ECE 795:

Quantitative Electrophysiology

Notes for Lecture #3

October 13, 2011

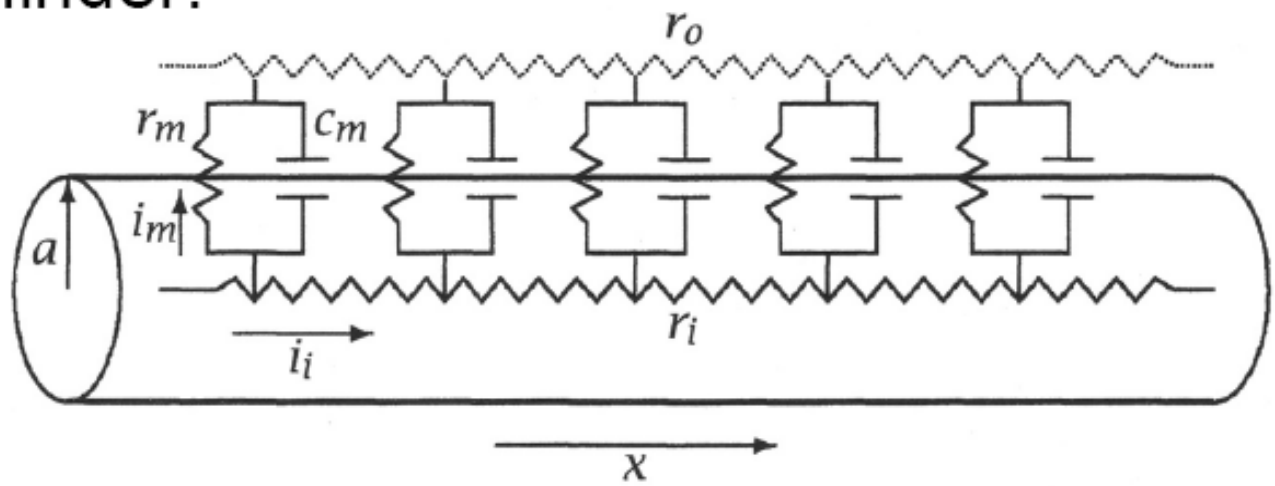
5. LINEAR CABLE EQUATIONS

We will look at:

- Core-conductor model
- Cable equations
- Linear (subthreshold) response of a cylindrical fiber

Core-conductor model:

In the *core-conductor model* we approximate an axon or a segment of a dendrite as a uniform cylinder.



(from Johnston and Wu)

Figure 4.6 Diagram for current flow in a uniform cylinder such as an axon or segment of dendrite.

Each small (cylindrical) segment of membrane is electrically linked (axially) to the next segment by the intra- and extra-cellular electrolytes.

Resistance and capacitance in a cylindrical fiber:

If the *resistivity* of the intracellular electrolyte is R_i ($\Omega \cdot \mathrm{cm}$), then for a cylindrical fiber of radius a the axial (longitudinal) *resistance per unit length* is:

$$r_i = \frac{R_i}{\pi a^2} \quad \Omega/\mathrm{cm}. \qquad (6.1)$$

(Note the convention that (i) resistivity or specific resistance/capacitance is designated by an uppercase letter and (ii) resistance or capacitance per unit length is designated by a lowercase letter.)

Resistance and capacitance in a cylindrical fiber (cont.):

If R_m ($\Omega \cdot \mathrm{cm}^2$) and C_m ($\mu\mathrm{F}/\mathrm{cm}^2$) are the *specific resistance* and the *specific capacitance*, respectively, of the membrane, then the *membrane resistance times length* is:

$$r_m = \frac{R_m}{2\pi a} \quad \Omega \text{ cm}, \tag{6.2}$$

and the *membrane capacitance per unit length* is:

$$c_m = C_m 2\pi a \quad \mu\text{F/cm}. \tag{6.3}$$

Core-conductor model (cont.):

If a single fiber described by the core-conductor model lies in a restricted extracellular space, then longitudinal current flow can occur in the extracellular electrolyte and longitudinal variations in the extracellular potential can result.

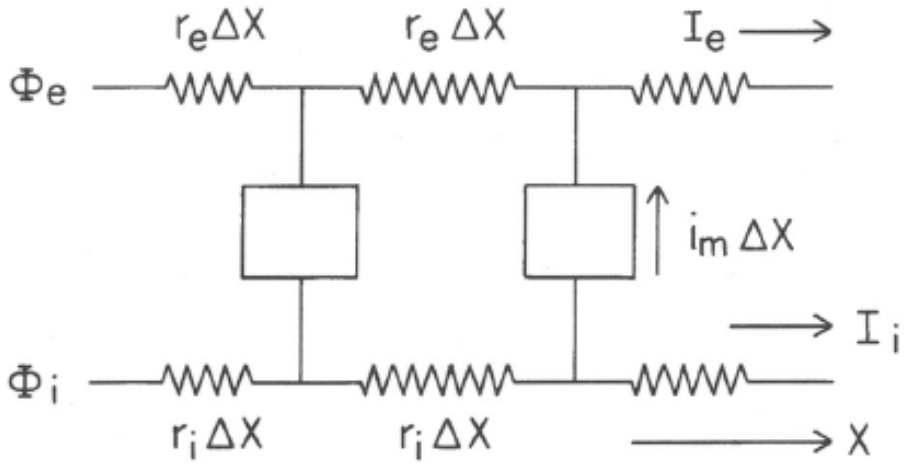


Figure 6.1. The linear core-conductor model for a single fiber lying in a restricted extracellular space. Longitudinal extracellular and intracellular currents are I_e and I_i, while extracellular and intracellular potentials per unit length are designated Φ_e and Φ_i, respectively.

Core-conductor model (cont.):

Under linear (i.e., subthreshold) conditions, each membrane patch of length Δx can be described by a lumped RC circuit.

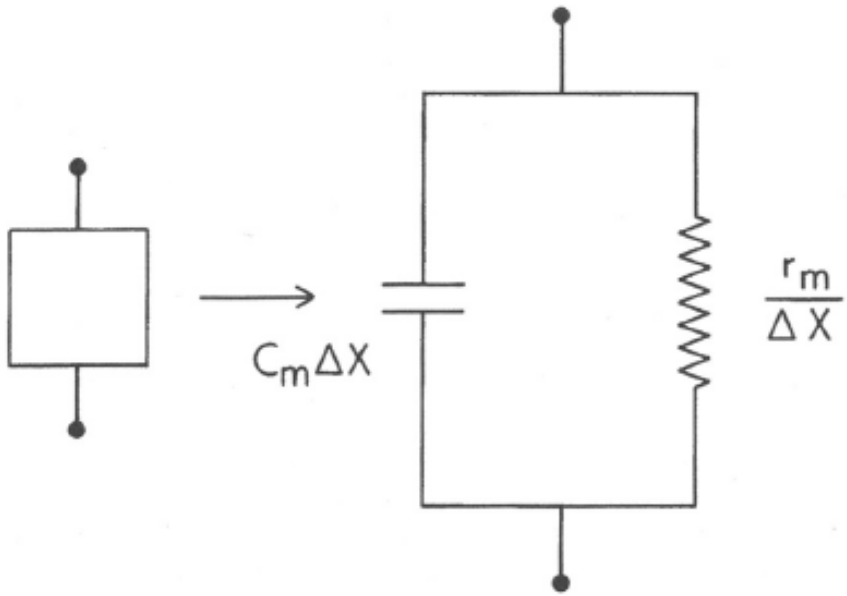


Figure 6.2. Electrical representation of a cylindrical fiber membrane element of length Δx under (linear) subthreshold conditions.

