EN580.435, APPLIED BIOELECTRICAL ENGINEERING I Feb. 14, 2019
The Johns Hopkins University

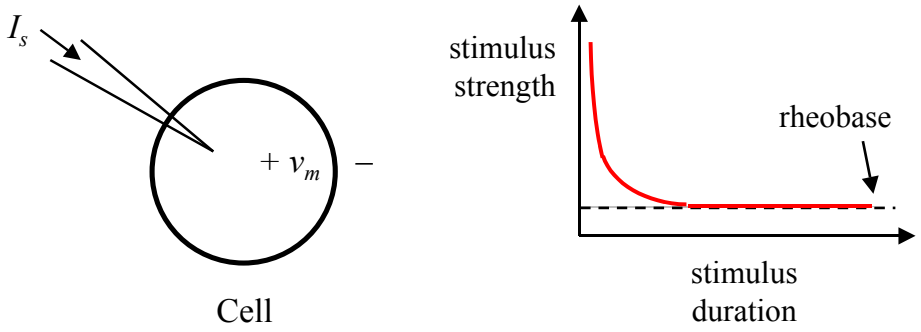
HANDOUT #5. ELECTRICAL STIMULATION

1. STIMULATON OF CELLS BY CURRENT INJECTION

A. Stimulus threshold

The electrical stimulation of excitable cells such as neurons or muscles cells involves the discharge of the resting potential across the cell membrane up to a threshold value, above which active membrane currents take over and control the time course of polarization change.

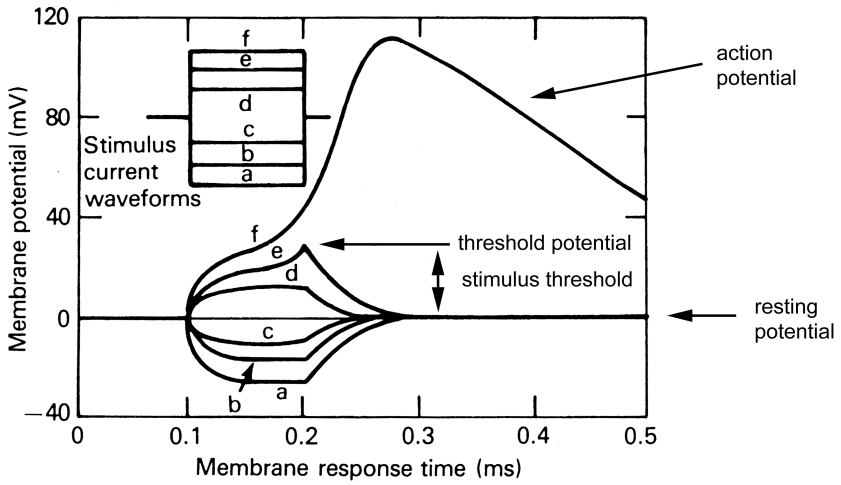
Figure 1



Let us consider the case of a single cell. The cell membrane has a characteristic passive resistance and capacitance. The *transmembrane potential* v_m is a voltage that exists across the cell membrane, with the inside defined positive relative to the outside. Stimulation can be achieved by passing a current i_s through a glass micropipette that is sharpened to a fine tip and impaled through the cell membrane. If a rectangular stimulus pulse is applied, there is in general an inverse relation between the pulse amplitude and pulse duration in terms of efficacy of the pulse. Thus, a shorter but larger pulse is just as effective for stimulation as a longer, smaller pulse. This inverse relation is reflected as a classical *strength-duration relation* for stimulation. Although stimulus strength drops as duration increases, there is a minimal level called the *rheobase*, below which stimulation cannot occur no matter how long the pulse duration.

In excitable cells, a regenerative *action potential* results when v_m is raised from its *resting potential* to the *threshold potential*. The figure below shows the result of injecting positive or negative current pulses into a computer model of a cell. For negative current pulses or small positive current pulses (traces a-d), the transmembrane potential exhibits the passive behavior of an RC circuit, just as it was analyzed above. However, if v_m is raised further to a threshold potential (trace e), a nonlinear behavior begins to appear, that at a still larger potential results in a fully manifested, active response.

