2)}, V^{(3)}, \cdots$ represent potential corrections due to current distributions on the membrane with zero surface averages. As a result, these higher order corrections produce no current efflux. Indeed, the integral constraints

$$\int\int_\Gamma V^{(n)}\,dS = 0, \qquad n = 2, 3, \cdots, \tag{18}$$

are a consequence of this result.

As an illustration of the asymptotic expansion method, let us reexamine the case of spherical cells which has previously been considered by Eisenberg and Engel [5]. Assuming that the dimensionless radius of the sphere is equal to one, we immediately deduce that

$$V^{(0)} = 1/(4\pi); \tag{19}$$

furthermore, the problem for $V^{(1)}$ becomes

$$\begin{aligned} \nabla^2 V^{(1)} &= -\,\delta(\mathbf{r} - \mathbf{R}) \quad \text{in } r < 1, \\ \partial V^{(1)}/\partial r &= -\,1/(4\pi) \quad \text{on } r = 1. \end{aligned} \tag{20}$$

We look for a solution of (20) made up of the fundamental solution of Laplace's equation in three dimensions, the "image" and an unknown harmonic function, ψ, with no singularities in the interior:

$$V^{(1)} = \frac{1}{4\pi}\left[\frac{1}{|\mathbf{r} - \mathbf{R}|} + \frac{1}{r|\mathbf{r}/r^2 - \mathbf{R}|} + \psi\right]. \tag{21}$$

Without loss of generality we can assume that $\mathbf{R}$ coincides with the axis $\theta = 0$, where θ is the polar angle. As a result ψ is solely a function of r and θ, and can be written

$$\psi = \sum_{n=0}^{\infty} A_n r^n P_n(\cos\theta), \tag{22}$$

where $P_n(\cos\theta)$ is the nth Legendre polynomial and the A_n's are unknown coefficients. From a consideration of the boundary condition we deduce that

$$A_n = R^n/n, \qquad n = 1, 2, \cdots, \tag{23}$$

A_0 being undetermined. Therefore

$$\psi = \sum_1^{\infty} \frac{1}{n}(rR)^n P_n(\cos\theta) + A_0; \tag{24}$$

this series expression for ψ can be summed by simply noting that ψ satisfies the differential equation

$$(rR)\frac{\partial\psi}{\partial(rR)} = \frac{1}{(r^2R^2 + 1 - 2rR\cos\theta)^{1/2}} - 1, \tag{25}$$

which can be easily deduced from (24) together with the generating function for the Legendre polynomials. Solving for ψ and evaluating A_0 in such a way as to satisfy the integral constraint

$$\int\int_\Gamma V^{(1)}\,dS = 0,$$

we deduce that

$$V^{(1)} = \frac{1}{4\pi}\left[\frac{1}{(r^2 + R^2 - 2rR\cos\theta)^{1/2}} + \frac{1}{(r^2R^2 + 1 - 2rR\cos\theta)^{1/2}}\right.$$
(26)
$$\left. -\log\{1 - rR\cos\theta + (1 + r^2R^2 - 2rR\cos\theta)^{1/2}\} - 2 + \log 2\right].$$

This very simple expression for $V^{(1)}$ is well-suited for computational purposes. In addition, it can be used to derive the average potential on a disc source of current [7] which would correspond to the potential recorded by the single probe method described above. Since there has been no basis for the interpretation of the results obtained by means of the single probe technique, the computation of the average potential on a disc source is of particular significance.

It should be noted that the expansion (8) is, strictly speaking, not uniformly valid inside the cell because of the source singularity in the $V^{(1)}$ term; however, it is valid for the difference of the potential from its singular part.

4. Infinitely long cells. We have previously deduced that for a finite cell the potential is of the form

$$V = \frac{1}{\varepsilon A} + V^{(1)} + \varepsilon V^{(2)} + \cdots. \tag{27}$$

For more and more elongated cells, the area of the membrane will become larger and larger, and for sufficiently large values of A the above representation will cease to be valid. For these elongated cells, the idealization of an infinitely long geometry might be appropriate. To that effect let us reexamine the specific case of an infinitely long cylindrical cell previously investigated by Eisenberg and Johnson [6].

