ECE 795:

Quantitative Electrophysiology

Notes for Lecture #6

November 17, 2011

10. GENERATION OF EXTRACELLULAR FIELDS

We will look at:

- Generation and measurement of extracellular fields
- Distributed-source models for APs in single fibers
- Lumped-source models for APs in single fibers
- Temporal considerations
- Classification of fields
- Example field recordings

Generation and measurement of extracellular fields:

The activity of excitable cells leads to flow of currents into the extracellular space.

These currents can be measured by extracellular electrodes or even electrodes on the body surface. Examples include:

- **ECG** (electrocardiogram)
- **EMG** (electromyogram)
- **EEG** (electroencephalogram)

Generation and measurement of extracellular fields (cont.):

Measurement of extracellular fields depends on:

- the spatial and temporal characteristics of the locally-generated extracellular fields, and
- the conductive characteristics of the tissue between the excited cell(s) and the electrodes, referred to as a *volume conductor*.

Observed extracellular potentials:

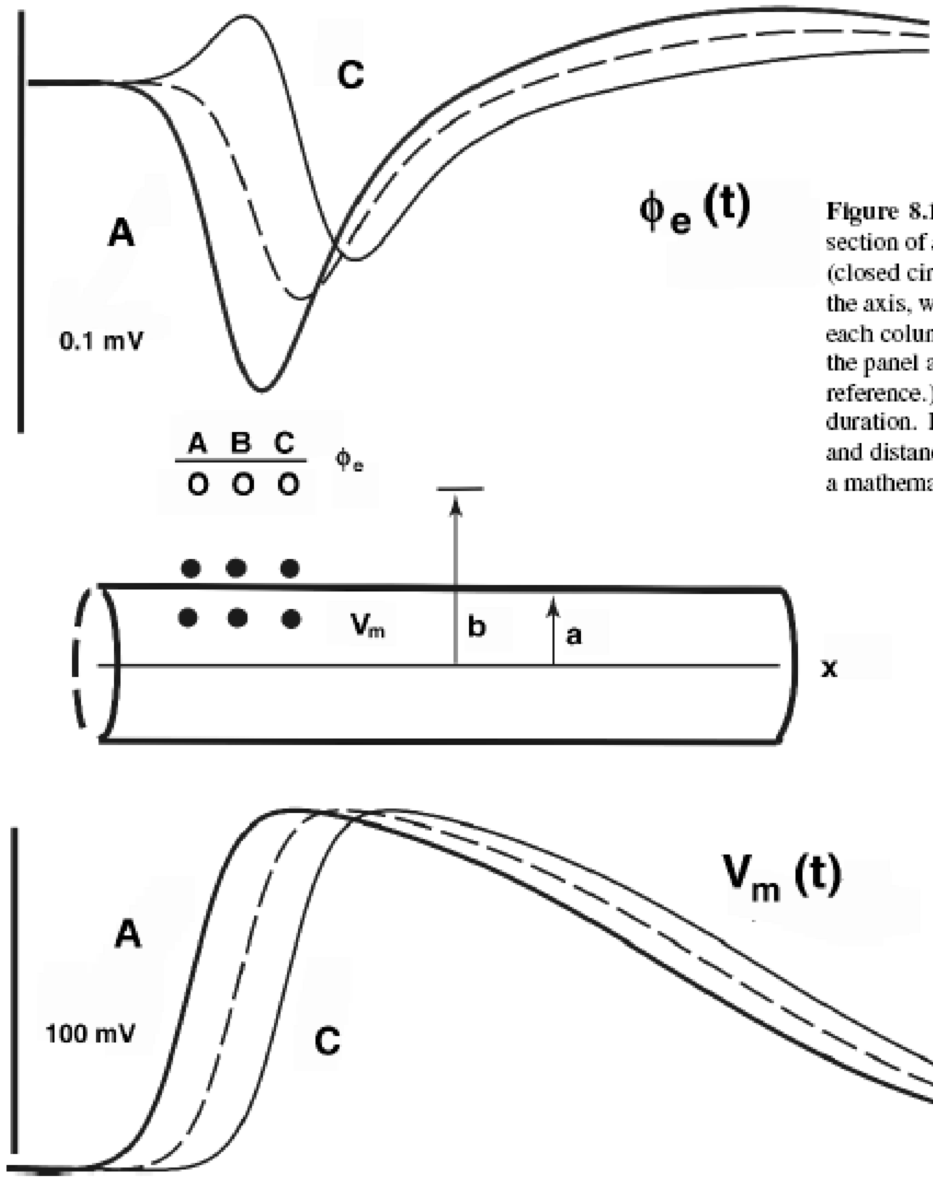


Figure 8.1. Intracellular and Extracellular Temporal Waveforms. A sketch of a short section of a long cylindrical fiber is shown in the middle panel. Transmembrane electrodes (closed circles) and extracellular electrodes (open circles) are drawn at three points along the axis, with their respective columns labeled A–C. Transmembrane potentials $V_m(t)$ for each column are shown in the panel below. Extracellular waveforms $\Phi_e(t)$ are shown in the panel at the top. (These are unipolar waveforms, i.e., potential with respect to a distant reference.) The vertical bars (top, bottom) give a voltage calibration. Each trace has a 10-ms duration. Locations A, B, and C are at $x = 0, 1, 2$ mm, respectively. Radius $a = 0.1$ mm and distance $b = 1.0$ mm. These waveforms are based on a computer simulation that uses a mathematically defined template function for $V_m(t)$. $R_i = 100$ and $R_e = 30\ \Omega$cm.

Observed extracellular potentials (cont.):

The temporal waveforms of extracellular potentials cannot be determined directly from the temporal waveforms for transmembrane potentials. Instead the following steps must be taken:

1. Convert transmembrane potential temporal waveform into spatial waveform.
2. Find transmembrane current and/or axial extracellular current.
3. Find extracellular spatial waveform produced by transmembrane current (or alternatively axial extracellular current).
4. Convert extracellular spatial waveform into temporal waveform.

Observed extracellular potentials (cont.):

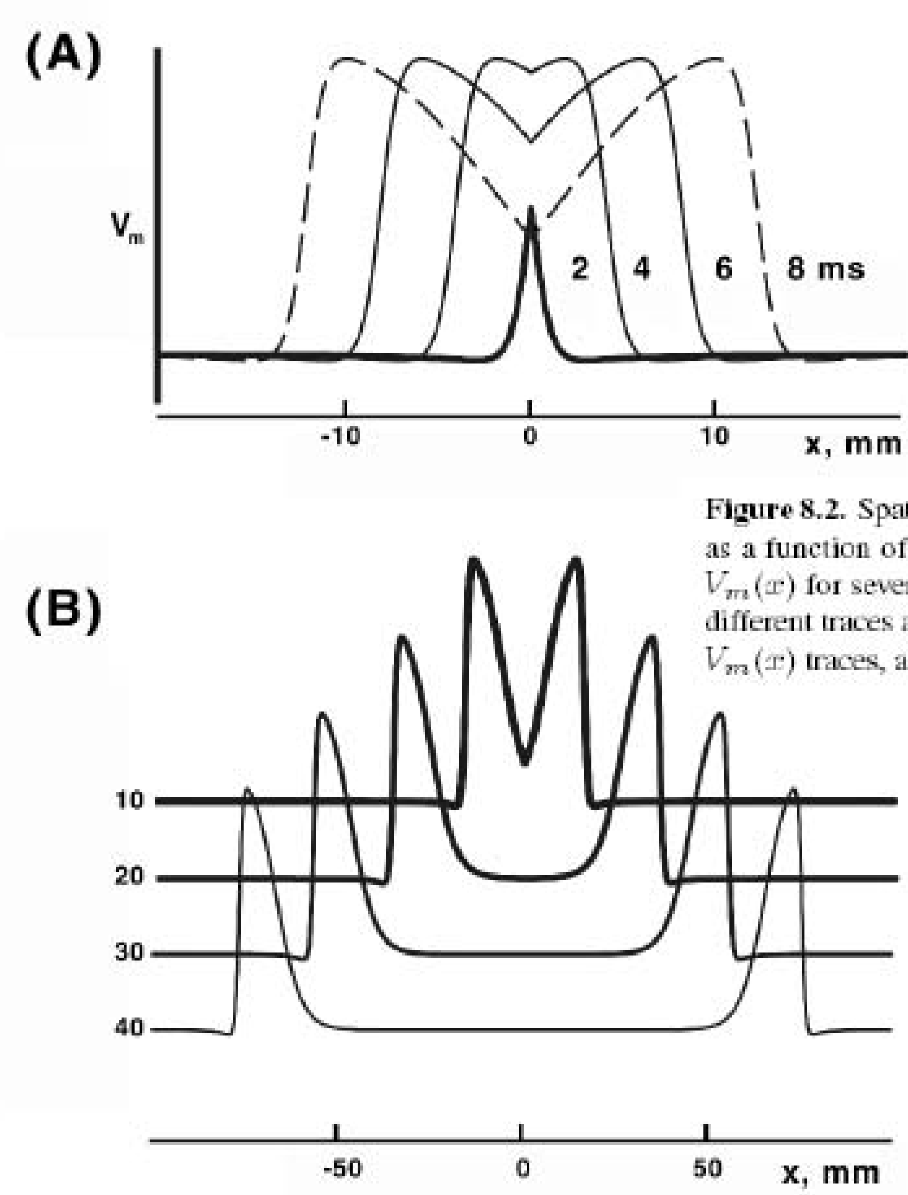


Figure 8.2. Spatial Transmembrane Potentials. Panel A shows the transmembrane potential as a function of distance along the fiber, for early times after excitation. Panel B shows $V_m(x)$ for several later times, given by the number beside each trace. For illustration, the different traces are displaced vertically. Note the multiplicity of wave shapes present in the $V_m(x)$ traces, as compared to $V_m(t)$, which is shown in Figure 8.1.

