

The Time-Dependent Potential in a Spherical Cell Using Matched Asymptotic Expansions

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Summary

A derivation is given of the equation and boundary condition for determining the electric potential in a cell. The potential is calculated for all time, everywhere inside a spherical cell and in the external bathing medium for the case of a point source of current inside the cell turned on abruptly at $t = 0$. The problem is solved by the singular perturbation technique of matching a short-time (inner) and a long time (outer) asymptotic expansion. The model for the cell consists of a sphere of radius a with an internal medium of conductivity σ_i , surrounded by a membrane of thickness δ , conductivity σ_m and surface capacity C_m , bathed in an external medium of conductivity σ_o . The solution is discussed for the physiologically interesting case of $\epsilon = \sigma_m a / \sigma_i$, $\delta \ll 1$, when the effective internal resistance is small compared to the effective membrane resistance. In the most important physiological case, for times much longer than $C_m a / \sigma_i$, simple analytic expressions are obtained for the inside potential, the outside potential and the transmembrane potential. The leading term in the expansion, the isopotential cell interior, is obtained for arbitrary finite-cell shape.

Introduction

Many experiments to determine the natural electrical activity and characteristics of cells and tissues involve the application of current to the inside of a cell and the recording of potential at nearby points also inside the cell. The current is usually applied through one microelectrode and the voltage recorded with another. In order to relate the observed potential to the properties of the cell — particularly to the resistance and capacitance of the cell membrane and the resistivity of the cell interior — an electrical model of the cell must be used. We consider here the model appropriate for a finite cell (one which is roughly spherical in shape) and analyze the electrical properties expected if a step function of current is applied to the cell. Our analysis differs from previous work (Rall, 1969; Pickard, 1968; Eisenberg and Johnson, 1970; Eisenberg and Engel, 1970; Hellerstein, 1968; Barcion, Cole and Eisenberg, 1971) in that it solves the complete problem including external resistance and time dependence of the voltage; the solution is also presented in rather compact form, so that it is easy to compare with experimental results.

Most importantly, we solve the problem using the techniques of singular perturbation theory (Murray, 1974; Cole, 1968; Eckhaus, 1973; Nayfeh, 1973), in particular, the technique of matched asymptotic expansions. It has been argued (Peskoff and Eisenberg, 1972) that this technique is particularly well suited to biological problems which contain a small parameter, because it emphasizes the physical meaning of the problem, and the way the solution to the problem depends on the biological parameters (e.g., the membrane and internal resistance and the membrane capacitance). Furthermore, the solutions generated by this technique are often in neat form, easy to compute and compare with experimental results. Finally, many of the properties of the solution can be deduced without detailed assumptions concerning the geometry. For instance, in our case the general properties of the solution can be predicted for cells of irregular shape provided all the dimensions of the cell are about the same (that is, the cell must not be too long).

The penalty paid for these advantages of singular perturbation is the length of the analysis; a large number of relatively simple problems must be solved instead of a single complex problem. We hope the reader will be patient with the length of the analysis and agree that the physical insight afforded by singular perturbation theory warrants it. The most relevant results for usual experimental situations are summarized in equations (73 a), (73 b) and (75). These show that the potential inside the cell (with respect to a distant external electrode) consists of two components. One component builds up slowly with time, is independent of position and of the resistance of the bathing solution, and corresponds to the usual assumption of an isopotential cell. The second, established quickly, is a local potential which near the current microelectrode is greater than or comparable to the first component, but a short distance from the microelectrode is small. Only this second component depends on the resistance of the bathing solution. At long times, and at distances far from the current microelectrode the isopotential term is dominant. The potential outside the cell follows a simple inverse distance law and at physiological times shows negligible dependence on angular position. The transmembrane potential has properties similar to the internal potential, except it is missing the component caused by the extracellular resistance. Thus, the transmembrane potential does not have a significant dependence on the extracellular resistance under physiological conditions.

The following paper (Peskoff and Ramirez, 1975) extends this analysis to include the case where the sink of current outside the cell is not at infinity but is at a finite distance from the cell. The solution is obtained by exact analysis and is shown to reduce to the perturbation solution presented here for the range of electrical parameters found in biological cells.

A report (Peskoff, Eisenberg and Cole, 1972)¹ is available which presents all the details of the derivation, including the solution of the partial differential equations and the summation of the series of Legendre polynomials.

¹ Available from Reports Group, School of Engineering and Applied Science, University of California, Los Angeles, CA 90024, U.S.A.

I. Cell Model

We consider the potential everywhere as a function of time for a point source of current turned on abruptly at $t=0$, somewhere in the interior of a cell. The model taken for the cell is a sphere of radius a , enclosed by a thin membrane of thickness δ , surrounded by an external conducting medium. We also obtain some results for a cell of arbitrary shape in which all dimensions are of comparable length. The current is collected by an electrode in the external medium. The geometry and coordinate system are shown in Fig. 1.

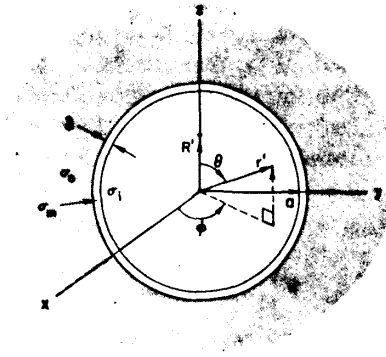


Fig. 1. Coordinate system for spherical cell

The conductivities of the cell interior, membrane and outside medium are σ_i , σ_m and σ_o (mhos/cm), respectively. The membrane thickness δ and conductivity σ_m are considered to approach zero individually in such a way that the ratio $\delta/\sigma_m = R_m$, the surface resistivity (ohm-cm²), remains finite. For a typical cell used in physiological experiments, $\delta = 10^{-6}$ cm and $a = 10^{-3}$ to 5×10^{-2} cm, so that the limit $\delta \rightarrow 0$ will lead to no appreciable error on the scale of the cell. The membrane is also assumed to have a capacity per unit area C_m (~ 1 μ farad/cm²).

The point source of current is a mathematical idealization of an electrolyte-filled tapered glass pipette with a tip diameter much smaller than the dimensions of a cell. In many cases, the electrical resistance of the pipette is large compared to the effective resistance across the cell interior and membrane, so that the source is naturally a current source. In other cases, the source can be made a current source by external electronics.

Typical values for σ_m and σ_i are 3×10^{-10} mhos/cm and 7×10^{-3} mhos/cm, respectively. Hence the quantity

$$\varepsilon = \frac{\sigma_m}{\delta} \cdot \frac{a}{\sigma_i} \quad (1)$$

is small ($< 10^{-3}$) and although a solution valid for arbitrary ε can be obtained (Peskoff, Eisenberg and Cole, 1972; Peskoff and Ramirez, 1975), we discuss in detail the physiologically interesting case of small ε , in which simpler analytic expressions are obtained.

We assume a point source of current of strength 4π amperes, at a position $\vec{r}' = \vec{R}'_1$ inside the cell, where \vec{r}' is the position vector for the observation point, and primes denote quantities measured in physical units. Unprimed quantities will be in nondimensional units, defined below. In addition, there is a current sink of equal magnitude at a point $\vec{r}' = \vec{R}'_2$ outside the cell. The equation for continuity of current is then

$$\nabla' \cdot \vec{J}' + \frac{\partial \rho'}{\partial t'} = 4\pi [\delta(\vec{r}' - \vec{R}'_1) - \delta(\vec{r}' - \vec{R}'_2)] u(t'), \quad (2)$$

where $\delta(\vec{r}' - \vec{R}'_i)$ is a Dirac delta function, $u(t')$ is a unit step function [$u(t') = 0$ for $t' < 0$ and $u(t') = 1$ for $t' > 0$] indicating that the source and sink are switched on abruptly at $t' = 0$, \vec{J}' is the current density in amps/m², and ρ' is the charge density in coulombs/m². According to (2) the 4π amperes flowing into the source electrode divides between current flowing into the cell from the electrode and the charge accumulation at the electrode tip.

The potential V' is assumed to be related to the current density by Ohm's law,

$$\vec{J}' = -\sigma \nabla' V', \quad (3)$$

where σ is σ_i , σ_m or σ_o in the respective regions. From Gauss' law, the potential may be related to the charge density by

$$\nabla'^2 V' = -\frac{\rho'}{\kappa \epsilon_0}, \quad (4)$$

where ϵ_0 is the permittivity of free space, κ is the dielectric constant and $\kappa = \kappa_i$, κ_m or κ_o inside the cell, within the membrane, and outside the cell, respectively. Equations (3) and (4) assume that the electric field is minus the gradient of a potential, and hence ignore magnetic field effects, which are negligible (Pickard, 1968). In addition, the simple proportionality (3) between current and electric field leads to charge neutrality and hence ignores effects on a scale comparable to a Debye length ($\sim 4 \text{ \AA}$).