Denoting by x, r, θ the cylindrical coordinates, we can assume without loss of generality that the source of current is located at $x = 0$, $r = R$, $\theta = 0$. As a result of the boundary value problem (5) can be written thus:

$$\left(\frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r} + \frac{1}{r^2}\frac{\partial^2}{\partial \theta^2}\right)V = -\frac{1}{r}\delta(x)\delta(r - R)\delta(\theta),$$
(28)
$$\frac{\partial V}{\partial r} + \varepsilon V = 0 \quad \text{on } r = 1,$$
$$V \to 0 \quad \text{as } |x| \to \infty.$$

The boundary condition at large x's is related to the fact that the outside potential was chosen to be zero.

The above problem can be solved by means of a Fourier transform in the x-direction; however, a method based on perturbation techniques presents the advantage that it can be generalized to other geometries.

Let us first observe that a "regular" expansion of the form

$$V = V^{(0)}(x, r, \theta) + \varepsilon V^{(1)}(x, r, \theta) + \cdots \tag{29}$$

is again not possible. This can be seen most easily by averaging the zeroth order problem over a cross section, viz.

$$\pi\frac{d^2}{dx^2}\bar{V}^{(0)}(x) = -\delta(x),$$
$$\bar{V}^{(0)}(x) \to 0 \quad \text{as } |x| \to \infty, \tag{30}$$

where

$$\bar{V}^{(0)}(x) = \frac{1}{\pi}\int_0^{2\pi} d\theta \int_0^1 rV^{(0)}(r, \theta, x)\,dr.^1 \tag{31}$$

Clearly, the boundary conditions at infinity cannot be satisfied. The following heuristic argument suggests the modification necessary for the derivation of a formal asymptotic expansion. Once again let us average the equation over a cross section, viz.

$$\pi\frac{d^2}{dx^2}\bar{V}(x) + \int_0^{2\pi} \left.\frac{\partial V}{\partial r}\right|_{r=1} d\theta = -\delta(x); \tag{32}$$

or making use of the boundary condition at $r = 1$ and assuming that, for large x's, $V(1, \theta, x)$ is nearly equal to the average $\bar{V}(x)$, we deduce that

$$d^2\bar{V}/dx^2 - 2\varepsilon\bar{V} \simeq 0. \tag{33}$$

This indicates that

$$\xi_1 = \sqrt{\varepsilon}x \tag{34}$$

is an appropriate far field variable and that half powers of ε will appear in the asymptotic expansion.

The multiple scale method [2] provides a means of removing nonuniformities at infinity. Let us introduce the following new variables:

$$\xi_n = \varepsilon^{n/2}x, \qquad n = 0, 1, 2, \cdots, \tag{35}$$

and regard them formally as independent variables. Let us furthermore look for an asymptotic approximation of the form

$$V = \frac{1}{\sqrt{\varepsilon}}\sum_{n=0}^{\infty} \varepsilon^{n/2}V^{(n)}(r, \theta, \xi_0, \xi_1, \cdots). \tag{36}$$

We shall require that (36) remain uniformly valid as $|x| \to \infty$. To that effect, the terms which lead to nonuniformity (viz. the secular terms) will have to be systematically eliminated. This process will generate the additional differential equations which determine the dependence of the different $V^{(n)}$'s on the various ξ's. Since all the new variables are formally independent variables, the operator $\partial/\partial x$ must be replaced by

$$\left(\frac{\partial}{\partial\xi_0}\right)_{\xi_1,\xi_2,\ldots} + \sqrt{\varepsilon}\left(\frac{\partial}{\partial\xi_1}\right)_{\xi_0,\xi_2,\ldots} + \varepsilon\left(\frac{\partial}{\partial\xi_2}\right)_{\xi_0,\xi_1,\xi_3,\ldots} + \cdots. \tag{37}$$

[1] Throughout the remainder of the paper we shall denote cross-sectional averages by an overbar.

It is convenient to use the symmetry of V and replace $\delta(x)$ by a boundary condition, and rewrite (28) thus:

$$
\begin{aligned}
&\nabla^2 V = 0,\\
&\partial V/\partial r + \varepsilon V = 0 \quad \text{on } r = 1,\\
&\frac{\partial V}{\partial x} = -\frac{1}{2r}\delta(r - R)\delta(\theta) \quad \text{on } x = 0,\\
&V \to 0 \quad \text{as } x \to \infty.
\end{aligned}
\tag{38}
$$

