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POTENTIAL INDUCED BY A POINT SOURCE OF CURRENT IN THE INTERIOR OF A SPHERICAL CELL

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INTRODUCTION

Laplace's equation arises in many physical problems which involve conservation laws and so has been well studied for a number of boundary conditions, most notably for the Dirichlet and Neumann conditions in which the potential or normal derivative of potential is specified on the boundary. There is a class of problems, common in heat, diffusion, and physiological situations, which have another less well studied boundary condition. This boundary condition is often called the mixed or general boundary condition since in its simplest form it specifies a linear combination of the potential and its normal derivative at the boundary. If the boundary separates two regions, in both of which Laplace's equation is obeyed, the mixed boundary condition takes on a more complicated form. This report is devoted to the solution of Laplace's equation for spherical geometry with a particular mixed boundary condition appropriate to the description of a thin layer or membrane. The problem is more general than the usual mixed boundary problem of heat or diffusion problems and can be specialized to the usual case.

While the solution to the problem can be written by classical eigenfunction techniques, the resulting formulae are of limited utility since they are barely computable and since they do not permit physical interpretation. We derive representations of obvious physical significance which are easy to compute by exploiting a particular property of the mixed boundary value problem; namely, in most physical situations the boundary condition, written in dimensionless units, involves a uniformly small parameter. The size of this parameter allows an expansion of the eigenfunction representation, which expansion can be made computable. The physical significance of the terms remains unclear, however, and this is particularly worrisome since some of the properties of the solution differ from one's a priori expectations.

A class of techniques called singular perturbation theory has been developed to exploit small parameters in problems specified by differential equations.[3] These techniques allow the derivation of expressions having simple physical meaning and indeed allow approximations to the solution of some otherwise unsolvable problems. In the case of our problem of Laplace's equation with mixed boundary conditions, singular perturbation techniques are helpful because the physical meaning given to each of the individual terms in the solution explains the conflict with a priori expectations. However, in our case, exact methods may also be used to obtain the solution.

There are no theorems available to justify the results of a singular perturbation analysis of partial differential equations and so it is particularly important to compare the representation derived by singular perturbation techniques with the corresponding exact solution. Such comparisons are quite rare and for that reason we solve our present problem in three ways--by classical exact methods based essentially on eigenfunction techniques; by the singular perturbation technique of matched asymptotic expansions; and by the singular perturbation technique of multiple scaling. A comparison of the results shows the representations to be equivalent, thus justifying in this case the techniques of singular perturbation. The several methods are presented in some detail with the hope that this report may serve as an effective teaching aid to our students and colleagues unfamiliar with some of the methods of eigenfunction expansions or singular perturbation theory.

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 the same order. The current is collected by an electrode a long distance away in the external medium. The geometry and coordinate system are shown in Figure 1.

The conductivities of the cell interior, membrane and outside medium are σ_i, σ_m and σ_o (mhos/cm), respectively. The membrane thickness and conductivity are considered to approach zero individually in such a way that the ratio σ_m/δ, the surface conductivity (mhos/cm^2) 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 ($\sim 1\,\mu$ farad/cm^2).

The point source of current is a mathematical idealization of a fluid-filled, tapered glass pipette which, in an actual experiment, is used to pierce the cell membrane and inject current into the cell. The open tip of the pipette is much smaller than the dimensions of a cell, so that for studying potential variations on a scale comparable to the cell size, a delta function is an adequate representation for the spatial distribution of the source.

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

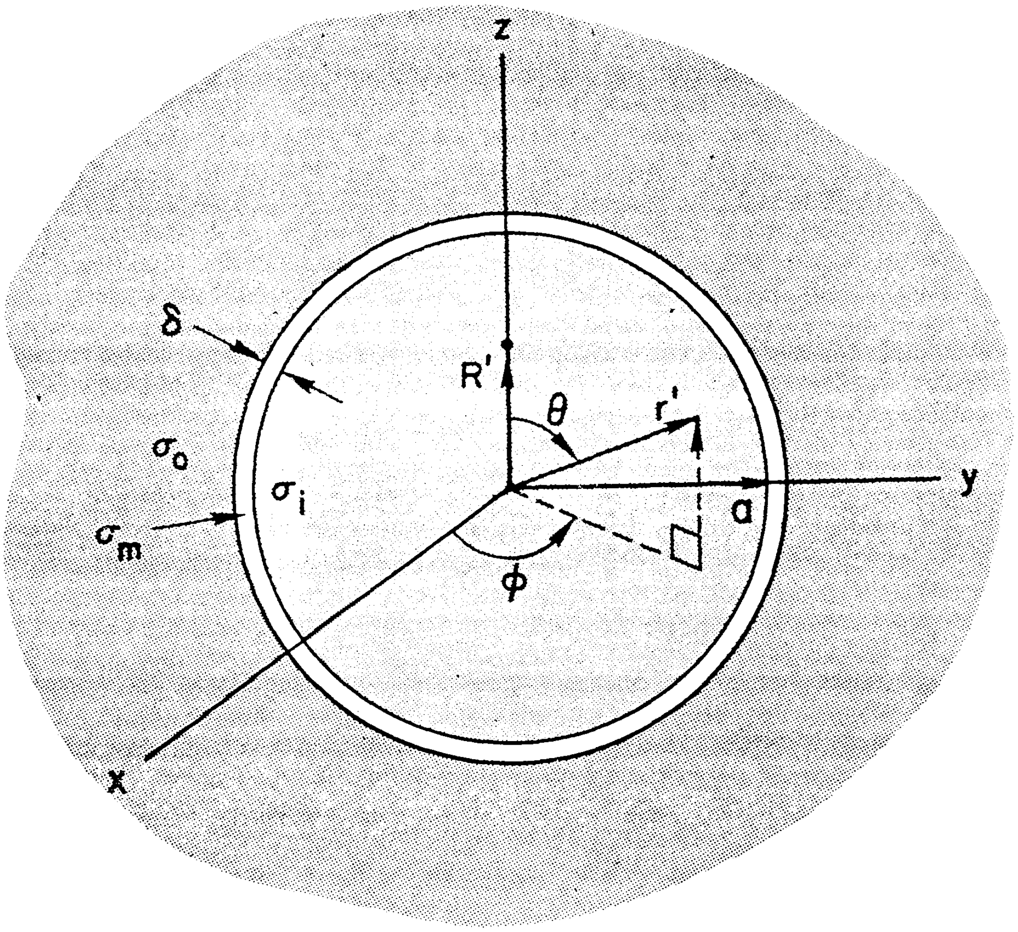

Figure 1. Coordinate System for Spherical Cell.

other cases, the source can be made a current source by external electronics. However, on a short time scale, capacitive coupling between the pipette and the cell is important, and in this case the current-source assumption breaks down. Hence, the results we obtain for the short time scale (defined below) may not apply to a physical micro-electrode. It should be pointed out, though, that if the electrical behavior of the source were well described, our analysis could be extended to short times for a real microelectrode.

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

$$\epsilon = \frac{\sigma_m}{\delta} \cdot \frac{a}{\sigma_i} \tag{1}$$

is small ($< 10^{-3}$) and although our solution is valid for all ϵ, we discuss the physiologically interesting case of small ϵ, in which case simpler analytic expressions are obtained.

If we assume a point current source of 4π amperes at a position $\vec{r}' = \vec{R}'$, inside the cell, then

$$\nabla' \cdot \vec{J}' = 4\pi \, \delta(\vec{r}' - \vec{R}') \, u(t') \tag{2}$$

where $\delta(\vec{r}' - \vec{R}')$ is a delta function, $u(t')$ a unit step function, J' is the current density in amps/cm^2, and primes denote quantities measured in physical units. Unprimed quantities will be in nondimensional units, defined below. The potential V' is related to the current density by Ohm's law,

$$\vec{J}' = - \sigma \nabla' V' \tag{3}$$

where σ is σ_i, σ_m or σ_o in the respective regions.

Substituting (3) in (2), we obtain the equation for the potential,

$$\nabla'^2 V' = -\frac{4\pi}{\sigma_i}\,\delta(\vec{r}' - \vec{R}')\,u(t') \quad . \tag{4}$$

We now derive the boundary condition appropriate for our membrane model. 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,

$$\frac{\partial q'^-}{\partial t'} = -\sigma_i \frac{\partial V'^-}{\partial n'} - J'_m \quad ,$$

$$\frac{\partial q'^+}{\partial t'} = \sigma_o \frac{\partial V'^+}{\partial n'} + J'_m \quad .$$

We assume that the membrane is thin ($\delta << a$) and that 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

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

where (+) and (-) superscripts denote quantities immediately outside and immediately inside the membrane. Conservation of charge then becomes

$$\frac{\partial q'^-}{\partial t'} = -\sigma_i \frac{\partial V'^-}{\partial n'} + \frac{\sigma_m}{\delta}\,(V'^+ - V'^-)$$

$$\frac{\partial q'^+}{\partial t'} = \sigma_o \frac{\partial V'^+}{\partial n'} - \frac{\sigma_m}{\delta}\,(V'^+ - V'^-) \quad .$$

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

$$q'^{+} = -K_o \frac{\partial V'^{+}}{\partial n'} + K_m \frac{V'^{+} - V'^{-}}{\delta}$$

$$q'^{-} = -K_m \frac{V'^{+} - V'^{-}}{\delta} + K_i \frac{\partial V'^{-}}{\partial n'}$$

where the K's are the permittivities in the respective regions, and the membrane capacitance per unit area is related to K_m by $C_m = K_m/\delta$. Taking the time derivative of this pair of equations we obtain

$$\frac{\partial q'^{+}}{\partial t'} = -K_o \frac{\partial^2 V'^{+}}{\partial t' \partial n'} + \frac{K_m}{\delta} \frac{\partial}{\partial t'} (V'^{+} - V'^{-})$$

$$\frac{\partial q'^{-}}{\partial t'} = -\frac{K_m}{\delta} \frac{\partial}{\partial t'} (V'^{+} - V'^{-}) + K_i \frac{\partial^2 V'^{-}}{\partial t' \partial n'}$$

Equating these two equations to the two charge conservation equations leads to

$$\left(\sigma_i + K_i \frac{\partial}{\partial t'}\right) \frac{\partial V'^{-}}{\partial n'} = \left(\sigma_m + K_m \frac{\partial}{\partial t'}\right) \frac{V'^{+} - V'^{-}}{\delta}$$

$$\left(\sigma_o + K_o \frac{\partial}{\partial t'}\right) \frac{\partial V'^{+}}{\partial n'} = \left(\sigma_m + K_m \frac{\partial}{\partial t'}\right) \frac{V'^{+} - V'^{-}}{\delta}$$

Making the change of variables

$$r = \frac{r'}{a}$$

$$V = a\,\sigma_i V'$$

$$t = \left(\sigma_m / K_m\right) t'$$

the last two equations become

$$\left(1 + \omega_i \frac{\partial}{\partial t}\right) \frac{\partial V^{-}}{\partial n} = \epsilon \left(1 + \frac{\partial}{\partial t}\right) (V^{+} - V^{-})$$

$$\frac{1}{\alpha} \left(1 + \omega_o \frac{\partial}{\partial t}\right) \frac{\partial V^{+}}{\partial n} = \epsilon \left(1 + \frac{\partial}{\partial t}\right) (V^{+} - V^{-})$$

where $\epsilon = \sigma_m a/\sigma_i \delta \sim 10^{-3}$, $\omega_i = K_i \sigma_m / K_m \sigma_i \sim 3 \times 10^{-9}$, $\omega_o = K_o \sigma_m / K_m \sigma_o \sim 10^{-9}$, and $\alpha = \sigma_i / \sigma_o$.

The ω_i and ω_o terms are negligible and if we ignore them we obtain for the membrane boundary condition,

$$\frac{\partial V^-}{\partial n} = \frac{1}{\alpha}\,\frac{\partial V^+}{\partial n} = \epsilon\left[V^+ - V^- + \frac{\partial V^+}{\partial t} - \frac{\partial V^-}{\partial t}\right], \tag{5}$$

or, in terms of physical variables

$$\sigma_i\,\frac{\partial V'^-}{\partial n'} = \sigma_o\,\frac{\partial V'^+}{\partial n'} = \frac{\sigma_m}{\delta}\left[V'^+ - V'^-\right] + C_m\left[\frac{\partial V'^+}{\partial t'} - \frac{\partial V'^-}{\partial t'}\right]. \tag{6}$$

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 within the membrane.

Making the same change of variables in Laplace's Equation (4), gives in nondimensional form,

$$\nabla^2 V = -\,4\pi\;\delta(\vec{r} - \vec{R})\;u(t)\;. \tag{7}$$

We now formulate the problem in spherical coordinates (r, θ, ϕ) with origin at the center of the spherical cell. With no loss in generality we take the point source on the $\theta = 0$ axis so that the potential becomes independent of the azimuthal angle ϕ.