Figure 2 [**1**]

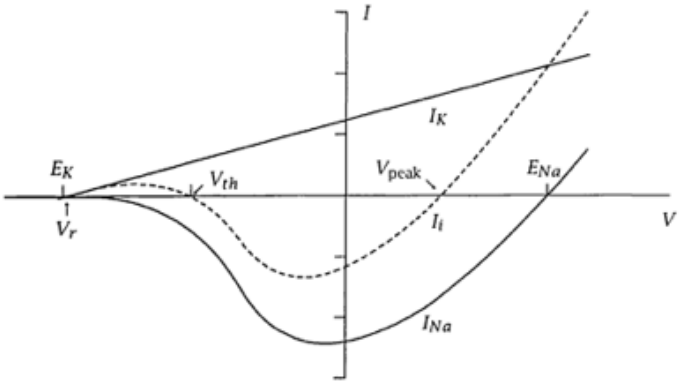


As we discussed in class the asumption that the threshold is a constant value and can be described with a passive RC circuit is limited. We can readily observe this by making use of the Noble model for excitation using the Hodgkin-Huxley equation for membrane current:

$$I_m = c_m \frac{dv_m}{dt} + g_k n^4 (v_m - E_k) + g_{Na} m^3 h (v_m - E_{Na}) + g_L (v_m - E_L) \qquad (1)$$

If we assume that *m* reaches its steady state value before *n* and *h* change from rest we can sketch the instantaneous I-V curve:

Figure 3 [**2**]



If we allow *h* and *n* to change slightly the dotted line will approach the curve for I_k (which in turn will increase in slope). As this happens v_{th} will increase before eventually disappearing. This demonstrates that the assumption of a static threshold is not valid for pulses that rise slowly compared to the time constants for *h* and *n* (~5-10 ms).

B. Strength-duration relation

Electrical stimulation follows a well-known strength-duration relation, first recognized by Hoorweg in 1892. In 1901, Weiss [**3**] used constant current rectangular pulses to stimulate nerve and muscle, and shortly afterward, in 1909 Lapicque [**4**] used capacitor discharge pulses to stimulate various tissues. This resultd in an impirical

formula for the strength-duration relationship and the definition of two parameters: I_{rh}, the rheobase (the lowest intensity with infinite pulse duration which just stimulates), and c, the chronaxie (the pulse duration having a threshold intensity of twice the rheobase).

2. UNIFORMLY POLARIZED CELL MEMBRANE

A. RC membrane. Under some conditions of stimulation, e.g., with small-sized cells stimulated by an intracellular source electrode and an extracellular return electrode, the transmembrane potential will be uniformly polarized, or isopotential, meaning that the membrane potential is the same across all segments of membrane along the cell surface. A theoretical strength-duration curve was described by Lapicque in 1907 [**4**] and extended by Hill in 1936 [**5**] for a current source charging a passive membrane, represented by a lumped resistor (R_m)–capacitor (C_m) circuit. In this case, as we derived in class, we have

$$v_m(t) = IR_m(1 - e^{-t/\tau_m}) \tag{2}$$

where τ_m is the membrane time constant R_mC_m, and $v_m(t)$ is the small signal deviation from resting potential. Assuming that the transmembrane potential must be depolarized to a threshold or "takeoff" potential[1] v_{th} over a pulse duration d, the threshold current I is given by

$$I = \frac{v_{th}}{R_m(1 - e^{-d/\tau_m})} \tag{3}$$

By definition, as $d \to \infty$, $I \to I_{rh}$, the rheobase. Therefore, (3) can be rewritten as

$$I = \frac{I_{rh}}{1 - e^{-d/\tau_m}} \tag{4}$$

where

$$I_{rh} = \frac{v_{th}}{R_m} \tag{5}$$

Note also, from (3) that as $d \to 0$,

$$\begin{aligned} Id &\to \left(\frac{v_{th}}{R_m}\frac{\tau_m}{d}\right)d = Q_{th} \\ \Rightarrow \quad I_{rh}\tau_m &= C_m v_{th} = Q_{th} \end{aligned} \tag{6}$$

[1] The threshold potential is usually defined as the maximal voltage obtained by a just subthreshold response. A just suprathreshold response leads to the upstroke of the action potential.

B. Current, charge, and energy. In the design of electrical stimulators, pacemakers and defibrillators, these three parameters have physical significance.

• Current (and hence, current density) through the electrode determines the electric field, which is the driving function for changes in transmembrane potential. It would be desirable to limit this parameter to minimize possible injury effects to the tissue.
• Charge is related to the storage capacity of the battery (usually expressed in Amp-hours, Ah), and it would be desirable to minimize this parameter to extend the number of shocks possible.
• Energy is the parameter used to characterize the strength of pulses applied during defibrillation (usually expressed in J) and is a function of pulse voltage and tissue resistance. The capacity of batteries is sometimes expressed as energy density, either in J/kg or J/cm^3. It is usually desirable to minimize this parameter to minimize possible injury effects to the tissue and to reduce the pain experience by the patient.