Using (3) and (4) to eliminate \vec{J}' and ρ' from (2), we obtain

$$\left. \begin{aligned} \left(1 + \frac{\kappa_i \epsilon_0}{\sigma_i} \frac{\partial}{\partial t'}\right) \nabla'^2 V' &= -\frac{4\pi}{\sigma_i} \delta(\vec{r}' - \vec{R}'_1) u(t'), \text{ inside cell,} \\ \left(1 + \frac{\kappa_m \epsilon_0}{\sigma_m} \frac{\partial}{\partial t'}\right) \nabla'^2 V' &= 0, \text{ in membrane,} \\ \left(1 + \frac{\kappa_o \epsilon_0}{\sigma_o} \frac{\partial}{\partial t'}\right) \nabla'^2 V' &= \frac{4\pi}{\sigma_o} \delta(\vec{r}' - \vec{R}'_2) u(t'), \text{ outside cell.} \end{aligned} \right\} \quad (5)$$

These first-order linear differential equations in t' may be integrated to obtain

$$\left. \begin{aligned} \nabla'^2 V' &= -\frac{4\pi}{\sigma_i} (1 - e^{-(\sigma_i/\kappa_i \varepsilon_0)t'}) \delta(\vec{r}' - \vec{R}'_1) u(t'), \text{ inside cell,} \\ \nabla'^2 V' &= 0, \text{ in membrane,} \\ \nabla'^2 V' &= \frac{4\pi}{\sigma_o} (1 - e^{-(\sigma_o/\kappa_o \varepsilon_0)t'}) \delta(\vec{r}' - \vec{R}'_2) u(t'), \text{ outside cell.} \end{aligned} \right\} \quad (6)$$

The *effective* point source and point sink of current and charge increase exponentially in time to their final value imposed by the external current source. This occurs because during a short transient period after the source is switched on at $t'=0$, charge accumulates at the tips of the microelectrodes. Taking $\kappa_i=80$, the time constant for this transient is found to be 1 nanosecond inside the cell, and a comparable value outside. Consequently, for times much longer than a nanosecond the transient is over and we may ignore the exponentials in (6), so that we have

$$\nabla'^2 V' = -\left[\frac{4\pi}{\sigma_i} \delta(\vec{r}' - \vec{R}'_1) - \frac{4\pi}{\sigma_o} \delta(\vec{r}' - \vec{R}'_2) \right] u(t'). \quad (7)$$

We now derive the boundary condition appropriate for our membrane model. According to (4) and (6) the volume charge density is zero everywhere within the interior of the cell, the interior of the membrane, and outside the cell, except for the infinite charge density just at the source and sink. At the interface between the interior of the cell and the membrane — and at the interface of the exterior solution and the membrane — there is free charge. Letting q'^- and q'^+ be the charge per unit area on the inner and outer surfaces of the membrane, respectively, and J'_m be the component of current density within the membrane, normal to the membrane surfaces, we have from conservation of charge,

$$\begin{aligned} \frac{\partial q'^-}{\partial t'} &= -\sigma_i \frac{\partial V'^-}{\partial n'} - J'_m, \\ \frac{\partial q'^+}{\partial t'} &= \sigma_o \frac{\partial V'^+}{\partial n'} + J'_m. \end{aligned} \quad (8)$$

We assume that the membrane is thin ($\delta \ll a$) and according to (6), no volume charge density exists in the interior of the membrane. The electric field within the membrane is then constant, and Ohm's law leads to

$$J'_m = -\frac{\sigma_m}{\delta} (V'^+ - V'^-), \quad (9)$$

where (+) and (−) superscripts denote quantities in the extracellular medium immediately outside the membrane, and in the intracellular medium immediately inside the membrane. Conservation of charge (8) then becomes

$$\begin{aligned} \frac{\partial q'^-}{\partial t'} &= -\sigma_i \frac{\partial V'^-}{\partial n'} + \frac{\sigma_m}{\delta} (V'^+ - V'^-), \\ \frac{\partial q'^+}{\partial t'} &= \sigma_o \frac{\partial V'^+}{\partial n'} - \frac{\sigma_m}{\delta} (V'^+ - V'^-). \end{aligned} \quad (10)$$

Using Gauss' law we can obtain another pair of equations relating the normal derivatives of the potential to the charge on each membrane surface:

$$\begin{aligned}\frac{q'^+}{\epsilon_0} &= -\kappa_o \frac{\partial V'^+}{\partial n'} + \kappa_m \frac{V'^+ - V'^-}{\delta}, \\ \frac{q'^-}{\epsilon_0} &= -\kappa_m \frac{V'^+ - V'^-}{\delta} + \kappa_i \frac{\partial V'^-}{\partial n'}.\end{aligned}\quad (11)$$

Taking the time derivative of this pair of equations we obtain

$$\begin{aligned}\frac{1}{\epsilon_0} \frac{\partial q'^+}{\partial t'} &= -\kappa_o \frac{\partial^2 V'^+}{\partial t' \partial n'} + \frac{\kappa_m}{\delta} \frac{\partial}{\partial t'} (V'^+ - V'^-), \\ \frac{1}{\epsilon_0} \frac{\partial q'^-}{\partial t'} &= -\frac{\kappa_m}{\delta} \frac{\partial}{\partial t'} (V'^+ - V'^-) + \kappa_i \frac{\partial^2 V'^-}{\partial t' \partial n'}.\end{aligned}\quad (12)$$

Equating these two equations to the two charge conservation equations leads to two equations relating the potential on either side of the membrane,

$$\begin{aligned}\left(\sigma_i + \kappa_i \epsilon_0 \frac{\partial}{\partial t'}\right) \frac{\partial V'^-}{\partial n'} &= \left(\sigma_m + \kappa_m \epsilon_0 \frac{\partial}{\partial t'}\right) \frac{V'^+ - V'^-}{\delta}, \\ \left(\sigma_o + \kappa_o \epsilon_0 \frac{\partial}{\partial t'}\right) \frac{\partial V'^+}{\partial n'} &= \left(\sigma_m + \kappa_m \epsilon_0 \frac{\partial}{\partial t'}\right) \frac{V'^+ - V'^-}{\delta}.\end{aligned}\quad (13)$$

The time derivatives on the left-hand side of these two equations, as was found for the corresponding terms in (5), lead to transients which occur on a nanosecond time scale, and will therefore be neglected. The derivatives on the right-hand side correspond to a much longer time constant. During the rapid transient period when charge is building up at the tip of the source (sink) electrode a charge of equal magnitude and opposite sign builds up at the inner (outer) surface of the membrane. For our purposes, henceforth, we will consider this to occur instantaneously and at $t'=0+$ this transient is over. Making the change of variables

$$\begin{aligned}r &= \frac{r'}{a}, \\ V &= a \sigma_i V', \\ t &= (\sigma_m / \kappa_m \epsilon_0) t',\end{aligned}$$

and letting $\alpha = \sigma_i / \sigma_o$, Poisson's equation, (7), becomes

$$\nabla^2 V = -4\pi [\delta (\tilde{r} - \tilde{R}_1) - \alpha \delta (\tilde{r} - \tilde{R}_2)] u(t) \quad (14)$$

and, the boundary condition (13) becomes

$$\frac{\partial V^-}{\partial n} = \frac{1}{\alpha} \frac{\partial V^+}{\partial n} = \epsilon \left[V^+ - V^- + \frac{\partial V^+}{\partial t} - \frac{\partial V^-}{\partial t} \right], \quad (15)$$

or, in terms of physical variables

$$\sigma_i \frac{\partial V'^-}{\partial n'} = \sigma_o \frac{\partial V'^+}{\partial n'} = \frac{\sigma_m}{\delta} [V'^+ - V'^-] + C_m \left[\frac{\partial V'^+}{\partial t'} - \frac{\partial V'^-}{\partial t'} \right]. \quad (15')$$

where $C_m = \kappa_m \varepsilon_0 / \delta$ is the capacitance per unit area. The physical interpretation of this boundary condition is that the normal component of current density is continuous across the membrane and is equal to the sum of the resistive and capacitive currents crossing the membrane. We shall call this the membrane boundary condition since it arises in many problems involving membranes.

In this paper we will consider the case for which the current sink is a long distance away from the cell in the extracellular medium. We therefore take $R_2 = \infty$ and let $R_1 = R$ so that (14) becomes

$$\nabla^2 V = -4 \pi \delta (\vec{r} - \vec{R}) u(t). \quad (16)$$

In the following paper (Peskoff and Ramirez, 1975), the solution is obtained for a sink at an arbitrary location outside the cell.

