THE POTENTIAL IN THE GAP BETWEEN TWO ABUTTING CARDIAC MUSCLE CELLS

A CLOSED SOLUTION

J. W. WOODBURY *and* W. E. CRILL

From the Department of Physiology and Biophysics, University of Washington School of Medicine, Seattle, Washington 98105

ABSTRACT An approximate differential equation is developed describing the potential in the gap (intercalated disc) between two closely abutting, coaxial cylindrical cardiac muscle cells. This permits approximate calculation of the degree of current spread from an active to an inactive cell. The equation has a closed solution in terms of the zero-order Bessel function $I_0(x)$. This result is different from one given by Woodbury and Crill (1961). The source of the original mistake is given and the magnitude of the error estimated. The new solution is compared with the exact, series solution to this problem given by Heppner and Plonsey (1970) in the preceding paper. It is shown analytically that our approximate solution differs negligibly from the series solution for the parameter values chosen. The closed solution not only considerably simplifies calculations but yields additional insights into the nature of the coupling resistances R and r used by Heppner and Plonsey in their detailed analysis of the cell-to-cell transmission process.

INTRODUCTION

The preceding paper by Heppner and Plonsey (1970) extends and elucidates some theoretical calculations made by us ten years ago (Woodbury and Crill, 1961). This paper discusses the nature and sources of the discrepancies between our original approximate solution for the voltage in the gap between two closely abutting cylindrical cardiac muscle cells and the rigorous series solution given by Heppner and Plonsey. The problem is to calculate the amount of current that spreads from an active cell to an abutting, inactive cell. The geometry and boundary conditions are given in Fig. 3 of Woodbury and Crill (1961), in Heppner and Plonsey's Fig. 1, and in Fig. 1 A of this paper.

The differential equation for the potential in the gap is Laplace's equation. Heppner and Plonsey solved this equation for the appropriate boundary conditions (their equation 3 and conditions *a*, *b*, and *c*). Their solution (equation 9) is an infinite series of zero-order Bessel functions of the first kind in radius, r, multiplied by hyperbolic functions in z, the axial distance through the gap. On the other hand, Woodbury and Crill derived the potential in the gap in terms of a differential equation in r only. They neglected the z-variation and used parameter values thought to apply to cardiac muscle. Heppner and Plonsey also used these same values of cell dimensions and resistances in their calculations of the gap potential. Hence, their more accurate calculations afford an excellent opportunity to check the accuracy of our original approximate solution. In the course of this checking, we discovered an embarrassing (but luckily not disastrous) error in our derivation. The purposes of this paper are (*a*) to correct the error, (*b*) to compare the results of the corrected theory with the rigorous Heppner-Plonsey solution, and (*c*) to show the analytical connection between the Heppner-Plonsey solution and our solution. This connection is useful because it leads to a considerable simplification of the calculations made by Heppner and Plonsey. One of us (J. W. Woodbury) refereed the Heppner-Plonsey paper and initiated correspondence which led to the writing of this paper.

APPROXIMATE DIFFERENTIAL EQUATION FOR THE POTENTIAL IN THE GAP

Fig. 1 A illustrates the important factors which determine current flow from an active cell (bottom) to a closely adjoining inactive cell (top). The apposing circular membranes, the disc membranes, are assumed to be inexcitable. This is necessary to maximize local current flow from the active to the inactive cell; if the disc membrane were excitable, then local current flow would cease when the disc became active. The fall in resistance in an active disc membrane would not aid transmission because the accompanying voltage changes reduce the driving voltage for local currents to zero and hence the voltage in the gap would also fall to zero. For simplicity, the complicated potential distribution during an action potential in the bottom cell is approximated by regarding the surface membrane of this cell as fully active and the disc membrane as completely polarized as shown by the + and − signs in Fig. 1 A. At this instant, the potential difference driving current through the lower disc membrane is the height of the action potential, ϵ_a. The assumptions are made that this current flows perpendicularly through the membrane and then either continues into the inactive cells and then depolarizes the surface membrane or turns out of the cleft into the extracellular fluid which is assumed to be at zero potential. Actually of course, the current paths are determined by Laplace's equation but if the gap is sufficiently narrow, the approximation should be quite good. This is shown to be the case for the parameter values assumed for heart (see below).