Substituting (36) and (37) in (38) and equating powers of $\sqrt{\varepsilon}$, we obtain a sequence of problems for the various $V^{(n)}$. In particular, the first five problems are:

$$
\begin{aligned}
&\Delta V^{(0)} = 0 \quad \text{in } r < 1, \quad 0 < \theta < 2\pi, \quad \xi_0 > 0, \quad \xi_1 > 0, \cdots,\\
&\partial V^{(0)}/\partial r = 0 \quad \text{on } r = 1,\\
&\partial V^{(0)}/\partial \xi_0 = 0 \quad \text{on } \xi_0 = \xi_1 = \cdots = 0,\\
&V^{(0)} \to 0 \quad \text{as } \xi_k \to \infty, \quad \text{whenever } \partial V^{(0)}/\partial \xi_n \equiv 0, \quad n = 0, 1, \cdots, k-1;
\end{aligned}
\tag{39}
$$

$$
\begin{aligned}
&\Delta V^{(1)} = -2\frac{\partial^2 V^{(0)}}{\partial \xi_0 \partial \xi_1},\\
&\partial V^{(1)}/\partial r = 0 \quad \text{on } r = 1,\\
&\frac{\partial V^{(1)}}{\partial \xi_0} = \frac{\partial V^{(0)}}{\partial \xi_1} - \frac{1}{2r}\delta(r - R)\delta(\theta) \quad \text{on } \xi_0 = \xi_1 = \cdots = 0,\\
&V^{(1)} \to 0 \quad \text{as } \xi_k \to \infty, \quad \text{where } \partial V^{(1)}/\partial \xi_n \equiv 0, \quad n = 0, \cdots, k-1;
\end{aligned}
\tag{40}
$$

$$
\begin{aligned}
&\Delta V^{(2)} = -2\frac{\partial^2 V^{(1)}}{\partial \xi_0 \partial \xi_1} - \frac{\partial^2 V^{(0)}}{\partial \xi_1^2} - 2\frac{\partial^2 V^{(0)}}{\partial \xi_0 \partial \xi_2},\\
&\partial V^{(2)}/\partial r = -V^{(0)} \quad \text{on } r = 1,\\
&\frac{\partial V^{(2)}}{\partial \xi_0} = -\frac{\partial V^{(1)}}{\partial \xi_1} - \frac{\partial V^{(0)}}{\partial \xi_2} \quad \text{on } \xi_0 = \xi_1 = \cdots = 0,\\
&V^{(2)} \to 0 \quad \text{as } \xi_k \to \infty, \quad \text{where } \partial V^{(2)}/\partial \xi_n \equiv 0, \quad n = 0, \cdots, k-1;
\end{aligned}
\tag{41}
$$

(42)
$$\Delta V^{(3)} = -2\frac{\partial^2 V^{(2)}}{\partial\xi_0\partial\xi_1} - \frac{\partial^2 V^{(1)}}{\partial\xi_1^2} - 2\frac{\partial^2 V^{(1)}}{\partial\xi_0\partial\xi_2} - 2\frac{\partial^2 V^{(0)}}{\partial\xi_0\partial\xi_3} - 2\frac{\partial^2 V^{(0)}}{\partial\xi_1\partial\xi_2},$$
$$\partial V^{(3)}/\partial r = -V^{(1)} \quad \text{on } r = 1,$$
$$\frac{\partial V^{(3)}}{\partial\xi_0} = -\frac{\partial V^{(2)}}{\partial\xi_1} - \frac{\partial V^{(1)}}{\partial\xi_2} - \frac{\partial V^{(0)}}{\partial\xi_3} \quad \text{on } \xi_0 = \xi_1 = \cdots = 0,$$
$$V^{(3)} \to 0 \quad \text{as } \xi_k \to \infty, \quad \text{where } \partial V^{(3)}/\partial\xi_n \equiv 0, \quad n = 0, \cdots, k-1;$$