As we will see later, it is not possible to have a stimulus pulse that minimizes all three parameters simultaneously.

From the expression for current (4) we can derive expressions similar for charge and energy.

Theoretical strength-duration relations for RC membrane

$$Q = \frac{I_{rh} d}{1 - e^{-d/\tau_m}} \tag{7a}$$

$$I = \frac{I_{rh}}{1 - e^{-d/\tau_m}} \tag{7b}$$

$$U = I_{rh}^2 R d \left(\frac{1}{1 - e^{-d/\tau_m}} \right)^2 \tag{7c}$$

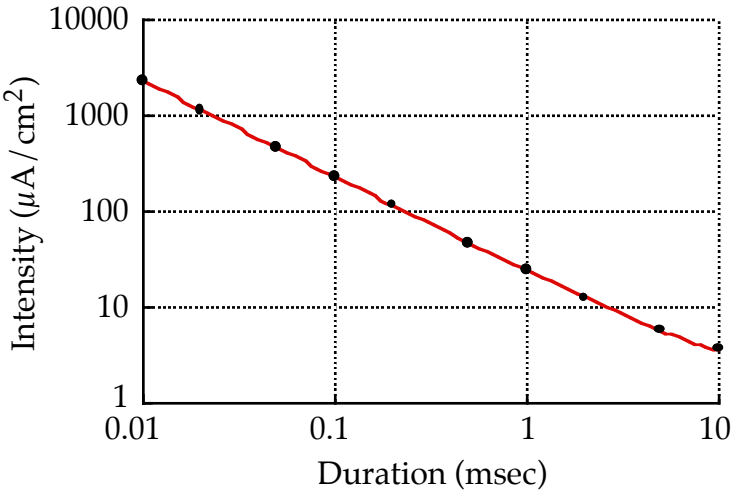
Under these conditions, the following statements can be made.

a) Given that c is defined as the pulse duration with intensity equal to twice rheobase, then from (7b), c is equal to $0.693\tau_m$.
b) The pulse duration with mimimum energy no longer equals c, but is equal to $1.255\ \tau_m$.

C. How good is the approximation of an RC membrane? In membrane biophysical models, R_m for example in cardiac muscle is essentially determined by the conductance of the inwardly rectifying potassium channel (corresponding to I_{K1}). Given that the conductance is nonlinear, and that other channels are time- and voltage-dependent, it is unclear whether a constant, time-invariant RC membrane is adequate to describe the passive, subthreshold behavior as the membrane depolarizes to its threshold potential during stimulation. Hill [**5**] showed that the strength-duration relation of an active, Hodgkin-Huxley membrane is affected to some extent by membrane nonlinearities, activation time, and accommodation. To address this question, we can use for example the simple 4 ionic current, Beeler-Reuter (BR) active membrane model for the cardiac

cell membrane [**6**] to solve for the strength-duration curve of cardiac cells, and to compare the result with that predicted by a constant, linear RC membrane. The results are plotted below.

Figure 4



The filled symbols are the results of the BR model simulation. The curve connecting the points is the best fit of the form given by (7b), with $I_{rh} = 2.084\ \mu\text{A/cm}^2$, and $\tau_m = 11.274$ ms. Clearly, the fit is very good! The simulation also shows that over the range of 0.01 to 10 ms, the excitation threshold varies only between -59.15 to -59.82 mV (not shown), so that the assumption of a constant V_{th} is very good. However, one discrepancy between the model and the fit is in the time constant. For a constant RC membrane, the time constant in (7b) is equal to $R_m C_m$. For the Beeler-Reuter model, this time constant should be approximately equal to C_m / g_{K1}, where g_{K1} is the slope conductance of the inwardly rectifying potassium channel at rest.[2] If we assume the resting potential is around -84 mV, then g_{K1} is calculated to be approximately 0.164 mS/cm^2, and therefore the calculated τ_m is around 6 ms, not 11 ms. The discrepancy apparently is a consequence of the nonlinearity of the model between resting and takeoff potentials.

3. ELECTRICAL STIMULATION OF CELLS BY UNIFORM ELECTRIC FIELDS

Unlike the case for intracellular current injection, which results in a uniformly polarized (or space-clamped) membrane, electrical stimulation by electric fields produces a nonuniform, differentially polarized membrane.