Source density $i_m(x)$:

The transmembrane current $i_m(x)$ acts as a current source in the extracellular electrolyte.

From the cable equations:

$$i_m = \frac{1}{r_i}\frac{\partial^2 \Phi_i}{\partial x^2}. \qquad (8.3)$$

For an axon with radius a and axoplasmic resistivity R_i, Eqn. (8.3) becomes:

$$i_m = \frac{\pi a^2}{R_i}\frac{\partial^2 \Phi_i}{\partial x^2} = \pi a^2 \sigma_i \frac{\partial^2 \Phi_i}{\partial x^2}. \qquad (8.5)$$

where $\sigma_i = 1/R_i$ is the conductance per unit length.

Source density $i_m(x)$:

However, one normally knows $V_m(x)$ but not $\Phi_i(x)$.

In the case where $r_e \ll r_i$, $V_m(x) \approx \Phi_i(x)$ and thus:

$$i_m = \frac{1}{r_i}\frac{\partial^2 \Phi_i}{\partial x^2} \approx \frac{1}{r_i}\frac{\partial^2 V_m}{\partial x^2}. \qquad (8.6)$$

Under this approximation:

$$I_i = -\frac{\pi a^2}{R_i}\frac{\partial \Phi_i}{\partial x} \approx -\pi a^2 \sigma_i \frac{\partial V_m}{\partial x} \qquad (8.7)$$

$$i_m = \frac{\pi a^2}{R_i}\frac{\partial^2 \Phi_i}{\partial x^2} \approx \pi a^2 \sigma_i \frac{\partial^2 V_m}{\partial x^2}. \qquad (8.8)$$

Source density $i_m(x)$ *(cont.):*

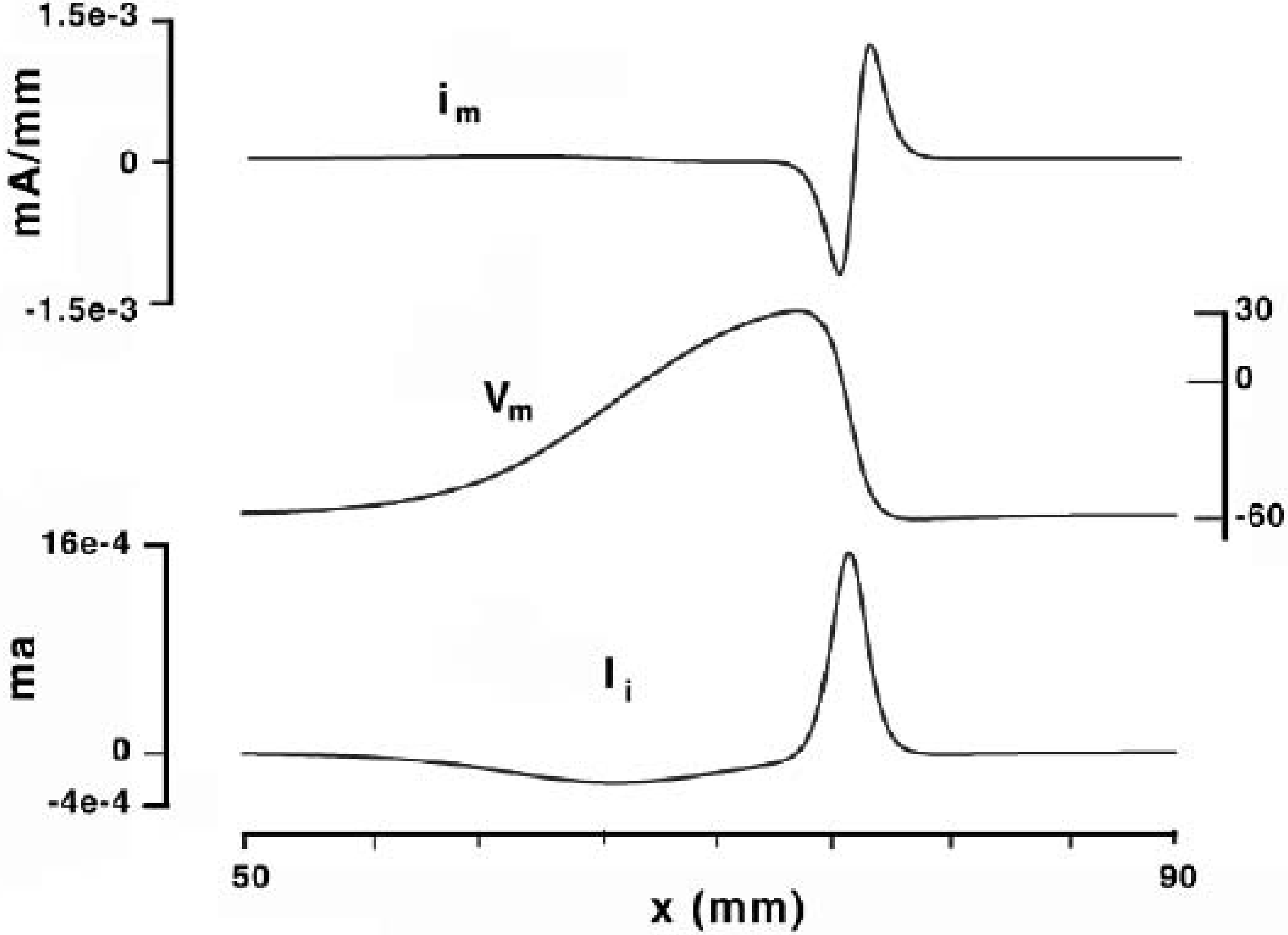


Figure 8.3. Transmembrane Potential V_m, Intracellular Current I_i, and Transmembrane Current i_m. The Figure shows a transmembrane potential (middle). Other traces give the transmembrane (top) and intracellular axial (bottom) currents, as determined from the transmembrane potential using Eqs. (8.7) and (8.8).

Observed extracellular potentials (cont.):