and

(43)
$$\Delta V^{(4)} = -2\frac{\partial^2 V^{(3)}}{\partial\xi_0\partial\xi_1} - \frac{\partial^2 V^{(2)}}{\partial\xi_1^2} - 2\frac{\partial^2 V^{(2)}}{\partial\xi_0\partial\xi_2} - 2\frac{\partial^2 V^{(1)}}{\partial\xi_0\partial\xi_3} - 2\frac{\partial^2 V^{(1)}}{\partial\xi_1\partial\xi_2} - \frac{\partial^2 V^{(0)}}{\partial\xi_2^2} - 2\frac{\partial^2 V^{(0)}}{\partial\xi_1\partial\xi_3} - 2\frac{\partial^2 V^{(0)}}{\partial\xi_0\partial\xi_4},$$
$$\partial V^{(4)}/\partial r = -V^{(2)} \quad \text{on } r = 1,$$
$$\frac{\partial V^{(4)}}{\partial\xi_0} = -\frac{\partial V^{(3)}}{\partial\xi_1} - \frac{\partial V^{(2)}}{\partial\xi_2} - \frac{\partial V^{(1)}}{\partial\xi_3} - \frac{\partial V^{(0)}}{\partial\xi_4} \quad \text{on } \xi_0 = \xi_1 = \cdots = 0,$$
$$V^{(4)} \to 0 \quad \text{as } \xi_k \to \infty, \quad \text{where } \partial V^{(4)}/\partial\xi_n \equiv 0, \quad n = 0, \cdots, k-1.$$

The operator Δ is defined thus:

(44)
$$\Delta = \frac{\partial^2}{\partial r^2} + \frac{1}{r}\frac{\partial}{\partial r} + \frac{1}{r^2}\frac{\partial^2}{\partial\theta^2} + \frac{\partial^2}{\partial\xi_0^2}.$$

The last boundary condition in each problem states that whenever the variable $V^{(j)}$ $(j = 0, 1, 2, 3, 4)$ is independent of the first k independent variables ξ_0, ξ_1, $\xi_2, \cdots, \xi_{k-1}$, it must decay to zero as $\xi_k \to \infty$.

It is usual in multiple scale methods to have to examine one or several of the higher order approximation equations in order to determine the first approximation.

Let us now consider each problem in turn. From (39) we can immediately deduce that $V^{(0)}$ is not a function of ξ_0, r and θ, viz.

(45)
$$V^{(0)} = V^{(0)}(\xi_1, \xi_2, \cdots);$$

furthermore

(46)
$$V^{(0)} \to 0 \quad \text{as } \xi_1 \to \infty.$$

As a result, the equation for $V^{(1)}$ is homogeneous. Averaging the latter over a cross section, we deduce that

(47)
$$\partial^2 \bar{V}^{(1)}/\partial\xi_0^2 = 0.$$

Furthermore, averaging the boundary condition at $\xi_0 = \xi_1 = \cdots = 0$, we see that

(48)
$$\pi\frac{\partial\bar{V}^{(1)}}{\partial\xi_0} = -\pi\frac{\partial V^{(0)}}{\partial\xi_1} - \frac{1}{2}.$$

Since $\bar{V}^{(1)}$ cannot have a linear dependence on ξ_0 on account of the boundary condition at large ξ_0's, we conclude that

$$\frac{\partial V^{(0)}}{\partial \xi_1} = -\frac{1}{2\pi} \quad \text{on } \xi_1 = \xi_2 = \cdots = 0. \tag{49}$$

The boundary value problem for $V^{(1)}$ can now be rewritten thus:

$$\begin{aligned} &\Delta V^{(1)} = 0, \\ &\partial V^{(1)}/\partial r = 0 \quad \text{on } r = 1, \\ &\frac{\partial V^{(1)}}{\partial \xi_0} = \frac{1}{2\pi} - \frac{1}{2r}\delta(r - R)\delta(\theta) \quad \text{on } \xi_0 = \xi_1 = \cdots = 0, \\ &V^{(1)} \to 0 \quad \text{as } \xi_0 \to \infty. \end{aligned} \tag{50}$$

The solution to the above problem can be expressed by an eigenfunction expansion:

$$V^{(1)} = \sum_m \sum_n a_{mn}^{(1)}(\xi_1, \xi_2, \cdots) U_{mn}^{(1)}(r, \theta, \xi_0), \tag{51}$$

where

$$U_{mn}^{(1)} = \frac{\alpha_m^{(n)} J_n(\alpha_m^{(n)} R) J_n(\alpha_m^{(n)} r)}{\pi\{\alpha_m^{(n)2} - n^2\}[J_n(\alpha_m^{(n)})]^2} \cos n\theta \exp(-\alpha_m^{(n)}\xi_0), \quad m, n = 1, 2, \cdots, \tag{52}$$

$$U_{m0}^{(1)} = \frac{J_0(\alpha_m^{(0)} R) J_0(\alpha_m^{(0)} r)}{2\pi\alpha_m^{(0)}[J_0(\alpha_m^{(0)})]^2} \exp(-\alpha_m^{(0)}\xi_0), \tag{53}$$