The radial current, i_2 (amperes), generates a potential gradient, $d\epsilon/dr$, in the gap. An annulus at r of width dr has a resistance of $dr/2\pi r\delta\sigma$ so this gradient is given by

$$-d\epsilon = \frac{dr}{2\pi r\delta\sigma}\, i_2, \qquad i_2 = -2\pi r\delta\sigma\frac{d\epsilon}{dr}, \tag{1}$$

where σ is the conductivity (mho/cm) of disc fluid and δ is the width of the gap (cm).

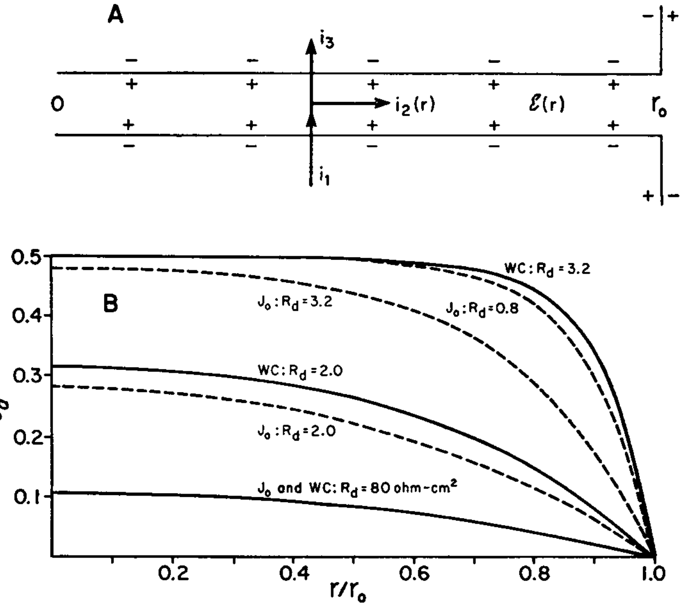

FIGURE 1 Potential in the gap (intercalated disc) between two cardiac muscle cells. (A) Geometry and boundary conditions used in calculating potential, $\epsilon(r)$. Surface membrane of lower cell is assumed to be at peak of action potential and the disc membrane at resting potential; driving voltage is ϵ_a. Current, i_1, divides in the gap into radial current, i_2, and axial current, i_3. (B) Plot of relative potential in the gap, $\epsilon(r)/\epsilon_a$, as a function of relative radius, r/r_0. Solid lines, values calculated from equation 7, the original solution given by Woodbury and Crill (1961) and labeled WC. Numbers are values of disc membrane resistance R_d. Dashed lines, labeled $J_0[I_0(x) \equiv J_0(ix)]$, values calculated from equation 5 for the values of R_d shown.

The current density entering the gap from below is $(\epsilon_a - \epsilon)R_d$ and that leaving above is ϵ/R_d where R_d is the specific resistance of the disc membrane (Ω-cm^2). The increment of radial current, di_2, added by an annulus $2\pi r\,dr$ is the difference between entering and exiting membrane currents. Hence

$$di_2 = 2\pi r\,dr\left(\frac{\epsilon_a - \epsilon}{R_d} - \frac{\epsilon}{R_d}\right) \quad \text{or} \quad \frac{di_2}{dr} = \frac{4\pi r}{R_d}\left(\frac{\epsilon_a}{2} - \epsilon\right). \tag{2}$$

Differentiating equation 1 and substituting in equation 2 gives

$$\frac{1}{r}\frac{d}{dr}\left(r\frac{d\epsilon}{dr}\right) - \frac{2}{\delta\sigma R_d}\epsilon = -\frac{2}{\delta\sigma R_d}\cdot\frac{\epsilon_a}{2}. \tag{3}$$

The left-hand side is the cable equation in cylindrical coordinates. The space constant is $\lambda_1^2 \equiv \delta\sigma R_d/2$. The factor $\frac{1}{2}$ appears because the two opposing membranes are effectively in parallel. The substitution $x = r/\lambda_1$ simplifies equation 3 to

$$\frac{1}{x}\frac{d}{dx}\left(x\frac{d\epsilon}{dx}\right) - \epsilon = -\epsilon_a/2. \tag{4}$$

The general solution of equation 4 is (Abramowitz and Stegun, 1964)

$$\epsilon(x) = AI_0(x) + BK_0(x) + \epsilon_a/2$$

where I_0 and K_0 are Bessel functions of zero order and of the first and second kinds, $\epsilon_a/2$ is the particular solution, and A and B are arbitrary constants.