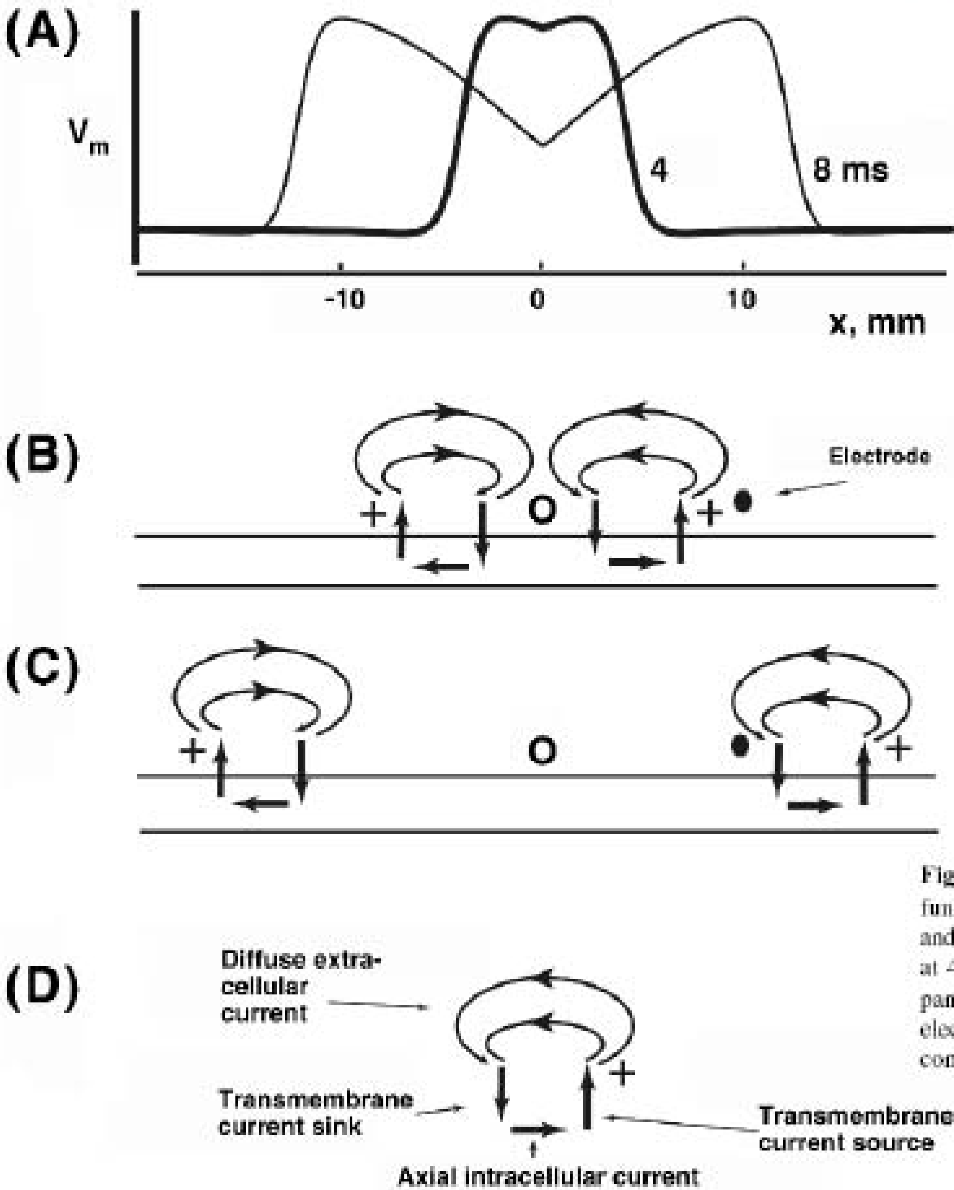


Figure 8.4. Action Current Cartoon. Panel A shows the transmembrane potential as a function of distance along the fiber for 4 and 8 milliseconds. Excitation began at $x = 0$ and spread from there in both directions. Panel B shows a cartoon of the current flow at 4 msec, and Panel C for 8 msec. Labels identifying elements of the current loops of panels B and C are given in panel D. The open and closed dots in B and C are hypothetical electrode positions. In B–D, for purposes of illustration the source–sink distance is widened, compared to that implied by the upstrokes of panel A.

Single-fiber source model:

The next step is to derive mathematical expressions for the potential at any point in the extracellular space, based on the transmembrane current source model of a single fiber.

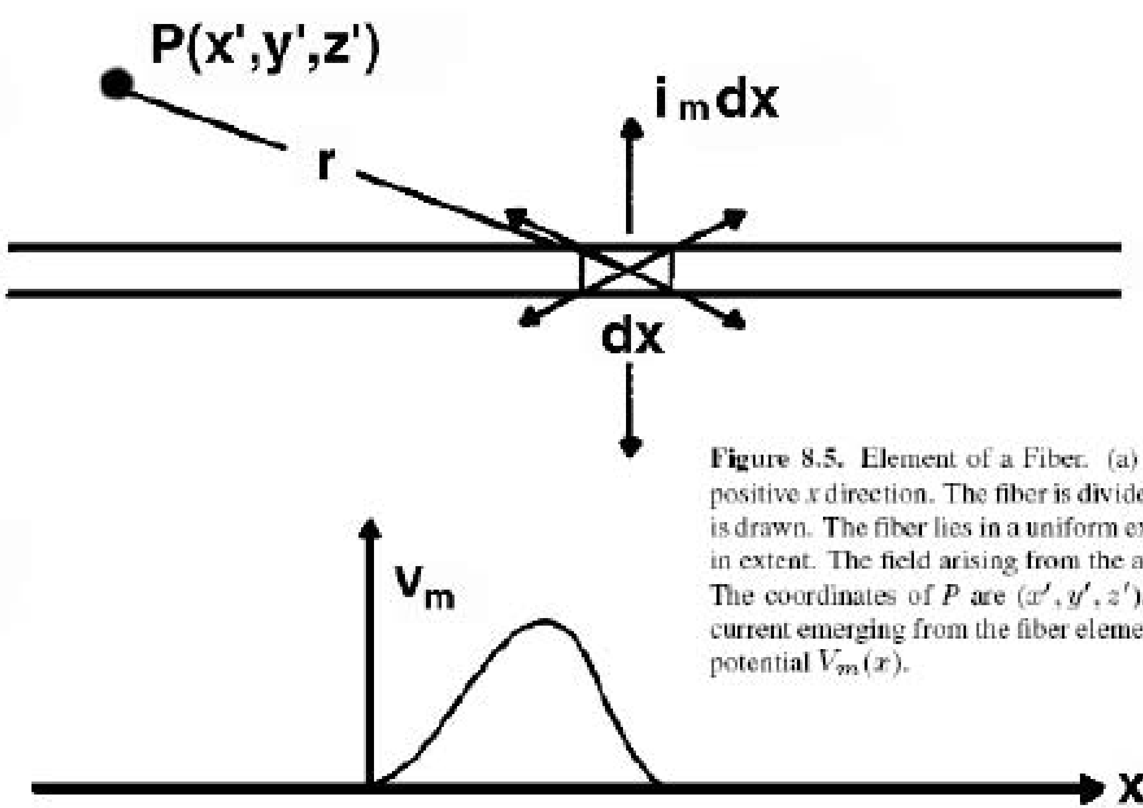


Figure 8.5. Element of a Fiber. (a) An action potential is propagating on a fiber in the positive x direction. The fiber is divided into mathematical segments, and one such segment is drawn. The fiber lies in a uniform extracellular medium of conductivity σ_e that is infinite in extent. The field arising from the action currents at an arbitrary field point P is desired. The coordinates of P are (x', y', z'). The source element is at (x, y, z). Shown is the current emerging from the fiber element dx (magnitude $i_m dx$). (b) The monophasic action potential $V_m(x)$.

Single-fiber source model (cont.):

For a fiber element of length $\mathrm{d}x$, the current I_0 passed into the extracellular space is:

$$I_0 = i_m \mathrm{d}x,$$

where i_m is the transmembrane current per unit length.

Although the element $\mathrm{d}x$ of fiber membrane is actually ring shaped, at distances that are large relative to the fiber's diameter, I_0 can be approximated as a point source.

Single-fiber source model (cont.):

For a point source, the extracellular field is:

$$\Phi_e = \frac{1}{4\pi\sigma_e}\frac{I_0}{r}, \qquad (8.9)$$

where $I_0 = i_m \mathrm{d}x$, σ_e is the conductivity of the extracellular medium, and r is the distance from the point source to an arbitrary field point.

Note that once again the effect of the fiber on the field is typically ignored.

Single-fiber source model (cont.):

The extracellular field for the fiber element $\mathrm{d}x$ is:

$$\mathrm{d}\Phi_e = \frac{1}{4\pi\sigma_e}\frac{i_m}{r}\mathrm{d}x\,, \tag{8.10}$$

and the total extracellular potential at point P is:

$$\Phi_e(P) = \frac{1}{4\pi\sigma_e}\int_L \frac{i_m}{r}\mathrm{d}x\,, \tag{8.11}$$

where L is the length of the fiber over which $i_m \neq 0$.

Single-fiber source model (cont.):

Substituting (8.8) into (8.11) gives:

$$\Phi_e = \frac{a^2\sigma_i}{4\sigma_e}\int \frac{\partial^2 V_m/\partial x^2}{r}\mathrm{d}x\,. \qquad (8.12)$$

The potential difference between two extracellular electrodes at positions a and b is then:

$$V_{ab} = \Phi_e(a) - \Phi_e(b)\,. \qquad (8.13)$$

Single-fiber source model (cont.):

If the element $\mathrm{d}x$ is located at point $(x,\, y,\, z)$ and the field potential is measured at $(x',\, y',\, z')$, then:

$$r = \sqrt{\left(x - x'\right)^2 + \left(y - y'\right)^2 + \left(z - z'\right)^2}. \quad (8.14)$$

Normally the coordinate origin is placed on the fiber so that $y = z = 0$. Since the source element is approximated by a point source, it too lies on the fiber's axis.