There is an arbitrary additive constant in the potential $V(r, \theta, t)$ which we choose so that the potential is zero at $r = \infty$. We assume that there are no sources for $t < 0$ so that the membrane capacitance is uncharged at $t = 0$ and hence the potential is continuous across the membrane at $t = 0$. Including this boundary condition at infinity, and initial condition, the problem becomes

$$\left\{\begin{array}{lr}
\nabla^2 V = -4\pi\, \delta(\vec{r} - \vec{R})\, u(t) & (7) \\[1ex]
V(\infty, \theta, t) = 0 & (8) \\[1ex]
\dfrac{1}{\epsilon} \dfrac{\partial V}{\partial r} (1^-, \theta, t) = \dfrac{1}{\epsilon \alpha} \dfrac{\partial V}{\partial r} (1^+, \theta, t) & \\[1ex]
\qquad\qquad = V(1^+, \theta, t) - V(1^-, \theta, t) & \\[1ex]
\qquad\qquad\quad + \dfrac{\partial V}{\partial t} (1^+, \theta, t) - \dfrac{\partial V}{\partial t} (1^-, \theta, t) & (9) \\[1ex]
V(1^+, \theta, 0) - V(1^-, \theta, 0) = 0\ . & (10)
\end{array}\right.$$

This problem is solved exactly in Section II and the solution is studied for small ϵ . In Section III and Section IV, we show how to obtain asymptotic expansions for small ϵ using two singular perturbation methods: the techniques of matching and multiple scaling, respectively.

II. EXACT SOLUTION IN SPHERICAL HARMONICS

A. General Solution

The general solution to Laplace's Equation in spherical coordinates may be expanded in a series of terms of the form $P_n(\cos\theta)\, a_n(t)\, r^n$ and $P_n(\cos\theta)\, b_n(t)\, r^{-n-1}$. $P_n(\cos\theta)$ is the n^{th}-order Legendre polynomial, $a_n(t)$ and $b_n(t)$ are functions of time, n is an integer, and we have assumed no ϕ dependence because of the rotational symmetry. The solution[1] to (7)-(10) must therefore be of this form in each of the three regions $0 \leqq r < R$, $R < r < 1$, $1 < r < \infty$, in each of which the right-hand side of (7) is zero. Requiring, in accordance with (8), that $V = 0$ at $r = \infty$, and in addition that V be finite at $r = 0$, the general solution may be written

$$V(r,\theta,t) = \sum_{n=0}^{\infty} P_n(\cos\theta) \begin{cases} a_n(t)\, r^n, & 0 \leqq r \leqq R, \\ b_n(t)\, r^{-n-1} + c_n(t)\, r^n, & R \leqq r \leqq 1, \\ d_n(t)\, r^{-n-1}, & 1 \leqq r \leqq \infty. \end{cases}$$

It is convenient, at this point, to extract the free-space potential of a point source of magnitude 4π at $\vec{r} = \vec{R}$, from the solution, so that we write the potential in the form

$$V(r,\theta,t) = \sum_{n=0}^{\infty} P_n(\cos\theta) \begin{cases} \frac{1}{R}\left(\frac{r}{R}\right)^n + A_n(t)\, r^n, & 0 \leqq r \leqq R, \\ \frac{1}{r}\left(\frac{R}{r}\right)^n + A_n(t)\, r^n, & R \leqq r \leqq 1, \\ B_n(t)\, r^{-n-1}, & 1 \leqq r \leqq \infty, \end{cases} \tag{11}$$

The delta-function source at $\vec{r} = \vec{R}$ in (7) is entirely accounted for by the known potential of a point source,[1]

$$\frac{1}{|\vec{r} - \vec{R}|} = (r^2 + R^2 - 2\, r\, R \cos\theta)^{-1/2}$$

$$= \sum_{n=0}^{\infty} P_n(\cos\theta) \begin{cases} \frac{1}{R}\left(\frac{r}{R}\right)^n , & 0 \leqq r \leqq R \,, \\ \frac{1}{r}\left(\frac{R}{r}\right)^n , & R \leqq r \leqq \infty \,. \end{cases}$$

We now find the functions $A_n(t)$ and $B_n(t)$ for which the potential (11) satisfies the membrane boundary condition (9) and initial condition (10). Substituting (11) in (9), we obtain the pair of coupled first-order differential equations,

$$- (n+1) R^n + n A_n(t) = - \frac{1}{\alpha} (n+1) B_n(t)$$
$$= \epsilon \left[B_n(t) - R^n - A_n(t) + \frac{dB_n}{dt} - \frac{dA_n}{dt} \right] . \qquad (12)$$

Applying the initial condition (10) to the potential (11), we obtain

$$B_n(0) - R^n - A_n(0) = 0 \,. \qquad (13)$$

The solution to the pair of equations (12) may be written in the form

$$A_n(t) = a_n + d_n e^{-\lambda_n t} ,$$

$$B_n(t) = b_n + c_n e^{-\lambda_n t} . \qquad (14)$$

Substituting (14) in (12) and equating the exponential and time-independent parts separately, we have

$$- (n+1) R^n + n a_n = - \frac{n+1}{\alpha} b_n = \epsilon \left[b_n - R^n - a_n \right] , \qquad (15)$$

$$n d_n = -\frac{n+1}{\alpha} c_n = \epsilon [c_n - d_n](1 - \lambda_n) . \tag{16}$$

Substituting (14) in (13) yields

$$b_n + c_n - R^n - a_n - d_n = 0 . \tag{17}$$

Solving the two equations (15) for a_n and b_n, we obtain

$$a_n = \frac{R^n [\epsilon(\alpha - 1) + n + 1]}{n + \epsilon\left(\frac{\alpha n}{n+1} + 1\right)} \tag{18}$$

and

$$b_n = \alpha R^n \left[1 - \frac{n[\epsilon(\alpha - 1) + n + 1]}{n(n+1) + \epsilon(\alpha n + n + 1)}\right] . \tag{19}$$

Using the second of equations (15), the first of equations (16) together with equation (17), we obtain the following expressions for c_n and d_n,

$$c_n = \frac{n(n+1)b_n}{\epsilon(1 + n + \alpha n)} , \tag{20}$$

$$d_n = -\frac{(n+1)^2 b_n}{\epsilon\alpha(1 + n + \alpha n)} . \tag{21}$$

Finally, solving Equations (16) for λ_n, we have

$$\lambda_n = 1 + \frac{n}{\epsilon} \frac{1+n}{1 + n + \alpha n} . \tag{22}$$

Substituting (18) through (22) in (14), and the resulting expressions for $A_n(t)$ and $B_n(t)$ in the expansion (11) for the potential we have for the potential inside the cell, i.e., for $r \leqq 1$,

$$V(r, \theta, t) = \frac{1}{|\vec{r} - \vec{R}|} + \sum_{n=0}^{\infty} \frac{(n+1)(rR)^n P_n(\cos\theta)}{n(n+1)+\epsilon(1+n+\alpha n)}$$

$$\cdot \left[1 + n + \epsilon(\alpha - 1) - \frac{(n+1)(2n+1)}{1+n+\alpha n} e^{-\left(\frac{n(n+1)}{1+n+\alpha n} + \epsilon\right)\frac{t}{\epsilon}} \right] \quad (23)$$

and for the potential outside the cell, i. e., for $r \geqq 1$,

$$V(r, \theta, t) = \frac{\alpha\epsilon}{r} \sum_{n=0}^{\infty} \frac{(2n+1)P_n(\cos\theta)\left(\frac{R}{r}\right)^n}{n(n+1)+\epsilon(\alpha n+n+1)} \cdot \left[1 + \frac{n(n+1)}{\epsilon(1+n+\alpha n)} e^{-\left(1+\frac{n}{\epsilon}\frac{1+n}{1+n+\alpha n}\right)t} \right]$$

$$(24)$$

Equations (23) and (24) are the unique solution to Equations (7) - (10). A direct substitution of (23) and (24) in (7) - (10) verifies that they are indeed the solution to the problem, and the uniqueness theorem[1] proves that they represent the only solution to the problem.

The solution given by (23) and (24) is unwieldy. We shall confine our discussion to the special case of small ϵ, which is the only case of physiological interest.

We can see from the solutions (23) and (24) that the potential contains two natural time constants. One is $\tau_m = 1$, the other $\tau_i = \epsilon$. We will refer to variations on a time scale $t \sim \tau_m$ as the slow transient, and variations on a time scale $t \sim \tau_i$, as the rapid transient. Converting to physical time (primed) these constants are $\tau_m' = C_m \delta / \sigma_m \sim 3 \times 10^{-3}$ sec and $\tau_i' = C_m a / \sigma_i \lesssim 7 \times 10^{-6}$ sec. The first is just the product of the membrane capacitance per unit area and the membrane surface resistivity, the second and shorter time is the product of the membrane capacitance per unit area and an effective surface resistivity of the interior of the cell.

B. Solution for Small ϵ

Since the parameter ϵ is small, the two time scales are of very different magnitudes and we obtain simplifications in formulas (23) and (24) for the two separate epochs $0 \leqq t \lesssim \epsilon$ (in which e^{-t} is essentially unity so that the slow transient has barely started) and $\epsilon << t \lesssim 1$ (in which $e^{-t/\epsilon}$ is essentially zero so that the rapid transient is over). First we expand the coefficients in (23) and (24) in powers of ϵ and retain terms of $0(\epsilon)$ and thereby obtain the following formulas valid for all t,

$$V(r,\theta,t) = \frac{1}{|\vec{r} - \vec{R}|} + \frac{1 - e^{-t}}{\epsilon} + \alpha - 1 + \sum_{n=1}^{\infty} \frac{(rR)^n}{n} P_n(\cos\theta) \cdot \left[(1+n) - \epsilon\left(2 + \frac{1}{n}\right) - (2n+1)\left(\frac{n+1}{1+n+\alpha n} - \frac{\epsilon}{n}\right) e^{-t} e^{-\frac{n(n+1)}{1+n+\alpha n}\frac{t}{\epsilon}} \right] + 0(\epsilon^2), \quad r \leqq 1, \tag{25}$$

and

$$V(\vec{r},t) = \frac{\alpha}{r} + \alpha \sum_{n=1}^{\infty} r^{-n-1} P_n(\cos\theta) R^n \frac{2n+1}{1+n+\alpha n} e^{-\left(1 + \frac{n}{\epsilon}\frac{1+n}{1+n+\alpha n}\right)t} + \epsilon\alpha \sum_{n=1}^{\infty} r^{-n-1} P_n(\cos\theta) R^n \left(\frac{1}{n} + \frac{1}{n+1}\right)\left[1 - e^{-\left(1 + \frac{n}{\epsilon}\frac{1+n}{1+n+\alpha n}\right)t}\right] + 0(\epsilon^2), \quad r > 1. \tag{26}$$

The $n = 0$ terms have been written separately to illustrate their simplicity. The summation of the first term in square brackets in (25) can be written in closed form, by noting that (letting $rR = a$)

$$\sum_{n=0}^{\infty} a^n P_n(\cos\theta) = \left(1 + a^2 - 2a\cos\theta\right)^{-1/2},$$

and

$$\sum_{n=1}^{\infty} \frac{a^n}{n} P_n(\cos\theta) = \int_0^a \frac{da'}{a'} \sum_{n=1}^{\infty} a'^{\,n} P_n(\cos\theta)$$

$$= \int_0^a \frac{da'}{a'} \left[\left(1 - 2a\cos\theta + a^2\right)^{-1/2} - 1 \right]$$

$$= \log 2 - \log \left[\left(1 + a^2 - 2a\cos\theta\right)^{1/2} + 1 - a\cos\theta \right],$$

so that, (25) becomes

$$V(r,t) = \frac{1 - e^{-t}}{\epsilon} + \frac{1}{|\vec{r} - \vec{R}|} + \frac{1}{R\left|\vec{r} - \frac{\vec{R}}{R^2}\right|}$$

$$- \log\left[1 - rR\cos\theta + \left(1 + r^2R^2 - 2rR\cos\theta\right)^{1/2}\right] - 2 + \log 2 + \alpha$$

$$- e^{-t} \sum_{n=1}^{\infty} \left[rR\,e^{-\frac{1+n}{1+n+\alpha n}\frac{t}{\epsilon}} \right]^n \frac{(n+1)(2n+1)}{n(n+1+\alpha n)} P_n(\cos\theta)$$

$$- \epsilon \sum_{n=1}^{\infty} (rR)^n \left(\frac{2}{n} + \frac{1}{n^2}\right) P_n(\cos\theta) \left[1 - e^{-\left(1 + \frac{n}{\epsilon}\frac{1+n}{1+n+\alpha n}\right)t}\right]$$

$$+ 0(\epsilon^2), \quad r \leqq 1 . \qquad (27)$$

The third term in (27) is the potential of an image source of magnitude $4\pi/R$, located at $r = 1/R$ on the $\theta = 0$ axis,

$$\left(1 + r^2R^2 - 2rR\cos\theta\right)^{-1/2} = \frac{1}{R\left|\vec{r} - \frac{\vec{R}}{R^2}\right|} .$$

C. Long-Time Solution

Examining (26) and (27), we see that the only remaining time dependence, when $t/\epsilon >> 1$, is in one term in the inside potential. The outside potential is independent of time during this epoch. The time-dependent term $(1 - e^{-t})/\epsilon$ in (25) represents the transient buildup of the cell interior to a large potential $(0[1/\epsilon])$ in a time $t \sim 1$.

We also can see from (26) that in the limit $\epsilon \to 0$, $t/\epsilon \to \infty$, the outside potential approaches an inverse r potential. The outer surface of the membrane becomes an equipotential surface, at potential $V = \alpha$, plus terms of $0(\epsilon,\ e^{-t/\epsilon})$. The deviation from isopotentiality is given to $0(\epsilon)$ by the time-independent part of the second sum in (26) (when $t/\epsilon >> 1$).