Core-conductor model (cont.):

Under nonlinear (i.e., suprathreshold/ transthreshold) conditions, each membrane patch of length Δx must be described by the HH model.

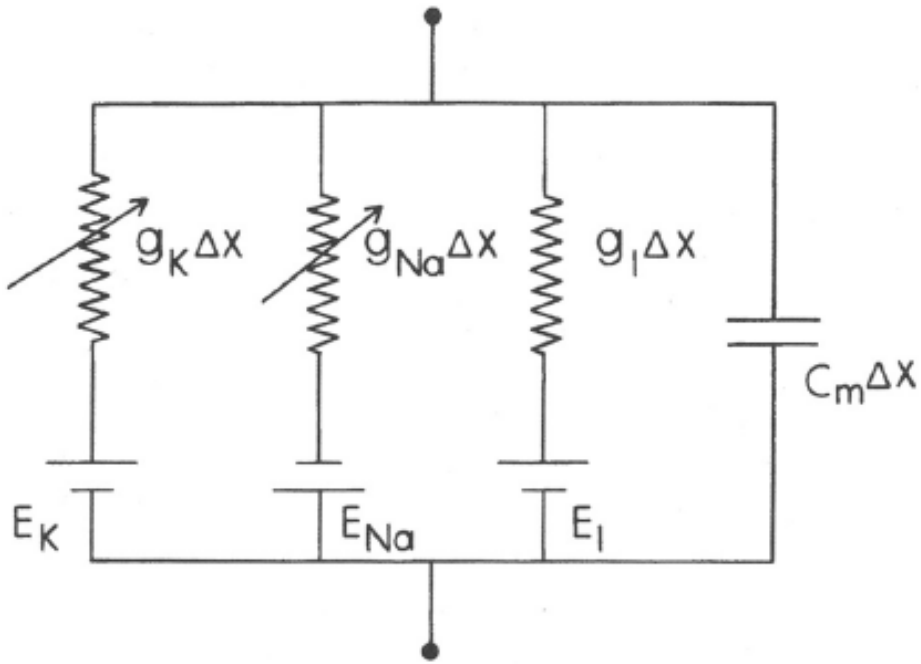


Figure 6.3. Electrical representation of the membrane for a fiber of length Δx under transthreshold conditions. The conductances g_K, g_{Na}, and g_ℓ are found from the Hodgkin–Huxley equations and are converted to units of S/cm for the linear core-conductor model.

Core-conductor model assumptions:

1. The transmembrane and longitudinal currents, as well as the intra- and extra-cellular potentials, are functions only of the axial (longitudinal) coordinate x. That is, we have a one-dimensional cable model.

2. For a fiber with a restricted extracellular space, the extracellular current can only flow in the axial (longitudinal) direction.
   In the case of a larger extracellular space, the resistance of the extracellular electrolyte is assumed to be negligible, i.e., $r_e \approx 0$.

Nerve fiber bundle showing restricted extracellular spaces:

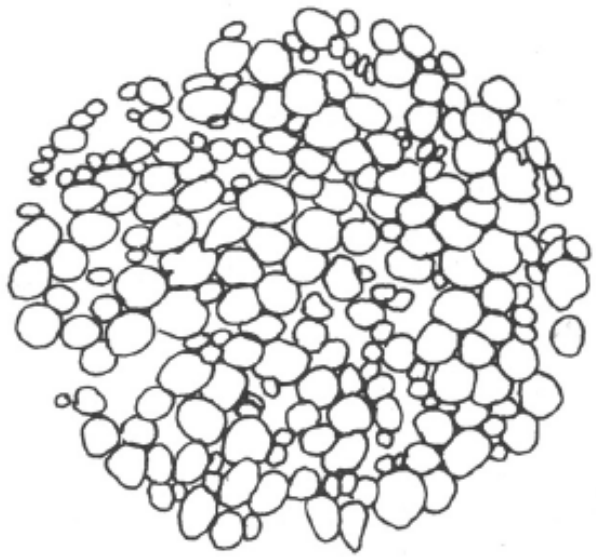


Figure 6.4. Photomicrograph of a transverse section of a cat saphenous nerve fascicle. Few fibers have a circular cross section and some are quite convoluted, but they can be approximated as circular or, better, as elliptical. Except near the periphery the interstitial currents can be expected to be essentially axial. If all fibers are approximately the same and behaving synchronously, and if the total number is N while the total interstitial cross-sectional area is A_e, then each fiber is associated with an interstitial cross-sectional area of A_e/N. Figure 6.1 would then apply to a typical fiber with $r_e = R_e/(A_e/N)$. This figure is from W. Olson, PhD dissertation, University of Michigan, 1985; also W. Olson, X. Wit, and S. L. BeMent, Compound action potential reconstructions and predicted fiber diameter distributions, in *Conduction Velocity Distributions*, L. J. Dorfman, K. L. Cummins, and L. J. Leifer, eds., A.R. Liss, New York, 1981. Reprinted by permission of Wiley-Liss Inc., a subsidiary of John Wiley and Sons.

Core-conductor model assumptions (cont.):

3. The radius of a fiber is typically many times smaller than its length, such that the intracellular current can be assumed only to flow in the axial (longitudinal) direction. The resistance per unit length of the intracellular electrolyte is found via Eqn. (6.1).
4. For nerve and muscle under passive conditions, the membrane is represented by passive components (shown in Fig. 6.2) with values for r_m and c_m found via Eqns. (6.2) and (6.3).
   Under active conditions, the HH model is utilized, as illustrated in Fig. 6.3.

Cable equations:

Ohm's and Kirchhoff's laws can be applied to the core-conductor circuit (shown in Fig. 6.1 of Plonsey and Barr) to obtain the *cable equations* for a uniform cylindrical fiber of arbitrary length.

It is then desirable to evaluate the cable equations in the limit as $\Delta x \to 0$, such that the equations describe the behaviour of the fiber as a *continuous* function of axial (longitudinal) position, rather than a set of discrete membrane patches.

Cable equations (cont.):

The resulting relationship between the extracellular potential gradient in the axial direction as a function of the axial current is:

$$\frac{\partial \Phi_e}{\partial x} = -I_e r_e, \qquad (6.4)$$

and likewise the intracellular potential gradient is:

$$\frac{\partial \Phi_i}{\partial x} = -I_i r_i. \qquad (6.5)$$

Cable equations (cont.):

If current leaves the intracellular space by crossing the membrane, then the intracellular current will show an axial *decrease*, while the transmembrane current will be *positive*. This conservation of current is described by:

$$\frac{\partial I_i}{\partial x} = -i_m, \qquad (6.6)$$

where i_m is the transmembrane current per unit length.

(Note that i_m is a linear function of the membrane potential under passive (subthreshold) conditions but is a nonlinear function under active (suprathreshold) conditions.)

Cable equations (cont.):

In contrast, the extracellular current will *increase* axially due to any transmembrane current.

In stating this relationship we will also allow for the possibility that a current may be injected into the extracellular space from polarizing electrodes, giving:

$$\frac{\partial I_e}{\partial x} = i_m + i_p, \qquad (6.7)$$

where i_p is the current per unit length injected from the polarizing electrodes.

Dependence of Φ_i and Φ_e on V_m:

Suppose I is defined as:

$$I = I_i + I_e. \tag{6.8}$$

From Eqns. (6.6) and (6.7):

$$\frac{\partial I}{\partial x} = \frac{\partial I_i}{\partial x} + \frac{\partial I_e}{\partial x} = -i_m + (i_m + i_p)$$

$$= i_p. \tag{6.10}$$

That is, any change in the total axial (longitudinal) current must come from the injected current i_p.