A. Field stimulation of RC membrane under step conditions. The step response of the spherical cell has been described by Plonsey, Schwann, Zimmermann, and others. This is reiterated in a recent paper by Cartee and Plonsey [**7**]. Assuming a spherical cell with the following coordinate system and an applied field along the *z*-axis, the transmembrane potential can be derived by solving Laplace's equation inside and outside the cell, with a boundary condition at the cell surface that reflects the passive properties of the cell membrane.

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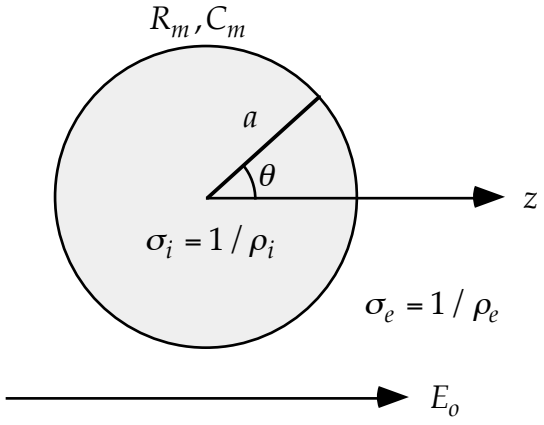
[2]Since there are several other channels in the membrane, the membrane conductance will be underestimated if taken to be g_{K1} only. Therefore, the calculated value of τ_m will be an overestimate.

Figure 5



$$v_m = \frac{3\sigma_i\sigma_e R_m E_o a\cos\theta}{a\sigma_i + 2a\sigma_e + 2\sigma_i\sigma_e R_m}\left(1-e^{-t/\tau'}\right)$$
$$= \frac{R_m}{R_m + R_a}\left(\frac{3}{2}E_o a\cos\theta\right)\left(1-e^{-t/\tau'}\right) \qquad (8)$$

where

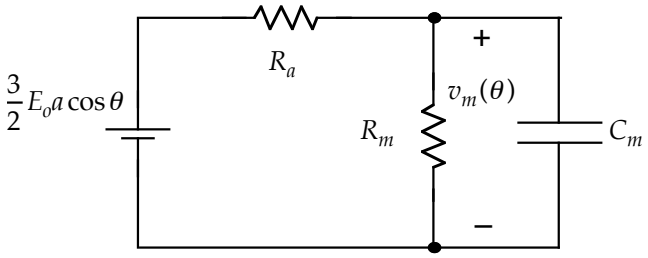
$$\frac{1}{\tau'} = \frac{1}{R_m C_m} + \frac{2\sigma_i\sigma_e}{aC_m(\sigma_i + 2\sigma_e)}$$
$$= \frac{1}{R_m C_m} + \frac{1}{R_a C_m} \qquad (9a)$$

and

$$R_a = a(\rho_i + 0.5\rho_e)\,. \qquad (9b)$$

Equation (8) can be interpreted in terms of an equivalent circuit where R_a is an equivalent access resistance to the membrane.

Figure 6



The source term is the field strength scaled by a spherical geometric form factor. The access resistance is the sum of intracellular and (half of the) extracellular resistivities integrated over a distance equal to the cell radius a. The transmembrane potential v_m varies with θ and charges with a time constant equal to τ'. For typical values of R_m ~ 1 kΩ-cm^2, C_m ~ 1 μF/cm^2, ρ_e ~ 50 Ω-cm, ρ_i ~ 200 Ω-cm, and a ~ 50 μm, we find that $R_m C_m$ ~ 1 ms, and $R_a C_m$ ~ 1.1 μs. Therefore, τ' ~ 1.1 μs, and the membrane essentially reaches steady-state instantaneously. From our previous discussion of the chronaxie, this would

seem to suggest that the chronaxie is on the order of microseconds, and that the strength-duration relation should be flat, at the rheobasic level for all practical pulse durations. However, this prediction is contradicted by actual measurements performed of the strength-duration relation in single cardiac cells [**8**], which show a chronaxie on the order of 2-3 milliseconds. Therefore, an additional factor must be contributing to the inverse relation of the strength-duration relation. This is accounted in large part by the voltage- and time-dependent kinetics of the Na channel, as we shall see in the next section.

B. Field stimulation of active membrane. The next step is to consider excitation under active membrane conditions. Since the charging time constant will be much faster than the kinetics of conductance change for an active membrane, we can regard the extracellular potential to be at equilibrium conditions during cell excitation. To solve for the transmembrane potential response, one can use the approximate extracellular potential distribution derived for a nonconducting cell as the driving function for a cell with active membrane [**9**]. Because the membrane is known to be nonuniformly polarized, the membrane must be partitioned into several segments, each with a different transmembrane potential as shown in Fig. 7. The cell membrane is mapped topologically onto a one-dimensional cable model. The upper panel shows the cell membrane partitioned into three membrane patches (M1-M3) along the perimeter of the cell. The lower panel is the corresponding cable representation. Each membrane patch includes ionic channels and lumped capacitance. The intracellular resistances represent pathways for ionic current flow through the cytoplasm.