There is an arbitrary additive constant in the potential $V(r, t)$ which we choose so that the potential is zero at $|\vec{r}| = \infty$. This implies the boundary condition at infinity,

$$V(\vec{r}, t) \rightarrow 0 \text{ as } |\vec{r}| \rightarrow \infty. \quad (17)$$

We have assumed that there are no sources for $t < 0$, i.e., the right-hand side of (16) is zero for $t < 0$. Consequently, at $t = 0^-$, before the source is switched on, $V = 0$ everywhere. There is a finite jump in $\partial V^- / \partial n$ between $t = 0^-$ and $t = 0^+$ and from (15) we see that there must be a corresponding finite jump in $\partial V^+ / \partial t - \partial V^- / \partial t$, but $V^+ - V^-$ must be continuous. Hence there is no potential difference across the membrane at $t = 0^+$, and we have the initial condition,

$$V^+(\vec{r}, 0^+) = V^-(\vec{r}, 0^+). \quad (18)$$

In Section 2, the problem defined by (15), (16), (17) and (18) is solved using the singular perturbation technique of matched asymptotic expansions.

II. Singular Perturbation Analysis Using Matched Asymptotic Expansions

There are two approaches that may be used to solve the problem specified by (15)–(18) in the case of physiological interest when $\varepsilon \rightarrow 0$ and $t/\varepsilon \rightarrow \infty$. First, we may find the exact solution to (15)–(18) for arbitrary ε and t and then study the limiting behaviour as $\varepsilon \rightarrow 0$ and $t/\varepsilon \rightarrow \infty$. The exact solution is derived in Peskoff, Eisenberg and Cole, 1972, and Peskoff and Ramirez, 1975, for a spherical cell and its asymptotic expansion in the $\varepsilon \rightarrow 0$ limit is obtained.

A second approach, which is taken here, is to solve the problem by singular perturbation theory. Rather than considering the limiting behaviour of the solution, we may apply a limiting process directly to (15)–(18) and bypass the exact solution, going directly to the solution in the form of an asymptotic expansion. This procedure has a number of advantages. The equations to be

solved are sometimes simpler (although there are more of them). In the case of the spherical cell under consideration, it is possible to obtain the exact solution to the problem in fairly simple form; in more complicated problems this may not be possible. For example, if we allow the cell to deviate from a spherical shape, we cannot directly see what changes will occur in the exact solution. We will see, however, that using perturbation theory, some knowledge of the solution may be obtained without any specification of the shape of the cell. The leading term in the asymptotic expansion is independent of the shape of the cell. We also will see that it is possible to gain greater insight into the physical process corresponding to each term from the boundary value problem which leads directly to the corresponding term.

A. Long-Time Expansion

First, we will obtain the solution valid for long times, i.e., $t \gg \varepsilon$. The initial condition (18) does not apply since $t=0$ is outside this period. We will therefore be left with some unknown constants in the solution which can only be evaluated by requiring that the long-time solution match to a short-time solution which does satisfy the initial condition.

We expand the potential in a series of the form

$$V(\vec{r}, t, \varepsilon) = \zeta_0(\varepsilon) V_0(\vec{r}, t) + \zeta_1(\varepsilon) V_1(\vec{r}, t) + \dots, \quad (19)$$

where $\zeta_{n+1}(\varepsilon)/\zeta_n(\varepsilon) \rightarrow 0$ as $\varepsilon \rightarrow 0$, and V_0, V_1, \dots are each independent of ε . Consequently, for small ε , each term is smaller than the preceding one. Equation (19) is an asymptotic expansion for $V(\vec{r}, t, \varepsilon)$ in the sense that each successive term improves the approximation, in the limit $\varepsilon \rightarrow 0$. Substituting the expansion (19) in (16) yields,

$$\nabla^2 V = \zeta_0(\varepsilon) \nabla^2 V_0 + \zeta_1(\varepsilon) \nabla^2 V_1 + \dots = -4\pi \delta(\vec{r} - \vec{R}). \quad (20)$$

Substituting (19) in the boundary condition (15), and grouping terms of successively decreasing magnitude yields the following set of boundary conditions for V_0, V_1 , and V_2 ,

$$\begin{aligned} \frac{\partial V_0^-}{\partial n} &= 0 = \frac{1}{\alpha} \frac{\partial V_0^+}{\partial n}, \\ \frac{\partial V_1^-}{\partial n} &= \frac{\varepsilon \zeta_0(\varepsilon)}{\zeta_1(\varepsilon)} \left(V_0^+ - V_0^- + \frac{\partial V_0^+}{\partial t} - \frac{\partial V_0^-}{\partial t} \right) = \frac{1}{\alpha} \frac{\partial V_1^+}{\partial n}, \\ \frac{\partial V_2^-}{\partial n} &= \frac{\varepsilon \zeta_1(\varepsilon)}{\zeta_2(\varepsilon)} \left(V_1^+ - V_1^- + \frac{\partial V_1^+}{\partial t} - \frac{\partial V_1^-}{\partial t} \right) = \frac{1}{\alpha} \frac{\partial V_2^+}{\partial n}. \end{aligned} \quad (21)$$

So that all terms in each equation in (21) have the same dependence on ε , we require that

$$\frac{\zeta_{n+1}(\varepsilon)}{\zeta_n(\varepsilon)} = \varepsilon. \quad (22)$$

The boundary condition for V_0 in (21) implies that no current crosses the membrane. Consequently there can be no current source in the equation for V_0 . The conclusion is that the second term in the expansion (20) of $\nabla^2 V$, rather than the first, must have the same dependence on ε as the current source, the delta function. This requires that $\zeta_1(\varepsilon) = 1$ and hence, by (22), $\zeta_0(\varepsilon) = \varepsilon^{-1}$. We therefore obtain for the expansion of the potential

$$V(\vec{r}, t; \varepsilon) = \frac{1}{\varepsilon} V_0(\vec{r}, t) + V_1(\vec{r}, t) + \varepsilon V_2(\vec{r}, t) + \dots, \tag{23}$$

and for the first three members of the sequence of problems

$$\left. \begin{aligned} \nabla^2 V_0 &= 0, \\ \frac{\partial V_0^-}{\partial n} &= 0 = \frac{\partial V_0^+}{\partial n}, \\ V_0 &\rightarrow 0 \text{ as } |\vec{r}| \rightarrow \infty, \end{aligned} \right\} \tag{24}$$

$$\left. \begin{aligned} \nabla^2 V_1 &= -4\pi \delta(\vec{r} - \vec{R}), \\ \frac{\partial V_1^-}{\partial n} &= V_0^+ - V_0^- + \frac{\partial V_0^+}{\partial t} - \frac{\partial V_0^-}{\partial t} = \frac{1}{\alpha} \frac{\partial V_1^+}{\partial n}, \\ V_1 &\rightarrow 0 \text{ as } |\vec{r}| \rightarrow \infty, \end{aligned} \right\} \tag{25}$$

$$\left. \begin{aligned} \nabla^2 V_2 &= 0, \\ \frac{\partial V_2^-}{\partial n} &= V_1^+ - V_1^- + \frac{\partial V_1^+}{\partial t} - \frac{\partial V_1^-}{\partial t} = \frac{1}{\alpha} \frac{\partial V_2^+}{\partial n}, \\ V_2 &\rightarrow 0 \text{ as } |\vec{r}| \rightarrow \infty. \end{aligned} \right\} \tag{26}$$

We now proceed to obtain the solutions to these three problems. The solution to the lowest-order problem (24) is:

$$V_0(\vec{r}, t) = \begin{cases} f_0(t), & \text{inside,} \\ 0, & \text{outside.} \end{cases} \tag{27}$$

There is no dependence on \vec{r} in the inside or outside solution and the outside potential must be zero to satisfy the boundary condition at $|\vec{r}| = \infty$. To determine the functional form of $f_0(t)$ it is necessary to go to the problem for V_1 . Performing a volume integral of the Laplacian in (25) over the volume enclosed by the surface S just inside the membrane,

$$\iiint \nabla^2 V_1 d^3 r = -4\pi = \iint \frac{\partial V_1}{\partial n} dS. \tag{28}$$

Using the boundary condition of (25) for $\frac{\partial V_1}{\partial n}$, and the result (27) for V_0 , (28) leads to

$$4\pi = \iint \left(f_0(t) + \frac{\partial f_0}{\partial t} \right) dS = A \left(f_0(t) + \frac{\partial f_0}{\partial t} \right), \tag{29}$$

where A is the surface area of the membrane. Solving the first order linear differential equation (29) for $f_0(t)$, we obtain

$$V_0(\vec{r}, t) = \begin{cases} \frac{4\pi}{A} + a_0 e^{-t}, & \text{inside,} \\ 0, & \text{outside.} \end{cases}$$

The constant a_0 can be determined by requiring the initial condition (18) to be satisfied, leading to

$$V_0(\vec{r}, t) = \frac{4\pi}{A} \begin{cases} 1 - e^{-t}, & \text{inside,} \\ 0, & \text{outside.} \end{cases} \quad (30)$$

Although we are able to satisfy the initial condition for the leading term in the expansion, V_0 , we will not be able to do so for higher order terms. In other words, while the first term in the expansion is valid for all t , we will see that the entire expansion (23) is only valid for $t \gg \varepsilon$. Note that (30) and (23) demonstrate that the cell interior builds up to a large potential $V = 4\pi/\varepsilon A$, which is just the reciprocal of the small parameter ε , times the total current of 4π amperes, divided by the area of the membrane. *This result is obtained independent of the shape of the cell.*

In physical (primed) units, this potential is $V' = V/\sigma_i a(\delta/\sigma_m)$, the potential necessary to drive a current density $4\pi/A'$ across a surface of surface resistivity δ/σ_m . There is no current crossing the membrane in the ε^{-1} problem of (24) but the voltage jump $V_0 = 4\pi/\varepsilon A$ across the membrane in the ε^{-1} problem is just the potential needed to drive the current in the ε^0 problem across the membrane.