Dependence of Φ_i and Φ_e on V_m (cont.):

We now consider the relationship between the transmembrane potential and the extra- and intra-cellular currents and potentials.

Since, by definition $V_m = \Phi_i - \Phi_e$, we have:

$$\frac{\partial V_m}{\partial x} = \frac{\partial \Phi_i}{\partial x} - \frac{\partial \Phi_e}{\partial x} = -r_i I_i + r_e I_e$$

$$= -r_i I_i + r_e \left(I - I_i\right) \qquad (6.9)$$

$$= -\left(r_i + r_e\right) I_i + r_e I. \qquad (6.11)$$

Expressions for membrane current:

If Eqns. (6.11) is differentiated with respect to x, then:

$$\frac{\partial^2 V_m}{\partial x^2} = -(r_i + r_e)\frac{\partial I_i}{\partial x} + r_e \frac{\partial I}{\partial x}. \qquad (6.23)$$

Substituting Eqns. (6.6) and (6.10) gives:

$$\frac{\partial^2 V_m}{\partial x^2} = (r_i + r_e)\, i_m + r_e i_p. \qquad (6.24)$$

Expressions for membrane current (cont.):

In comparison, if Eqn. (6.5) is differentiated with respect to x and Eqn. (6.6) is substituted for $\partial I_i/\partial x$, then:

$$i_m = \frac{1}{r_i}\frac{\partial^2 \phi_i}{\partial x^2}. \qquad (6.25)$$

- Note that Eqn. (6.24) shows the dependence of the transmembrane current i_m on the transmembrane potential, the injected current and the extra- and intracellular resistances.
- In contrast, Eqn. (6.25) describes the dependence of the transmembrane current on the intracellular potential and resistance only.

Linear (subthreshold) response of a cylindrical fiber:

Under subthreshold conditions, the transmembrane current per unit length $i_m\ (\mathrm{mA/cm})$ in a cylindrical fiber is:

$$i_m = \frac{v_m}{r_m} + c_m \frac{\mathrm{d}v_m}{\mathrm{d}t}, \qquad (7.9)$$

where r_m is the membrane resistance times unit length $(\Omega \cdot \mathrm{cm})$ and c_m is the membrane capacitance per unit length $(\mu\mathrm{F/cm})$.

Linear (subthreshold) response of a cylindrical fiber (cont.):

Substituting Eqn. (7.9) into cable equation (6.24) gives:

$$\lambda^2 \frac{\partial^2 v_m}{\partial x^2} - \tau \frac{\partial v_m}{\partial t} - v_m = r_e \lambda^2 i_p \,, \quad (7.11)$$

where:

$$\lambda = \sqrt{\frac{r_m}{r_i + r_e}} \quad \text{and} \quad \tau = r_m c_m \,. \quad (7.12)$$

Linear (subthreshold) response of a cylindrical fiber (cont.):

For steady-state conditions $(\partial v_m/\partial t = 0)$, Eqn. (7.11) simplifies to:

$$\lambda^2 \frac{\mathrm{d}^2 v_m}{\mathrm{d}x^2} - v_m = r_e \lambda^2 i_p \,. \qquad (7.13)$$

In the case of $i_p = 0$, Eqn. (7.13) becomes:

$$\lambda^2 \frac{\mathrm{d}^2 v_m}{\mathrm{d}x^2} - v_m = 0 \,. \qquad (7.14)$$

Linear (subthreshold) response of a cylindrical fiber (cont.):

The solution of Eqn. (7.14) :

$$v_m = A\mathrm{e}^{-x/\lambda} + B\mathrm{e}^{x/\lambda}, \qquad (7.15)$$

where A and B are constants, the values of which are determined by boundary conditions.

Note that in cases where $i_p \neq 0$, rather than solving Eqn. (7.13) for the particular solution, is possible to apply Eqn. (7.14) to regions of a fiber where $i_p = 0$ and use the region where $i_p \neq 0$ to impose the boundary conditions and solve for A and B.

Space and time constants:

In Eqn. (7.12) we introduced:

- the **space constant** λ, and
- the **time constant** τ.

Space constant:-

Under steady-state conditions, Eqn. (7.15) describes the space constant λ as the distance over which the transmembrane voltage and current decay by the factor $1/\mathrm{e}$.

Space and time constants (cont.):

For a cylindrical fiber with uniform membrane properties and with $r_e \approx 0$:

$$\lambda = \sqrt{\frac{r_m}{r_i + r_e}} \approx \sqrt{\frac{r_m}{r_i}}. \qquad (7.16)$$

Substituting for r_i and r_m in Eqn. (7.16) using Eqns. (6.1) and (6.2) gives:

$$\lambda = \sqrt{\frac{R_m/2\pi a}{R_i/\pi a^2}} \qquad (7.17)$$

$$= \sqrt{\frac{aR_m}{2R_i}}. \qquad (7.18)$$

Space and time constants (cont.):

Time constant:-

For an *isopotential patch of membrane* (e.g., a small spherical cell), we saw in Eqn. (7.4) that the time constant τ corresponds to the time over which the transmembrane potential grows towards its steady-state value by the factor $1-1/\mathrm{e}$.

For a *cylindrical fiber*, the transmembrane potential grows to a particular fraction its steady-state value by the time τ, where the fraction depends on the distance from the site of stimulation.

Steady-state solution for stimulus current at the origin:

Injection of a small current into the extracellular space at the origin (center) of an infinitely-long cylindrical fiber can be approximated by a spatial delta function source:

$$i_p = I_0\,\delta(x)\ , \qquad (7.19)$$

where I_0 is the total applied current (mA) and $\delta(x)$ is the unit delta function.

Note that i_p is zero everywhere except at the origin, where it is infinite, and integrating i_p around the origin gives the total current I_0.

Steady-state solution for stimulus current at the origin (cont.):

Given the current injection described by Eqn. (7.19), the steady-state membrane equation (7.13) becomes:

$$\lambda^2 \frac{\mathrm{d}^2 v_m}{\mathrm{d}x^2} - v_m = r_e \lambda^2 I_0 \, \delta(x) \ . \qquad (7.21)$$

Except at the origin, the fiber is described by the homogeneous equation (7.14), which yields the homogeneous solution given in Eqn. (7.15).

Steady-state solution for stimulus current at the origin (cont.):

However, $v_m(x)$ must be continuous at the origin, so Eqn. (7.15) must apply everywhere.

Now we need to apply the boundary conditions of:

- a source at the origin $x = 0$, and
- the transmembrane potential at $|x| = \infty$,

to determine the constants A and B.

Steady-state solution for stimulus current at the origin (cont.):

- The relative transmembrane potential at $x = \infty$ must be zero, so the constant B must be zero for the region $x \geq 0$.
- Likewise, the relative transmembrane potential at $x = -\infty$ must be zero, so the constant A must be zero for the region $x \leq 0$.
- Because of the continuity of $v_m(x)$ at the origin, the value of the constant A for the region $x \geq 0$ must be equal to the constant B for the region $x \leq 0$. We will call this constant C.