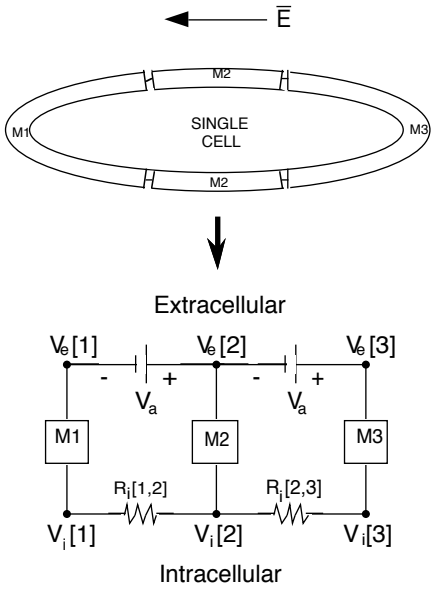


Figure 7 [**9**]

Using this model, an excitation strength-duration relation (ESD) can be determined. Compared with that for intracellular current injection, the ESD for field stimulation is flatter but nevertheless exhibits an inverse relation between pulse strength and duration. The model shows that the curvature results in part from the voltage- and time-dependent kinetics of the Na channel. Once activated, the resulting inward Na current then serves to charge the membrane capacitance up to threshold with a complex, nonexponential time course. A comparison of the ESDs for these two

modes of stimulation is shown in Fig. 8 using a 13 ionic current, Luo-Rudy active membrane model for the cardiac cell membrane [**10**].

Figure 8 [**9**]

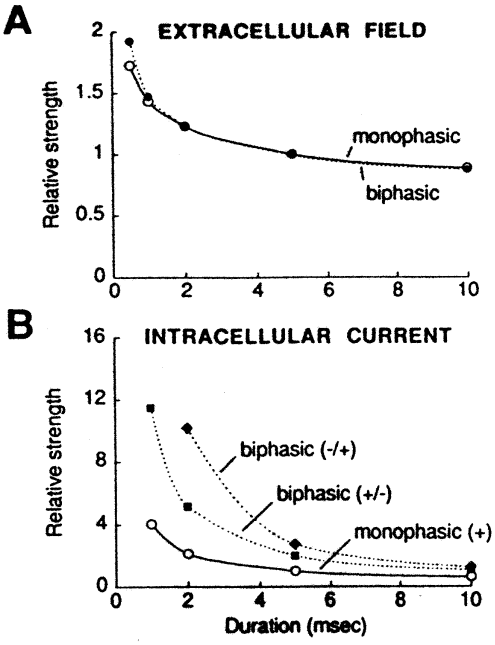


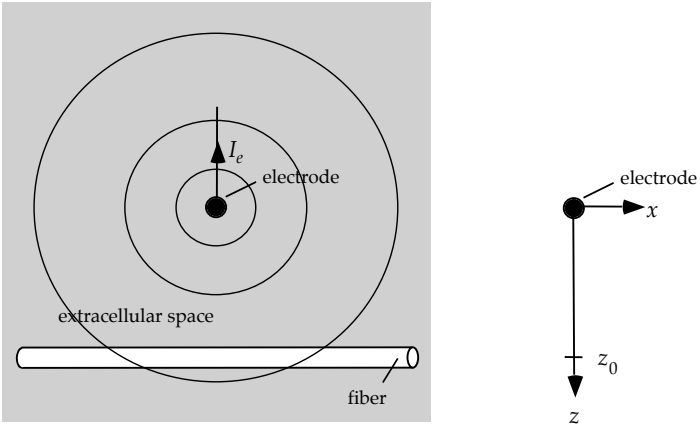
FIGURE 9 Excitation thresholds for extracellular and intracellular stimulation. Thresholds have been normalized to the 5 ms values (21.189 mV for field, 6.86 $\mu A/cm^2$ for current). (*A*) Stimulus thresholds for extracellular monophasic (○) and extracellular biphasic (●) field pulses at five stimulus durations (0.5, 1, 2, 5, and 10 ms). (*B*) Stimulus thresholds for intracellular (+) monophasic (○), intracellular (+/−) biphasic (■), and intracellular (−/+) biphasic (◆) current pulses at the same five stimulus durations. Intensities in each panel have been normalized to the intensity for monophasic stimulation at the 5 ms pulse duration.