Single-fiber source model (cont.):

With this expression for r, the field potential is given by:

$$\Phi_e(x', y', z') = \frac{1}{4\pi\sigma_e} \int_L \frac{i_m(x)\,\mathrm{d}x}{\sqrt{(x-x')^2 + (y')^2 + (z')^2}} \,. \quad (8.15)$$

Eqn. (8.15) can be written as the convolution:

$$\Phi_e(x', y', z') = \frac{1}{4\pi\sigma_e} \int_L H(x-x')\, i_m(x)\,\mathrm{d}x \,, \quad (8.16)$$

where $$H(x-x') = \frac{1}{\sqrt{(x-x')^2 + (y')^2 + (z')^2}} \,. \quad (8.17)$$

Single-fiber source model (cont.):

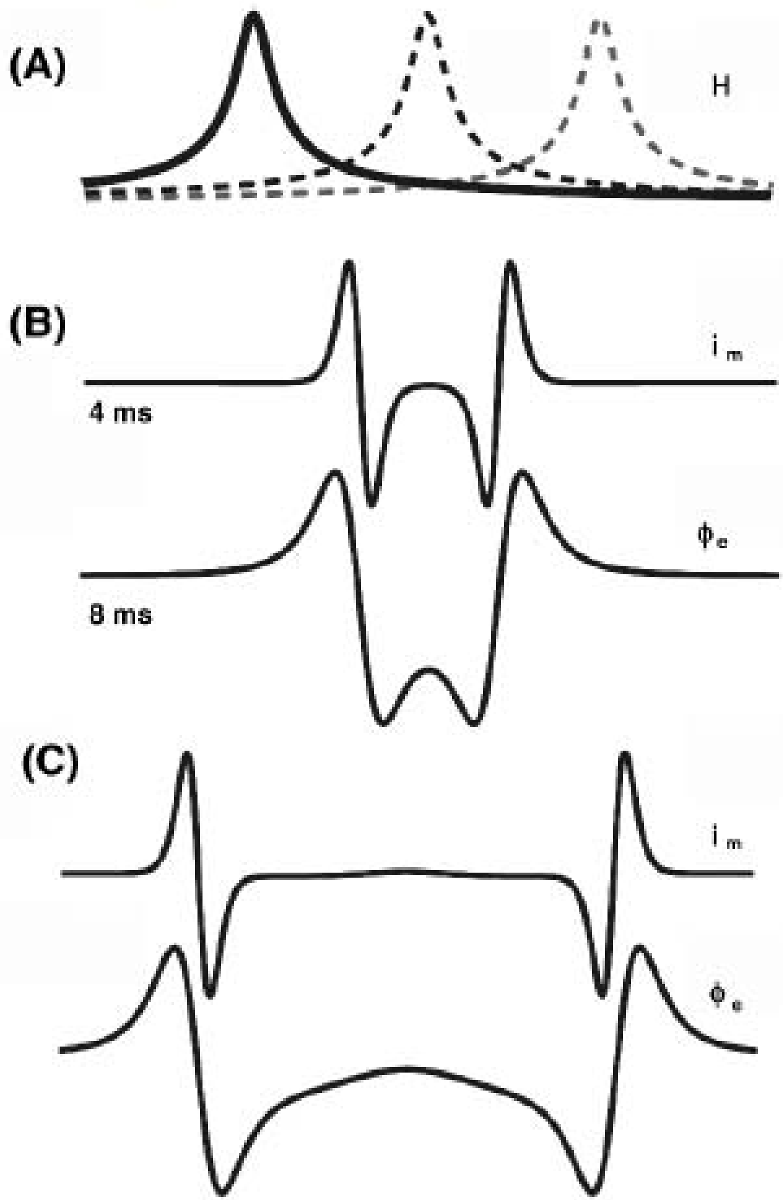


Figure 8.6. Transfer Function H, Membrane Current $i_m(x)$, and Extracellular Potentials $\Phi_e(x)$. Panel A: Plots of the transfer function H. Transfer function $H(x - x')$ is given for three values of x'. The solid line is for $x' = -10$ mm, while the two dashed lines are for $x' = 0$ (centered) and $x' = 10$ (on right). Panel B: Membrane current $i_m(x)$ at 4 milliseconds and extracellular potential $\Phi_e(x)$ along a line a distance of 1 mm from the fiber axis. Panel C: Membrane current $i_m(x)$ at 8 milliseconds and extracellular potential $\Phi_e(x)$ along a line a distance of 1 mm from the fiber axis. The extracellular potential distribution $\Phi_e(x)$ for 4 ms (thick line) and 8 ms (thin line). The 4-ms potential function comes from the convolution of H with i_m for 4 ms, and similarly for 8 ms.

Single-fiber source model (cont.):

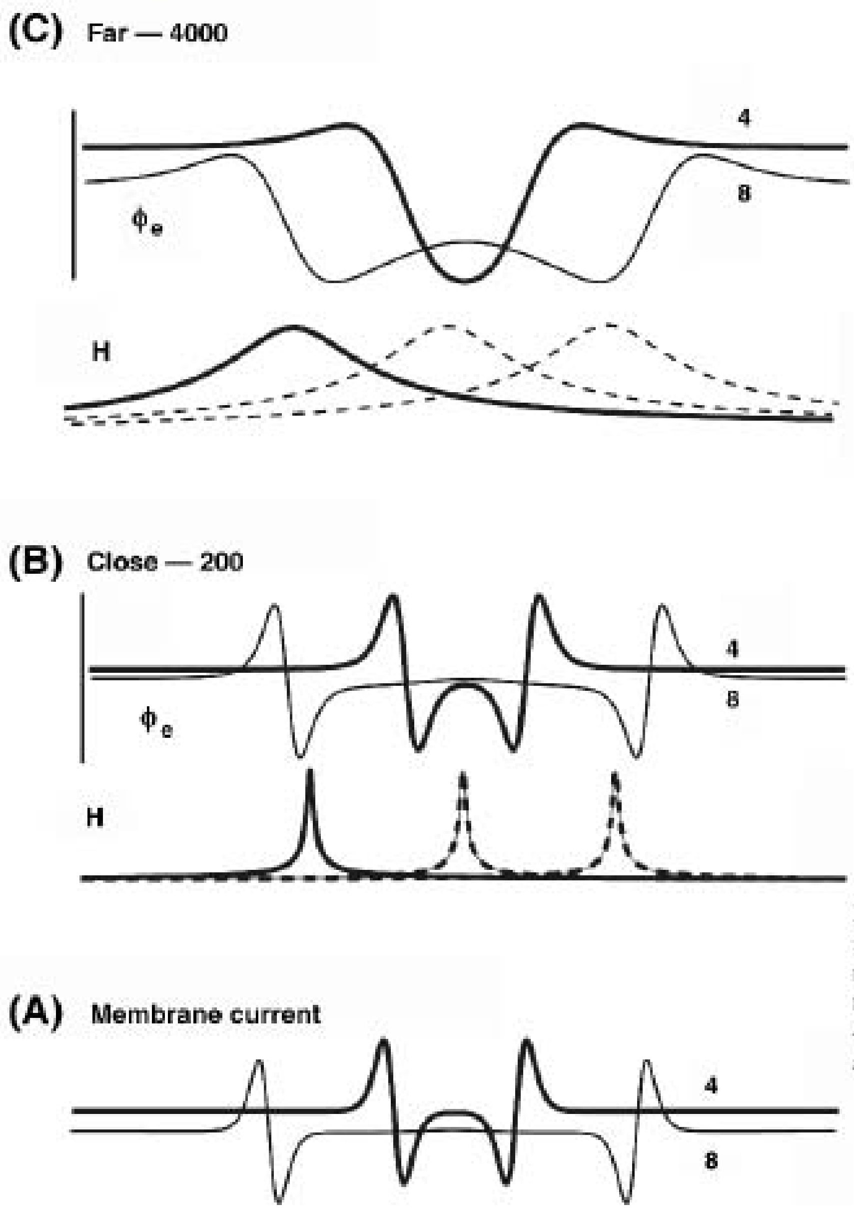


Figure 8.7. Changes with Distance of Extracellular Waveforms. Panel A shows the trans-membrane current waveform. Panel B shows data for a distance of 200 micrometers from the fiber axis. Data plotted is H for positions $-10, 0,$ and 10 mm, and $\phi_e(x)$. Panel C shows the same data at a distance of 4000 micrometers (4 mm). In all panels, the small numbers 4 and 8 are to identify curves for 4 milliseconds and 8 milliseconds after excitation begins at the center. (For illustration, the 8-ms plot is slightly displaced downward.)

Single-fiber source model (cont.):

Eqn. (8.12) can be considered the integral:

$$\Phi_e = \frac{1}{4\pi\sigma_e}\int \frac{I_\ell}{r}\,\mathrm{d}x \qquad (8.18)$$

of the **monopole source density** I_ℓ (with units of current per unit length):

$$I_\ell = \pi a^2 \sigma_i \frac{\partial^2 V_m}{\partial x^2}\,. \qquad (8.19)$$

Lumped monopole source model:

For a typical action potential waveform, the monopole source density is triphasic, with the three phases each extending over a fairly short section of the fiber, as illustrated in the next slide.

Consequently, these three source density regions can be approximated by three lumped monopoles M_1, M_2 & M_3.