Substituting the potential V_0 from (30) in (25) yields

$$\left. \begin{aligned} \nabla^2 V_1 &= -4\pi\delta(\vec{r} - \vec{R}), \\ \frac{\partial V_1^-}{\partial n} &= -\frac{4\pi}{A} = \frac{1}{\alpha} \frac{\partial V_1^+}{\partial n}, \\ V_1 &\rightarrow 0 \text{ as } |\vec{r}| \rightarrow \infty \end{aligned} \right\} \quad (31)$$

for the ε^0 problem.

By performing a volume integral of $\nabla^2 V_2$ and using the $\partial V_2^-/\partial n$ boundary condition in (26) we obtain

$$\begin{aligned} \iiint \nabla^2 V_2 d^3r &= 0 = \iint \frac{\partial V_2^-}{\partial n} dS \\ &= \iint \left(V_1^+ - V_1^- + \frac{\partial V_1^+}{\partial t} - \frac{\partial V_1^-}{\partial t} \right) dS \end{aligned} \quad (32)$$

This is an integral constraint on V_1 , which combined with (31) determines V_1 .

The potential $V_1(\vec{r}, t)$ may be written as the sum of two functions

$$V_1(\vec{r}, t) = G(\vec{r}) + f_1(\vec{r}, t), \tag{33}$$

where G is a time-independent Green's function satisfying

$$\left. \begin{aligned} \nabla^2 G &= -4\pi \delta(\vec{r} - \vec{R}), \\ \frac{\partial G^-}{\partial n} &= -\frac{4\pi}{A} = \frac{1}{\alpha} \frac{\partial G^+}{\partial n}, \\ \iint (G^+ - G^-) dS &= 0, \\ G &\rightarrow 0 \text{ as } |\vec{r}| \rightarrow \infty. \end{aligned} \right\} \tag{34}$$

G is the steady state solution of (31) and (32). With the definition of G given by (33) and (34) we find, by subtracting G from V_1 in (31) and (32), that f_1 must be the solution of

$$\left. \begin{aligned} \nabla^2 f_1 &= 0, \\ \frac{\partial f_1^-}{\partial n} &= 0 = \frac{1}{\alpha} \frac{\partial f_1^+}{\partial n}, \\ f_1 &\rightarrow 0, \text{ as } |\vec{r}| \rightarrow \infty, \\ \iint \left(f_1^+ - f_1^- + \frac{\partial f_1^+}{\partial t} - \frac{\partial f_1^-}{\partial t} \right) dS &= 0. \end{aligned} \right\} \tag{35}$$

This problem (35) is identical to that of (24) and (29) for V_0 , except that the surface integral in (35) is zero rather than 4π . The problem (34) has a physical interpretation. It represents the potential of a point source of current inside the spherical cell subject to the boundary condition that the current leaves the cell across the membrane with uniform current density, $4\pi/A$, and the average intracellular potential just inside the membrane is constrained to be equal to the average extracellular potential just outside the membrane. The uniform distribution of current flux across the membrane occurs because the ratio of the voltage drop between two points in the interior of the cell to the voltage drop across the membrane is proportional to ϵ , and consequently small. If the interior conductivity were infinite, the uniform interior distribution would be precise; in our case the interior conductivity is large, so that this is only an approximation which will be corrected by the higher-order terms in our solution for $V(\vec{r}, t)$.

The problem (34) with $\alpha=0$ is identical to a problem which has been solved in connection with a special case of the present analysis (Barclon, Cole and Eisenberg, 1972) in which the steady state solution is obtained when the outer surface of the membrane is constrained to zero potential (i.e., the $\alpha=0, t \rightarrow \infty$ limit of our solution). The solution to (34) can be expressed in terms of elementary functions:

$$\begin{aligned} G(\vec{r}) &= (r^2 + R^2 - 2rR \cos \theta)^{-1/2} + (1 + r^2 R^2 - 2rR \cos \theta)^{-1/2} \\ &- \log [1 - rR \cos \theta + (1 + r^2 R^2 - 2rR \cos \theta)^{1/2}] - 2 + \log 2 + \alpha, \end{aligned} \tag{36 a}$$

for $r < 1$, and

$$G(\vec{r}) = \alpha/r, \quad (36 \text{ b})$$

for $r > 1$. The solution for $r < 1$ also may be expressed as an expansion in Legendre polynomials,

$$G(\vec{r}) = \alpha - 1 + \sum_{n=1}^{\infty} P_n(\cos \theta) (r/R)^n \left(1 + \frac{1}{n}\right) + \sum_{n=0}^{\infty} P_n(\cos \theta) \begin{cases} \frac{1}{R} \left(\frac{r}{R}\right)^n, & r \leq R, \\ \frac{1}{r} \left(\frac{R}{r}\right)^n, & r \geq R. \end{cases} \quad (37)$$

The most direct way to obtain the solution to (34) is to assume a general form in terms of an expansion in Legendre polynomials with unknown coefficients. Substituting the form in (34) then determines the coefficients, yielding (36 b) and (37). The latter can then be converted to (36 a) using known summation formulas. Equation (36 a) is clearly more useful than (37) for numerical calculation; the alternate (37) is given here because it is useful in calculating higher-order potentials, for which there are no known closed-form expressions.

The solution inside the cell consists of the free-space potential of a point source of strength 4π at $\vec{r} = \vec{R}$, an image source of strength $4\pi/R$ at $\vec{r} = \vec{R}/R^2$, a logarithmic function of position and some constant terms. The solution outside the cell ($r > 1$) is inversely proportional to the radial distance. At $t = \infty$, G is the complete part of the potential independent of ε .

For finite t , the solution $f_1(t)$ to (35) must be added to (36 a) and (36 b). The first three of equations (35) imply

$$f_1(\vec{r}, t) = \begin{cases} f_1(t), & \text{inside,} \\ 0, & \text{outside.} \end{cases}$$

Substituting this in the fourth of (25) yields

$$f_1 + \frac{\partial f_1}{\partial t} = 0, \text{ inside,}$$

so that

$$f_1(\vec{r}, t) = \begin{cases} a_1 e^{-t}, & \text{inside,} \\ 0, & \text{outside.} \end{cases} \quad (38)$$

The constant a_1 is undetermined. Trying to satisfy the initial condition (18) would require a_1 to be equal to $\Delta G = G^+(\vec{r}) - G^-(\vec{r})$, but since ΔG is a function of position and a_1 is a constant, this is not possible for all points on the membrane. The conclusion is that the expansion (23) is not valid at $t = 0$. In Fig. 2 the solid curve represents the first two terms in the long-time expansion for the transmembrane potential. It can be seen that as $t \rightarrow 0$, the long-time expansion for the transmembrane potential, $\Delta(V_0 + V_1 + \dots)$, approaches a nonzero value, violating the initial condition $\Delta V = 0$ at $t = 0$. In the next subsection, we will define another expansion, valid at short times, including $t = 0$, which joins smoothly to the long-time expansion. The short-time expansion is shown as the dotted curve in Fig. 2.