The boundary conditions are the following. (*a*) The potential of extracellular fluid is taken as zero, thus $\epsilon(x_0) = 0$, where $x_0 = r_0/\lambda_1$ and r_0 is the cell radius. (*b*) The potential at $r = 0$ is finite. Since $K_0(0) = \infty$, B must be zero. Substituting these in the general solution gives $\epsilon(x_0) = 0 = AI_0(x_0) + \epsilon_a/2$; $A = -\epsilon_a/(2I_0[x_0])$. The complete solution is thus

$$\frac{\epsilon(x)}{\epsilon_a} = \frac{1}{2}\left(1 - \frac{I_0(x)}{I_0(x_0)}\right). \tag{5}$$

This is to be compared with the solution of Laplace's equation for the gap but first equation 5 must be compared with the Woodbury-Crill result.

THE ERROR IN THE WOODBURY-CRILL DIFFERENTIAL EQUATION

Ten years ago we obtained a rather different result: a differential equation

$$-\frac{d\epsilon}{dr} = r(\epsilon_a - 2\epsilon)/\lambda_2^2, \qquad \lambda_2^2 \equiv 2\delta\sigma R_d \tag{6}$$

with solution

$$\frac{\epsilon(r)}{\epsilon_a} = \frac{1}{2}\left(1 - \frac{e^{(r/\lambda_2)^2}}{e^{(r_0/\lambda_2)^2}}\right). \tag{7}$$

This result was obtained apparently through an inadvertent error (we cannot find our original notes) which fortunately only slightly modifies our original conclusion that R_d's $\sim$ 1 Ω-cm² are necessary for effective transmission at the disc. Careful investigation showed that equations 6 and 7 result if equation 2 is integrated on the assumption that $(\epsilon_{a/2} - \epsilon)$ is independent of r. Physically this means that ϵ is close to zero for all r, the situation where there is little electrical coupling between cells. Integration of equation 2 on this assumption gives

$$i_2 \simeq \frac{2\pi r^2}{R_d}\left(\frac{\epsilon_a}{2} - \epsilon\right).$$

Combining this with equation 1 gives equation 6.

The natural definition of the space constant in equation 6 is twice the natural space constant of equation 3: $\lambda_2 = 2\lambda_1$. Hence, in order to compare the two solutions, equation 7 and equation 5, they must be properly scaled. Thus equation 7 must be rewritten with argument $x/2 = r/\lambda_2$:

$$\frac{\epsilon(x)}{\epsilon_a} = \frac{1}{2}\left(1 - \frac{e^{(x/2)^2}}{e^{(x_0/2)^2}}\right). \tag{8}$$

It follows that this solution is equivalent to equation 5 to the extent that $e^{(x/2)^2} = I_0(x)$. Series expansion of these two functions gives

$$e^{(x/2)^2} = 1 + x^2/4 + x^4/32 + \cdots$$

and

$$I_0(x) = 1 + x^2/4 + x^4/64 + \cdots$$

These two are nearly equal for values of $x \leq 1$, ($e^{1/4} = 1.284$, $I_0[1] = 1.266$).

Fig. 1 B shows plots of equations 5 and 8 for various values of R_d and with $r_0 = 8 \times 10^{-4}$ cm, $\delta = 8 \times 10^{-7}$ cm, and $\sigma = 0.02$ mho/cm (Woodbury and Crill, 1961). The error in equation 7 is progressively greater as r_0/λ is increased; the error for $R_d = 80$ Ω-cm^2 ($r_0/\lambda = 1$) is about one line width on the graph (Fig. 1 B) but is very large for $R_d = 3.2$ Ω-cm^2.