where $\alpha_m^{(n)}$ is the mth root of $J_n'(z)$, and the $a_{mn}^{(1)}(\xi_1, \xi_2, \cdots)$ are unknown functions of $\xi_1, \xi_2, \cdots$ such that

$$a_{mn}^{(1)}(0, 0, \cdots) = 1. \tag{54}$$

We now turn our attention to (41) which becomes

$$\begin{aligned} &\Delta V^{(2)} = -\frac{\partial^2 V^{(0)}}{\partial \xi_1^2} - 2\frac{\partial^2 V^{(1)}}{\partial \xi_1 \partial \xi_0}, \\ &\partial V^{(2)}/\partial r = -V^{(0)} \quad \text{on } r = 1, \\ &\frac{\partial V^{(2)}}{\partial \xi_0} = -\frac{\partial V^{(1)}}{\partial \xi_1} - \frac{\partial V^{(0)}}{\partial \xi_2} \quad \text{on } \xi_0 = \xi_1 = \cdots = 0. \end{aligned} \tag{55}$$

The solution to the above problem is of the form

$$\begin{aligned} V^{(2)} = &-\frac{r^2}{2}V^{(0)} - \frac{\xi_0^2}{2}\left[\frac{\partial^2 V^{(0)}}{\partial \xi_1^2} - 2V^{(0)}\right] - \xi_0\frac{\partial V^{(1)}}{\partial \xi_1} \\ &+ W^{(2)}(r, \theta, \xi_0, \xi_1, \cdots), \end{aligned} \tag{56}$$

where

$$\begin{aligned} &\Delta W^{(2)} = 0, \\ &\partial W^{(2)}/\partial r = 0 \quad \text{on } r = 1, \\ &\partial W^{(2)}/\partial \xi_0 = -\partial V^{(0)}/\partial \xi_2 \quad \text{on } \xi_0 = \xi_1 = \cdots = 0. \end{aligned} \tag{57}$$

Clearly, in order to maintain the uniform validity of the asymptotic expansion we must eliminate the secular terms appearing in (56) and require that

$$\partial^2 V^{(0)}/\partial\xi_1^2 - 2V^{(0)} = 0 \tag{58}$$

and

$$\partial V^{(1)}/\partial\xi_1 = 0. \tag{59}$$

Making use of (49), we deduce that

$$\begin{aligned} V^{(0)} &= \frac{v(\xi_2, \cdots)}{2\sqrt{2\pi}}\exp(-\sqrt{2}\xi_1), \\ V^{(1)} &= \sum_{n=0}^{\infty}\sum_{m=1}^{\infty} a_{mn}^{(1)}(\xi_2, \cdots)U_{mn}^{(1)}(r, \theta, \xi_0), \\ V^{(2)} &= -\frac{r^2}{2}V^{(0)} + W^{(2)}(\xi_1, \xi_2, \cdots). \end{aligned} \tag{60}$$

The only other information contained in (57) is

$$\partial v/\partial\xi_2 = 0 \quad \text{on } \xi_1 = \cdots = 0. \tag{61}$$

It is perhaps worth noting that since $V^{(1)}$ depends on ξ_0 and $V^{(1)} \to 0$ as $\xi_0 \to \infty$, the expression for $V^{(1)}$ cannot contain an additive unknown function of $\xi_1, \xi_2, \cdots$ as is the case for $V^{(2)}$.

Let us now consider (42) for $V^{(3)}$ which becomes

$$\begin{aligned} \Delta V^{(3)} &= -2\frac{\partial^2 V^{(1)}}{\partial\xi_0\partial\xi_2} - 2\frac{\partial^2 V^{(0)}}{\partial\xi_1\partial\xi_2}, \\ \partial V^{(3)}/\partial r &= -V^{(1)} \quad \text{on } r = 1, \\ \frac{\partial V^{(3)}}{\partial\xi_0} &= -\frac{\partial V^{(2)}}{\partial\xi_1} - \frac{\partial V^{(1)}}{\partial\xi_2} - \frac{\partial V^{(0)}}{\partial\xi_3} \quad \text{on } \xi_0 = \xi_1 = \cdots = 0. \end{aligned} \tag{62}$$