This is readily shown by approximating the AP waveform as a triangle (see next slide).

Lumped monopole source model (cont.):

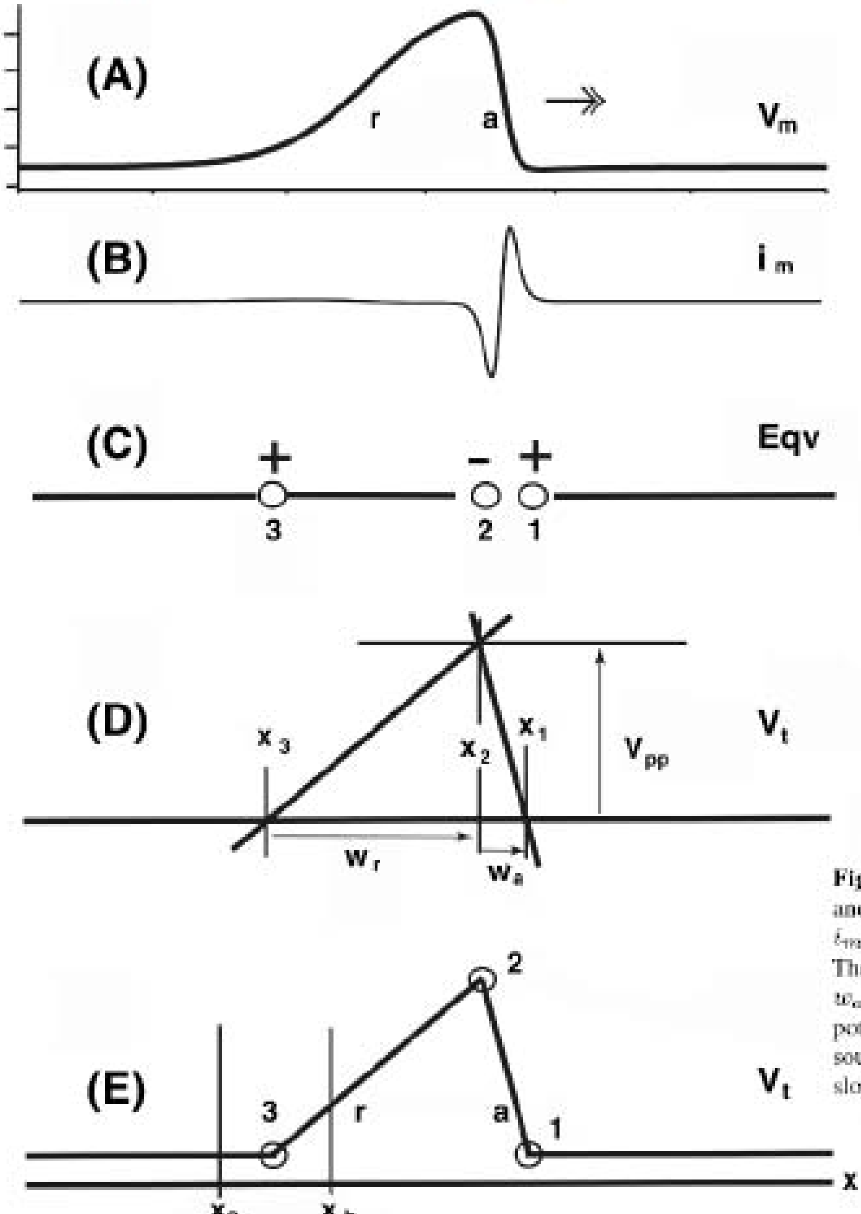


Figure 8.8. Monopole Sources. (A) Monophasic action potential $V_m(x)$. The activation and recovery phases are identified with the small letters a and r. (B) Membrane current $i_m(x)$. (C) Lumped equivalent monopole sources. (D) Triangularized action potential. The sides of the triangle have a slope equal to the maximum slope of V_m of panel A. Widths w_a and w_r are for the activation and recovery phases, spatially. (E) Triangular action potential with encircled sites where there is a slope change. Sites 1 to 3 lead to monopole sources M_1 to M_3. The activation phase of V_t has slope A_{max} and the recovery phase has slope B_{max}.

Lumped monopole source model (cont.):

From Eqn. (8.19), the total monopole strength arising from the distributed monopole densities in any interval x_a to x_b is given by:

$$M = \pi a^2 \sigma_i \int_{x_a}^{x_b} \frac{\partial^2 V_m}{\partial x^2} \, \mathrm{d}x$$

$$= \pi a^2 \sigma_i \left(\left. \frac{\partial V_m}{\partial x} \right|_{x = x_b} - \left. \frac{\partial V_m}{\partial x} \right|_{x = x_a} \right). \quad (8.21)$$

Lumped monopole source model (cont.):

The *magnitude* of the slope of the activation phase of width w_a and peak potential V_{pp} is:

$$A_{\mathsf{max}} = V_{\mathsf{pp}}/w_a\,, \tag{8.22}$$

and the *magnitude* of the slope of the repolarization phase of width w_r is:

$$B_{\mathsf{max}} = V_{\mathsf{pp}}/w_r\,. \tag{8.22}$$

Lumped monopole source model (cont.):

Consequently:

$$M_1 = \pi a^2 \sigma_i A_{\max}, \tag{8.24}$$

$$M_2 = -\pi a^2 \sigma_i \left(A_{\max} + B_{\max} \right), \tag{8.25}$$

$$M_3 = \pi a^2 \sigma_i B_{\max}. \tag{8.26}$$

These three lumped (i.e., discrete) monopole sources are located at the activation onset, AP peak & repolarization offset and approximate the actual distributed monopole source densities.

Lumped monopole source model (cont.):

The net extracellular field potential generated by these three sources is then:

$$\Phi_p = \frac{a^2\sigma_i}{4\sigma_e}\left(\frac{M_1}{r_1} + \frac{M_2}{r_2} + \frac{M_3}{r_3}\right) \qquad (8.27)$$

$$= \frac{a^2\sigma_i}{4\sigma_e}\left(\frac{A_{\mathrm{max}}}{r_1} - \frac{A_{\mathrm{max}} + B_{\mathrm{max}}}{r_2} + \frac{B_{\mathrm{max}}}{r_3}\right), \qquad (8.28)$$

where r_1, r_2 & r_3 are the respective distances from the sources to the field point.

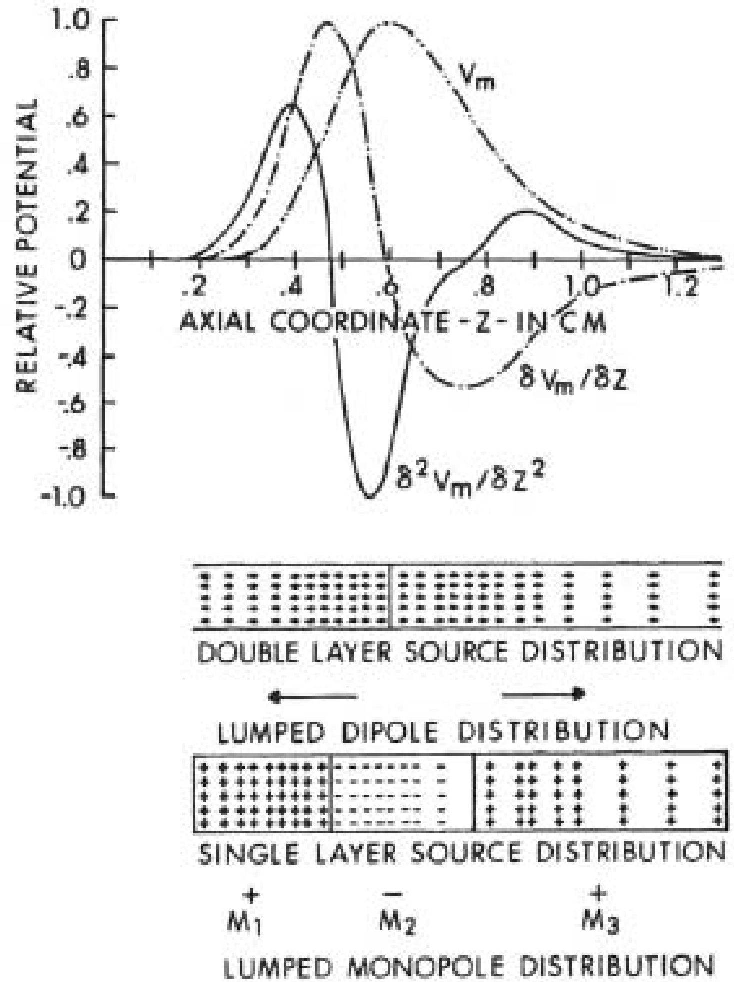
Lumped monopole source model (cont.):

Note:-

1. A lumped monopole source is a good approximation only at a reasonable distance from the fiber.
2. Eqn. (8.21) can be used to determine three lumped monopoles directly from the AP waveform, rather than the triangular approximation. In this case, each monopole is located at the "center of gravity" of the monopole source density that it is approximating.