Also shown in Fig. 9 are the ESDs for rectangular biphasic stimulus pulses. Different behaviors are predicted for the relative efficacy of biphasic stimulation compared with monophasic stimulation, depending on the mode of stimulation.

4. ELECTRICAL STIMULATION OF FIBERS BY ELECTRIC FIELDS

A. The activating function. We now consider the case of a cylindrical fiber stimulated by an extracellular point electrode. In the region adjacent to the stimulus electrode, there will generally be relatively steep gradients in electric field. These gradients can induce a pattern of polarization in the fiber. A simple example was described by Rattay [**11**] for nerve fibers lying under a point electrode (as drawn below).

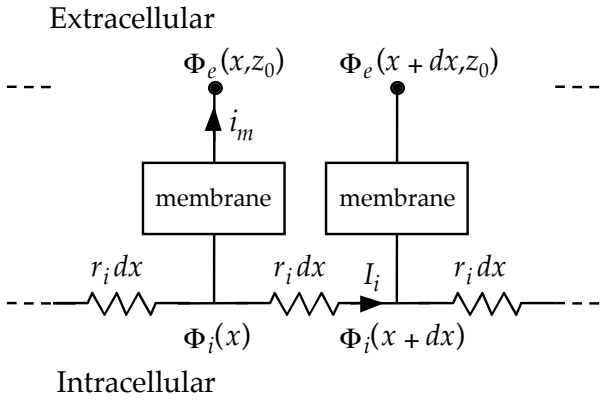
Figure 9



An electrode is placed in a slab of tissue, and its location is defined as the origin of the coordinate system. Surfaces of equipotential are shown as circular lines. A cylindrical

cardiac fiber is located a distance z_0 beneath the tissue surface. The 1-D cable representation for the fiber is shown below in Fig. 10. Unlike the usual assumption of the core-conductor model, the extracellular space is not confined to be close to the fiber, and current does not flow through the extracellular space along a single pathway. For simplicity, all other sources (e.g., locally applied current sources) are assumed to be absent. Using the same model we used previously for the active fiber as a bioelectric source,

Figure 10



The transmembrane current i_m contains two components – the capacitive current i_C and total ionic current i_{ion} (all with units of amp/cm):

$$i_m = i_C + i_{ion} = c_m \frac{\partial v_m}{\partial t} + i_{ion} \tag{10}$$

where c_m is the length-specific membrane capacitance (units of μF/cm). Along the intracellular pathway within the fiber, we have

$$\frac{\partial I_i}{\partial x} = -i_m \tag{11}$$

$$r_i I_i = -\frac{\partial \Phi_i}{\partial x}\,. \tag{12}$$

Inserting (10) and (12) into (11), and utilizing the relation $\Phi_i = v_m + \Phi_e$,

$$-\frac{1}{r_i}\left(\frac{\partial^2 v_m}{\partial x^2} + \frac{\partial^2 \Phi_e}{\partial x^2}\right) = -c_m \frac{\partial v_m}{\partial t} - i_{ion}\,. \tag{13}$$

We can rewrite (13) in the following form,

$$\frac{1}{r_i}\frac{\partial^2 v_m}{\partial x^2} - c_m \frac{\partial v_m}{\partial t} - i_{ion} = -\frac{1}{r_i} A \tag{14}$$

where

Activating function

$$\boxed{A = \left.\frac{\partial^2 \Phi_e}{\partial x^2}\right|_{S_e} = -\nabla E_x\big|_{S_e}} \qquad (15)$$

A is the so-called activating function [**11**] and is equal to the second spatial derivative of Φ_e along the axis of the fiber at the extracellular surface, S_e. A can also be written as the negative gradient of the x-component of the extracellular electric field (E_x) along S_e. From (14), we see that A acts as an input forcing function for $v_m(x,t)$.