We can immediately see that we must set

$$\partial V^{(0)}/\partial\xi_2 = 0 \tag{63}$$

to prevent a term of the form $\xi_0^2\,\partial^2 V^{(0)}/\partial\xi_1\partial\xi_2$ from entering the expression for $V^{(3)}$. As a matter of fact, it should already be apparent at this stage that the fields with even (odd) superscripts are independent of the variables with even (odd) subscripts, viz.

$$\begin{aligned} V = \frac{1}{\sqrt{\varepsilon}} &\sum_{n=0}^{\infty} \varepsilon^n V^{(2n)}(r, \xi_1, \xi_3, \cdots, \xi_{2k+1}, \cdots) \\ &+ \sum_{n=0}^{\infty} \varepsilon^n V^{(2n+1)}(r, \theta, \xi_0, \xi_2, \cdots, \xi_{2k}, \cdots); \end{aligned} \tag{64}$$

from now on we shall assume that this is the case.

Returning now to (62), we look for a solution of the form

$$V^{(3)} = \sum_{m=1}^{\infty}\sum_{n=0}^{\infty} \frac{a_{mn}^{(1)}}{\alpha_m^{(n)2} - n^2} r\frac{\partial U_{mn}^{(1)}}{\partial r} + W^{(3)}(r, \theta, \xi_0, \cdots), \tag{65}$$

where

$$\Delta W^{(3)} = \sum_{m=1}^{\infty}\sum_{n=0}^{\infty} 2\alpha_m^{(n)}\left\{\frac{\alpha_m^{(n)}}{\alpha_m^{(n)2}-n^2}a_{mn}^{(1)} + \frac{\partial a_{mn}^{(1)}}{\partial \xi_2}\right\}U_{mn}^{(1)},$$

(66)

$$\partial W^{(3)}/\partial r = 0 \quad \text{on } r = 1,$$

$$\frac{\partial W^{(3)}}{\partial \xi_0} = -\sum_{m=1}^{\infty}\sum_{n=0}^{\infty}\frac{\alpha_m^{(n)}}{\alpha_m^{(n)2}-n^2}r\frac{\partial U_{mn}^{(1)}}{\partial r}\bigg|_{\xi_0=0} - \frac{r^2}{4\pi} - \frac{\partial W^{(2)}}{\partial \xi_1}$$

$$-\sum_{m=1}^{\infty}\sum_{n=0}^{\infty}\frac{\partial a_{mn}^{(1)}}{\partial \xi_2}U_{mn}^{(1)}(r,\theta,0) - \frac{\partial V^{(0)}}{\partial \xi_3} \quad \text{on } \xi_0 = \cdots = 0.$$

For regularization purposes, we require that

$$\frac{\partial a_{mn}^{(1)}}{\partial \xi_2} + \frac{\alpha_m^{(n)}}{\alpha_m^{(n)2}-n^2}a_{mn}^{(1)} = 0, \tag{67}$$

or, using (54),

$$a_{mn}^{(1)} = b_{mn}^{(1)}(\xi_4,\cdots)\exp\left(-\frac{\alpha_m^{(n)}}{\alpha_m^{(n)2}-n^2}\xi_2\right), \tag{68}$$

where

$$b_{mn}^{(n)}(0,0,\cdots) = 1.$$

The evaluation of $W^{(3)}$ has to await the determination of the dependence of $V^{(0)}$ on ξ_3 and that of $W^{(2)}$ on ξ_1. However, by averaging the boundary condition on $\xi_0 = \xi_1 = \cdots = 0$ over a cross section we get

$$0 = -2\pi\sum_{m=1}^{\infty}\frac{1}{a_{m0}}\int_0^1 r^2\frac{\partial U_{m0}^{(1)}}{\partial r}dr - \frac{1}{8} - \pi\frac{\partial W^{(2)}}{\partial \xi_1} - \pi\frac{\partial V^{(0)}}{\partial \xi_3},$$

i.e.,

$$\frac{\partial W^{(2)}}{\partial \xi_1} + \frac{\partial V^{(0)}}{\partial \xi_3} = -\frac{1}{8\pi} - \frac{1}{\pi}\sum_{m=1}^{\infty}\frac{J_0(\alpha_m^{(0)}R)}{\alpha_m^{(0)2}J_0(\alpha_m^{(0)})} \quad \text{on } \xi_1 = \cdots = 0. \tag{69}$$

Let us now turn to the boundary value problem for $V^{(4)}$, viz.