Neglecting terms of $0(\epsilon,\ e^{-t/\epsilon})$, Equation (27) yields a closed-form expression for the inside potential,

$$V(\vec{r}, t) = \frac{1 - e^{-t}}{\epsilon} + \frac{1}{|\vec{r} - \vec{R}|} + \frac{1}{R\left|\vec{r} - \frac{\vec{R}}{R^2}\right|}$$

$$- \log\left[1 - rR\cos\theta + \left(1 + r^2R^2 - 2rR\cos\theta\right)^{1/2}\right]$$

$$- 2 + \log 2 + \alpha + 0\left(\epsilon, e^{-t/\epsilon}\right), \quad r < 1 . \qquad (27')$$

Equation (27') represents the entire part of the interior potential that is within the current realm of measurability in physiological experiments. The terms of higher order in ϵ are too small to detect; the terms of higher order in $e^{-t/\epsilon}$ are too rapid to detect, and also occur during a period when the assumption of a pure current source is questionable.

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.[2]

Examination of Equation (27') shows that the effect of the finite conductivity of the external medium or, equivalently, the removal of the isopotentiality assymption, is merely to increase the inside potential by an additive constant, α, relative to the potential a long distance away from the cell.

We now give a closed-form expression for the outside potential when $t >> \epsilon$, neglecting terms of $0(\epsilon^2, e^{-t/\epsilon})$. We note that the following sum can be evaluated:

$$\sum_{n=1}^{\infty} \frac{a^{n+1}}{n+1} P_n(\cos\theta) = \int_0^a da' \sum_{n=1}^{\infty} a'^{\,n} P_n(\cos\theta)$$

$$= \int_0^a da' \left[\left(1 - 2a' \cos\theta + a'^{\,2}\right)^{-1/2} - 1 \right]$$

$$= \log\left[\left(1 + a^2 - 2a\cos\theta\right)^{1/2} + a - \cos\theta \right] - a - \log(1 - \cos\theta),$$

so that (26) becomes

$$V(\vec{r}, t) = \frac{\alpha}{r} + \frac{\epsilon\alpha}{R} \sum_{n=1}^{\infty} \left(\frac{R}{r}\right)^{n+1} P_n(\cos\theta) \left(\frac{1}{n} + \frac{1}{n+1}\right) + 0\left(\epsilon^2, e^{-t/\epsilon}\right)$$

$$= \frac{\alpha}{r} + \frac{\epsilon\alpha}{R} \left[\log\left\{ \frac{R}{r} - \cos\theta + \left(1 - 2\frac{R}{r}\cos\theta + \frac{R^2}{r^2}\right)^{1/2} \right\} - \log(1 - \cos\theta) - \frac{R}{r} \right.$$

$$\left. - \frac{R}{r} \log\left\{ 1 - \frac{R}{r}\cos\theta + \left(1 - 2\frac{R}{r}\cos\theta + \frac{R^2}{r^2}\right)^{1/2} \right\} + \frac{R}{r}\log 2 \right]$$

$$+ 0\left(\epsilon^2, e^{-t/\epsilon}\right), \quad r > 1. \qquad (28)$$

Equation (28) shows that the deviation from a simple inverse distance potential in the external medium is of $0(\epsilon)$, and hence hardly detectable. This is an extremely interesting result. It indicates that to $0(1)$ 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 appears in the $0(\epsilon)$ term, whereas for the interior potential it appears already in the $0(1)$ term. On physical grounds, although we have not actually proved it, 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 could be shown by moving the second electrode from infinity to a finite position.

D. Transmembrane Potential

Defining the transmembrane potential by

$$\Delta V = V(1^-, \theta, t) - V(1^+, \theta, t),$$

we obtain from (26) and (27),

$$\Delta V = \frac{1 - e^{-t}}{\epsilon} + 2\left(1 + R^2 - 2R\cos\theta\right)^{-1/2} - \log\left[1 - R\cos\theta + \left(1 + R^2 - 2R\cos\theta\right)^{1/2}\right]$$

$$-2 + \log 2 - e^{-t}\sum_{n=1}^{\infty}\left[R e^{-\frac{1+n}{1+n+\alpha n}\frac{t}{\epsilon}}\right]^n \left(2 + \frac{1}{n}\right) P_n(\cos\theta)$$

$$-\epsilon\sum_{n=1}^{\infty} R^n \frac{(2n+1)(1+n+\alpha n)}{n^2(n+1)} P_n(\cos\theta)\left[1 - e^{-\left(1 + \frac{n}{\epsilon}\frac{1+n}{1+n+\alpha n}\right)t}\right]$$

$$+ 0(\epsilon^2), \qquad (29)$$

for all t. For long times, $t/\epsilon \to \infty$, (29) becomes

$$\Delta V = \frac{1 - e^{-t}}{\epsilon} + 2\left(1 + R^2 - 2R\cos\theta\right)^{-1/2} - \log\left[1 - R\cos\theta + \left(1 + R^2 - 2R\cos\theta\right)^{1/2}\right]$$

$$- 2 + \log 2 - \epsilon \sum_{n=1}^{\infty} R^n \frac{(2n+1)(1+n+\alpha n)}{n^2(n+1)} P_n(\cos\theta)$$

$$+ 0(\epsilon^2, e^{-t/\epsilon}) . \qquad (30)$$

Thus, to 0(1), for long times ΔV is independent of the external conductivity. Almost all experimental measurements are taken in the domain in which Equation (30) is valid.

E. Infinite External Conductivity

It is of some mathematical interest that in the special case of $\alpha = 0$, corresponding to infinite external conductivity or outer membrane surface constrained to a constant potential of zero, a great simplification of (25) occurs and a closed-form expression can be obtained to 0(1), for all t. Letting $\alpha = 0$ in (25) we obtain

$$V(\vec{r}, t) = \frac{1 - e^{-t}}{\epsilon} + \frac{1}{|\vec{r} - \vec{R}|} + \frac{1}{R\left|\vec{r} - \frac{\vec{R}}{R^2}\right|}$$

$$- \log\left[1 - rR\cos\theta + \left(1 + r^2R^2 - 2rR\cos\theta\right)^{1/2}\right] - 2 + \log 2$$

$$- e^{-t} \sum_{n=1}^{\infty} \left(rR\, e^{-t/\epsilon}\right)^n \left(2 + \frac{1}{n}\right) P_n(\cos\theta)$$

$$- \epsilon \sum_{n=1}^{\infty} (rR)^n \left(\frac{2}{n} + \frac{1}{n^2}\right) P_n(\cos\theta) \left[1 - e^{-\left(1 + \frac{n}{\epsilon}\right)t}\right]$$

$$+ 0(\epsilon^2)$$

$$
\begin{aligned}
&= \frac{1 - e^{-t}}{\epsilon} + \left(r^2 + R^2 - 2rR\cos\theta\right)^{-1/2} + \left(1 + r^2R^2 - 2rR\cos\theta\right)^{-1/2} \\
&\quad - 2e^{-t}\left(1 + r^2R^2e^{-2t/\epsilon} - 2rRe^{-t/\epsilon}\cos\theta\right)^{-1/2} \\
&\quad - \log\left[(1 - rR\cos\theta) + \left(1 + r^2R^2 - 2rR\cos\theta\right)^{1/2}\right] \\
&\quad + e^{-t}\log\left[1 - rRe^{-t/\epsilon}\cos\theta + \left(1 + r^2R^2e^{-2t/\epsilon} - 2rRe^{-t/\epsilon}\cos\theta\right)^{1/2}\right] \\
&\quad - (2 - \log 2)(1 - e^{-t}) + 0(\epsilon), \quad r \leqq 1, \qquad (29)
\end{aligned}
$$

and $V = 0$ for $r > 1$.

F. 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 (27') shows that the external conductivity (and thus the external potential) enters into the 0(1) term (the second term) 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 potential.

This is not the case for two reasons. First, under most conditions $\epsilon \lesssim 0.005$ and so the 0(1) term in most locations is insignificant compared to the total potential. Close to the point source, at distances less than a ϵ, the 0(1) term is approximately equal to the leading term (of order

$1/\epsilon$). However, at this location and under these conditions, the contribution of the external conductivity to the $0(1)$ term is small. Secondly, the most important potential for physiological purposes is the transmembrane potential ΔV and this is independent of the external conductivity to two orders of magnitude of ϵ; that is to say, the external resistance appears multiplied by ϵ in the expression for ΔV whereas, for instance, the terms involving the membrane capacitance appear divided by ϵ. The earlier analyses are then not in serious error.

It is rather interesting to pursue this latter point concerning the dependence of ΔV on ϵ. 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 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 independent of the external resistance to two orders of magnitude. This result may be rationalized by saying that 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 secondary.

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 given by the O(1) term 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 O(1) term of the transmembrane potential, 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 shape would be insulated from the effect of changes in the extracellular space.

Our analysis shows that the effects of external resistance (and thus external potential) on a transmembrane potential like the action potential are extremely small, occurring only in a high order term. 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 the transmembrane potential from the external potential is probably 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.

III. SINGULAR PERTURBATION ANALYSIS USING MATCHED ASYMPTOTIC EXPANSIONS

The Legendre polynomial expansions (23) and (24) represent the exact solution to the problem defined by Equations (7), (8), (9) and (10) for a spherical cell. It is valid for all values of ϵ and t. For the case of physiological interest in which $\epsilon << 1$ and $t/\epsilon >> 1$ we were able to study the limiting behavior of the solution (23) and (24), as $\epsilon \rightarrow 0$ and $t/\epsilon \rightarrow \infty$.

Another approach that may be taken is to solve the problem by singular perturbation theory. Rather than considering the limiting behavior of the solution, we may apply a limiting process directly to Equations (7), (8), (9) and (10) and bypass the exact solution going directly to the solution in various limiting cases of interest. This procedure has a number of advantages. The equations to be solved are simpler (although there are more of them). In the case of the spherical cell under consideration, it was 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 solution (23) and (24). 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. We also will see that it is possible to gain greater insight into the physical process corresponding to each limit from the limiting forms of the equations which lead directly to the corresponding limiting solutions.

A. Long-Time Solution

First, we will obtain the solution valid for long times, i.e., $t >> \epsilon$. The solution in this epoch will be obtained using Equations (7), (8) and (9) generalized to arbitrary geometry. The initial condition (10) does not apply during 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 we will subsequently obtain.

We expand the potential in a series in which each successive term is of higher order in ϵ than the preceding one:[3]

$$V(\vec{r}, t, \epsilon) = \zeta_0(\epsilon)\, V_0(\vec{r}, t) + \zeta_1(\epsilon)\, V_1(\vec{r}, t) + \cdots , \tag{32}$$

where $\zeta_{n+1}(\epsilon)/\zeta_n(\epsilon) \rightarrow 0$ as $\epsilon \rightarrow 0$, and $V_0, V_1, \ldots$ are all of $0(1)$. Equation (32) is an asymptotic expansion for $V(\vec{r}, t, \epsilon)$ in the sense that each term improves the approximation, in the limit $\epsilon \rightarrow 0$, that is,

$$\lim_{\epsilon \rightarrow 0} \frac{1}{\zeta_N(\epsilon)} \left[V(\vec{r}, t, \epsilon) - \sum_{n=1}^{N} \zeta_n(\epsilon) V_n(\vec{r}, t) \right] = 0 .$$

Substituting the expansion (32) in Equation (7) yields,

$$\nabla^2 V = \zeta_0(\epsilon) \nabla^2 V_0 + \zeta_1(\epsilon) \nabla^2 V_1 + \cdots = -4\pi\, \delta(\vec{r} - \vec{R}) . \tag{33}$$