Lumped fiber source models (cont.):

The spatial waveform of an action potential propagating in the negative x direction, and its first two spatial derivates, with the resultant source densities.



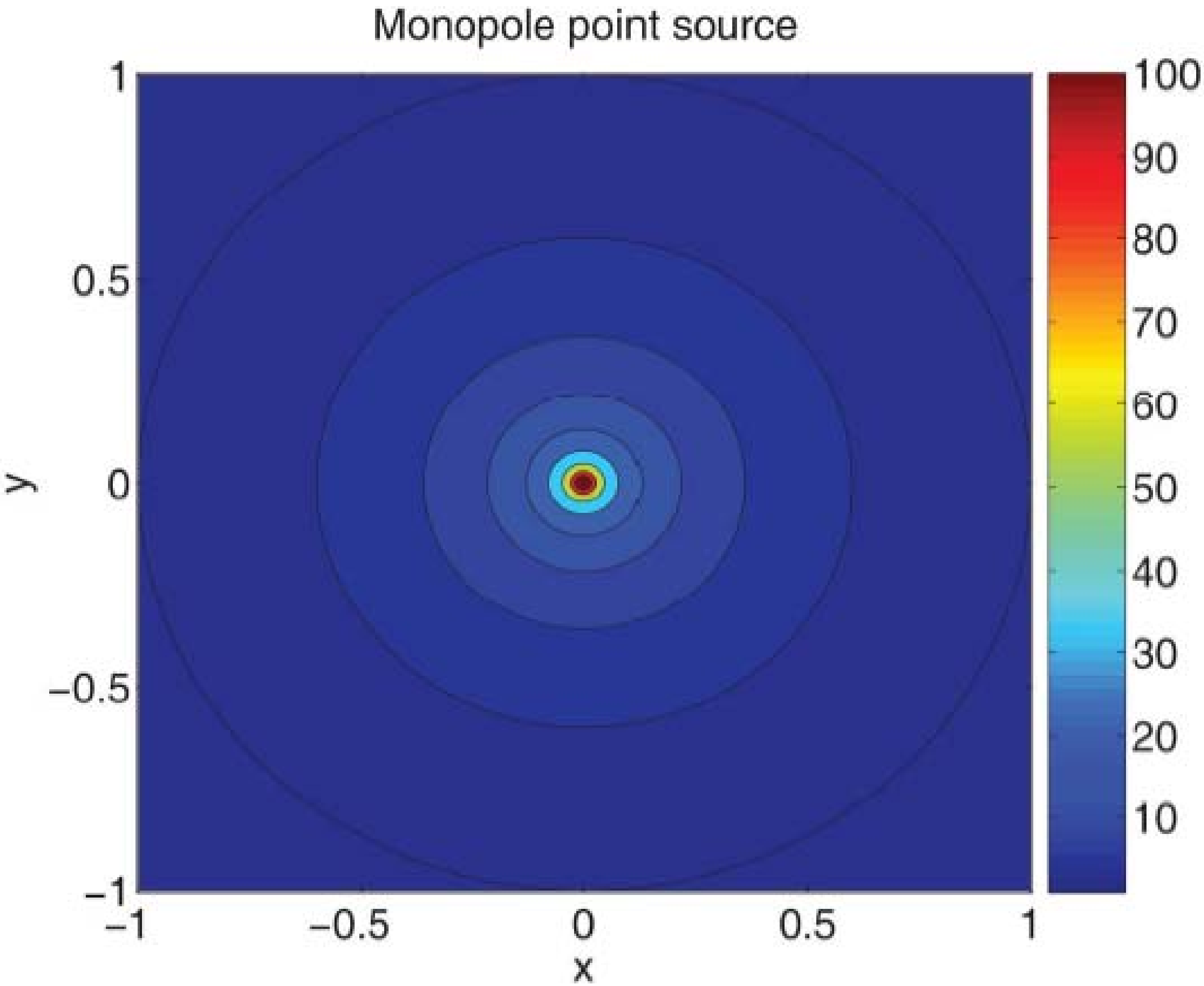
(From Plonsey & Barr, 2nd Edition)

Figure 8.2. Monophasic action potential v_m and its first two spatial derivatives. The corresponding double-layer and single-layer distributed sources are also indicated. Lumped dipole and monopole sources are shown (their locations are approximate). [From R. Plonsey, Action potential sources and their volume conductor fields, *Proc. IEEE* **65**:601–611 (1977). Copyright 1977, IEEE.]

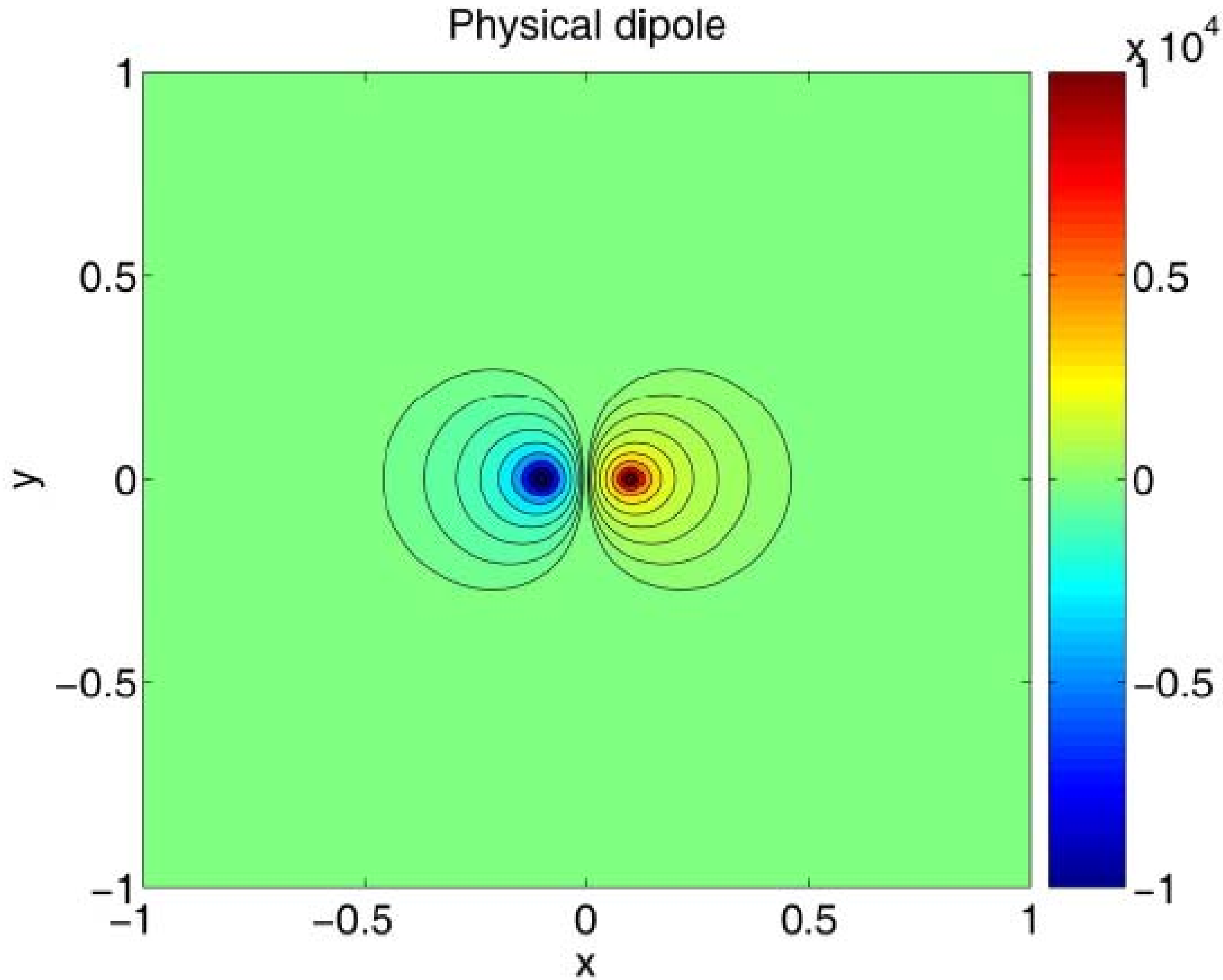
Dipole source definition:

The “tripole” lumped monopole model derived in the last lecture could also be interpreted as a pair of physical dipoles, one with current strength $+\pi a^2 \sigma_i A_{\max}$ at the onset of activation and $-\pi a^2 \sigma_i A_{\max}$ at the peak of the AP, and another with current strength $+\pi a^2 \sigma_i B_{\max}$ at the offset of repolarization and $-\pi a^2 \sigma_i B_{\max}$ at the peak of the AP.