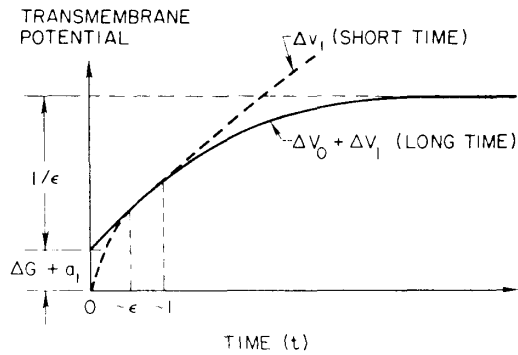


Fig. 2. Matching of short-time and long-time expansions

Continuing the procedure one order higher, we obtain for the ϵ problem, by substituting (33) and (38) in (26)

$$\left. \begin{aligned} \nabla^2 V_2 &= 0, \\ \frac{\partial V_2^-}{\partial n} &= G^+ - G^- = \frac{1}{\alpha} \frac{\partial V_2^+}{\partial n}, \\ V_2 &\rightarrow 0 \text{ as } |\vec{r}| \rightarrow \infty, \end{aligned} \right\} \quad (39)$$

and by integrating $\nabla^2 V_3$ over the cell interior,

$$\iiint \nabla^2 V_3 d^3 r = 0 = \iint \frac{\partial V_3^-}{\partial n} dS = - \iint \left(V_2^- - V_2^+ + \frac{\partial V_2^-}{\partial t} - \frac{\partial V_2^+}{\partial t} \right) dS \quad (40)$$

As in the preceding problem, we break up the potential V_2 into two parts,

$$V_2(\vec{r}, t) = \Phi(\vec{r}) + f_2(\vec{r}, t) \quad (41)$$

and require the two surface integral constraints

$$\iint (\Phi^+ - \Phi^-) dS = 0, \quad (42)$$

$$\iint \left(f_2^- - f_2^+ + \frac{\partial f_2^-}{\partial t} - \frac{\partial f_2^+}{\partial t} \right) dS = 0. \quad (43)$$

The problem for f_2 is identical to (35) for f_1 , which leads to

$$f_2(\vec{r}, t) = \begin{cases} a_2 e^{-t}, & \text{inside,} \\ 0, & \text{outside.} \end{cases} \quad (44)$$

where a_2 is a constant to be determined by matching to the short-time solution, and Φ is a solution of the problem

$$\left. \begin{aligned} \nabla^2 \Phi(\vec{r}) &= 0, \\ \frac{\partial \Phi^-}{\partial n} &= -G^+ + G^- = \frac{1}{\alpha} \frac{\partial \Phi^+}{\partial n}, \\ \iint (\Phi^- - \Phi^+) dS &= 0, \\ \Phi &\rightarrow 0 \text{ as } |\vec{r}| \rightarrow \infty. \end{aligned} \right\} \quad (45)$$

The boundary value problem for Φ may be solved by assuming a Legendre polynomial expansion and evaluating the expansion coefficients. The result is

$$\Phi(r, \theta) = - \sum_{n=1}^{\infty} \frac{2n+1}{n^2} r^n R^n P_n(\cos \theta) \quad (46 \text{ a})$$

for $r < 1$ and

$$\begin{aligned} \Phi(r, \theta) &= \frac{\alpha}{R} \sum_{n=1}^{\infty} \left(\frac{R}{r}\right)^{n+1} \frac{2n+1}{n(n+1)} P_n(\cos \theta) \\ &= \frac{\alpha}{R} \left[\log \left\{ \frac{R}{r} - \cos \theta + \left(1 - 2 \frac{R}{r} \cos \theta + \frac{R^2}{r^2}\right)^{1/2} \right\} - \log(1 - \cos \theta) \right] \\ &\quad - \frac{\alpha}{r} \left[1 + \log \left\{ 1 - \frac{R}{r} \cos \theta + \left(1 + \frac{R^2}{r^2} - 2 \frac{R}{r} \cos \theta\right)^{1/2} \right\} - \log 2 \right] \end{aligned} \quad (46 \text{ b})$$

for $r > 1$. For the potential Φ outside the cell a closed-form expression has been obtained for the Legendre polynomial expansion, but inside the cell this cannot be done.

B. Short-Time Expansion

Initially, the membrane capacitance is uncharged, and the transmembrane potential is zero. However, the time derivative of the transmembrane potential need not be small. If we (incorrectly) extrapolate the long-time solution back to $t=0$ we see above and in Fig. 2, that there is a finite discontinuity in the transmembrane potential, ΔV , between $t=0^-$ and $t=0^+$. That is, the time derivative is infinite at $t=0$. We therefore look for an initially valid, short-time expansion which satisfies the initial condition and joins smoothly to the long-time solution (the dotted curve in Fig. 2). In the limit of $\varepsilon \rightarrow 0$ we expect the region of validity of the long-time solution to get closer to $t=0$ and the time derivative of ΔV to approach infinity at $t=0$. Hence we see that the reason for the breakdown of the long-time expansion near $t=0$ is the assumption that $\partial V_n / \partial t$ and V_n are both independent of ε . We therefore expect that in the initially valid expansion for $V(\tilde{r}, t)$, $(\partial V_n^- / \partial t - \partial V_n^+ / \partial t)$ is much greater than $(V_n^- - V_n^+)$. There is another time variable, $\tilde{t} = t/\mu(\varepsilon)$, for which $(\partial V_n^- / \partial \tilde{t} - \partial V_n^+ / \partial \tilde{t})$ is comparable in magnitude to $(V_n^- - V_n^+)$, and the short-time solution should be written in terms of this variable, for convenience in grouping terms of comparable magnitude. We write the expansion for V in the form

$$V(\tilde{r}, t) = V(\tilde{r}, \mu \tilde{t}) \equiv v(\tilde{r}, \tilde{t}) = v_1(\varepsilon) v_1(\tilde{r}, \tilde{t}) + v_2(\varepsilon) v_2(\tilde{r}, \tilde{t}) + \dots \quad (47)$$

Substituting (47) in (16)

$$\nabla^2 V = v_1(\varepsilon) \nabla^2 v_1 + v_2(\varepsilon) \nabla^2 v_2 + \dots = -4\pi \delta(\tilde{r} - \bar{R}) u(\tilde{t}), \quad (48)$$

and substituting (47) in (15)

$$\begin{aligned}
& v_1 \frac{\partial v_1^-}{\partial n} + v_2 \frac{\partial v_2^-}{\partial n} + \dots \\
&= \frac{v_1}{\alpha} \frac{\partial v_1^+}{\partial n} + \frac{v_2}{\alpha} \frac{\partial v_2^+}{\partial n} + \dots \\
&= \varepsilon v_1 (v_1^+ - v_1^-) + \frac{\varepsilon v_1}{\mu} \left(\frac{\partial v_1^+}{\partial \tilde{t}} - \frac{\partial v_1^-}{\partial \tilde{t}} \right) \\
&+ \varepsilon v_2 (v_2^+ - v_2^-) + \frac{\varepsilon v_2}{\mu} \left(\frac{\partial v_2^+}{\partial \tilde{t}} - \frac{\partial v_2^-}{\partial \tilde{t}} \right) + \dots
\end{aligned}$$

We make the following separation for v_1 and v_2 ,

$$\begin{aligned}
\frac{\partial v_1^-}{\partial n} &= \frac{1}{\alpha} \frac{\partial v_1^+}{\partial n} = \frac{\varepsilon}{\mu} \left(\frac{\partial v_1^+}{\partial \tilde{t}} - \frac{\partial v_1^-}{\partial \tilde{t}} \right) \\
\frac{\partial v_2^-}{\partial n} &= \frac{1}{\alpha} \frac{\partial v_2^+}{\partial n} = \varepsilon \frac{v_1}{v_2} (v_1^+ - v_1^-) + \frac{\varepsilon}{\mu} \left(\frac{\partial v_2^+}{\partial \tilde{t}} - \frac{\partial v_2^-}{\partial \tilde{t}} \right)
\end{aligned} \tag{49}$$

This separation requires the choices

$$\mu(\varepsilon) = \varepsilon \quad \text{or} \quad \tilde{t} = \frac{t}{\varepsilon}, \tag{50}$$

and

$$\frac{v_{n+1}}{v_n} = \varepsilon. \tag{51}$$

Unlike in the long-time expansion, here the lowest-order potential has a nonzero normal derivative, and so placing the delta function source in the lowest-order problem leads to no inconsistency. If this is done, we must require $v_1(\varepsilon) = 1$. The first two of the sequence of problems then become, for $t \geq 0$,

$$\left. \begin{aligned}
& \nabla^2 v_1 = -4\pi \delta(\vec{r} - \vec{R}) \\
& \frac{\partial v_1^-}{\partial n} = \frac{\partial v_1^+}{\partial \tilde{t}} - \frac{\partial v_1^-}{\partial \tilde{t}} = \frac{1}{\alpha} \frac{\partial v_1^+}{\partial n} \\
& v_1^-(\vec{r}, 0+) = v_1^+(\vec{r}, 0+) \\
& v_1(\infty, \tilde{t}) = 0
\end{aligned} \right\} \tag{52}$$

$$\left. \begin{aligned}
& \nabla^2 v_2 = 0 \\
& \frac{\partial v_2^-}{\partial n} = v_1^+ - v_1^- + \frac{\partial v_2^+}{\partial \tilde{t}} - \frac{\partial v_2^-}{\partial \tilde{t}} = \frac{1}{\alpha} \frac{\partial v_2^+}{\partial n} \\
& v_2^-(\vec{r}, 0+) = v_2^+(\vec{r}, 0+) \\
& v_2(\infty, \tilde{t}) = 0
\end{aligned} \right\} \tag{53}$$

In the v_1 , problem, only the membrane capacitance enters; in the v_2 and higher problems, the resistance enters also, via the potential in the next-lower-order problem.