Steady-state solution for stimulus current at the origin (cont.):

These boundary conditions can be summarized as:

Table 7.1. Boundary Conditions

Constants	A	B
$x > 0$	C	0
$x < 0$	0	C

Given these boundary conditions, Eqn. (7.15) can be rewritten as:

$$v_m = C\mathrm{e}^{-|x|/\lambda}. \qquad (7.27)$$

Steady-state solution for stimulus current at the origin (cont.):

Integrating Eqn. (7.21) around the origin and imposing these boundary conditions to solve for the constant C, we obtain:

$$C = -\frac{r_e \lambda I_0}{2} . \qquad (7.30)$$

Substituting Eqn. (7.30) into Eqn. (7.27) gives:

$$v_m = -\frac{r_e \lambda I_0}{2} \mathrm{e}^{-|x|/\lambda} . \qquad (7.31)$$

Steady-state solution for stimulus current at the origin (cont.):

Inspection of Eqn. (7.31) leads to the following conclusions:

1. The stimulus clearly affects the transmembrane potential, since v_m is nonzero for all finite values of x.
2. The effects of the stimulus varies markedly with x. The largest change in v_m occurs where $x = 0$. v_m decreases exponentially with distance, falling by a factor of $1/\mathrm{e}$ every length λ from the stimulus site.

Steady-state solution for stimulus current at the origin (cont.):

3. For a given stimulus I_0, the change in v_m increases with increasing r_e, increasing r_m and/or decreasing r_i.
4. From the sign of Eqn. (7.31), a positive current injected into the extracellular space leads to a negative v_m, i.e., the membrane is *hyperpolarized*.
5. The space constant λ gives a nominal measure of how far the disturbance in v_m extends from the site of stimulation.

Step current at origin – general time-varying solution:

Consider the homogeneous version of Eqn. (7.11):

$$\lambda^2 \frac{\partial^2 v_m}{\partial x^2} - \tau \frac{\partial v_m}{\partial t} - v_m = 0. \qquad (7.32)$$

As before, we will apply the boundary condition of an injected current at the origin.

If we assume an unbounded extracellular space and an intracellular injected current, we can assume that $r_e \approx 0$.

Step current at origin – general time-varying solution (cont.):

To simplify our notation, we introduce the normalized space and time variables:

$$X = \frac{x}{\lambda} \quad \text{and} \quad T = \frac{t}{\tau}, \tag{7.33}$$

such that Eqn. (7. 32) becomes:

$$\frac{\partial^2 v_m}{\partial X^2} - \frac{\partial v_m}{\partial T} - v_m = 0. \tag{7.34}$$

Step current at origin – general time-varying solution (cont.):

The solution to Eqn. (7.34) for an infinite cable with an intracellularly-injected current I_0 at the origin can be obtained by using:

- the *Laplace transform* to turn the differential equation into an algebraic equation, and
- the *boundary conditions* of the injected current at $X = 0$ and $v_m(X) = 0$ at $X = \pm\infty$.

Step current at origin – general time-varying solution (cont.):

In the normalized space and time variables the solution is:

$$v_m(X,T) = \frac{r_i \lambda I_0}{4}\left\{ e^{-X}\left[1-\mathrm{erf}\left(\frac{X}{2\sqrt{T}}-\sqrt{T}\right)\right] - e^{X}\left[1-\mathrm{erf}\left(\frac{X}{2\sqrt{T}}+\sqrt{T}\right)\right]\right\}, \qquad (7.45)$$

where:

$$\mathrm{erf}(y) \triangleq \frac{2}{\sqrt{\pi}}\int_0^y e^{-z^2}\,dz. \qquad (7.47)$$

Step current at origin – general time-varying solution (cont.):

Converting back to the original coordinates gives:

$$v_m(x,t) = \frac{r_i \lambda I_0}{4}\left\{ e^{-|x|/\lambda}\left[1 - \operatorname{erf}\left(\frac{|x|}{2\lambda}\sqrt{\frac{\tau}{t}} - \sqrt{\frac{t}{\tau}}\right)\right] - e^{|x|/\lambda}\left[1 - \operatorname{erf}\left(\frac{|x|}{2\lambda}\sqrt{\frac{\tau}{t}} + \sqrt{\frac{t}{\tau}}\right)\right]\right\} \quad (7.46)$$

Step current at origin – general time-varying solution (cont.):

For a given value of time, the spatial behaviour is exponential-like. For $t > \tau$, $v_m(x)$ tends towards a true exponential, as was obtained for the steady-state response described by Eqn. (7.31).

This continuous decrement of $v_m(x)$ with increasing $|x|$ is due to the leakage of current through the membrane, while λ describes the rate of this effect.

Step current at origin – general time-varying solution (cont.):

For a given position x along a fiber, the membrane potential reaches its steady-state in an exponential-like manner over time.

Only at $x = \lambda$ is it truly exponential, i.e., the fraction of the steady-state potential that is achieved at $t = \tau$ is $1-1/\mathrm{e}$.

Table 7.2. Temporal Morphology at Different Values of x Due to Current Step at $x = 0$

x	Fraction of steady-state value reached at $t = \tau$
0	0.843
λ	0.632
2λ	0.372
3λ	0.157
4λ	0.0453
5λ	0.00862

Step current at origin – general time-varying solution (cont.):