(70)

$$\Delta V^{(4)} = -\frac{\partial^2 V^{(2)}}{\partial \xi_1^2} - 2\frac{\partial^2 V^{(0)}}{\partial \xi_1 \partial \xi_3},$$

$$\partial V^{(4)}/\partial r = -V^{(2)} \quad \text{on } r = 1,$$

$$V^{(4)} \to 0 \quad \text{as } \xi_1 \to \infty;$$

the boundary condition on $\xi_0 = \xi_1 = \cdots = 0$ is identically satisfied on account of (64). We now look for a solution of the form

$$V^{(4)} = \frac{r^4}{16}V^{(0)} + r^2\left(\frac{V^{(0)}}{8} - \frac{W^{(2)}}{2}\right) + W^{(4)}; \tag{71}$$

then

(72)

$$\Delta W^{(4)} = -\frac{\partial^2 W^{(2)}}{\partial \xi_1^2} + 2\dot{W}^{(2)} + \frac{1}{\pi}\frac{\partial v}{\partial \xi_3}e^{-\sqrt{2}\xi_1} - \frac{v}{4\sqrt{2}\pi}e^{-\sqrt{2}\xi_1},$$

$$\partial W^{(4)}/\partial r = 0,$$

$$W^{(4)} \to 0 \quad \text{as } \xi_1 \to \infty.$$

By the usual arguments we deduce that

$$\frac{\partial^2 W^{(2)}}{\partial \xi_1^2} - 2W^{(2)} = \frac{e^{-\sqrt{2}\xi_1}}{\pi}\left\{\frac{\partial v}{\partial \xi_3} - \frac{v}{4\sqrt{2}}\right\}. \tag{73}$$

In turn, to eliminate secularities in $W^{(2)}$ we must set

$$\frac{\partial v}{\partial \xi_3} - \frac{v}{4\sqrt{2}} = 0, \tag{74}$$

which, on account of (49), implies that

$$v = \mu(\xi_5, \cdots)\exp\left(\frac{\sqrt{2}}{8}\xi_3\right), \tag{75}$$

where

$$\mu(0, 0, \cdots) = 1. \tag{76}$$

Finally, solving (73) together with (69), we get

$$W^{(2)} = \left\{\frac{3}{16\pi\sqrt{2}} + \frac{1}{\sqrt{2}\pi}\sum_{m=1}^{\infty}\frac{J_0(\alpha_m^{(0)}R)}{\alpha_m^{(0)2}J_0(\alpha_m^{(0)})}\right\}e^{-\sqrt{2}\xi_1}\omega(\xi_3, \cdots), \tag{77}$$

where

$$\omega(0, 0, \cdots) = 1. \tag{78}$$

In summary, if we truncate the series expansion after the first two terms and let x range from $-\infty$ to $+\infty$, we get

$$\begin{aligned} V = {} & \frac{1}{2\pi\sqrt{2\varepsilon}}\exp\left\{-\left(\sqrt{2\varepsilon} - \varepsilon\frac{\sqrt{2\varepsilon}}{8}\right)|x|\right\} \\ & + \sum_{m=1}^{\infty}\frac{J_0(\alpha_m^{(0)}R)J_0(\alpha_m^{(0)}r)}{2\pi\alpha_m^{(0)}[J_0(\alpha_m^{(0)})]^2}\exp\left\{-\left(\alpha_m^{(0)} + \frac{\varepsilon}{\alpha_m^{(0)}}\right)|x|\right\} \\ & + \sum_{m=1}^{\infty}\sum_{n=1}^{\infty}\frac{\alpha_m^{(n)}J_n(\alpha_m^{(n)}R)J_n(\alpha_m^{(n)}r)}{\pi\{\alpha_m^{(n)2} - n^2\}[J_n(\alpha_m^{(n)})]^2}\cos n\theta\exp\left\{-\alpha_m^{(n)}\left\{1 + \frac{\varepsilon}{\alpha_m^{(n)2} - n^2}\right\}|x|\right\} \\ & + O(\sqrt{\varepsilon}). \end{aligned} \tag{79}$$

From the point of view of the expansion procedure, it is interesting to note that the first series in the representation (64) coincides with the far field that would be obtained by an inner and outer expansion. In fact, one can show that the far field, say $V^{(f)}$, is of the form

$$V^{(f)} = \left[\sum_{n=0}^{\infty}\varepsilon^n P_{2n}(r)\right]\exp[-l(\varepsilon)|x|], \tag{80}$$

where $P_{2n}(r)$ is a polynomial of degree $2n$, and $l(\varepsilon)$ is a coefficient dependent on ε, viz.

$$l(\varepsilon) \cong \sqrt{2}\left(\varepsilon - \frac{\varepsilon^{3/2}}{8}\right) + O(\varepsilon^{5/2}). \tag{81}$$

The far field is independent of θ but it displays a dependence on r, the distance of the source from the axis (cf. (77)).