Integrating the first of equations (52) over the cell volume,

$$\iiint \nabla^2 v_1 d^3 r = -4 \pi = \iint \frac{\partial v_1^-}{\partial n} dS = \frac{\partial}{\partial \tilde{t}} \iint (v_1^+ - v_1^-) dS. \quad (54)$$

Integrating over \tilde{t} , and using the initial condition in (52), we find

$$\iint (v_1^+ - v_1^-) dS = -4 \pi \tilde{t}. \quad (55)$$

This implies that there is a part of v_1 , which increases linearly with \tilde{t} . The potential v_1 can therefore be broken into the following three parts,

$$v_1(\vec{r}, t) = G(\vec{r}) + w_1(\vec{r}, \tilde{t}) + h(\vec{r})\tilde{t}, \quad (56)$$

where G is the same Green's function that was defined in (34), (36 a) and (36 b) and accounts completely for the singular part of v_1 , and $w_1(\vec{r}, \tilde{t})$ is bounded.

Using (34) to eliminate G from the boundary condition in (52),

$$\frac{\partial w_1^-}{\partial n} + \frac{\partial h^-}{\partial n} \tilde{t} = \frac{4 \pi}{A} + \frac{\partial w_1^+}{\partial \tilde{t}} - \frac{\partial w_1^-}{\partial \tilde{t}} + h^+ - h^- = \frac{1}{\alpha} \frac{\partial w_1^+}{\partial n} + \frac{1}{\alpha} \frac{\partial h^+}{\partial n} \tilde{t}. \quad (57)$$

The only way (57) can be satisfied is if the coefficients of \tilde{t} are zero, so that

$$\frac{\partial h^-}{\partial n} = \frac{\partial h^+}{\partial n} = 0. \quad (58)$$

Since $\nabla^2 h = 0$ and $h(\infty) = 0$,

$$h(\vec{r}) = \begin{cases} \text{constant, inside,} \\ 0, \text{ outside.} \end{cases}$$

Using (55) to evaluate the constant, we have

$$h(\vec{r}) = \begin{cases} 4 \pi / A, \text{ inside,} \\ 0, \text{ outside.} \end{cases} \quad (59)$$

The remaining part of $v_1(\vec{r}, \tilde{t})$, that is, $w_1(\vec{r}, \tilde{t})$, can be expanded in a series of eigenfunctions in a spatial coordinate system \vec{r} appropriate for the particular cell shape. The problem for determining $w_1(\vec{r}, \tilde{t})$ is obtained by substituting (56)–(59) in (52) and is

$$\left. \begin{aligned} \nabla^2 w_1 &= 0 \\ \frac{\partial w_1^-}{\partial n} &= \frac{\partial w_1^+}{\partial \tilde{t}} - \frac{\partial w_1^-}{\partial \tilde{t}} = \frac{1}{\alpha} \frac{\partial w_1^+}{\partial n} \\ w_1^-(\vec{r}, 0+) - w_1^+(\vec{r}, 0+) &= G^+(\vec{r}) - G^-(\vec{r}) \\ w_1(\infty, \tilde{t}) &= w_1(\vec{r}, \infty) = 0. \end{aligned} \right\} \quad (60)$$

For a spherical cell of unit radius, the solution to (60) is

$$w_1(\tilde{r}, \tilde{t}) = - \sum_{n=1}^{\infty} r^n R^n \exp\left(-\frac{n(n+1)\tilde{t}}{n+\alpha n+1}\right) \frac{(n+1)(2n+1)}{n(n+\alpha n+1)} P_n(\cos\theta) \quad (61)$$

for $r < 1$, and

$$w_1(\tilde{r}, \tilde{t}) = \alpha \sum_{n=1}^{\infty} r^{-n-1} R^n \exp\left(-\frac{n(n+1)\tilde{t}}{n+\alpha n+1}\right) \frac{2n+1}{n+\alpha n+1} P_n(\cos\theta) \quad (62)$$

for $r > 1$. This completes the solution for $v_1(\tilde{r}, \tilde{t})$. We now continue by finding $v_2(\tilde{r}, \tilde{t})$.

Substituting the expressions (56), (59), (61), (62), (36 b) and (37) in the membrane boundary condition in (53) for a spherical cell of unit radius the boundary condition becomes

$$\begin{aligned} \frac{\hat{c}v_2}{\hat{c}r} &= -\tilde{t} - \sum_{n=1}^{\infty} \frac{2n+1}{n} R^n P_n(\cos\theta) \left[1 - \exp\left(-\frac{n(n+1)\tilde{t}}{n+\alpha n+1}\right) \right] + \frac{\partial v_2^+}{\partial \tilde{t}} - \frac{\partial v_2^-}{\partial \tilde{t}} \\ &= \frac{1}{\alpha} \frac{\hat{c}v_2^+}{\hat{c}r} \end{aligned} \quad (63)$$

Proceeding in a manner similar to the way we treated $v_1(\tilde{r}, \tilde{t})$, the solution to the boundary value problem (53) and (63) can be decomposed into a term quadratic in \tilde{t} , and an eigenfunction expansion bounded at $\tilde{t} = \infty$:

$$\begin{aligned} v_2(\tilde{r}, \tilde{t}) &= -\frac{\tilde{t}^2}{2} + \tilde{t} \sum_{n=1}^{\infty} \frac{(n+1)(2n+1)}{n(n+\alpha n+1)} r^n R^n P_n(\cos\theta) \exp\left(-\frac{n(n+1)\tilde{t}}{n+\alpha n+1}\right) \\ &\quad - \sum_{n=1}^{\infty} r^n R^n \frac{2n+1}{n^2} P_n(\cos\theta) \left[1 - \exp\left(-\frac{n(n+1)\tilde{t}}{n+\alpha n+1}\right) \right] \end{aligned} \quad (64)$$

for $r < 1$, and

$$\begin{aligned} v_2(\tilde{r}, \tilde{t}) &= \alpha \sum_{n=1}^{\infty} r^{-n-1} R^n P_n(\cos\theta) \left\{ \frac{2n+1}{n(n+1)} \left[1 - \exp\left(-\frac{n(n+1)\tilde{t}}{n+\alpha n+1}\right) \right] \right. \\ &\quad \left. - \frac{2n+1}{n+\alpha n+1} \tilde{t} \exp\left(-\frac{n(n+1)\tilde{t}}{n+\alpha n+1}\right) \right\} \end{aligned} \quad (65)$$

for $r > 1$. It should be noted that the $\tilde{t} \rightarrow \infty$ limit of the eigenfunction expansions in $v_2(\tilde{r}, \tilde{t})$ is just $\Phi(r, \theta)$ given by (46 a) and (46 b).

Summarizing the results for the short-time potential inside the cell we have, for $r < 1$,

$$\begin{aligned} v(\tilde{r}, \tilde{t}) &= \tilde{t} + (r^2 + R^2 - 2rR \cos\theta)^{-1/2} + (1 + r^2 R^2 - 2rR \cos\theta)^{-1/2} - 2 + \alpha + \log 2 \\ &\quad - \log [1 - rR \cos\theta + (1 + r^2 R^2 - 2rR \cos\theta)^{1/2}] \\ &\quad - \sum_{n=1}^{\infty} (rR)^n \exp\left(-\frac{n(1+n)\tilde{t}}{1+n+\alpha n}\right) \frac{(n+1)(2n+1)}{n(n+1+\alpha n)} P_n(\cos\theta) \end{aligned}$$

$$\begin{aligned}
& + \varepsilon \left[-\frac{\tilde{t}^2}{2} + \tilde{t} \sum_{n=1}^{\infty} (rR)^n \exp\left(-\frac{n(1+n)}{1+n+\alpha n} \tilde{t}\right) \frac{(n+1)(2n+1)}{n(n+1+\alpha n)} P_n(\cos \theta) \right. \\
& \left. - \sum_{n=1}^{\infty} (rR)^n \left(\frac{2}{n} + \frac{1}{n^2}\right) P_n(\cos \theta) \left(1 - \exp\left(-\frac{n(1+n)}{1+n+\alpha n} \tilde{t}\right)\right) \right] + \dots \quad (66)
\end{aligned}$$

and outside the cell, for $r > 1$

$$\begin{aligned}
v(\tilde{r}, \tilde{t}) = & \frac{\alpha}{r} + \frac{\alpha}{r} \sum_{n=1}^{\infty} \left(\frac{R}{r}\right)^n P_n(\cos \theta) \frac{2n+1}{1+n+\alpha n} e^{-\frac{n(1+n)}{1+n+\alpha n} \tilde{t}} \\
& + \varepsilon \left[\frac{\alpha}{r} \sum_{n=1}^{\infty} \left(\frac{R}{r}\right)^n P_n(\cos \theta) \left\{ \frac{2n+1}{n(n+1)} \left(1 - e^{-\frac{n(1+n)}{1+n+\alpha n} \tilde{t}}\right) \right. \right. \\
& \left. \left. - \frac{2n+1}{1+n+\alpha n} \tilde{t} e^{-\frac{n(1+n)}{1+n+\alpha n} \tilde{t}} \right\} \right] + \dots \quad (67)
\end{aligned}$$

We see that the first (independent of ε) term in the short-time expansion of v in the cell interior, (66), has a linear growth in \tilde{t} . This behaviour is shown by the dotted curve for Δv_1 in Fig. 2. Thus we see that although the first term in the short-time expansion does satisfy the initial condition, it does not correctly represent the solution for long times, $t \gtrsim 1$. Equation (66) also indicates that the second (proportional to ε) term in the short-time expansion is quadratic in \tilde{t} . The effect of adding this term would be to make the dotted curve a parabola which more closely follows the solid curve as t increases. In fact, we can see that these are just the first two terms in the Taylor series for $(1 - e^{-t})/\varepsilon$, and if we continued the expansion indefinitely to higher powers of ε , we would recover the term proportional to $1/\varepsilon$ in the long-time expansion (30).