Substituting (32) in the boundary condition (5), and equating terms of the same order in ϵ yields the following set of boundary conditions for each order,

$$\frac{\partial V_0^-}{\partial n} = 0 = \frac{1}{\alpha} \frac{\partial V_0^+}{\partial n}$$

$$\frac{\partial V_1^-}{\partial n} = \frac{\epsilon \zeta_0(\epsilon)}{\zeta_1(\epsilon)} \left(V_0^+ - V_0^- + \frac{\partial V_0^+}{\partial t} - \frac{\partial V_0^-}{\partial t} \right) = \frac{1}{\alpha} \frac{\partial V_1^+}{\partial n}$$

$$\frac{\partial V_2^-}{\partial n} = \frac{\epsilon \zeta_1(\epsilon)}{\zeta_2(\epsilon)} \left(V_1^+ - V_1^- + \frac{\partial V_1^+}{\partial t} - \frac{\partial V_1^-}{\partial t} \right) = \frac{1}{\alpha} \frac{\partial V_2^+}{\partial n}$$

$$\cdots\cdots \tag{34}$$

In order that all terms in each equation in (34) be of the same order in ϵ we require that

$$\frac{\zeta_{n+1}(\epsilon)}{\zeta_n(\epsilon)} = \epsilon \; . \tag{35}$$

Returning to Equation (33), we might be tempted to try $\zeta_0(\epsilon) = 1$, leading to the lowest order equation,

$$\nabla^2 V_0 = -4\pi\, \delta(\vec{r} - \vec{R}) \; .$$

This equation for V_0 cannot be consistent with the lowest-order boundary condition for V_0 in (34). The equation states that there is a source of current within the cell; the boundary condition implies that no current crosses the membrane. No steady state is possible under these conditions. The conclusion is that the second term in the expansion of $\nabla^2 V$, rather than the first, must be of the same order as the delta function. This requires that $\zeta_1(\epsilon) = 1$ and hence, by (35), $\zeta_0(\epsilon) = \epsilon^{-1}$. We therefore obtain the following sequence of problems, for the potential

$$V(\vec{r}, t\, ;\epsilon) = \frac{1}{\epsilon}\, V_0(\vec{r}, t) + V_1(\vec{r}, t) + \epsilon\, V_2(\vec{r}, t) + \cdots , \tag{36}$$

$$\begin{cases} \nabla^2 V_0 = 0 \, , \\ \dfrac{\partial V_0^-}{\partial n} = 0 = \dfrac{\partial V_0^+}{\partial n} \, , \\ V_0 \to 0 \text{ as } |\vec{r}| \to \infty , \end{cases} \tag{37}$$

$$
\begin{cases}
\nabla^2 V_1 = -4\pi\ \delta(\vec{r}-\vec{R}) , \\
\dfrac{\partial V_1^-}{\partial n} = V_0^+ - V_0^- + \dfrac{\partial V_0^+}{\partial t} - \dfrac{\partial V_0^-}{\partial t} = \dfrac{1}{\alpha}\dfrac{\partial V_1^+}{\partial n} , \\
V_1 \to 0 \text{ as } |\vec{r}| \to \infty ,
\end{cases}
\tag{38}
$$

$$
\begin{cases}
\nabla^2 V_2 = 0 , \\
\dfrac{\partial V_2^-}{\partial n} = V_1^+ - V_1^- + \dfrac{\partial V_1^+}{\partial t} - \dfrac{\partial V_1}{\partial t} = \dfrac{1}{\alpha}\dfrac{\partial V_2^+}{\partial n} , \\
V_2 \to 0 \text{ as } |\vec{r}| \to \infty ,
\end{cases}
\tag{39}
$$

. . . .

The solution to the lowest-order problem (37) is:

$$
V_0(\vec{r}, t) = \begin{cases} f_0(t) , & \text{inside,} \\ 0 , & \text{outside .} \end{cases}
\tag{40}
$$

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 $|\vec{r}| = \infty$.

Performing a volume integral of the Laplacian (38) over the volume enclosed by the surface S just inside the membrane,

$$
\iiint \nabla^2 V_1 \, d^3 r = -4\pi = \iint \frac{\partial V_1^-}{\partial n} \, dS .
\tag{41}
$$

Using the boundary condition of (38) for $\partial V_1^- / \partial n$, and the result (40) for V_0 , (41) leads to

$$
4\pi = \iint \left(f_0(t) + \frac{\partial f_0}{\partial t} \right) dS = A \left(f_0(t) + \frac{\partial f_0}{\partial t} \right) ,
\tag{42}
$$

where A is the surface area of the membrane. Solving the first order linear differential Equation (42) 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 (10) to be satisfied, leading to

$$V_0(\vec{r}, t) = \frac{4\pi}{A} \begin{cases} 1-e^{-t}, & \text{inside,} \\ 0, & \text{outside} \end{cases} \quad . \tag{43}$$

Although we are able to satisfy the initial condition for the $0(\epsilon^{-1})$ term, 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 (32) is only valid for $t \gg \epsilon$. Note that (43) and (36) demonstrate that the cell interior builds up to a large potential $4\pi/\epsilon A$ which is just the reciprocal of the small parameter ϵ multiplied by the current per unit area crossing the membrane, $4\pi/A$. This result is obtained independent of the shape of the cell and may be considered a generalization of the $1/\epsilon$ term in Equation (25) for the potential within a spherical cell. Converting to physical (primed) units, this potential corresponds to $V' = (4\pi/A')(\delta/\sigma_m)$, 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 (37), but the voltage jump $V_0 = 4\pi/\epsilon A$ 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 (43) in (38) yields

$$\begin{cases} \nabla^2 V_1 = -4\pi \ \delta(\vec{r} - \vec{R}), \\ \dfrac{\partial V_1^-}{\partial n} = -\dfrac{4\pi}{A} = \dfrac{1}{\alpha} \dfrac{\partial V_1^+}{\partial n}, \end{cases} \tag{44}$$

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 (39), we obtain

$$\iiint \nabla^2 V_2 \, d^3 r = 0 = \iint \frac{\partial V_2^-}{\partial n} \, dS$$

$$= \iint \left(V_1^+ - V_1^- + \frac{\partial V_1^+}{\partial t} - \frac{\partial V_1^-}{\partial t} \right) dS \tag{45}$$

This is an integral constraint on V_1, which combined with (44) determines V_1.

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

$$V_1(\vec{r}, t) = G_1(\vec{r}) + f_1(\vec{r}, t) \quad , \tag{46}$$

where G_1 is a time-independent Green's function satisfying

$$\begin{cases} \nabla^2 G_1 = -4\pi \, \delta(\vec{r} - \vec{R}) \, , \\ \dfrac{\partial G_1^-}{\partial n} = -\dfrac{4\pi}{A} = \dfrac{1}{\alpha} \dfrac{\partial G_1^+}{\partial n} , \\ \iint \left(G_1^+ - G_1^- \right) dS = 0 \, , \\ G_1(\infty) = 0 \quad . \end{cases} \tag{47}$$

With the definition of G_1 given by (46) and (47), we find, from (44) and (45), that f_1 must be the solution of

$$\begin{cases} \nabla^2 f_1 = 0 \, , \\ \dfrac{\partial f_1^-}{\partial n} = 0 = \dfrac{1}{\alpha} \dfrac{\partial f_1^+}{\partial n} \, , \\ f_1(\infty, t) = 0 \, , \\ \iint \left(f_1^+ - f_1^- + \dfrac{\partial f_1^+}{\partial t} - \dfrac{\partial f_1^-}{\partial t} \right) dS = 0 \, . \end{cases} \tag{48}$$

This problem is identical to that of (37) and (42) for V_0, except that the surface integral in (48) is zero rather than 4π.

The first three of Equations (48) imply

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

Substituting this in the fourth of Equations (48) yields

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

so that

$$f_1(\vec{r}, t) = \begin{cases} a_1 e^{-t} , & \text{inside} \\ 0 , & \text{outside} \end{cases} \qquad (49)$$

The constant a_1 is undetermined. Trying to satisfy the initial condition (10) would require a_1 to be equal to $-\Delta G_1 = G_1^+(\vec{r}) - G_1^-(\vec{r})$, but since ΔG_1 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 (32) is not valid at $t = 0$. In Figure 2, the solid curve represents the first two terms in the long-time expansion for the transmembrane potential. It can be seen that as $t \to 0$, the long-time expansion for the transmembrane potential, $\Delta(V_0 + V_1 + \ldots)$, 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 Figure 2.

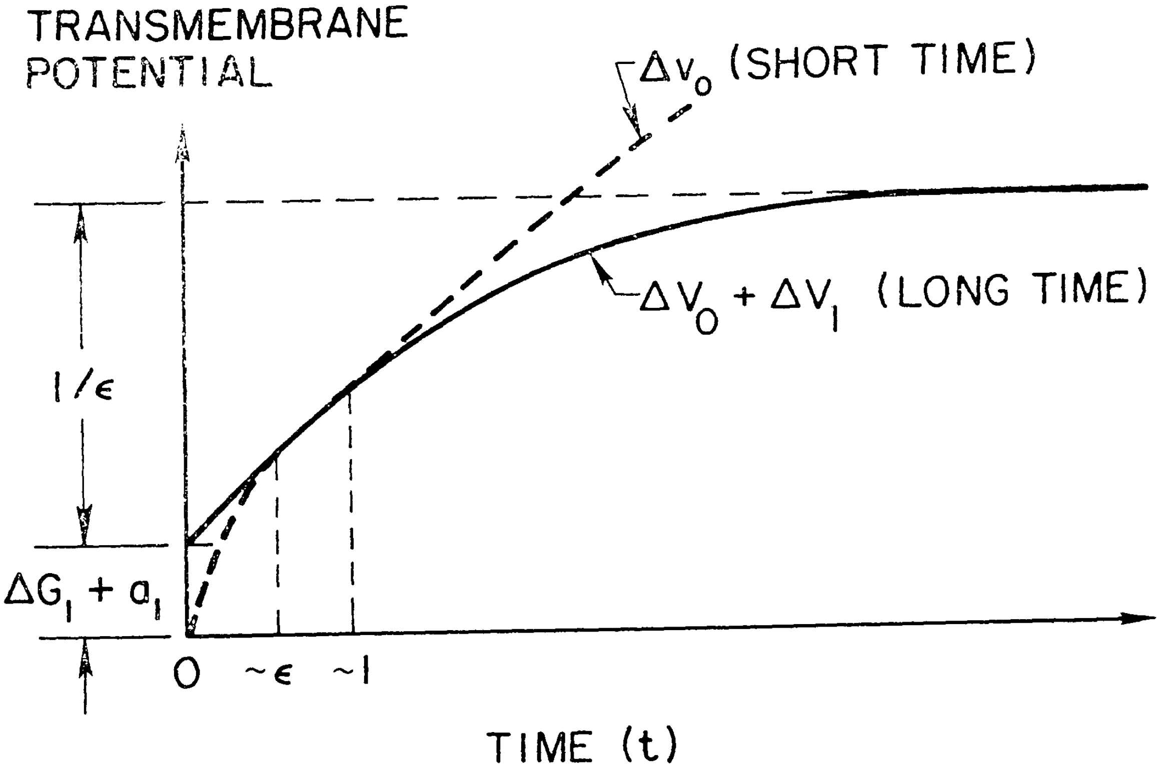

Figure 2. Matching of Short-Time and Long-Time Expansions.

The constants a_1, a_2, ... will be determined by matching, that is, by requiring that the short-time expansion be identical, term by term, to the long-time expansion in some intermediate range of t ($\epsilon \lesssim t \lesssim 1$) where they are both valid.

Continuing the procedure one order higher, we obtain for the ϵ problem, by substituting (46) and (49) in (39),

$$\begin{cases} \nabla^2 V_2 = 0 , \\ \dfrac{\partial V_2^-}{\partial n} = G_1^+ - G_1^- = \dfrac{1}{\alpha} \dfrac{\partial V_2^+}{\partial n} , \\ V_2 \to 0 \quad \text{as } |\vec{r}| \to \infty , \end{cases} \tag{50}$$

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

$$\iiint \nabla^2 V_3 \, d^3r = 0 = \iint \frac{\partial V_3^-}{\partial n} dS = -\iint \left(V_2^- - V_2^+ + \frac{\partial V_2^-}{\partial t} - \frac{\partial V_2^+}{\partial t} \right) dS \tag{51}$$

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

$$V_2 (\vec{r}, t) = G_2 (\vec{r}) + f_2(\vec{r}, t) \tag{52}$$

and require the two surface integral constraints

$$\iint \left(G_2^- - G_2^+ \right) dS = 0 , \tag{53}$$

$$\iint \left(f_2^- - f_2^+ + \frac{\partial f_2^-}{\partial t} - \frac{\partial f_2^+}{\partial t} \right) dS = 0 . \tag{54}$$

This leads to

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

and G_2 is a solution of the problem

$$\begin{cases} \nabla^2 G_2(\vec{r}) = 0 , \\ \dfrac{\partial G_2^-}{\partial n} = - G_1^- + G_1^+ = \dfrac{1}{\alpha} \dfrac{\partial G_2^+}{\partial n} , \\ \iint (G_2^- - G_2^+)\, dS = 0 , \\ G_2(\infty) = 0 . \end{cases} \tag{56}$$

B. Short-Time Solution

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 saw above and in Figure 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 Figure 2). In the limit of $\epsilon \to 0$ 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 $\partial V_n / \partial t$ is of the same order in ϵ as V_n. We therefore expect that in the initially valid expansion for $V(\vec{r}, t)$,

$$\left(\frac{\partial V_n^-}{\partial t} - \frac{\partial V_n^+}{\partial t} \right) >> \left(V_n^- - V_n^+ \right) .$$

There is another time variable, $\tilde{t} = t/\mu(\epsilon)$, for which

$$\left(\frac{\partial V_n^-}{\partial \tilde{t}} - \frac{\partial V_n^+}{\partial \tilde{t}} \right) \sim \left(V_n^- - V_n^+ \right) ,$$

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,

$$V(\vec{r}, t; \epsilon) = \nu_1(\epsilon)\, v_1(\vec{r}, \tilde{t}) + \nu_2(\epsilon)\, v_2(\vec{r}, \tilde{t}) + \cdots \tag{58}$$