Dipole source definition (cont.):



Dipole source definition (cont.):



Dipole source definition (cont.):

For a physical dipole with current strengths $+I_0$ and $-I_0$ separated by a distance d, the amount of uncancelled field created by the two monopoles is dependent on the product $p = I_0 d$.

Thus, the physical dipole equation:

$$\Phi_d = -\frac{I_0}{4\pi\sigma}\frac{1}{r_0} + \frac{I_0}{4\pi\sigma}\frac{1}{r_1}, \qquad (2.23)$$

is well approximated by the expression:

$$\Phi_d = \frac{I_0}{4\pi\sigma}\frac{\partial\,(1/r)}{\partial d}d, \qquad (2.25)$$

for d small compared to r_0 and r_1.

Dipole source definition (cont.):

The directional derivate of $(1/r)$ is the component of the gradient of $(1/r)$ in the direction of d, i.e.:

$$\frac{\partial}{\partial d}\left(\frac{1}{r}\right) = \nabla\left(\frac{1}{r}\right)\cdot \bar{a}_d\,, \qquad (2.26)$$

where $\bar{a}_d$ is the unit vector in the direction of the displacement $\bar{d}$.

Consequently, Eqn. (2.25) can be reformulated as:

$$\Phi_d = \frac{I_0}{4\pi\sigma}\nabla\left(\frac{1}{r}\right)\cdot \bar{d}\,. \qquad (2.28)$$

Dipole source definition (cont.):

An idealized or "perfect" dipole is the point source equivalent of a physical dipole. It is created by letting $d \to 0$ and $I_0 \to \infty$ such that $p = I_0 d$ remains constant and finite. Eqn. (2.28) then becomes:

$$\Phi_d = \frac{1}{4\pi\sigma} \nabla \left(\frac{1}{r} \right) \cdot \bar{p}, \tag{2.29}$$

where the dipole vector $\bar{p}$ = $p\bar{a}_d$ is typically located at a point midway between the positive and negative physical dipoles sources and oriented in the direction of the positive source.

Dipole source definition (cont.):

The gradient of $(1/r)$ can be shown to equal:

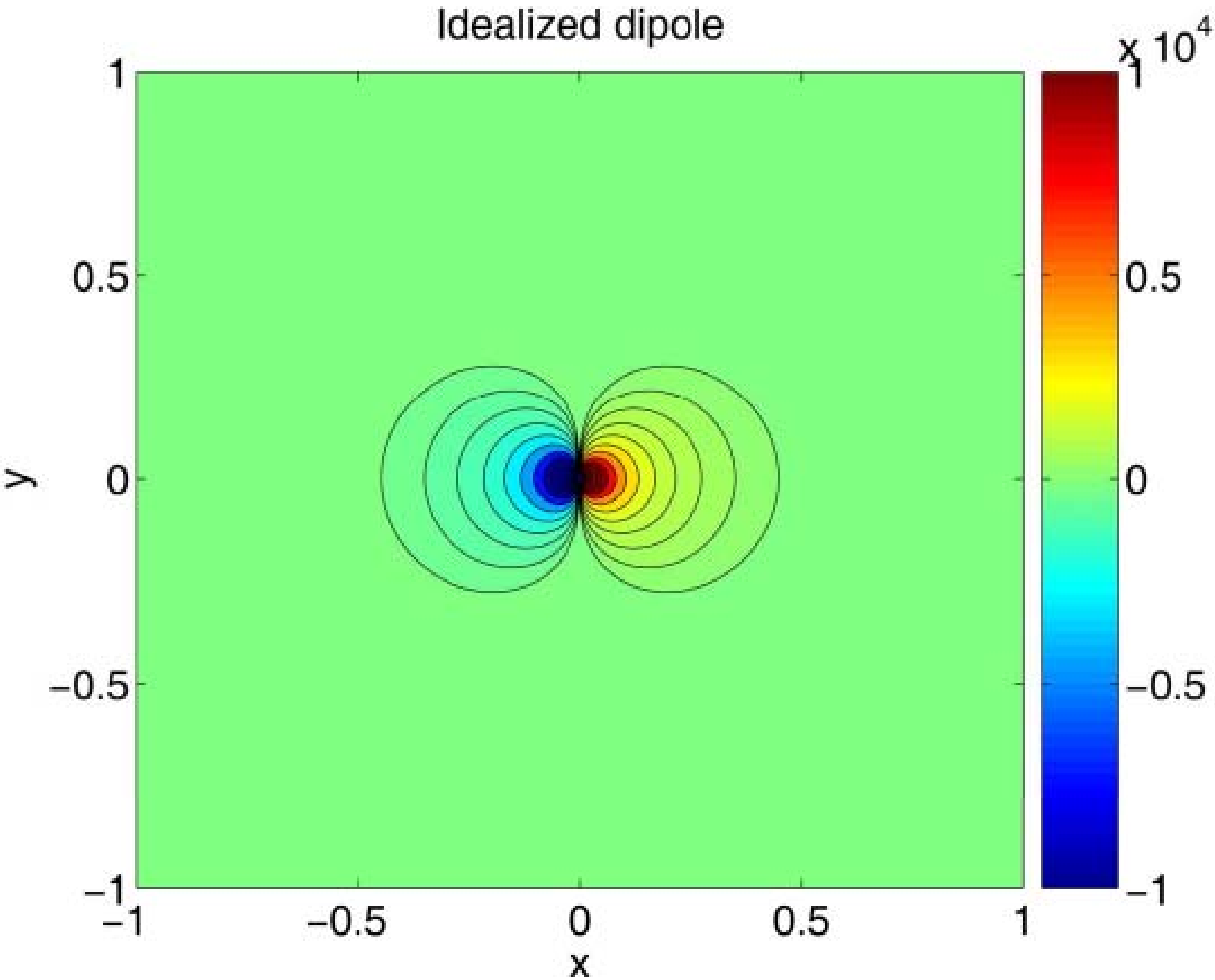
$$\nabla\left(\frac{1}{r}\right) = \frac{\bar{a}_r}{r^2}, \tag{2.32}$$

where $\bar{a}_r$ is the unit vector from the dipole source location to the field point. If θ is the angle between $\bar{a}_r$ and $\bar{p}$, then:

$$\Phi_d = \frac{\bar{a}_r \cdot \bar{p}}{4\pi\sigma r^2} \tag{2.33}$$

$$= \frac{1}{4\pi\sigma}\frac{p\cos\theta}{r^2}. \tag{2.34}$$

Dipole source definition (cont.):



Single-fiber dipole source model:

Eqn. (8.12) can be rewritten in the form:

$$\Phi_e = \frac{a^2\sigma_i}{4\sigma_e}\int_{-\infty}^{\infty}\frac{\partial}{\partial x}\left(\frac{\partial V_m}{\partial x}\right)\frac{1}{r}\,\mathrm{d}x\,. \qquad (8.32)$$

Integrating by parts gives:

$$\Phi_e = \frac{a^2\sigma_i}{4\sigma_e}\left\{\left[\frac{\partial V_m}{\partial x}\frac{1}{r}\right]\Bigg|_{-\infty}^{\infty} - \int_{-\infty}^{\infty}\frac{\partial V_m}{\partial x}\frac{\mathrm{d}(1/r)}{\mathrm{d}x}\,\mathrm{d}x\right\}. \qquad (8.34)$$

Single-fiber dipole source model (cont.):

The integrated part of (8.34) is zero if the action potential is not at the ends of the fiber, and it is only necessary to integrate over the region L of the fiber where $\partial V_m/\partial x$ $\neq 0$, giving:

$$\Phi_e = \frac{a^2\sigma_i}{4\sigma_e}\int_L \left[-\frac{\partial V_m}{\partial x}\right]\frac{\mathrm{d}(1/r)}{\mathrm{d}x}\,\mathrm{d}x. \quad (8.35)$$

Again, the directional derivative is:

$$\frac{\mathrm{d}(1/r)}{\mathrm{d}x} = \bar{a}_x \cdot \nabla\left(\frac{1}{r}\right). \quad (8.36)$$

Single-fiber dipole source model (cont.):

Substituting (8.36) into (8.35) gives:

$$\Phi_e = \frac{a^2\sigma_i}{4\sigma_e}\int\left[-\frac{\partial V_m}{\partial x}\bar{a}_x\right]\cdot\left[\nabla\left(\frac{1}{r}\right)\right]\mathrm{d}x. \quad (8.37)$$

Eqn. (8.37) can be considered the integral of the **dipole source density**:

$$\bar{\tau}_\ell \equiv -\pi a^2\sigma_i\frac{\partial V_m}{\partial x}\bar{a}_x \approx I_i\bar{a}_x\,, \quad (8.41)$$

with units of current (current times length per unit length) oriented in the x direction. Note the final approximation in (8.41) is true for $r_e \ll r_i$.