C. Matching

When $t \rightarrow 0$ in the long-time solution and $\tilde{t} \rightarrow \infty$ in the short-time solution, the two potentials, written in some intermediate time variable, must be equal, to all orders of ε . This requirement permits evaluation of the constants a_0, a_1, a_2, \dots appearing in the long-time solution. The value of a_0 must be consistent with the value of a_0 determined previously in (30). An intermediate time variable can be defined by

$$t_\eta = t/\eta(\varepsilon),$$

where

$$\eta(\varepsilon) \rightarrow 0 \text{ as } \varepsilon \rightarrow 0$$

but η approaches zero less rapidly than ε does, so that

$$\eta(\varepsilon)/\varepsilon \rightarrow \infty \text{ as } \varepsilon \rightarrow 0.$$

Thus the limiting behaviour of t_η as $\varepsilon \rightarrow 0$ is intermediate between t and \tilde{t} .

If we hold t_η fixed at some value in the overlap region of Fig. 2, say t_η^* , and take the limit $\varepsilon \rightarrow 0$, the point t_η^* remains in the overlap region while the lower extremity of the overlap region approaches $t = 0$. The corresponding limiting values of t and \tilde{t} are

$$t = \eta(\epsilon) t_\eta \rightarrow 0 \text{ as } \epsilon \rightarrow 0,$$

and

$$\tilde{t} = [\eta(\epsilon)/\epsilon] t_\eta \rightarrow \infty \text{ as } \epsilon \rightarrow 0.$$

In order to match the long-time and short-time expansions in the overlap region, it is convenient to write the $t \rightarrow 0$ limit of the long-time expansion and the $\tilde{t} \rightarrow \infty$ limit of the short-time expansion both in terms of \tilde{t} , and require that the two limits be identical, that is,

$$\lim_{t \rightarrow 0} \left[\frac{1}{\epsilon} V_0 + V_1 + \epsilon V_2 + \dots \right] = \lim_{\tilde{t} \rightarrow \infty} [v_1 + \epsilon v_2 + \dots].$$

The long-time solution given by (23), (30), (33), (38), (41), and (44) is, for $r < 1$,

$$V(\tilde{r}, t) = \frac{1}{\epsilon} [1 - e^{-t}] + [G(\tilde{r}) + a_1 e^{-t}] + \epsilon [\Phi(\tilde{r}) + a_2 e^{-t}] + \dots \tag{68}$$

Letting $t = \epsilon \tilde{t}$ in (68) we obtain

$$\begin{aligned} V(\tilde{r}, \epsilon \tilde{t}) &= \frac{1}{\epsilon} \left[\epsilon \tilde{t} - \frac{\epsilon^2 \tilde{t}^2}{2} + \dots \right] + [G(\tilde{r}) + a_1 (1 - \epsilon \tilde{t} + \dots)] + \epsilon [\Phi(\tilde{r}) + a_2 (1 - \epsilon \tilde{t} + \dots)] \\ &= \tilde{t} + G(\tilde{r}) + a_1 + \epsilon \left(\frac{\tilde{t}^2}{2} + \Phi(\tilde{r}) - a_1 \tilde{t} + a_2 \right) + \dots \end{aligned} \tag{69 a}$$

by expanding the exponentials in powers of ϵ , and for $r > 1$,

$$V(\tilde{r}, \tilde{t}) = \frac{\alpha}{r} + \epsilon \Phi(\tilde{r}) + \dots \tag{69 b}$$

Ignoring the exponentially small terms in the short-time solution (66) and (67), as $\tilde{t} \rightarrow \infty$, the short-time solution becomes, for $r < 1$,

$$\lim_{\tilde{t} \rightarrow \infty} v(\tilde{r}, \tilde{t}) = \tilde{t} + G(\tilde{r}) - \frac{\epsilon \tilde{t}^2}{2} + \epsilon \Phi(\tilde{r}) + \dots \tag{70 a}$$

and for $r > 1$,

$$\lim_{\tilde{t} \rightarrow \infty} v(\tilde{r}, \tilde{t}) = \frac{\alpha}{r} + \epsilon \Phi(\tilde{r}) + \dots \tag{70 b}$$

Comparing (69) and (70) we find that our earlier choice of $a_0 = -4\pi/A = -1$ is satisfactory, and in order that (69) and (70) be identical we must have

$$a_1 = a_2 = \dots = 0. \tag{71}$$

Using these values of a_0, a_1, \dots and (33), (36), (38), (41), (44), (46), the long-time expansion for the potential is consequently

$$\begin{aligned} V(\tilde{r}, t) &= \frac{1}{\epsilon} [1 - \exp(-t)] + (r^2 + R^2 - 2rR \cos \theta)^{-1/2} + (1 + r^2 R^2 - 2rR \cos \theta)^{-1/2} \\ &\quad - \log [1 - rR \cos \theta + (1 + r^2 R^2 - 2rR \cos \theta)^{1/2}] - 2 + \log 2 + \alpha \tag{72 a} \\ &\quad - \epsilon \sum_{n=1}^{\infty} \frac{2n+1}{n^2} r^n R^n P_n(\cos \theta) + \dots \end{aligned}$$

for $r < 1$, and

$$V(\bar{r}, t) = \frac{\alpha}{r} - \varepsilon \alpha \sum_{n=1}^{\infty} r^{-n-1} R^n \frac{2n+1}{n(n+1)} P_n(\cos \theta) + \dots \quad (72 \text{ b})$$

for $r > 1$.

Examining (72 a) and (72 b) we see that the only time dependence in the long-time expansion is in one term in the inside potential. The outside potential is independent of time during this epoch. The time-dependent term $(1 - e^{-t})/\varepsilon$ in (72 a) represents the transient buildup of the cell interior to a large potential in a time $t \sim 1$. This term by itself is the "isopotential approximation" to the potential of the cell. In physical units, the potential builds up to this large value in a time $t' \sim R_m C_m$.

All other terms in (72) switch on abruptly at $t=0$, and thenceforth are independent of time. As noted before, this abrupt change does not satisfy the initial condition, but does represent the potential at successively smaller values of t as $\varepsilon \rightarrow 0$. The short-time expansion correctly extrapolates the long-time expansion back to $t=0$.

We also can see from (72 b) that in the long-time epoch, the outside potential approaches an inverse- r potential. The outer surface of the membrane becomes an equipotential surface, at potential $V=\alpha$, plus terms containing higher powers of ε . The deviation of the outside surface from isopotentiality is given, neglecting terms proportional to ε and higher powers of ε , by the sum in (72 b).

Neglecting terms proportional to ε^m , $m = 1, 2, 3, \dots$ (72 a) yields the closed form expression, for $r < 1$,

$$\begin{aligned} V(\bar{r}, t) = & \frac{1}{\varepsilon} [1 - \exp(-t)] + (r^2 + R^2 - 2rR \cos \theta)^{-1/2} \\ & + (1 + r^2 R^2 - 2rR \cos \theta)^{-1/2} - 2 + \log 2 + \alpha \\ & - \log [1 - rR \cos \theta + (1 + r^2 R^2 - 2rR \cos \theta)^{1/2}] + \dots \end{aligned} \quad (73 \text{ a})$$

and (72 b) yields, for $r > 1$,

$$V(\bar{r}, t) = \frac{\alpha}{r} + \dots \quad (73 \text{ b})$$

Equations (73 a) and (73 b) represent the entire part of the interior potential that is normally within the current realm of measurability in physiological experiments. The terms containing higher powers of ε are too small to detect; the transient terms in the short-time expansion (66) and (67) are too rapid to detect.

If the outside conductivity were infinite, $\sigma_o = \infty$, then we have $\alpha=0$. Also, infinite outside conductivity would imply the outer surface of the membrane, as well as the entire external medium, is at a constant potential of $V=0$. Thus, the assumption $\alpha=0$ is equivalent to the condition of isopotentiality (to all orders of ε) of the outside surface of the membrane. This condition has been used in the literature (Barcilon, Cole and Eisenberg, 1972).