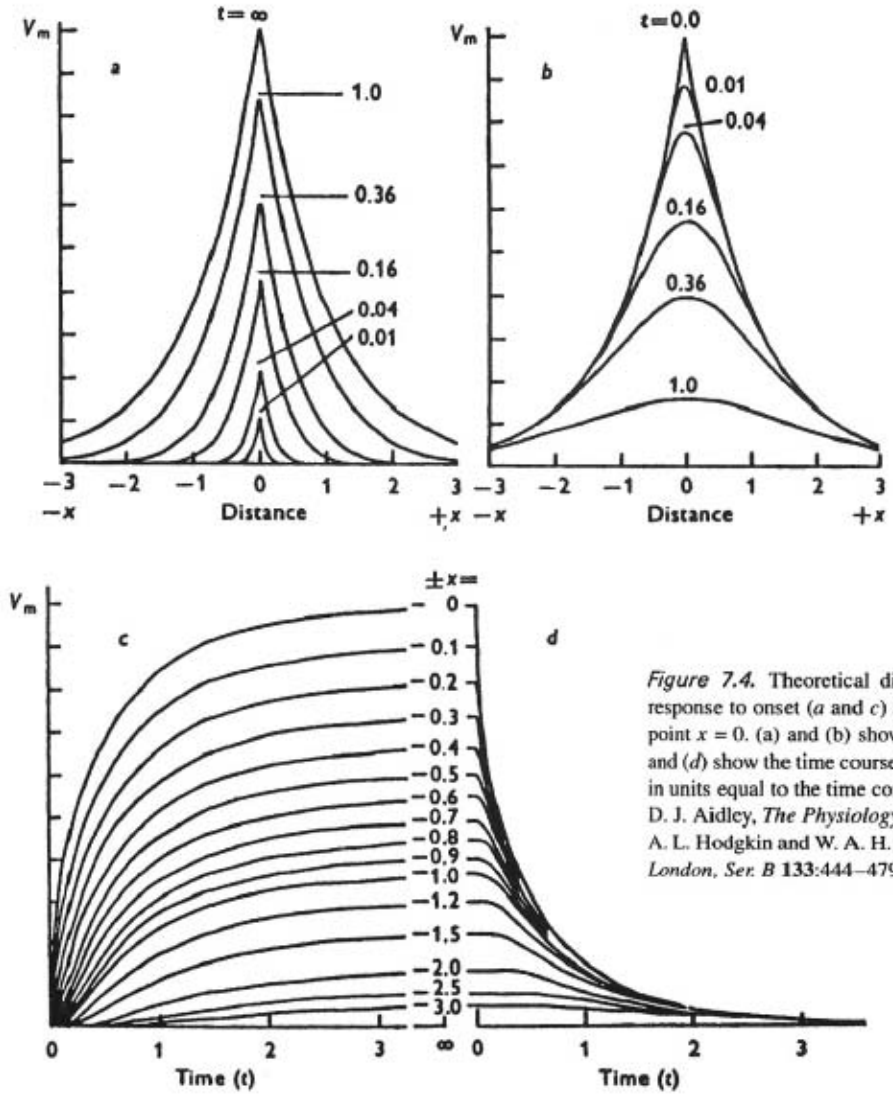


Figure 7.4. Theoretical distribution of potential difference across a passive nerve membrane in response to onset (*a* and *c*) and cessation (*b* and *d*) of a constant current applied intracellularly at the point $x = 0$. (a) and (b) show the spatial distribution of potential difference at different times, and (*c*) and (*d*) show the time course of the potential at different distances along the axon. Time (t) is expressed in units equal to the time constant, τ, and distance (x) is expressed in units of space constant, λ. [From D. J. Aidley, *The Physiology of Excitable Cells*, Cambridge University Press, Cambridge, 1978. After A. L. Hodgkin and W. A. H. Rushton, The electrical constants of a crustacean nerve fiber, *Proc. R. Soc. London, Ser. B* **133**:444–479 (1946). Reprinted with permission of Cambridge University Press.]

6. PROPAGATION OF ELECTRICAL POTENTIAL WAVEFORMS

We will look at:

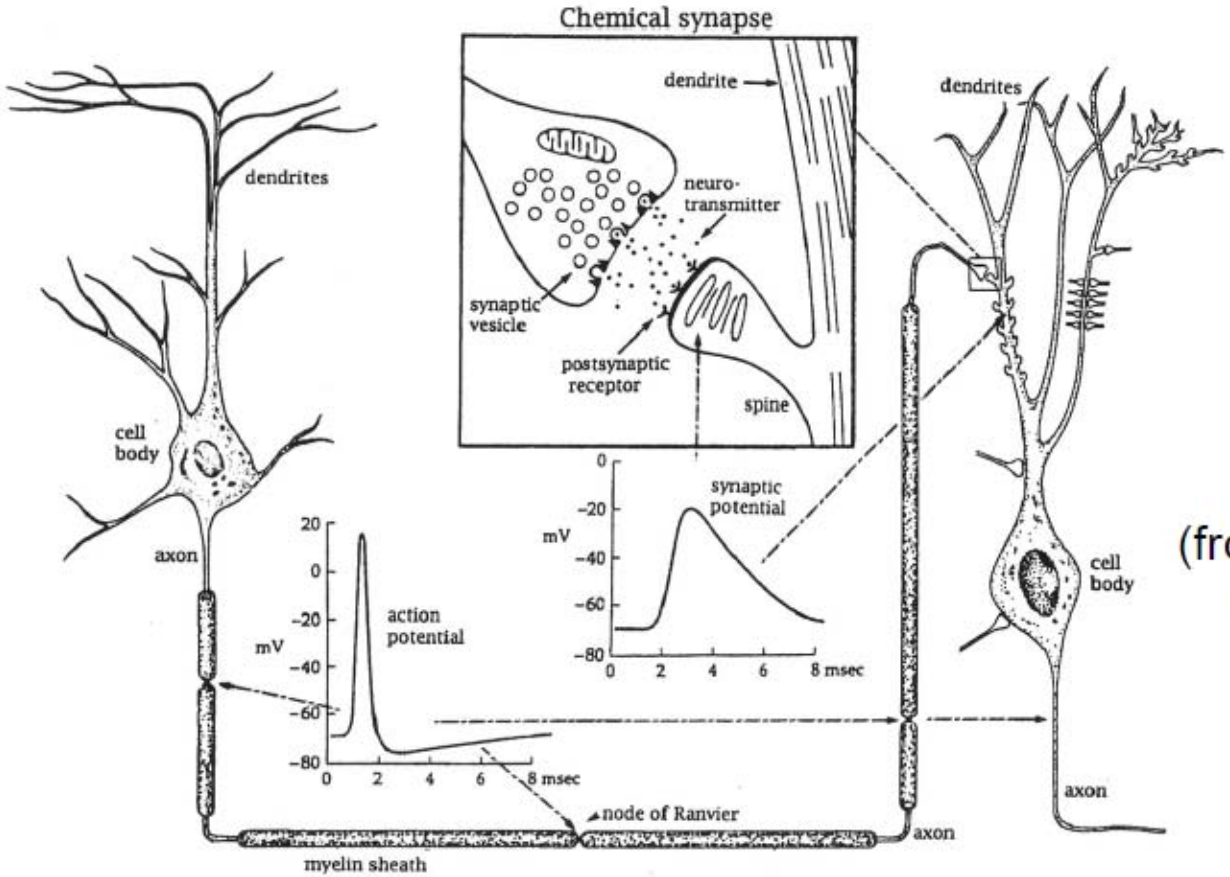
- Axonal delays & propagation velocity in linear cable
- Local circuit currents during propagation
- Mathematics of propagating action potentials
- Numerical solutions for propagating action potentials
- Propagation velocity constraint for uniform fiber
- Propagation in myelinated nerve fibers

Impulse propagation:

In the previous lecture we considered excitation and action potential generation in an isopotential patch of membrane.

However, in practice we are often concerned about the *propagation* of transmembrane potential impulses (i.e., waveforms), particularly action potentials, along the length of axons, dendrites or muscle fibers.

Impulse propagation (cont.):



(from Johnston and Wu)

Figure 1.2 Neurons convey information by electrical and chemical signals. Electrical signals travel from the cell body of a neuron (left) to its axon terminal in the form of action potentials. Action potentials trigger the secretion of neurotransmitters from synaptic terminals (upper insert). Neurotransmitters bind to postsynaptic receptors and cause electric signals (synaptic potential) in the postsynaptic neuron (right). Synaptic potentials trigger action potentials, which propagate to the axon terminal and trigger secretion of neurotransmitters to the next neuron. (Adapted from Kandel et al. 1991 and from L.L. Iversen, copyright © 1979 by Scientific American, Inc. All rights reserved.)

Axonal delays & propagation velocity in linear cable:

Figure 7.4 on slide # 42 shows a delay in depolarizing sites far away from the site of current injection. Is this delay somehow proportional to the distance, i.e., can one define a propagation velocity?

There is no wave solution for a linear cable:

1. waveforms must dissipate due to the low-pass character of the linear membrane, and
2. there must be an infinitely-quick response at distant sites if the cable contains no inductive elements.

Axonal delays & propagation velocity (cont.):

However, it is possible to define a propagation delay/velocity based on the *centroid* (first moment) of potentials in a linear cable. For a current or voltage waveform $h(x,t)$, the centroid at location x is:

$$\hat{t}_x^h = \frac{\int_{-\infty}^{\infty} t\, h(x,t)\, \mathrm{d}t}{\int_{-\infty}^{\infty} h(x,t)\, \mathrm{d}t}\,. \qquad \text{(K2.43)}$$

Axonal delays & propagation velocity (cont.):

The *transfer delay* D is the difference between the centroid of the induced *voltage* measured at location y and the centroid of the *current* that was injected at location x:

$$D_{x \to y} = D_{xy} = \hat{t}_y^V - \hat{t}_x^I. \qquad \text{(K2.45)}$$

The *local* or *input* delay is then D_{xx}.

The *propagation delay* P is the difference in the voltage centroids at x and y:

$$P_{xy} = \hat{t}_y^V - \hat{t}_x^V = D_{xy} - D_{xx}. \qquad \text{(K2.51)}$$

Axonal delays & propagation velocity (cont.):

These delays can be obtained for a linear cable by multiplying the cable equations by t and integrating over t. The resulting equation is an ODE similar to the steady-state cable equations.