Single-fiber dipole source model (cont.):

The field potential generated by a dipole source density is then:

$$\Phi_e = \frac{1}{4\pi\sigma_e}\int \bar{\bar{\tau}}_\ell \cdot \left[\nabla\left(\frac{1}{r}\right)\right] \mathrm{d}x\,. \qquad (8.43)$$

Because the first derivate of a typical AP spatial waveform is biphasic, a propagating AP produces a pair of dipole source regions, each with the dipoles pointing away from the peak of the AP.

Note that these dipole source regions are consistent with the diffuse axial extracellular currents I_e produced by a propagating AP.

Lumped dipole source model:

The two dipole source density regions can be approximated by two lumped dipoles, a dipole D_p pointing in the $+\mathrm{ve}\ x$ direction at the activation phase and a dipole D_n pointing in the $-\mathrm{ve}\ x$ direction at the repolarization phase of an AP propagating in the $+\mathrm{ve}\ x$ direction.

Note that these dipoles would be switched if the AP were propagating in the $-\mathrm{ve}\ x$ direction.

Lumped dipole source model (cont.):

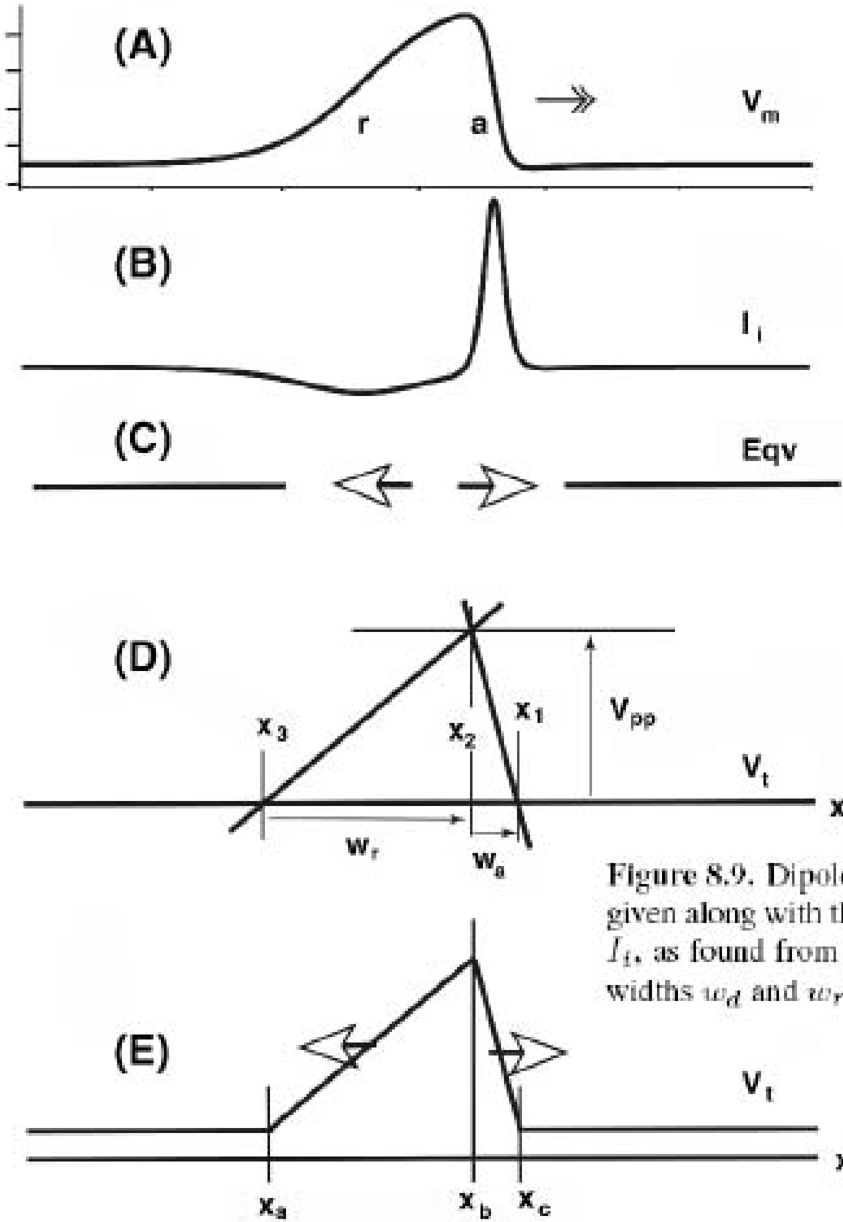


Figure 8.9. Dipole Sources. The action potential $V_m(x)$ and its first spatial derivative are given along with the approximating triangularized action potential $V_t(x)$ and axial current I_t, as found from the spatial derivative of V_m. Depolarization and repolarization spatial widths w_d and w_r are for the approximating triangular action potential.

Lumped dipole source model (cont.):

From Eqn. (8.41), the total dipole strength arising from the distributed dipole densities in any interval x_1 to x_2 is given by:

$$D = -\pi a^2 \sigma_i \int_{x_1}^{x_2} \frac{\partial V_m}{\partial x} \, \mathrm{d}x$$

$$= \pi a^2 \sigma_i \left[V_m(x_1) - V_m(x_2) \right] . \qquad (8.46)$$

Lumped dipole source model (cont.):

Hence, the lumped dipole strength associated with the activation interval x_b to x_c is:

$$
\begin{aligned}
D_p &= \pi a^2 \sigma_i \left[V_{\text{peak}} - V_{\text{rest}} \right] \\
&= \pi a^2 \sigma_i V_{\text{pp}} \, , \qquad (8.47)
\end{aligned}
$$

and the lumped dipole strength for the repolarization interval x_a to x_b is:

$$
\begin{aligned}
D_n &= \pi a^2 \sigma_i \left[V_{\text{rest}} - V_{\text{peak}} \right] \\
&= -\pi a^2 \sigma_i V_{\text{pp}} \, . \qquad (8.48)
\end{aligned}
$$

Lumped monopole source model (cont.):

Note:-

1. Each lumped dipole is located at the "center of gravity" of the dipole source density that it approximates.
2. A lumped dipole source is a good approximation only at a reasonable distance from the fiber.
3. Eqn. (8.46) can be used to determine lumped dipoles directly from the AP waveform, rather than the triangular approximation.

Temporal considerations:

The temporal waveform of external field potentials will depend on the locations of the recording electrodes.

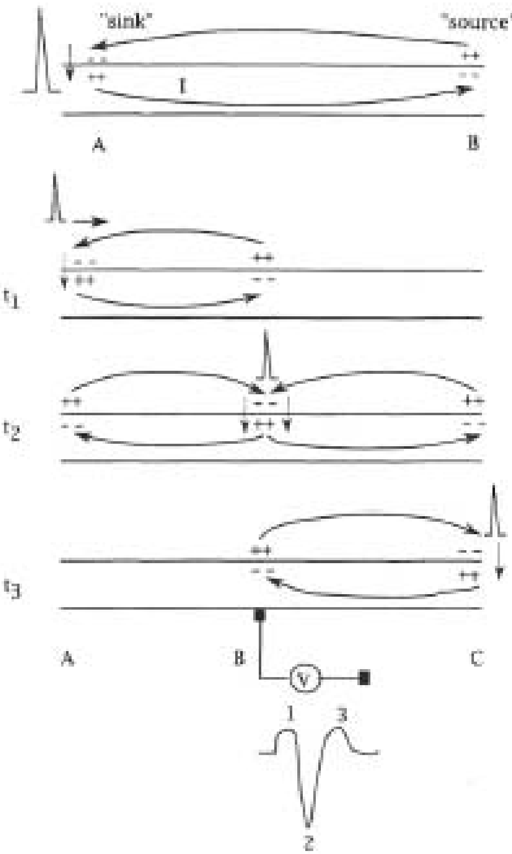


Figure 14.1 Action potential propagation along an axon. In the upper diagram an action potential is initiated at A and the current flow (I) from A to B is indicated. The bottom three diagrams illustrate a time sequence ($t_1 < t_2 < t_3$) for the propagation of an action potential from A to B to C. The recording at B indicates a positivity (1), a negativity (2), and a positivity (3) corresponding to this time sequence of AP propagation (see text for further explanation).

(from Johnston and Wu)

Temporal considerations (cont.):

While the action potential is propagating along an axon, it is producing a pair of dipole sources (or a quadrupole source).

However, while the action potential is being initiated (typically at the axon hillock, the patch of membrane where the axon joins the soma) and when the action potential reaches the axon terminals, only one dipole source exists.

The dendritic tree acts as a passive source during action potential initiation.