Substituting (58) in (6),

$$\nabla^2 V = \nu_1(\epsilon)\nabla^2 v_1 + \nu_2(\epsilon)\nabla^2 v_2 + \ldots = -4\pi\, \delta(\vec{r} - \vec{R})\, u(\tilde{t}), \tag{59}$$

and substituting (58) in (51),

$$\nu_1 \frac{\partial v_1^-}{\partial n} + \nu_2 \frac{\partial v_2^-}{\partial n} + \cdots$$

$$= \frac{\nu_1}{\alpha}\frac{\partial v_1^+}{\partial n} + \frac{\nu_2}{\alpha}\frac{\partial v_2^+}{\partial n} + \cdots$$

$$= \epsilon\,\nu_1\left(v_1^+ - v_1^-\right) + \frac{\epsilon\,\nu_1}{\mu}\left(\frac{\partial v_1^+}{\partial \tilde{t}} - \frac{\partial v_1^-}{\partial \tilde{t}}\right)$$

$$+ \epsilon\,\nu_2\left(v_2^+ - v_2^-\right) + \frac{\epsilon\,\nu_2}{\mu}\left(\frac{\partial v_2^+}{\partial \tilde{t}} - \frac{\partial v_2^-}{\partial \tilde{t}}\right) + \cdots$$

We make the following separation in orders of ϵ,

$$\frac{\partial v_1^-}{\partial n} = \frac{1}{\alpha}\frac{\partial v_1^+}{\partial n} = \frac{\epsilon}{\mu}\left(\frac{\partial v_1^+}{\partial \tilde{t}} - \frac{\partial v_1^-}{\partial \tilde{t}}\right)$$

$$\frac{\partial v_2^-}{\partial n} = \frac{1}{\alpha}\frac{\partial v_2^+}{\partial n} = \epsilon\frac{\nu_1}{\nu_2}\left(v_1^+ - v_1^-\right) + \frac{\epsilon}{\mu}\left(\frac{\partial v_2^+}{\partial \tilde{t}} - \frac{\partial v_2^-}{\partial \tilde{t}}\right)$$

$$\cdot\quad\cdot\quad\cdot\quad\cdot\quad\cdot\quad\cdot\quad\cdot\quad\cdot\quad\cdot \tag{60}$$

This separation requires the choices

$$\mu(\epsilon) = \epsilon \quad \text{or} \quad \tilde{t} = \frac{t}{\epsilon}\ , \tag{61}$$

and

$$\frac{\nu_{n+1}}{\nu_n} = \epsilon\ . \tag{62}$$

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 $\nu_1(\epsilon) = 1$. The sequence of problems then becomes, for $t \geqq 0$,

$$\left\{\begin{array}{l} \nabla^2 v_1 = -4\pi\ \delta(\vec{r} - R) \\ \\ \dfrac{\partial v_1^-}{\partial n} = \dfrac{\partial v_1^+}{\partial \tilde{t}} - \dfrac{\partial v_1^-}{\partial \tilde{t}} = \dfrac{1}{\alpha}\dfrac{\partial v_1^+}{\partial n} \\ \\ v_1^-(\vec{r}, 0) = v_1^+(\vec{r}, 0) \\ \\ v_1(\infty, \tilde{t}) = 0 \end{array}\right. \tag{63}$$

$$\left\{\begin{array}{l} \nabla^2 v_2 = 0 \\ \\ \dfrac{\partial v_2^-}{\partial n} = v_1^+ - v_1^- + \dfrac{\partial v_2^+}{\partial \tilde{t}} - \dfrac{\partial v_2^-}{\partial \tilde{t}} = \dfrac{1}{\alpha}\dfrac{\partial v_2^+}{\partial n} \\ \\ v_2^-(\vec{r}, 0) = v_2^+(\vec{r}, 0) \\ \\ v_2(\infty, \tilde{t}) = 0 \end{array}\right. \tag{64}$$

. . . .

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 (63) over the cell volume,

$$\iiint \nabla^2 v_1\, d^3r = -4\pi = \iint \frac{\partial v_1^-}{\partial n}\, dS = \frac{\partial}{\partial \tilde{t}} \iint \left(v_1^+ - v_1^-\right) dS\ . \tag{65}$$

Integrating over $\tilde{t}$, and using the initial condition in (63), we find

$$\iint \left(v_1^+ - v_1^- \right) dS = -4\pi \tilde{t} . \tag{66}$$

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,

$$v_1(\vec{r}, t) = G_1(\vec{r}) + w_1(\vec{r}, \tilde{t}) + h(\vec{r})\tilde{t} , \tag{67}$$

where G_1 is the same Green's function that was defined in (46) and (47) and accounts completely for the singular part of v_1, and $w_1(\vec{r}, \tilde{t})$ is bounded.

Using (47) to eliminate G_1 from the boundary condition in (6.3),

$$\frac{\partial w_1^-}{\partial n} + \frac{\partial h^-}{\partial n} \tilde{t} = \frac{4\pi}{A} + \frac{\partial w_1^+}{\partial \tilde{t}} - \frac{\partial w_1^-}{\partial \tilde{t}} + h^+ - h^- = \frac{1}{\alpha} \frac{\partial w_1^+}{\partial n} + \frac{1}{\alpha} \frac{\partial h^+}{\partial n} \tilde{t} . \tag{68}$$

The only way (68) can be satisfied is if the coefficients of $\tilde{t}$ are zero, so that

$$\frac{\partial h^-}{\partial n} = \frac{\partial h^+}{\partial n} = 0 . \tag{69}$$

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

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

Using (66) to evaluate the constant, we have

$$h(\vec{r}) = \begin{cases} 4\pi / A , & \text{inside,} \\ 0 \quad , & \text{outside.} \end{cases} \tag{70}$$

The remainder of $v_1(\vec{r},\tilde{t})$, that is, $w_1(\vec{r},\tilde{t})$, can be expanded in a series of eigenfunctions in some 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 (67) - (70) in (63), and is

$$\begin{cases} \nabla^2 w_1 = 0 \\[4pt] \dfrac{\partial w_1^-}{\partial n} = \dfrac{\partial w_1^+}{\partial \tilde{t}} - \dfrac{\partial w_1^-}{\partial \tilde{t}} = \dfrac{1}{\alpha}\dfrac{\partial w_1^+}{\partial n} \\[4pt] w_1^-(\vec{r},0) - w_1^+(\vec{r},0) = G_1^+(\vec{r}) - G_1^-(\vec{r}) \\[4pt] w_1(\infty,\tilde{t}) = w_1(\vec{r},\infty) = 0\,. \end{cases} \tag{71}$$

We assume an eigenfunction expansion for $w_1(\vec{r},\tilde{t})$ of the form

$$w_1(\vec{r},t) = \begin{cases} \sum\limits_k g_k^i(\tilde{t})\,\phi_k^i(\vec{r})\,, & \text{inside,} \\[4pt] \sum\limits_k g_k^o(\tilde{t})\,\phi_k^o(\vec{r})\,, & \text{outside.} \end{cases} \tag{72}$$

In the case of the spherical cell considered in Section II, $\phi_k^i(\vec{r}) = P_k(\cos\theta)r^k$, and $\phi_k^o(\vec{r}) = P_k(\cos\theta)r^{-k-1}$; in general, ϕ_k^i and ϕ_k^o are eigenfunctions which are the solutions of Laplace's equation bounded inside and outside the cell, respectively. Substituting the form (72) in the membrane boundary condition in (71), we find

$$w_1(\vec{r}, t) = \sum_k a_k \, e^{-\lambda_k \tilde{t}} \begin{cases} \phi_k^i(\vec{r}) \ , & \text{inside,} \\ \dfrac{\alpha \, \partial\phi_k^-/\partial n}{\partial\phi_k^+/\partial n} \ \phi_k^o(\vec{r}), & \text{outside,} \end{cases} \tag{73}$$

where

$$\lambda_k = \left[\frac{\phi_k^-}{\partial\phi_n^-/\partial n} - \frac{\phi_k^+}{\partial\phi_n^+/\partial n} \right]^{-1} . \tag{74}$$

The Green's function G_1 may be expanded in terms of the same eigenfunctions ϕ_k^i and ϕ_k^o. Substituting this expansion for G_1, and the expansion (73) for w_1 in the initial condition in (71) yields values for the coefficients a_k in (73). We will not carry out this process in the general case, which is somewhat cumbersome, but return now to the special case of the spherical cell.

We have a general procedure for obtaining a solution to (63) for v_1 , and we could apply this to the special case of a sphere. We could also continue and similarly obtain a solution to (64) for v_2. However, we can more easily write down the solutions by taking the limit of the solutions (26) and (27) as $\epsilon \to 0$, and $\tilde{t} = t/\epsilon$ is held fixed, and then verify by direct substitution that the $0(1)$, $0(\epsilon)$, . . . terms are the solutions to (63), (64). . . , respectively.

Letting $t = \epsilon\tilde{t}$ in (26) and (27) and expanding $e^{-t} = e^{-\epsilon\tilde{t}}$ in powers of ϵ , we obtain for the inside potential

$$
\begin{aligned}
V(\vec{r}, t) = {} & \tilde{t} + \frac{1}{|\vec{r} - \vec{R}|} + \frac{1}{R\left|\vec{r} - \frac{\vec{R}}{R^2}\right|} - 2 + \alpha + \log 2 \\
& - \log\left[1 - rR\cos\theta + \left(1 + r^2R^2 - 2rR\cos\theta\right)^{1/2}\right] \\
& - \sum_{n=1}^{\infty}\left[rR\, e^{-\frac{1+n}{1+n+\alpha n}\tilde{t}}\right]^n \frac{(n+1)(2n+1)}{n(n+1+\alpha n)} P_n(\cos\theta) \\
& + \epsilon\left[-\frac{\tilde{t}^2}{2} + \tilde{t}\sum_{n=1}^{\infty}\left(rR\, e^{-\frac{1+n}{1+n+\alpha n}\tilde{t}}\right)^n \frac{(n+1)(2n+1)}{n(n+1+\alpha n)} P_n(\cos\theta)\right. \\
& \qquad \left. - \sum_{n=1}^{\infty}(rR)^n\left(\frac{2}{n} + \frac{1}{n^2}\right)P_n(\cos\theta)\left(1 - e^{-\frac{n(1+n)}{1+n+\alpha n}\tilde{t}}\right)\right] \\
& + 0(\epsilon^2), \quad r \leqq 1,
\end{aligned} \tag{75}
$$

and for the outside potential,

$$
\begin{aligned}
V(\vec{r}, t) = {} & \frac{\alpha}{r} + \frac{\alpha}{r}\sum_{n=1}^{\infty}\left(\frac{R}{r}\right)^n P_n(\cos\theta)\frac{2n+1}{1+n+\alpha n}\, e^{-\frac{n(1+n)}{1+n+\alpha n}\tilde{t}} \\
& + \epsilon\left[\frac{\alpha}{r}\sum_{n=1}^{\infty}\left(\frac{R}{r}\right)^n P_n(\cos\theta)\left\{\frac{2n+1}{n(n+1)}\left[1 - e^{-\frac{n(1+n)}{1+n+\alpha n}\tilde{t}}\right]\right.\right. \\
& \qquad \left.\left. - \frac{2n+1}{1+n+\alpha n}\,\tilde{t}\; e^{-\frac{n(1+n)}{1+n+\alpha n}\tilde{t}}\right\}\right] \\
& + 0(\epsilon^2), \quad r \geqq 1.
\end{aligned} \tag{76}
$$

We see that the $0(\epsilon^0)$ term in the short-time expansion of V in the cell interior, (75), has a linear growth in $\tilde{t}$. This behavior is shown by the dotted curve for Δv_0 in Figure 2. Thus we see that the first term in the short-time expansion does not correctly represent the solution for long times, $t \gtrsim 1$. Equation (75) also indicates that the $0(\epsilon)$ 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 $(1-e^{-t})/\epsilon$, and if we continued the expansion indefinitely to higher orders of ϵ, we would recover the $0(\epsilon^{-1})$ term in (27'), or (43). In most problems that can be handled by singular perturbation theory one is not able to obtain an exact solution or sum the expansion. It is instructive to compare (75) in this way with the exact solution. However, we should point out that it is in the other cases, where asymptotic expansions like (75) are the best that can be done, that the singular perturbation approach is seen to be mathematically more powerful than the exact method of Section II. In the present case the singular perturbation approach yields greater physical insight, although the formulation is a bit more clumsy than the exact formulation of Section II.

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 $a_0, a_1, a_2, \ldots$ appearing in the long-time solution. The value of a_0 must be consistent with the value of a_0 determined previously in (43). The intermediate time variable is defined as

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

where

$$\eta(\epsilon) \to 0 \text{ as } \epsilon \to 0$$

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

$$\eta(\epsilon)/\epsilon \to \infty \text{ as } \epsilon \to 0.$$

Thus the limiting behavior of t_η as $\epsilon \to 0$ is intermediate between t and $\tilde{t}$.

If we hold t_η fixed at some value in the overlap region of Figure 2, say t_η^*, and take the limit $\epsilon \to 0$, 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

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

and

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

In order to match the long-time and short-time expansions in the overlap region, it is most convenient to write the $t \to 0$ limit of the long-time expansion and the $\tilde{t} \to \infty$ limit of the short-time expansion both in terms of t.