Some important properties are:

1. $D_{xy} > 0$
2. D_{xy} is independent of the form of I_{inj}, i.e., it is a properties of *the cable not the input*, and
3. $D_{xy} = D_{yx}$.

Axonal delays & propagation velocity (cont.):

For an *isopotential neuron*, $D_{xx} = \tau_m$.

For an *infinite cable*, $D_{xx} = \tau_m/2$,

$$D_{xy} = \left(1 + \frac{|x-y|}{\lambda}\right)\frac{\tau_m}{2}, \qquad \text{(K2.50)}$$

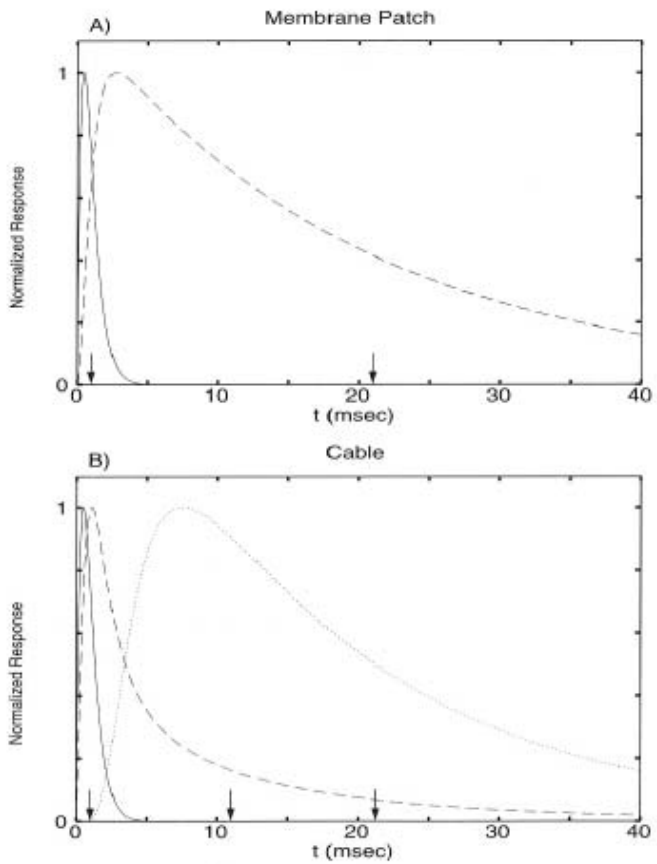
and

$$P_{xy} = \left(\frac{|x-y|}{\lambda}\right)\frac{\tau_m}{2}, \qquad \text{(K2.52)}$$

such that the nominal propagation velocity is:

$$v = 2\frac{\lambda}{\tau_m} = \sqrt{\frac{d}{R_m R_i C_m^2}}. \qquad \text{(K2.53)}$$

Axonal delays & propagation velocity (cont.):



(from Koch)

Fig. 2.11 Neuronal Input and Propagation Delays An elegant way to define propagation delays in passive cables involves tracking the *centroid* or *center of mass* of voltages or currents in passive cable (Agmon-Snir and Segev, 1993). This is illustrated in **(A)** for an isopotential patch of membrane with $\tau_m = 20$ msec. A brief current pulse (solid profile with $t_{peak} = 0.5$ msec) gives rise to a rapidly rising but very slowly decaying depolarizing potential (shown dashed using normalized units). The centroids of the two signals (see arrows at 1 and 21 msec) are displaced by one time constant. In **(B)**, the same current is injected into a very long cable, and the normalized potential at the same location (dashed) and at a location one space constant displaced (dotted) are plotted. In an infinite cable, the *transfer delay* $D_{x,y}$ between the centroid of the current at x and the centroid of the voltage at y is $(1 + |x - y|/\lambda)\tau_m/2$ (see the arrows at 1, 11, and 21 msec). As witnessed already in Fig. 2.8A, the potential decays faster in a cable than in an isopotential patch of membrane.

Local circuit currents in active membranes:

Propagation of action potentials in active (nonlinear) membranes can be understood qualitatively by considering the patterns of local currents that are produced by an action potential (site A in the figure below).

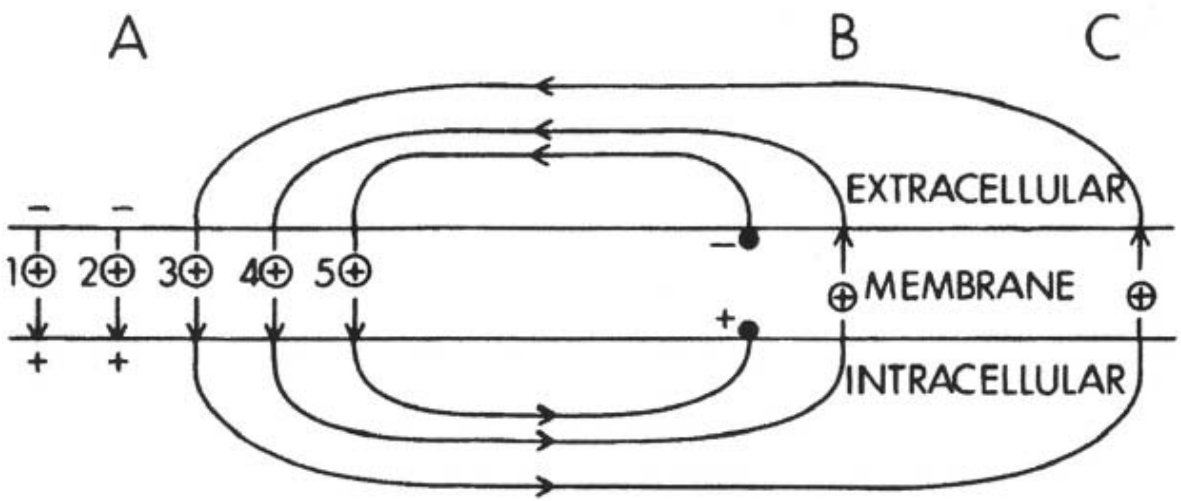
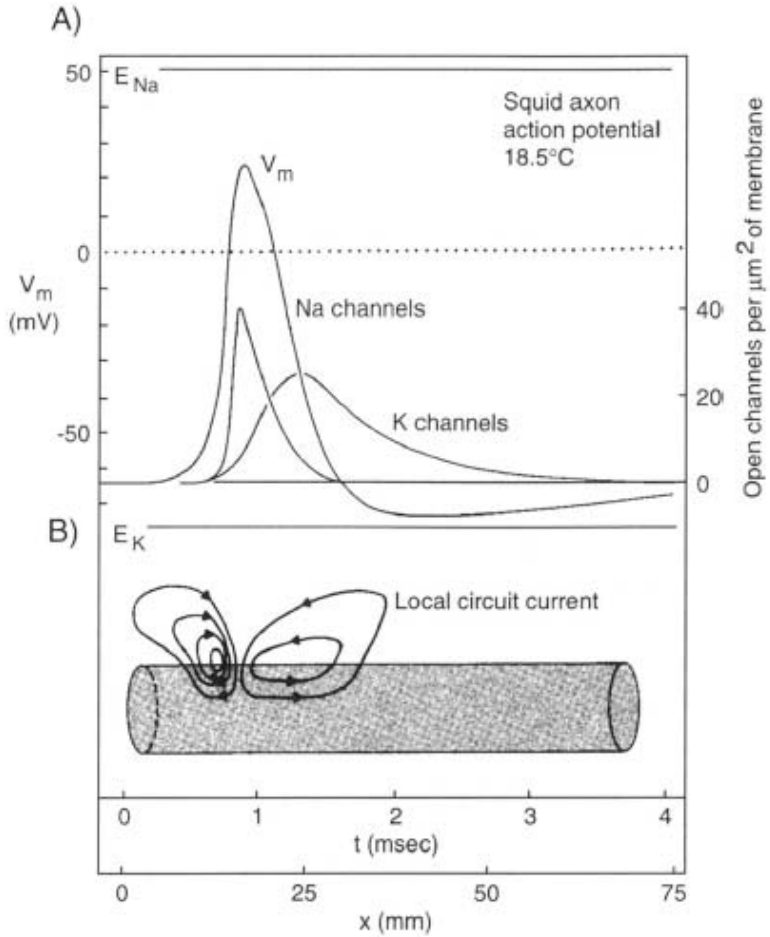


Figure 6.5. Local circuit or action current pattern.