Examination of Equation (72 a) shows that the effect of the finite conductivity of the external medium or, equivalently, the removal of the isopotentiality

assumption, is merely to increase the inside potential by an additive constant, α , relative to the potential a long distance away from the cell.

Equation (72 b) shows that the deviation from a simple inverse distance potential in the external medium is hardly detectable. This is an extremely interesting result. It indicates that to a good approximation the external potential is independent of the position of the source inside the cell. The membrane, because of its high resistance, shields the external world from the events occurring inside the cell. The dependence of the exterior potential on θ and on the location R of the current source first appears in the term proportional to ε , whereas for the interior potential it appears already in the term which is independent of ε . On physical grounds, we would expect the opposite to be true as well, that is, that the membrane shields the interior of the cell from electrical events outside the cell. This will be seen in the following paper (Peskoff and Ramirez, 1975).

It is also possible to write down a single expansion which is valid for all t , i. e., except for exponentially small terms, it reduces to the long-time solution when $\varepsilon \rightarrow 0$ and t is fixed and it reduces to the short-time solution when $\varepsilon \rightarrow 0$ and \tilde{t} is fixed. This expansion is

$$\begin{aligned}
 V(\tilde{r}, t) = & \frac{1}{\varepsilon} (1 - e^{-t}) \\
 & + G(\tilde{r}) - \sum_{n=1}^{\infty} r^n R^n \frac{(n+1)(2n+1)}{n(n+\alpha n+1)} P_n(\cos \theta) \exp\left(-\frac{n(n+1)t}{(n+\alpha n+1)\varepsilon}\right) \\
 & + \varepsilon \left\{ \Phi(\tilde{r}) + \sum_{n=1}^{\infty} r^n R^n P_n(\cos \theta) \exp\left(-\frac{n(n+1)t}{(n+\alpha n+1)\varepsilon}\right) \frac{2n+1}{n^2} \right. \\
 & \quad \left. \cdot \left[1 + \frac{n(n+1)t}{(n+\alpha n+1)\varepsilon} \right] \right\} + \dots
 \end{aligned} \tag{74a}$$

for $r < 1$, and

$$\begin{aligned}
 V(r, t) = & \frac{\alpha}{r} + \alpha \sum_{n=1}^{\infty} r^{-n-1} R^n P_n(\cos \theta) \frac{2n+1}{n+\alpha n+1} \exp\left(-\frac{n(n+1)t}{(n+\alpha n+1)\varepsilon}\right) \\
 & + \varepsilon \left\{ \Phi(\tilde{r}) - \alpha \sum_{n=1}^{\infty} r^{-n-1} R^n P_n(\cos \theta) \frac{2n+1}{n(n+1)} \left[1 + \frac{n(n+1)t}{(n+\alpha n+1)\varepsilon} \right] \right. \\
 & \quad \left. \cdot \exp\left(-\frac{n(n+1)t}{(n+\alpha n+1)\varepsilon}\right) \right\} + \dots
 \end{aligned} \tag{74b}$$

for $r > 1$. It is obtained by adding the short-time and long-time expansions and subtracting the common part, $[1 - \exp(-t)]/\varepsilon + G(\tilde{r}) + \varepsilon \Phi(\tilde{r}) + \dots$.

D. Transmembrane Potential

Defining the transmembrane potential by

$$\Delta V = V^- - V^+,$$

we obtain from (74a) and (74b)

$$\begin{aligned}
\Delta V = & \frac{1-e^{-t}}{\varepsilon} + 2(1+R^2-2R\cos\theta)^{-1/2} - \log [1-R\cos\theta+(1+R^2-2R\cos\theta)^{1/2}] \\
& - 2 + \log 2 - \sum_{n=1}^{\infty} \frac{2n+1}{n} R^n P_n(\cos\theta) \exp\left(-\frac{n(n+1)t}{(n+\alpha n+1)\varepsilon}\right) \\
& - \varepsilon \sum_{n=1}^{\infty} \frac{(2n+1)(1+n+\alpha n)}{n^2(n+1)} R^n P_n(\cos\theta) \left[1 - \exp\left(-\frac{n(n+1)t}{(n+\alpha n+1)\varepsilon}\right) \right. \\
& \quad \left. \left\{ 1 + \frac{n(n+1)t}{(n+\alpha n+1)\varepsilon} \right\} \right] + \dots
\end{aligned} \tag{75}$$

for all t . For long times, $t/\varepsilon \rightarrow \infty$, (75) becomes

$$\begin{aligned}
\Delta V = & \frac{1-e^{-t}}{\varepsilon} + 2(1+R^2-2R\cos\theta)^{-1/2} - \log [1-R\cos\theta+(1+R^2-2R\cos\theta)^{1/2}] \\
& - 2 + \log 2 + \dots
\end{aligned} \tag{76}$$

Thus, neglecting terms proportional to ε and higher powers of ε , for long times ΔV is independent of the external conductivity. Almost all experimental measurements are taken in the domain in which (76) is valid. Equation (76) can be converted to physical units using the change of variables defined above, Eq. (14). The solution is for a current source of 4π amperes.

E. Physiological Significance of Extracellular Fields

Previous analyses of the potential inside spherical cells have assumed the external potential to be zero and so it is interesting to investigate the validity of that assumption now that the external potential can be explicitly determined. Equation (73 a) shows that the external conductivity (and thus the external potential) enters into the second term V_1 (the local potential) of the expression for the potential inside the cell. It might seem then that the potential recorded inside the cell depends in a significant manner on the external conductivity and thus the external potential.

This is not the case for two reasons. First, in many cases $\varepsilon \leq 0.005$ and so in most locations the entire V_1 term is insignificant compared to $V(\vec{r}, t)$, the total potential. Close to the point source (at distances less than the cell radius times ε) V_1 is at least equal to the leading term (proportional to $1/\varepsilon$) and so there the local potential is important. However, at such locations the relative contribution of the external conductivity to the V_1 term is small. Thus, even when the local potential is important, the α -dependent part of it is not very important. Secondly, the most important potential for physiological purposes is the transmembrane potential ΔV and this potential is independent of the external conductivity to two powers of ε ; that is, both ΔV_0 and ΔV_1 are entirely independent of α ; only the third term ΔV_2 , which is almost always negligible, depends on α .

It is rather interesting to analyze physically the dependence of the transmembrane potential ΔV on the external resistance. The reason that the transmembrane potential does not depend significantly on the external resistance is that the

external potential, produced by current flow through the external resistance, is in the first approximation independent of the angular coordinate θ . The external potential then changes the internal potential by a constant amount, independent of position, and the *difference* of the external potential and the internal potential (the transmembrane potential) is essentially independent of the external resistance. This result may be restated: the primary effect of the external resistance is to uniformly raise the potential immediately outside the cell; redistribution of current outside the cell (which creates circumferential gradients of external potential) is a secondary effect. Thus the effect of the external potential on *transmembrane* potential is negligible.

This result is of some use in understanding the role of small extracellular spaces in excitable tissues, including the heart and the central nervous system. Although the local internal potentials which are independent of ε are not terribly important under resting conditions in nerve cells, they do become important during fast phenomena and phenomena characterized by large values of membrane conductance (and so by relatively large values of ε). Since the action potential, and some synaptic potentials, are states of high conductance and rapidly changing potential, the local potential does become important in normal physiological states. If the external resistance were to be important in the local component of the transmembrane potential ΔV_1 , then the external resistance would influence the local potentials during an action potential and the shape and properties of the action potential would be expected to depend on the detailed properties of the extracellular space. This would seem to be an unfortunate situation from the teleological point of view, since the detailed properties of the extracellular space are quite variable and not well controlled. One would hope that the properties and shape of the action potential would be insulated from the effect of changes in the extracellular space.

Our analysis suggests then that the effects of external resistance (and thus external potential) even on a nonlinear membrane phenomenon like the action potential would be small, occurring only as a small correction. Thus, during an action potential the effect of external resistance would be expected to be small, even if the external potential itself is not negligible. This relative independence of transmembrane potential from external potential might well be significant in allowing the nervous system to function with so little extracellular space and thus with such a high density of information processing and transmitting units.

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ERRATA

"The Time-Dependent Potential in a Spherical Cell Using Matched Asymptotic Expansions" by A. Peskoff & R.S. Eisenberg

1. Page 278, paragraph 2, line 6 should read "(76)" not "(75)".

2. Page 286, line beginning with "In physical (primed) units..." should read as follows:

"In physical (primed) units, this potential is $V' = V/\sigma_i$ a = $(4\pi/A')(\delta/\sigma_m)$, the potential..."

3. Page 289, line 2 of equations (45) should read as follows:

$$\frac{\partial \phi^-}{\partial n} = G^+ - G^- = \frac{1}{\alpha} \frac{\partial \phi^+}{\partial n},$$