As $t \to 0$ in the long-time solution given by (36), (43), (46), (49), (52), and (55), we obtain the expansion in powers of ϵ, for $r \leqq 1$,

$$\begin{aligned} V(\vec{r},t) &= \frac{1}{\epsilon}\left[1-e^{-t}\right] + \left[G_1(\vec{r}) + a_1e^{-t}\right] + \epsilon\left[G_2(\vec{r}) + a_2e^{-t}\right] + \dots \\ &\to \frac{1}{\epsilon}\left[t - \frac{t^2}{2} + \dots\right] + \left[G_1(\vec{r}) + a_1(1-t+\dots)\right] \\ &\quad + \epsilon\left[G_2(\vec{r}) + a_2(1-t+\dots)\right] + \dots \qquad (77a) \end{aligned}$$

where we have taken $a_0 = -4\pi/A = -1$ for a sphere, and for $r \geqq 1$,

$$V(\vec{r},t) = G_1(\vec{r}) + \epsilon\, G_2(\vec{r}) + \ldots \tag{77b}$$

Ignoring the exponentially small terms in (75), as $\tilde{t} \rightarrow \infty$, the short-time solution becomes, for $r \leqq 1$,

$$\begin{aligned} V(\vec{r},t) = {} & \frac{t}{\epsilon} + \frac{1}{|\vec{r} - \vec{R}|} + \frac{1}{R\left|\vec{r} - \frac{\vec{R}}{R^2}\right|} - 2 + \alpha + \log 2 \\ & - \log\left[1 - rR\cos\theta + \left(1 + r^2R^2 - 2rR\cos\theta\right)^{1/2}\right] \\ & - \frac{t^2}{2\epsilon} - \epsilon \sum_{n=1}^{\infty} (rR)^n \left(\frac{2}{n} + \frac{1}{n^2}\right) P_n(\cos\theta)\;. \\ & + \cdot\cdot\cdot \end{aligned} \tag{78a}$$

and for $r \geqq 1$,

$$V(\vec{r},t) = \frac{\alpha}{r} + \epsilon\frac{\alpha}{r}\sum_{n=1}^{\infty}\left(\frac{R}{r}\right)^n P_n(\cos\theta)\,\frac{2n+1}{n(n+1)} + \cdots \tag{78b}$$

Comparing (77) and (78) we find that our earlier choice of $a_0 = -4\pi/A = -1$ is satisfactory, and

$$a_1 = a_2 = \ldots = 0 \tag{79}$$

We also find that the solution $G_1(\vec{r})$ to Equations (47) is

$$\begin{aligned} G_1(\vec{r}) = {} & \frac{1}{|\vec{r} - \vec{R}|} + \frac{1}{R\left|\vec{r} - \frac{\vec{R}}{R^2}\right|} - 2 + \alpha + \log 2 \\ & - \log\left[1 - rR\cos\theta + (1 + r^2R^2 - 2rR\cos\theta)^{1/2}\right], \; r \leqq 1, \end{aligned} \tag{80a}$$

and

$$G_1(\vec{r}) = \frac{\alpha}{r}, \quad r \geqq 1, \tag{80b}$$

and the solution $G_2(\vec{r})$ to Equations (56) is

$$G_2(\vec{r}) = -\sum_{n=1}^{\infty} (rR)^n \left(\frac{2}{n} + \frac{1}{n^2}\right) P_n(\cos\theta), \quad r \leqq 1, \tag{81a}$$

and

$$G_2(\vec{r}) = \frac{\alpha}{r} \sum_{n=1}^{\infty} \left(\frac{R}{r}\right)^n \frac{2n+1}{n(n+1)} P_n(\cos\theta), \quad r \geqq 1 . \tag{81b}$$

IV. SINGULAR PERTURBATION ANALYSIS USING TWO TIME-VARIABLES

In this Section we repeat the analysis of the problem solved previously in Section II by exact methods and in Section III by using matched asymptotic expansions. We use instead a perturbation technique, introduced by Poincaré for analyzing the motion of a slightly nonlinear damped oscillator, which is particularly useful for problems in which there are two (or more) time constants of widely differing magnitude.[4] In the case of a damped oscillator, the two time constants are the period of oscillation and the damping time. In our case, the two time constants are the relaxation time associated with the membrane capacitance and membrane resistance, $\tau'_m = C_m \delta/\sigma_m$, and the relaxation time associated with the membrane capacitance and the interior medium resistance, $\tau'_i = C_m a/\sigma_i$, for which $\tau'_m/\tau'_i = \epsilon \ll 1$ (see discussion following Equation 24).

It is assumed that the potential may be represented by an asymptotic expansion of the form

$$V(\vec{r},t;\epsilon) = \zeta_0(\epsilon)\overline{V}_0(\vec{r},t,\tilde{t}) + \zeta_1(\epsilon)\,\overline{V}_1(\vec{r},t,\tilde{t}) + \ldots \qquad (82)$$

in which the quantities $\zeta_0, \zeta_1, \zeta_2, \ldots$ form an asymptotic sequence[5] of increasing order in ϵ, i.e.,

$$\lim_{\epsilon \to 0} \frac{\zeta_{n+1}(\epsilon)}{\zeta_n(\epsilon)} = 0$$

and,

$$\lim_{\epsilon \to 0} \frac{1}{\zeta_N(\epsilon)} \left[V(\vec{r},t;\epsilon) - \sum_{n=1}^{N} \zeta_n(\epsilon)\overline{V}_n(\vec{r},t,\tilde{t}) \right] = 0 \quad ,$$

so that each successive term in (82) improves the approximation, in the limit $\epsilon \to 0$. In anticipation of the result that the ζ_n's are identical to the ζ_n's in (32), we have used the same symbol. Also, $\tilde{t}$ will be found to be related to t by the same relation (61), and hence we use the same notation in anticipation of this result. It should be pointed out that $\overline{V}_n$ is considered to be a function of the space variable $\vec{r}$ and the two independent time variables t and $\tilde{t}$.

The specific functional form $\zeta_n(\epsilon)$ will be determined in the course of the perturbation analysis. The quantities $\overline{V}_0$, $\overline{V}_1$, $\overline{V}_2$, ... are all of the same order, 0(1), in ϵ. That is, they do not depend on ϵ, but are each functions of position $\vec{r}$, and two time variables, t, the slow time variable, and $\tilde{t}$, the fast time variable. The relationship between t and $\tilde{t}$ also will be determined by the perturbation analysis.

The problem which must be solved to determine the potential $V(\vec{r}, t; \epsilon)$ is again

$$\left\{\begin{array}{l} \nabla^2 V = -4\pi\,\delta(\vec{r}-\vec{R}) \\[6pt] \dfrac{\partial V^-}{\partial r} = \dfrac{1}{\alpha}\,\dfrac{\partial V^+}{\partial r} = \epsilon\left[V^+ - V^- + \dfrac{\partial V^+}{\partial t} - \dfrac{\partial V^-}{\partial t}\right] \\[6pt] V^+(\vec{r}, 0; \epsilon) - V^-(\vec{r}, 0; \epsilon) = 0 \\[6pt] V(\vec{\infty}, t; \epsilon) = 0 \quad . \end{array}\right. \tag{83}$$

As above, superscripts (+) and (-) indicate quantities on the outer and inner surfaces of the membrane.

Substituting the expansion (82) for V in (83), we have

$$\zeta_0 \nabla^2 \overline{V}_0 + \zeta_1 \nabla^2 \overline{V}_1 + \ldots = -4\pi\,\delta(\vec{r}-\vec{R}) \tag{84}$$

and substituting (82) in the membrane boundary condition in (83) we have

$$\zeta_0 \frac{\partial \overline{V}_0^-}{\partial r} + \zeta_1 \frac{\partial \overline{V}_1^-}{\partial r} + \ldots = \frac{1}{\alpha} \zeta_0 \frac{\partial \overline{V}_0^+}{\partial r} + \frac{1}{\alpha} \zeta_1 \frac{\partial \overline{V}_1^+}{\partial r} + \ldots$$
$$= \epsilon \Bigg[\zeta_0 \overline{V}_0^+ + \zeta_1 \overline{V}_1^+ + \ldots - \zeta_0 \overline{V}_0^- - \zeta_1 \overline{V}_1^- - \ldots$$
$$+ \zeta_0 \frac{\partial \overline{V}_0^+}{\partial t} + \zeta_1 \frac{\partial \overline{V}_1^+}{\partial t} + \ldots - \zeta_0 \frac{\partial \overline{V}_0^-}{\partial t} - \zeta_1 \frac{\partial \overline{V}_1^-}{\partial t} - \ldots$$
$$+ \frac{d\tilde{t}}{dt} \left(\zeta_0 \frac{\partial \overline{V}_0^+}{\partial \tilde{t}} + \zeta_1 \frac{\partial \overline{V}_1^+}{\partial \tilde{t}} + \ldots - \zeta_0 \frac{\partial \overline{V}_0^-}{\partial \tilde{t}} - \zeta_1 \frac{\partial \overline{V}_1^-}{\partial \tilde{t}} - \ldots \right) \Bigg] \qquad (85)$$

The procedure now is to collect terms of each order in ϵ in (84) and (85), and require that the equation and boundary condition be satisfied in each order. If we assume

$$\frac{d\tilde{t}}{dt} = \frac{1}{\epsilon} , \quad \tilde{t} = \frac{t}{\epsilon} \qquad (86)$$

the lowest-order boundary condition is

$$\frac{\partial \overline{V}_0^-}{\partial r} = \frac{1}{\alpha} \frac{\partial \overline{V}_0^+}{\partial r} = \frac{\partial \overline{V}_0^+}{\partial \tilde{t}} - \frac{\partial \overline{V}_0^-}{\partial \tilde{t}} . \qquad (87)$$

The choice (86) for $\tilde{t}$ is motivated by $\tau'_m / \tau'_i = \epsilon$, but its ultimate justification is that with this choice we will obtain a consistent set of problems for determining $\overline{V}_0$, $\overline{V}_1$, $\overline{V}_2$, ... Note that the partial derivative of $\overline{V}_0$ with respect to the slow variable, t, does not appear in the lowest-order boundary condition (87), nor does $\overline{V}_0$ itself. These quantities will appear in the next order boundary condition, which is

$$\frac{\partial \overline{V}_1^-}{\partial r} = \frac{1}{\alpha} \frac{\partial \overline{V}_1^+}{\partial r} = \overline{V}_0^+ - \overline{V}_0^- + \frac{\partial \overline{V}_0^+}{\partial t} - \frac{\partial \overline{V}_0^-}{\partial t} + \frac{\partial \overline{V}_1^+}{\partial \tilde{t}} - \frac{\partial \overline{V}_1^-}{\partial \tilde{t}} . \qquad (88)$$

To obtain (88), we set

$$\zeta_1(\epsilon) = \epsilon \, \zeta_0(\epsilon). \qquad (89)$$

Continuing the process to the next order, we have

$$\frac{\partial \overline{V}_2^-}{\partial r} = \frac{1}{\alpha}\frac{\partial \overline{V}_2^+}{\partial r} = \overline{V}_1^+ - \overline{V}_1^- + \frac{\partial \overline{V}_1^+}{\partial t} - \frac{\partial \overline{V}_1^-}{\partial t} + \frac{\partial \overline{V}_2^+}{\partial \tilde{t}} - \frac{\partial \overline{V}_2^-}{\partial \tilde{t}} \tag{90}$$

and

$$\zeta_2(\epsilon) = \epsilon\ \zeta_1(\epsilon)\ . \tag{91}$$

Returning to Equation (84), we might be tempted to assume $\zeta_0(\epsilon) = 1$, which places the δ function in the lowest-order problem, leading to

$$\nabla^2 \overline{V}_0 = -4\pi\ \delta(\vec{r}-\vec{R})\ .$$

If there is to be a steady state, however, in the limit $\tilde{t} \to \infty$, the lowest-order boundary condition becomes

$$\frac{\partial \overline{V}_0^-}{\partial r} = \frac{1}{\alpha}\frac{\partial \overline{V}_0^+}{\partial r} = 0 \quad \text{as } \tilde{t} \to \infty\ ,$$

i.e., the time derivatives must vanish in this limit. This equation and boundary condition are clearly inconsistent. The equation states that there is a source of current within the cell; the boundary condition states that no current crosses the boundary. To avoid this difficulty, we take

$$\zeta_0(\epsilon) = \frac{1}{\epsilon} \tag{92}$$

which places the δ function in the second problem rather than the first. As a result, (82) becomes

$$V(r,\theta,t;\epsilon) = \frac{1}{\epsilon}\ \overline{V}_0(r,\theta,t,\tilde{t}\,) + \overline{V}_1(r,\theta,t,\tilde{t}\,) + \ldots \tag{93}$$

and the problem (83) is replaced by the sequence of problems

$$\left\{\begin{aligned} &\nabla^2 \bar{V}_0 = 0 \\ &\frac{\partial \bar{V}_0^-}{\partial r} = \frac{1}{\alpha}\frac{\partial \bar{V}_0^+}{\partial r} = \frac{\partial \bar{V}_0^+}{\partial \tilde{t}} - \frac{\partial \bar{V}_0^-}{\partial \tilde{t}} \\ &\bar{V}_0(1,\theta,t,\tilde{t}) = 0 \\ &\bar{V}_0^+(1,\theta,0,0) = \bar{V}_0^-(1,\theta,0,0) \end{aligned}\right. \tag{94}$$

$$\left\{\begin{aligned} &\nabla^2 \bar{V}_1 = -4\pi\,\delta(\vec{r} - \vec{R}) \\ &\frac{\partial \bar{V}_1^-}{\partial r} = \frac{1}{\alpha}\frac{\partial \bar{V}_1^+}{\partial r} = \bar{V}_0^+ - \bar{V}_0^- + \frac{\partial \bar{V}_0^+}{\partial t} - \frac{\partial \bar{V}_0^-}{\partial t} + \frac{\partial \bar{V}_1^+}{\partial \tilde{t}} - \frac{\partial \bar{V}_1^-}{\partial \tilde{t}} \\ &\bar{V}_1(\infty,\theta,t,\tilde{t}) = 0 \\ &\bar{V}_1^+(1,\theta,0,0) = \bar{V}_1^-(1,\theta,0,0) \end{aligned}\right. \tag{95}$$

$$\left\{\begin{aligned} &\nabla^2 \bar{V}_2 = 0 \\ &\frac{\partial \bar{V}_2^-}{\partial r} = \frac{1}{\alpha}\frac{\partial \bar{V}_2^+}{\partial r} = \bar{V}_1^+ - \bar{V}_1^- + \frac{\partial \bar{V}_1^+}{\partial t} - \frac{\partial \bar{V}_1^-}{\partial t} + \frac{\partial \bar{V}_2^+}{\partial \tilde{t}} - \frac{\partial \bar{V}_2^-}{\partial \tilde{t}} \\ &\bar{V}_2(\infty,\theta,t,\tilde{t}) = 0 \\ &\bar{V}_2^+(1,\theta,0,0) = \bar{V}_2^+(1,\theta,0,0) \end{aligned}\right. \tag{96}$$