For the extracellular *cathodal* point source of Fig. 9, the potential in the volume conductor is:

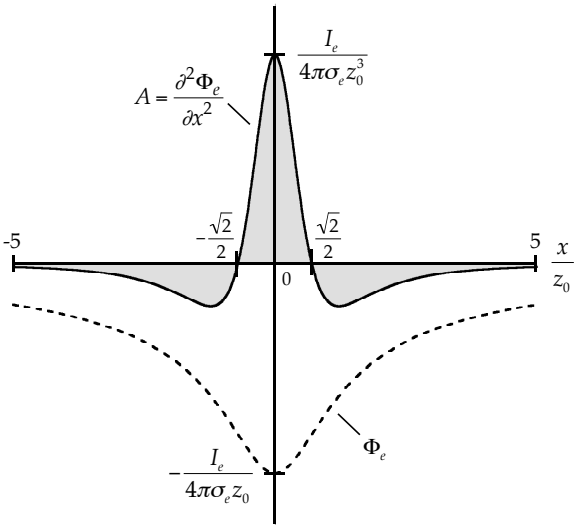
$$\Phi_e = -\frac{I_e}{4\pi\sigma_e r} = -\frac{I_e}{4\pi\sigma_e \sqrt{x^2 + z_0^2}} \qquad (16)$$

For a fiber located a distance z_0 from the point electrode as shown in Fig. 9, it is readily seen that the equipotential lines are not parallel to the fiber axis nor are they equally spaced (i.e., the electric field strength is dropping with distance from the electrode). This implies that there will be a gradient in electric field along the fiber axis, and a non-zero activating function will develop. Indeed, the activating function is,

$$A = \frac{I_e}{4\pi\sigma_e} \frac{z_0^2 - 2x^2}{(x^2 + z_0^2)^{5/2}} \,. \qquad (17)$$

Φ_e and A are plotted in Fig. 11.

Figure 11



Directly under the cathode in the region $|x| < (\sqrt{2}/2)z_0$, A is greater than 0, which from (14) leads to depolarization. We might choose to call this the "virtual cathode" response, since the solution to the core-conductor model for an extracellular cathode decays exponentially with distance and has this polarity. On the other hand, there are

side lobes of membrane hyperpolarization, which could be referred to as the "virtual anode" response. These lobes may be significant during cathodal stimulation since they can cause conduction block of the electrical impulse. Conversely, during *anodal* stimulation, the side lobes may become positive in sign and at sufficiently large intensities can lead to fiber excitation. In the cardiac literature, the reciprocal responses were initially described by Hoshi and Matsuda **[12]** and Bonke **[13]**, and are commonly referred to as a "virtual electrode" effect.

Some concluding comments are in order with respect to A. First, it is only the forcing function, and is not the transmembrane potential response v_m. Second, A is usually computed from the potential field associated with the source electrode in a homogeneous volume conductor, whereas the presence of the fiber must have some, albeit small, effect on the equipotential surfaces and flowlines of current. Although the relation (15) of A to Φ_e is exact, Φ_e is the actual (perturbed) potential on the fiber surface and not the unperturbed potential. Third, the flow of transmembrane i_{ion} in response to the developing v_m must necessarily alter Φ_e. However, if the sum total of perturbations in Φ_e and its second derivative is small, then it is reasonable use the unperturbed Φ_e from the stimulus electrode to determine A.

B. Subthreshold step response. Up to excitation threshold, we can model the membrane as a passive RC circuit; i.e.,

$$i_{ion} = \frac{v_m}{R_m} \tag{18}$$

This means that (14) can be rewritten as,

$$\lambda^2 \frac{\partial^2 v_m}{\partial x^2} - \tau \frac{\partial v_m}{\partial t} - v_m = -\lambda^2 A \tag{19}$$

where,

Space constant

$$\boxed{\lambda = \sqrt{\frac{R_m}{r_i}}} \tag{20a}$$

Time constant

$$\boxed{\tau = R_m C_m} \tag{20b}$$

Now, let the stimulus current I_e be a step function at time 0 with amplitude I_0; i.e.,

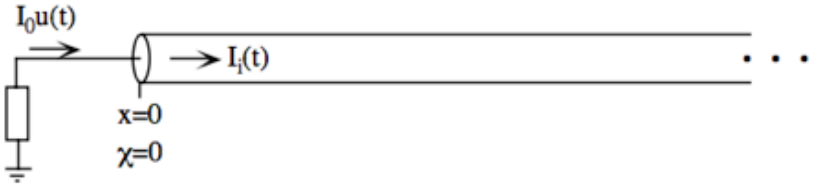
$$I_e = I_0 u(t) \tag{21}$$

so that for $t \geq 0$, $A(x)$ is given by (17). At $t = 0^+$ (the instant right after the stimulus current has turned on), v_m and its derivatives are zero (assuming zero initial conditions), and at this instant, but this instant only, (19) simplifies to,

$$\tau \frac{\partial v_m}{\partial t} = \lambda^2 A \tag{22}$$

This means that *the activating function governs the initial polarization change* of v_m. Referring to Fig. 11, v_m will initially depolarize in the region $-\sqrt{2}z_0/2 < x < \sqrt{2}z_0/2$, and hyperpolarize outside that region.