Our conclusion in 1961 was that efficient transmission requires that $r_0/\lambda_2 \geq 4$ ($r_0/\lambda_1 \geq 8$). This implies that $R_d \leq 1.2$ Ω-cm^2. Fig. 1 A shows that a rather higher value for r_0/λ_1 (lower value for R_d) must be chosen for efficient transmission. The comparable figure is $R_d \leq 0.3$ Ω-cm^2 ($r_0/\lambda_1 \geq 16$). Thus, the mistake made in our original derivation results in a less than order of magnitude error for the parameter values chosen. This is fortunate considering that the inadvertent approximation is a poor one under the conditions of efficient cell-to-cell transmission. Nevertheless, the change in the limit on R_d is rather inappreciable considering the uncertainties in tissue geometry and other parameters and in the assumptions leading to the equations.

COMPARISON WITH THE HEPPNER-PLONSEY RESULTS

Comparison of the $I_0(x)$ curves in Fig. 1 B with the curves, $\epsilon(r, \delta/2)$, in Fig. 2 of Heppner and Plonsey reveals that there is no detectable difference. Hence, it is desirable to find some analytical means of comparison so that the adequacy of the approximate equation (equation 5) can be evaluated.

The Heppner-Plonsey solution (Heppner-Plonsey equation 3) with $z = \delta/2$ is

$$\frac{\epsilon(r, \delta/2)}{\epsilon_a} = \sum_{n=1}^{\infty} \frac{[d_n \cosh(k_n\delta/2) - \sinh(k_n\delta/2)]}{k_n r_0(d_n + \sigma R_d k_n)} \cdot \frac{2J_0(k_n r)}{J_1(k_n r_0)} \tag{9}$$

where

$$d_n = (\sigma R_d k_n + \tanh (k_n \delta])/(1 + \sigma R_d k_n \tanh [k_n \delta])$$

and the k_n's are defined by $J_0(k_n r_0) = 0$. $J_0(x)$ is the zero-order Bessel function of the first kind. The form of this solution suggests that the relationships between equations 5 and 9 can be found by expanding equation 5 into a series of Bessel functions of $k_n r$ so that a term by term comparison can be made. This is done by setting

$$\epsilon(r) = \frac{1}{2}\left(1 - \frac{I_0(r/\lambda_1)}{I_0(r_0/\lambda_1)}\right) = \sum_{n=1}^{\infty} A_n J_0(k_n r), \tag{10}$$

where the A_n's are constants to be evaluated by means of the orthogonality properties of $J_0(k_n r)$. The A_n's are obtained by multiplying the center and right-hand sides of equation 10 by $rJ_0(k_n r)$ and integrating between the limits 0 and r_0. The final result is

$$\epsilon(r) = \sum_{n=1}^{\infty} \frac{1}{k_n r_0(1 + \lambda_1^2 k_n^2)} \cdot \frac{J_0(k_n r)}{J_1(k_n r_0)}. \tag{11}$$

Comparison of equations 9 and 11 shows some resemblance but apparently large differences. However, equation 9 can be greatly simplified by making an approximation that introduces a negligible error for the parameter values used. Heppner and Plonsey point out that since $\delta = 10^{-3} r_0$, then $\cosh (k_n \delta/2) \simeq 1$, and $\sinh (k_n \delta/2) \simeq 0$, for k_n values which contribute significantly to the value of $\epsilon(r, \delta/2)$. A similar approximation can be made in the equation for d_n; the $\tanh (k_n \delta)$ term in the numerator is negligible (i.e. $\sigma R_d \gg \delta k_n$). The $\tanh (k_n \delta)$ term in the denominator must be retained but is accurately approximated by $k_n \delta$. Thus d_n reduces to

$$d_n = \frac{R_d \sigma k_n}{1 + \sigma R_d \delta k_n^2} = \frac{R_d \sigma k_n}{1 + 2\lambda_1^2 k_n^2}, \tag{12}$$

since $\lambda_1^2 \equiv \delta R_d \sigma/2$. Substituting equation 12 in equation 9 and rearranging terms gives

$$\frac{\epsilon_a(r, \delta/2)}{\epsilon_a} = \sum_{n=1}^{\infty} \frac{1}{k_n r_0(1 + \lambda_1^2 k_n^2} \cdot \frac{J_0(k_n r)}{J_1(k_n r_0)}. \tag{13}$$

Comparison of equations 11 and 13 shows that the two series are identical and thus the approximation given by equation 5 is entirely adequate for the parameters chosen. Thus, the error in equation 5 can be estimated by comparing the values of the A_n's given by equation 13 with those given by equation 11.