We now can proceed to solve these problems in succession. Taking the volume integral over the entire interior of the cell, of the Laplacian in (94):

$$\iiint\limits_{\text{cell}} \nabla^2 \bar{V}_0 \, d^3 r = 0 = \iint\limits_{r=1} \frac{\partial \bar{V}_0^-}{\partial r}\, dS = \frac{\partial}{\partial \tilde{t}} \iint\limits_{r=1} (\bar{V}_0^+ - \bar{V}_0^-)\,dS. \tag{97}$$

The second equality in (97) relates the volume integral of $\nabla^2\overline{V}_0$ to the surface integral of $\partial\overline{V}_0/\partial r$ over the inner surface of the membrane by application of the divergence theorem; the last equality in (97) follows from the boundary condition at r=1 in (94).

The solution to (94) is clearly independent of θ since there is no source term or boundary condition to introduce θ-dependence. Therefore $\overline{V}_0^+$ and $\overline{V}_0^-$ are constant, the surface integral in (97) becomes simply 4π times the integrand and consequently,

$$\frac{\partial\overline{V}_0^+}{\partial\tilde{t}} - \frac{\partial\overline{V}_0^-}{\partial\tilde{t}} = 0 \quad . \tag{98}$$

Since there is no θ dependence, and in addition $\overline{V}_0 \rightarrow 0$ as $r \rightarrow \infty$, the potential $\overline{V}_0$ must be of the form

$$\overline{V}_0(r,t,\tilde{t}\,) = \begin{cases} A(t,\tilde{t}\,), & \text{for } r < 1, \\ \frac{1}{r}\,B(t,\tilde{t}\,), & \text{for } r > 1. \end{cases}$$

Now, if we take a volume integral like (97) over a sphere of radius $\rho > 1$,

$$\iiint_{\rho > 1} \nabla^2\overline{V}_0 \, d^3r = 0 = 4\pi\, B(t,\tilde{t})$$

so that B=0 and $\overline{V}_0 = 0$ for $r > 1$. In particular, $\overline{V}_0^+ = 0$. Consequently, (98) becomes $\partial\overline{V}_0^-/\partial\tilde{t} = 0 = \partial A/\partial\tilde{t}$, and the inside potential is independent of $\tilde{t}$, the fast time variable. The potential is thus of the form

$$\overline{V}_0(r,\theta,t,\tilde{t}\,) = \begin{cases} A(t), & r < 1 \\ 0\,, & r > 1\,. \end{cases} \tag{99}$$

To obtain the functional form of A(t) we must go on to the next problem, (95). Taking the volume integral of the Laplacian in (95) over the entire cell interior, we have

$$\iiint\limits_{\text{cell}} \nabla^2 \overline{V}_1 d^3 r = -4\pi = \iint\limits_{r=1} \frac{\partial \overline{V}_1^-}{\partial r} dS$$

$$= \iint\limits_{r=1} \left(\overline{V}_0^+ - \overline{V}_0^- + \frac{\partial \overline{V}_0^+}{\partial t} - \frac{\partial \overline{V}_0^-}{\partial t} + \frac{\partial \overline{V}_1^+}{\partial \tilde{t}} - \frac{\partial \overline{V}_1^-}{\partial \tilde{t}} \right) dS$$

$$= -4\pi \left(A + \frac{dA}{dt} \right) + \frac{\partial}{\partial \tilde{t}} \iint\limits_{r=1} (\overline{V}_1^+ - \overline{V}_1^-) \, dS. \qquad (100)$$

Rearranging terms in (100),

$$A + \frac{dA}{dt} = 1 - \frac{1}{4\pi} \frac{\partial}{\partial \tilde{t}} \iint\limits_{r=1} (\overline{V}_1^+ - \overline{V}_1^-) \, dS \, . \qquad (101)$$

Since the left-hand-side of (101) is independent of $\tilde{t}$, the right-hand-side must be also, and therefore

$$\frac{\partial}{\partial \tilde{t}} \iint\limits_{r=1} (\overline{V}_1^+ - \overline{V}_1^-) \, dS = h(t) \quad .$$

Integrating,

$$\iint\limits_{r=1} (\overline{V}_1^+ - \overline{V}_1^-) \, dS = f(t) + h(t) \, \tilde{t} \, .$$

For a steady state to exist, there cannot be linear growth in $\tilde{t}$ and hence $h(t) = 0$ and

$$A + \frac{dA}{dt} = 1 \, . \qquad (102)$$

From (99) and the initial condition in (94),

$$A(0) = 0 \quad . \qquad (103)$$

The solution (102) and (103) is

$$A(t) = 1 - e^{-t} \quad ,$$

and consequently, from (99),

$$V_0 = \begin{cases} 1 - e^{-t}, & r < 1 \\ 0 \ , & r > 1 \ . \end{cases} \tag{104}$$

Thus in the lowest-order term in our expansion of the potential, the whole interior of the cell builds up exponentially in time to a large potential $1/\epsilon$, with a time constant of unity in nondimensional units, or τ'_m in seconds.

We now continue by solving for $\overline{V}_1$. Substituting the result (104) for $\overline{V}_0$ in the boundary condition in (95), we obtain

$$\frac{\partial \overline{V}_1^-}{\partial r} = \frac{1}{\alpha} \frac{\partial \overline{V}_1^+}{\partial r} = \frac{\partial \overline{V}_1^+}{\partial \tilde{t}} - \frac{\partial \overline{V}_1^-}{\partial \tilde{t}} - 1 \quad . \tag{105}$$

Just as we found it necessary to consider the volume integral of $\nabla^2 \overline{V}_1$ in order to determine $\overline{V}_0$, we must consider the volume integral of $\nabla^2 \overline{V}_2$ to determine $\overline{V}_1$:

$$\iiint\limits_{\text{cell}} \nabla^2 \overline{V}_2 \, d^3 r = 0 = \iint\limits_{r=1} \left(\overline{V}_1^+ - \overline{V}_1^- + \frac{\partial \overline{V}_1^+}{\partial t} - \frac{\partial \overline{V}_1^-}{\partial t} + \frac{\partial \overline{V}_2^+}{\partial \tilde{t}} - \frac{\partial \overline{V}_2^-}{\partial \tilde{t}} \right) dS \tag{106}$$

It is now convenient to decompose $\overline{V}_1$ into

$$\overline{V}_1(r, \theta, t, \tilde{t}\,) = G_1(r, \theta) + g_1(r, \theta, t, \tilde{t}\,) \tag{107}$$

where $G_1(r, \theta)$ is defined as independent of the time variables and satisfies the problem:

$$\begin{cases} \nabla^2 G_1 = -4\pi\,\delta(\vec{r}-\vec{R}) \\ \dfrac{\partial G_1^-}{\partial r} = \dfrac{1}{\alpha}\,\dfrac{\partial G_1^+}{\partial r} = -1 \\ \displaystyle\iint (G_1^+ - G_1^-)dS = 0 \\ G_1(\infty, \theta) = 0 \end{cases} \tag{108}$$

Note that this is identical to (47).

The leftover $g_1(r, \theta, t, \tilde{t})$ satisfies:

$$\begin{cases} \nabla^2 g_1 = 0 \\ \dfrac{\partial g_1^-}{\partial r} = \dfrac{1}{\alpha}\,\dfrac{\partial g_1^+}{\partial r} = \dfrac{\partial g_1^+}{\partial \tilde{t}} - \dfrac{\partial g_1^-}{\partial \tilde{t}} \\ g_1(\infty, t, \tilde{t}) = 0 \\ g_1^-(1^-, \theta, 0, 0) - g_1^+(1^+, \theta, 0, 0) = G_1^+(1, \theta) - G_1^-(1, \theta) \\ \displaystyle\iint \left(g_1^+ - g_1^- + \frac{\partial g_1^+}{\partial t} - \frac{\partial g_1^-}{\partial t} + \frac{\partial \overline{V}_2^+}{\partial \tilde{t}} - \frac{\partial \overline{V}_2^-}{\partial \tilde{t}} \right) dS = 0 \end{cases} \tag{109}$$

We note that this becomes (48) if $\partial/\partial\tilde{t} = 0$.

The division of (96) into the two problems (108) and (109) is not essential, but it is convenient. The problem for G_1 was obtained from (95) and (106) by setting the t and $\tilde{t}$ derivatives equal to zero and G_1 is thus the solution as $t \to \infty$; g_1 is the remainder after substracting G_1 from $\overline{V}_1$. The first three lines in (109) for g_1 are identical to the first three lines in (94) for $\overline{V}_0$. However, the initial condition is different (we will see this introduces θ dependence to g_1) and the integral constraint is zero in (109) whereas it is -4π in (100).

The initial condition in the problem (109) for g_1 depends on the solution of (108) for G_1, but (108) is self contained and hence we start by solving (108). The solution for G_1 outside the cell is

$$G_1(r) = \frac{\alpha}{r} \text{ for } r > 1. \tag{110}$$

Substituting (110) in (108) yields:

$$\left\{\begin{aligned} &\nabla^2 G_1 = -4\pi\, \delta(\vec{r} - \vec{R}) \\ &\frac{\partial G_1^-}{\partial r} = -1 \\ &\iint\limits_{r=1} G_1^- \, dS = 4\pi\alpha \end{aligned}\right. \tag{111}$$

The problem (111) has a simple physical interpretation. It represents a point source of current inside the spherical cell. The current leaves the cell across the boundary with uniform current density, and the average potential just inside the boundary is constrained to be equal to α, the potential just outside the boundary. The uniform distribution of current flux across the membrane occurs because the voltage drop in going from the point $\vec{R}$ to any point on the membrane is small $[0(\epsilon)]$ compared to the voltage drop across the membrane. If the interior conductivity were infinite, the uniform distribution would be the exact condition; 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 $V(\vec{r}, \theta, t)$.

The problem (111) with $\alpha = 0$ is identical to a problem which has been solved in connection with a special case of the present analysis[2] in which the steady state solution is obtained when the outer membrane is constrained to zero potential (i.e., the $\alpha = 0$, $t \to \infty$, $\tilde{t} \to \infty$ limit of our solution). The solution to (111) can be expressed in terms of elementary functions:

$$G_1(\vec{r}) = (r^2 + R^2 - 2rR\cos\theta)^{-1/2} + (1 + r^2R^2 - 2rR\cos\theta)^{-1/2} - \log\left[1 - rR\cos\theta + (1 + r^2R^2 - 2rR\cos\theta)^{1/2}\right] - 2 + \log 2 + \alpha, \tag{112a}$$

or it may be expressed as an expansion in Legendre polynomials, $P_n(\cos\theta)$:

$$G_1(\vec{r}) = \alpha - 1 + \sum_{n=1}^{\infty} P_n(\cos\theta)(rR)^n\left(1 + \frac{1}{n}\right) + \sum_{n=0}^{\infty} P_n(\cos\theta)\begin{cases} \frac{1}{R}\left(\frac{r}{R}\right)^n, & r \leq R \\ \frac{1}{r}\left(\frac{R}{r}\right)^n, & r \geq R \,. \end{cases}$$

Equations (110) and (112a) are identical to Equations (80a) and (80b). The most direct way to obtain the solution to (111) is to assume a general form in terms of an expansion in Legendre polynomials with unknown coefficients, as was done in Section II. Substituting the form in (111) then determines the coefficients, yielding (112b) which can then be converted to (112a) using summation formulas given in Section II. Equation (112a) is clearly more useful for numerical calculation; the alternate (112b) is given here because it will be useful in calculating higher-order potentials.