It is not possible to give a simple physical interpretation to each $V^{(n)}$. This is due to the fact that the various order fields are intricately coupled, as can be seen from the boundary conditions at $\xi_0 = \xi_1 = \cdots = 0$. However, if we restrict our attention to $V^{(0)}$ and $V^{(1)}$, we can see that the first term represents the potential in a transmission line, while the second is the potential due to a point source of current lying on a transverse, uniform disc sink in an insulated cylinder. Strictly speaking, this interpretation of $V^{(1)}$ is correct provided that its dependence on ε is neglected. A similar restriction is not necessary for $V^{(0)}$; in fact, the entire ε-dependence of $V^{(0)}$ can be taken into account by means of the parameter $l(\varepsilon)$ introduced in (80), which can be looked upon as a "loss" coefficient characteristic of the nerve cell. In previous physiological studies of the transmission line model, $l(\varepsilon)$ was approximated by the first term in the series expansion (81).

Finally, we should mention that the procedure used for a cylindrical cell can also be used for an infinitely long axially symmetric cell of variable cross section. The case of greatest interest is that for which the "wavelength" of the corrugations is comparable to $1/\sqrt{\varepsilon}$, i.e., the equation of the membrane is of the form

$$r = f(\sqrt{\varepsilon}x). \tag{82}$$

Because of the slowly varying cross-sectional area of the cell, the variable

$$X = \frac{1}{\sqrt{\varepsilon}} \int_0^{\xi} \frac{d\xi_0}{\rho(\xi_0)} \tag{83}$$

must be introduced. Otherwise, the basic procedure for deriving the potential is unchanged. In particular, the $O(1/\sqrt{\varepsilon}\,)$ field equation becomes

$$\frac{d}{d\xi_1}\left[f(\xi_1)\frac{dV^{(0)}}{d\xi_1} \right] - 2V^{(0)} = -\frac{1}{\pi}\delta(\xi_1). \tag{84}$$

5. Concluding remarks. In § 3 and § 4 we have examined the problem for the finite and infinite cells. Mathematically, the results are rather different. Continuing to denote the area of the surface membrane by A, we can look upon these results as representations of the solution in different regions of the ε-A space. An investigation of the range of validity of the finite and infinite cell representations reveals that they are valid when $A \ll 1/\sqrt{\varepsilon}$ and $A \gg 1/\sqrt{\varepsilon}$, respectively.

Finally, the rather surprising result derived in § 3, regarding the uniform $O(1)$ current flux across the membrane, might be better understood by considering a transient problem. Since the transient problem for the electric current is rather delicate, our discussion will be given in terms of a simpler heat conduction problem with a steady state analogous to that of the electrostatic problem under investigation. Denoting the temperature field by T and time by t, we consider the following transient problem:

$$\begin{aligned} -T_t + \nabla^2 T &= -\delta(\mathbf{r} - \mathbf{R}) \quad \text{in } D, \\ \partial T/\partial n + \varepsilon T &= 0 \quad \text{on } \Gamma, \\ T &= 0 \quad \text{at } t = 0. \end{aligned} \tag{85}$$

We shall omit all calculations, and simply write down the first few terms of the solution which is *uniformly* valid in t, viz.

$$T = +\frac{1}{\varepsilon}T^{(0)} + T^{(1)} + O(\varepsilon), \tag{86}$$

where

$$T^{(0)} = +\frac{1}{A}\left\{1 - \exp\left(-\frac{A}{K}\tau\right)\right\}, \tag{87}$$

$\tau = \varepsilon t$ and K is the volume of the region. The transient problem reveals that over a rather long time, viz $t \sim 1/\varepsilon$, for all intents and purposes heat does not flow across the surface. As a result the temperature in D builds up and becomes *uniform.* When the temperature reaches a magnitude of $O(1/\varepsilon)$ (i.e., for $t \geqq 1/\varepsilon$), heat starts to flow, and the heat flux is roughly uniform over the entire boundary.

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