THE HEPPNER-PLONSEY QUANTITIES *R* AND *r*

The simpler, closed solution, equation 5, can also be used to obtain closed solutions for the values of the quantities R and r used by Heppner and Plonsey to calculate cell-to-cell coupling (their Table I). To do this, substitute equation 5 in equation 1 to obtain the radial current, i_2 at $r = r_0$:

$$i_2 = \epsilon_a \frac{r_0}{\lambda_1} \cdot \frac{2\pi r_0^2}{R_d} \cdot \frac{I_1(r_0/\lambda_1)}{I_0(r_0/\lambda_1)}. \tag{14}$$

Similarly the total incoming, i_1, and outgoing, i_3, axial currents can be obtained from integration of the current densities $(\epsilon_a - \epsilon)R_d$ and ϵ/R_d over the surface area:

$$\begin{aligned} i_1 &= i_2 + i_3 \\ \text{where} \quad i_3 &= \epsilon_a \cdot \frac{\pi r_0^2}{2R_d}\left[1 - \frac{2\lambda_1}{r_0} \cdot \frac{I_1(r_0/\lambda_1)}{I_0(r_0/\lambda_1)}\right]. \end{aligned} \tag{15}$$

Heppner and Plonsey equations 8 *a* and *b* can then be solved for the longitudinal and shunt resistances R and r. Our result is

$$R = R_d/\pi r_0^2 = 5 \times 10^5 R_d \text{ ohms}, \tag{16}$$

$$\begin{aligned} r &= \left[\frac{r_0}{4\lambda_1} \cdot \frac{I_0(r_0/\lambda_1)}{I_1(r_0/\lambda_1)} - \frac{1}{2}\right]\frac{R_d}{\pi r_0^2}, \\ &= \left[\sqrt{\frac{5}{R_d}} \cdot \frac{I_0(\sqrt{80/R_d})}{I_1(\sqrt{80/R_d})} - \frac{1}{2}\right] 5 \times 10^5 R_d. \end{aligned} \tag{17}$$

Equation 16 shows analytically what Heppner and Plonsey suspected: R is simply the resistance of the whole disc membrane. Values of r calculated from equation 17 agree well with the values given in Heppner and Plonsey's Table I.

Equation 17 can be simplified for the case where the radius is much larger than the space constant $(r_0/\lambda_1 \gg 1)$. In this case, the asymptotic relations for I_0 and I_1 can be used (Abramowitz and Stegun, 1964, p. 377).

$$I_n(x) \simeq \frac{e^x}{\sqrt{2\pi x}}\left(1 - \frac{4n^2 - 1}{8x} + \cdots\right).$$

Hence, $I_0(x)/I_1(x) \simeq (8x + 1)/(8x - 3)$. The error is less than 5% at $x \simeq 3$ and less than 2% for $x > 4$. Substituting in equation 17 gives

$$\begin{aligned} r &= \left[\frac{r_0(8r_0/\lambda_1 + 1)}{4\lambda_1(8r_0/\lambda_1 - 3)} - \frac{1}{2}\right]\frac{R_d}{\pi r_0^2}, \\ &= \left[\sqrt{\frac{5}{R_d}} \cdot \frac{(32\sqrt{5/R_d} + 1)}{(32\sqrt{5/R_d} - 3)} - \frac{1}{2}\right] 5 \times 10^5 R_d. \end{aligned} \tag{18}$$

This approximation is sufficiently accurate for most purposes if $R_d < 5$ Ω-cm² $(x > 4)$.

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