We now turn to the problem (109) for the transient part g_1 of $\overline{V}_1$. Expanding in Legendre polynomials,

$$g_1(r,\theta,t,\tilde{t}) = \sum_{n=0}^{\infty} P_n(\cos\theta)\begin{cases} a_n^{(1)}(t,\tilde{t})r^n, & 0 \leq r \leq 1 \\ b_n^{(1)}(t,\tilde{t})r^{-n-1}, & 1 \leq r \leq \infty \,. \end{cases} \tag{113}$$

in which the steady state solution is obtained when the outer membrane is constrained to zero potential (i.e., the $\alpha = 0$, $t \to \infty$, $\tilde{t} \to \infty$ limit of our solution). The solution to (111) can be expressed in terms of elementary functions:

$$G_1(\vec{r}) = (r^2 + R^2 - 2rR\cos\theta)^{-1/2} + (1 + r^2R^2 - 2rR\cos\theta)^{-1/2} - \log\left[1 - rR\cos\theta + (1 + r^2R^2 - 2rR\cos\theta)^{1/2}\right] - 2 + \log 2 + \alpha, \tag{112a}$$

or it may be expressed as an expansion in Legendre polynomials, $P_n(\cos\theta)$:

$$G_1(\vec{r}) = \alpha - 1 + \sum_{n=1}^{\infty} P_n(\cos\theta)(rR)^n\left(1 + \frac{1}{n}\right) + \sum_{n=0}^{\infty} P_n(\cos\theta)\begin{cases}\frac{1}{R}\left(\frac{r}{R}\right)^n, & r \le R\\ \frac{1}{r}\left(\frac{R}{r}\right)^n, & r \ge R\,.\end{cases}$$

Equations (110) and (112a) are identical to Equations (80a) and (80b). The most direct way to obtain the solution to (111) is to assume a general form in terms of an expansion in Legendre polynomials with unknown coefficients, as was done in Section II. Substituting the form in (111) then determines the coefficients, yielding (112b) which can then be converted to (112a) using summation formulas given in Section II. Equation (112a) is clearly more useful for numerical calculation; the alternate (112b) is given here because it will be useful in calculating higher-order potentials.

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$$g_1(r,\theta,t,\tilde{t}) = \sum_{n=0}^{\infty} P_n(\cos\theta)\begin{cases}a_n^{(1)}(t,\tilde{t})r^n, & 0 \le r \le 1\\ b_n^{(1)}(t,\tilde{t})r^{-n-1}, & 1 \le r \le \infty\,.\end{cases} \tag{113}$$

Substituting (113) in the r=1 boundary condition and initial condition in (109) and using the orthogonality properties of $P_n(\cos\theta)$,

$$n\, a_n^{(1)}(t,\tilde{t}) = -\frac{1}{\alpha}(n+1)\, b_n^{(1)}(t,\tilde{t}) = \frac{\partial}{\partial\tilde{t}}\left(b_n^{(1)} - a_n^{(1)}\right), \tag{114}$$

$$a_n^{(1)}(0,0) - b_n^{(1)}(0,0) = \begin{cases} 0 \quad, & n = 0 \\ -\dfrac{2n+1}{n} R^n, & n \geq 1 \, . \end{cases} \tag{115}$$

We have used (110) and (112b) to evaluate the nth term in the eigenfunction expansion of $(G_1^+ - G_1^-)$ which appears on the right-hand-side of (115). Except for an as yet unknown dependence on t, Equations (114) and (115) determine $a_n^{(1)}$ and $b_n^{(1)}$:

$$a_n^{(1)}(t,\tilde{t}) = \begin{cases} 0, & n = 0 \\ -\dfrac{(n+1)(2n+1)}{n(1+n+\alpha n)} R^n e^{-\lambda_n \tilde{t}} f_n(t), & n \geq 1 \end{cases} \tag{116a}$$

$$b_n^{(1)}(t,\tilde{t}) = \begin{cases} 0, & n = 0 \\ \dfrac{\alpha(2n+1)}{1+n+\alpha n} R^n e^{-\lambda_n \tilde{t}} f_n(t), & n \geq 1 \end{cases} \tag{116b}$$

$$\lambda_n = \frac{n(n+1)}{1+n+\alpha n} \;, \tag{116c}$$

where $f_n(0) = 1$. For the functional form of $f_n(t)$ we must go on to the problem (96) for $\overline{V}_2(\vec{r},t,\tilde{t})$.

As we did in the $\overline{V}_1$ problem we now break the $\overline{V}_2$ problem (96) into two problems by separating $\overline{V}_2$ into the steady state and transient parts,

$$\overline{V}_2(\vec{r},t,\tilde{t}) = G_2(\vec{r}) + g_2(\vec{r},t,\tilde{t}) \tag{117}$$

where $G_2(\vec{r})$ satisfies:

$$\begin{cases} \nabla^2 G_2 = 0 \\ \dfrac{\partial G_2^-}{\partial r} = \dfrac{1}{\alpha} \dfrac{\partial G_2^+}{\partial r} = G_1^+ - G_1^- \\ G_2(\infty, \theta) = 0 \end{cases} \tag{118}$$

and $g_2(\vec{r}, t, \tilde{t})$ satisfies:

$$\begin{cases} \nabla^2 g_2 = 0 \\ \dfrac{\partial g_2^-}{\partial r} = \dfrac{1}{\alpha} \dfrac{\partial g_2^+}{\partial r} = g_1^+ - g_1^- + \dfrac{\partial g_1^+}{\partial t} - \dfrac{\partial g_1^-}{\partial t} + \dfrac{\partial g_2^+}{\partial \tilde{t}} - \dfrac{\partial g_2^-}{\partial \tilde{t}} \\ g_1(\infty, t, \tilde{t}) = 0 \\ g_2^-(1^-, 0, 0) - g_2^+(1^+, 0, 0) = G_2^+(1, \theta) - G_2^-(1, \theta) \end{cases} \tag{119}$$

We expand G_2 and g_2 in eigenfunctions:

$$G_2(\vec{r}) = \sum_{n=0}^{\infty} P_n(\cos\theta) \begin{cases} A_n^{(2)} r^n , & 0 \leq r < 1, \\ B_n^{(2)} r^{-n-1}, & 1 < r \leq \infty , \end{cases} \tag{120}$$

$$g_2(\vec{r}, t, \tilde{t}) = \sum_{n=0}^{\infty} P_n(\cos\theta) \begin{cases} a_n^{(2)}(t, \tilde{t}) r^n , & 0 \leq r < 1 , \\ b_n^{(2)}(t, \tilde{t}) r^{-n-1}, & 1 < r \leq \infty. \end{cases} \tag{121}$$

Substituting (120) in the r=1 boundary condition in (118), and using (110) and (112b) we have

$$n A_n^{(2)} = - \frac{n+1}{\alpha} B_n^{(2)} = \begin{cases} 0, & n = 0 \\ - \dfrac{2n+1}{n} R^n, & n \geq 1 \end{cases}$$

so that

$$A_n^{(2)} = \begin{cases} 0, & n = 0 \\ -\dfrac{2n+1}{n^2} R^n, & n \geq 1 \end{cases} \tag{122a}$$

$$B_n^{(2)} = \begin{cases} 0, & n = 0 \\ \dfrac{\alpha(2n+1)}{n(n+1)} R^n, & n \geq 1 \end{cases} \tag{122b}$$

Substituting (122a, b) in (120), for $r \leqq 1$,

$$G_2(\vec{r}) = -\sum_{n=1}^{\infty} P_n(\cos\theta) \frac{2n+1}{n^2} (rR)^n \tag{123a}$$

and for $r \geqq 1$,

$$\begin{aligned} G_2(\vec{r}) &= \frac{\alpha}{R} \sum_{n=1}^{\infty} \left(\frac{1}{n} + \frac{1}{n+1}\right)\left(\frac{R}{r}\right)^{n+1} P_n(\cos\theta) \\ &= \frac{\alpha}{R}\left[\log\left\{\frac{R}{r} - \cos\theta + \left(1 - 2\frac{R}{r}\cos\theta + \frac{R^2}{r^2}\right)^{1/2}\right\}\right. \\ &\quad - \log(1-\cos\theta) - \frac{R}{r}\log\left\{1 - \frac{R}{r}\cos\theta + \left(1 - 2\frac{R}{r}\cos\theta + \frac{R^2}{r^2}\right)^{1/2}\right\} \\ &\quad \left. - \frac{R}{r} + \frac{R}{r}\log 2\right] \end{aligned} \tag{123b}$$

where in the case of the outside potential (123b) it is possible to obtain the sum in terms of elementary functions.

We now continue by considering the problem for the transient part, g_2, of the potential, $\overline{V}_2$. Substituting (121) in the r=1 boundary condition in (119) and using the results (116) for $a_n^{(1)}(t,\tilde{t})$ and $b_n^{(1)}(t,\tilde{t})$, we obtain

$$\begin{aligned} n\, a_n^{(2)}(t,\tilde{t}) &= -\frac{n+1}{\alpha} b_n^{(2)}(t,\tilde{t}) \\ &= \frac{\partial b_n^{(2)}}{\partial \tilde{t}} - \frac{\partial a_n^{(2)}}{\partial \tilde{t}} + \left[f_n(t) + \frac{df_n}{dt}\right] \begin{cases} 0 & , n = 0 \\ \dfrac{2n+1}{n} R^n e^{-\lambda_n \tilde{t}} & , n \geq 1 \end{cases} \end{aligned} \tag{124}$$

which yields, on elimination of $b_n^{(2)}$, the equation for $a_n^{(2)}$

$$\frac{\partial a_n^{(2)}}{\partial \tilde{t}} + \frac{n(n+1)}{1+n+\alpha n} a_n^{(2)}(t,\tilde{t}) = \left[f_n(t) + \frac{df_n}{dt}\right] \begin{cases} 0 & , n = 0 \\ \frac{(n+1)(2n+1)}{n(1+n+\alpha n)} R^n e^{-\lambda_n \tilde{t}} & , n \geq 1 \end{cases} \tag{125}$$

The homogeneous solution to (125) is $e^{-\lambda_n \tilde{t}}$, where λ_n is the same as in the solution for $a_n^{(1)}$ and $b_n^{(1)}$. Since the right-hand-side of (125) contains the homogeneous solution, the particular solution to (125) would contain a term of the form $\tilde{t} e^{-\lambda_n \tilde{t}}$ so that as $\tilde{t} \to \infty$, $(\overline{V}_2/\overline{V}_1) \to \infty$. This is not permissible as successive terms in the asymptotic expansion (93) for V must be decreasing in magnitude. We are thus led to the conclusion that

$$\frac{df_n}{dt} + f_n(t) = 0 \tag{126}$$

and hence, since $f_n(0) = 1$,

$$f_n(t) = e^{-t} \tag{127}$$

Substituting (127) in (116), we have the complete functional form of $\overline{V}_1(\vec{r}, t, \tilde{t})$.

We continue the solution for $a_n^{(2)}$ and $b_n^{(2)}$ by substituting (121) and (123) in the initial condition in (119), and we obtain

$$a_n^{(2)}(0,0) - b_n^{(2)}(0,0) = \begin{cases} 0 & , n = 0 \\ \frac{(\alpha n+n+1)(2n+1)}{n^2(n+1)} & , n \geq 1 \end{cases} \tag{128}$$

Using the result (126) in (124) and (125), and then solving (124), (125) and (128) for $a_n^{(2)}$ and $b_n^{(2)}$, we obtain

$$a_n^{(2)}(t,\tilde{t}) = \begin{cases} 0 , & n = 0 \\ \frac{2n+1}{n^2} R^n e^{-\lambda_n \tilde{t}} h_n(t) , & n \geq 1 \end{cases} \tag{129a}$$

$$b_n^{(2)}(t,\tilde{t}) = \begin{cases} 0 , & n = 0 \\ -\frac{\alpha(2n+1)}{n(n+1)} R^n e^{-\lambda_n \tilde{t}} h_n(t) , & n \geq 1 \end{cases} \tag{129b}$$

where $h_n(0) = 1$ and λ_n is given by (116c).

As before, if we continue with the problem for $\overline{V}_3$, we can show that to avoid terms proportional to $\tilde{t}$ in $\overline{V}_3$, we obtain a condition on $h_n(t)$ identical to (126) for $f_n(t)$, which determines the functional form of $h_n(t)$ to be e^{-t}. Hence

$$a_n^{(2)}(t,\tilde{t}) = \begin{cases} 0 , & n = 0 \\ \frac{2n+1}{n^2} R^n e^{-\lambda_n \tilde{t}} e^{-t} , & n \geq 1 \end{cases} \tag{130a}$$

$$b_n^{(2)}(t,\tilde{t}) = \begin{cases} 0 , & n = 0 \\ -\frac{\alpha(2n+1)}{n(n+1)} R^n e^{-\lambda_n \tilde{t}} e^{-t} , & n \geq 1 . \end{cases} \tag{130b}$$

References

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4. Ibid., Sec. 3.1-3.3.
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ABSTRACT

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 turned on abruptly at $t = 0$. The problem is solved by exact methods and by singular perturbation theory. 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 $\epsilon = \sigma_m a/\sigma_i \delta << 1$, that is, when the effective internal resistance is small compared to the effective membrane resistance. The most important physiological results are when the rapid transient has died out, for times much greater than $C_m a/\sigma_i$. In this case simple analytic expressions are obtained for the inside potential, Equation (27'), the outside potential, Equation (28), and the transmembrane potential, Equation (30). Some results are obtained for an arbitrarily shaped finite cell. The potential problem is solved, in addition to the exact solution, by the singular perturbation technique of matching a short-time and a long-time asymptotic expansion, and independently by the perturbation technique of multiple scaling. The presentation is designed to give not only the solution to the problem, but to show how three different methods can be applied to potential problems containing a small parameter.