As discussed in class, we can take advantage of the similarity of (19) to the linear cable equation (with a bounded extracellular space) with an intracellular injected current:



$$\chi = \frac{x}{\lambda} \quad and\, T = t/\tau$$

Figure 12

In this case we obtain the solution:

$$v(\chi,T) = \frac{I_0}{2G_\infty}\left\{e^{-\chi}\,\mathrm{erfc}\left[\frac{\chi}{2\sqrt{T}} - \sqrt{T}\right] - e^{\chi}\,\mathrm{erfc}\left[\frac{\chi}{2\sqrt{T}} + \sqrt{T}\right]\right\}$$

Where

$$G_\infty = \frac{1}{R_\infty} = \sqrt{r_i R_m} = \frac{1}{r_i \lambda} \tag{20}$$

is the is the input conductance looking into the semi-infinite fiber. From this we can obtain the impulse response of the system.

Fig. 13 shows the v_m response in steady-state to an extracellular cathode at a distance of $z_0 = \lambda$ from the fiber. Panel A shows $A(x)$. Panel B shows the impulse response of the the system, $h(x,t)$, in steady-state: an exponentially decaying function with decay constant λ. Panel C shows the convolution of $A(x)$ and $h(x)$. $A(x)$, $h(x)$ and $v_m(x)$ have been normalized to their peak intensities at $x = 0$.

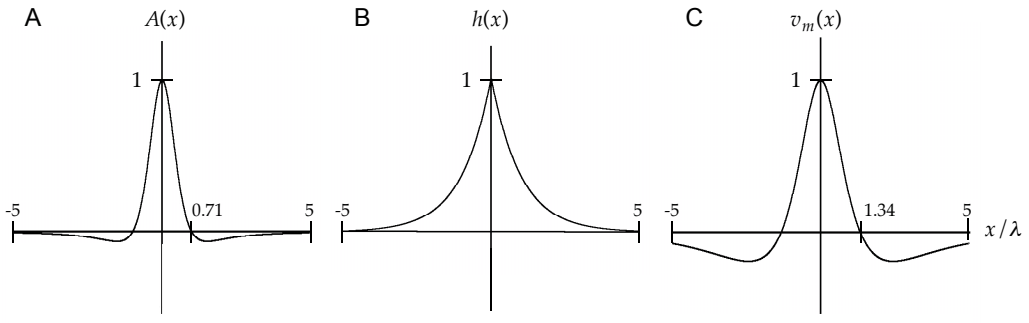


Figure 13

References

1. Reilly, J.P. Applied Bioelectricity – From Electrical Stimulation to Electropathology. Springer, 1998.
2. Johnston, D., Wu, M.S. Foundations of Cellular Neurophysiology. MIT Press, 1995.
3. Weiss, G. G. Sur la possibilite de rendre comparables entre eux les appareils: a l'excitation. Arch Ital de Biol 35:413-446, 1901.
4. Lapicque, L. Recherches quantitative sur l'excitation electriques des nerfs traitée comme une polarisation. J Physiol (Paris) 9:620-635, 1907.
5. Hill, A. V. Excitation and accommodation in nerve. Proc R Soc B 119:305-355, 1936.
6. Beeler, G.W. and Reuter, H. Reconstruction of the action potential of ventricular myocardial fibres. J Physiol 268:177-210, 1977.
7. Cartee, L. and Plonsey, R. The transient subthreshold response of spherical and cylindrical cell models to extracellular stimulation. IEEE Trans Biomed Eng 39:76-85, 1992.
8. Tung, L, Sliz, N. and Mulligan, M.R. Influence of electrical axis of stimulation on excitation of cardiac muscle cells. Circ Res 69:722-730, 1991.
9. Tung, L. and Borderies, J.-R. Analysis of electrical excitation of cardiac muscle cells. Biophys J 63:371-386, 1992.
10. Luo, C.-H. and Rudy, Y. A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes. Circ Res 74:1071-1096, 1994.
11. Rattay, F. Analysis of models for external stimulation of axons. IEEE Trans Biomed Eng 33:974-977, 1986.
12. Hoshi, T. and Matsuda, K. Excitability cycle of cardiac muscle examined by intracellular stimulation. Jpn J Physiol 12:433-446, 1962.
13. Bonke, F. I. M. Passive electrical properties of atrial fibers of the rabbit heart. Pflugers Arch 339:1-15, 1973.