Local circuit currents (cont.):



(from Koch)

Fig. 6.13 Local Circuit Current in the Squid Axon Illustration of the events occurring in the squid axon during the propagation of an action potential. Since the spike behaves like a wave traveling at constant velocity, these two panels can be thought of either as showing the voltages and currents in time at one location or as providing a snapshot of the state of the axon at one particular instant (see the space/time axes at the bottom). **(A)** Distribution of the voltage (left scale) or the number of open channels (right scale) as inferred from the Hodgkin–Huxley model at 18.5° C. **(B)** *Local circuit currents* that spread from an excited patch of the axon to neighboring regions bringing them above threshold, thereby propagating the action potential. The diameter of the axon (0.476 mm) is not drawn to scale. Reprinted by permission from Hille (1992).

Mathematics of propagating action potentials:

The **cable equations** describe the behaviour of the extra- and intra-cellular (and consequently transmembrane) currents and potentials as a function of **space**, specifically the axial (longitudinal) coordinate x.

In order to describe the **propagation** of transmembrane potentials, i.e., movement in **space** over **time**, we must couple the cable equations with a description of how a patch of membrane behaves as a function of **time**, i.e., the linear (passive) RC circuit equation or the nonlinear (active) HH model equations.

Mathematics of propagating action potentials (cont.):

Evaluating Eqn. (6.24) in a *source free region* gives:

$$\frac{\partial^2 V_m}{\partial x^2} = (r_i + r_e)\, i_m. \qquad (6.26)$$

Assuming that the extracellular space is large ($\Rightarrow r_e = 0$) and using Eqn. (6.1), we have:

$$i_m = \frac{\pi a^2}{R_i} \frac{\partial^2 V_m}{\partial x^2}. \qquad (6.27)$$

Mathematics of propagating action potentials (cont.):

The transmembrane current per unit area, I_m, is related to i_m (the current per unit length) via the cylindrical geometry, such that:

$$2\pi a I_m = i_m, \tag{6.28}$$

and consequently:

$$I_m = \frac{a}{2R_i}\frac{\partial^2 V_m}{\partial x^2}. \tag{6.29}$$

Mathematics of propagating action potentials (cont.):

To model the propagation of action potentials, the description of the transmembrane current per unit area, I_m, given by Eqn. (6.29) can be equated to the HH model equation for I_m:

$$\begin{aligned} I_m = & \bar{g}_{\mathrm{K}} n^4 (V_m - E_{\mathrm{K}}) \\ & + \bar{g}_{\mathrm{Na}} m^3 h (V_m - E_{\mathrm{Na}}) \\ & + g_L (V_m - E_L) \\ & + C_m \frac{\mathrm{d}V_m}{\mathrm{d}t}. \end{aligned} \tag{6.30}$$

Mathematics of propagating action potentials (cont.):

Thus:

$$\frac{\partial V_m}{\partial t} = \frac{1}{C_m}\left(\frac{a}{2R_i}\frac{\partial^2 V_m}{\partial x^2}\right) - \frac{\sum I_{\text{ion}}}{C_m}, \quad (6.31)$$

where the total ionic current is given by:

$$\begin{aligned}\sum I_{\text{ion}} = {} & \bar{g}_{\text{K}} n^4 (V_m - E_{\text{K}}) + \bar{g}_{\text{Na}} m^3 h (V_m - E_{\text{Na}}) \\ & + g_L (V_m - E_L) + I_0, \qquad (6.32)\end{aligned}$$

and I_0 is a current applied (normally briefly) at a particular spatial location.

Numerical solutions for propagating action potentials:

- Eqn. (6.31) is a nonlinear *partial differential equation* (PDE) that is *first-order in time* and *second-order in space*.
- Numerical solution is required because of the nonlinear nature of Eqn. (6.32) and hence Eqn. (6.31).
- The fiber must be discretized into sequential points (or nodes of Ranvier) spaced at intervals of Δx (say $25\ \mu\mathrm{m}$).
- The solution is then computed for each time interval Δt (say $10\ \mu\mathrm{s}$).

Numerical solutions for propagating action potentials:

One method for numerical solution is to compute these four steps at each time interval:

1. Solve for the change in transmembrane potential ΔV_m by approximating the partial derivates for discrete intervals.
2. Update V_m.
3. Compute the updated gating particle time constants α_n, β_n, etc.
4. Compute the new ionic currents based on the updated gating time constants and V_m.

This has updated I_m and V_m by one time step.

Numerical solutions for propagating action potentials (cont.):

Note that it is often desirable to have a variable time step Δt, to optimize computation speed.

This can be achieved with:

- Matlab, which has a set of numerical PDE solvers, or
- software packages for simulating axons and dendrites, including:
  - NEURON: For computer simulations of neurons and neural networks
  - The GEneral NEural SImulation System (GENESIS)

Example propagating action potential:

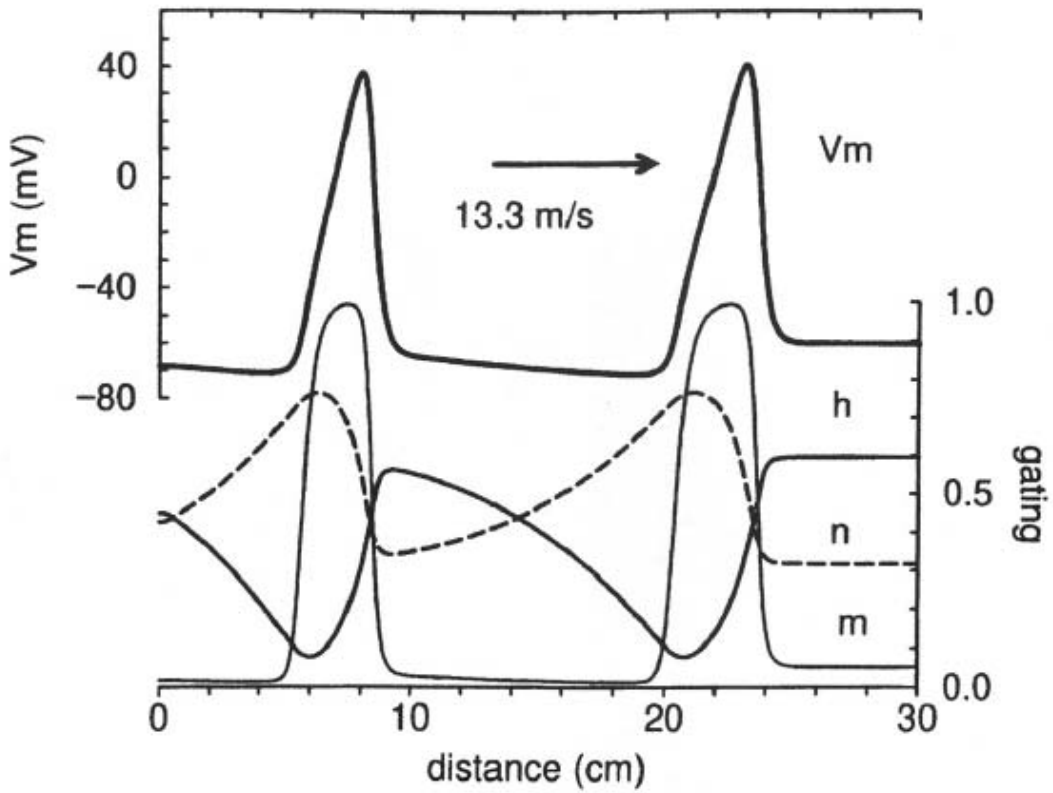


Figure 6.9. Simulation of propagation on squid axon of diameter 600 μm at $T = 6.3$ °C. Hodgkin–Huxley membrane parameters and equations are utilized. The figure describes the behavior of gating variables and transmembrane potential as functions of the axial coordinate. The velocity of propagation is 13.3 m/sec.

Example propagating action potential (cont.):

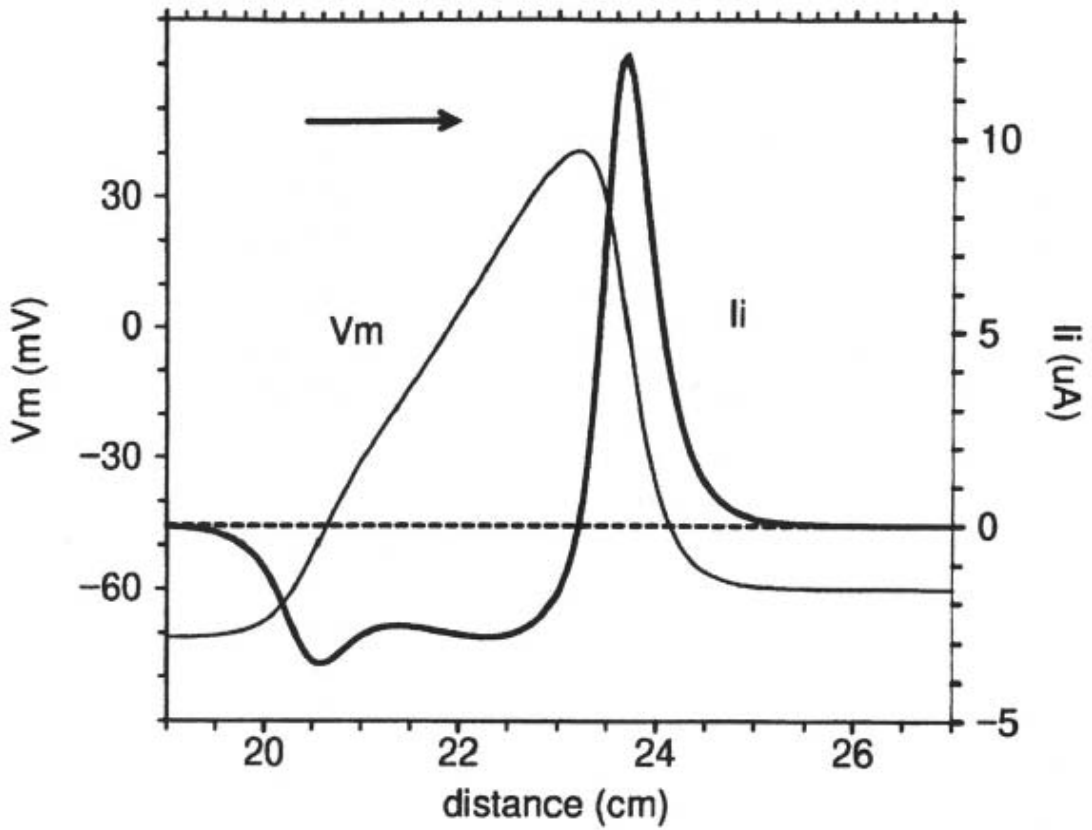


Figure 6.10. Simulation of propagation on squid axon of diameter 600 μm at $T = 6.3$ °C. Hodgkin–Huxley membrane parameters and equations are utilized. The figure describes the spatial behavior of transmembrane potential and the intracellular (longitudinal) current; v_m is given in mV and I_i in μA.

Example propagating action potential (cont.):

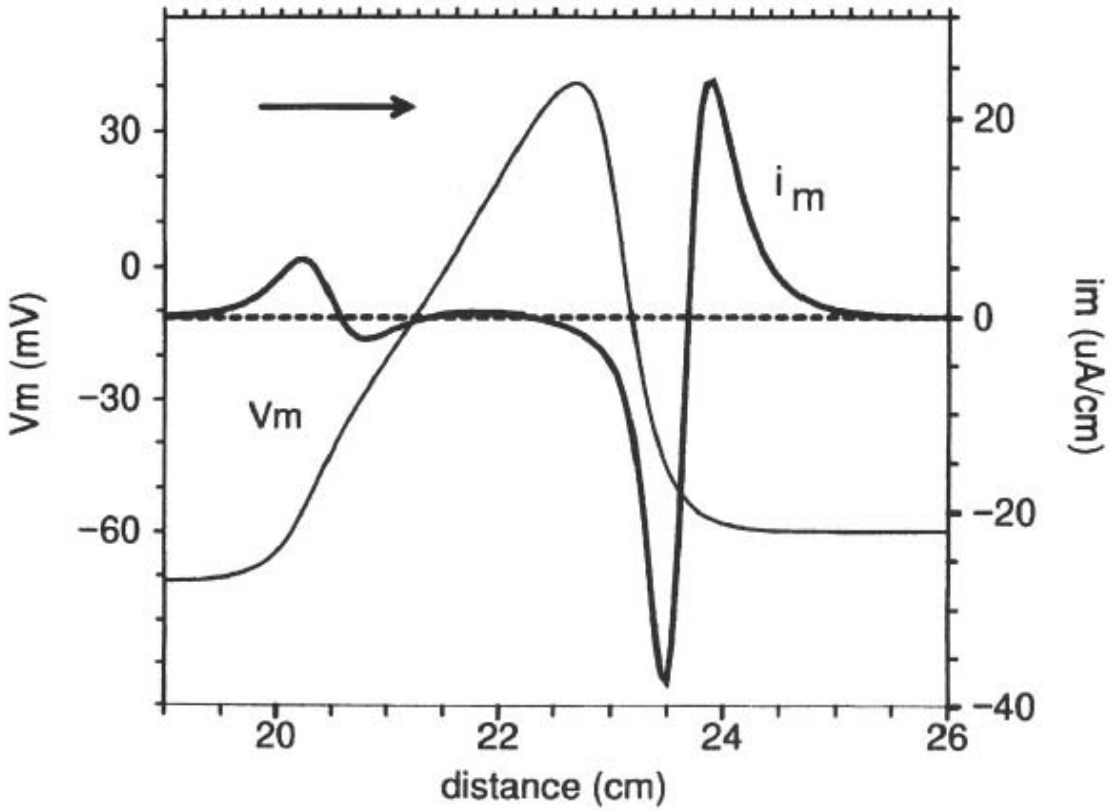


Figure 6.11. Simulation of propagation on squid axon of diameter 600 μm at $T = 6.3$ °C. Hodgkin–Huxley membrane parameters and equations are utilized. The figure describes the spatial behavior of the transmembrane potential and the transmembrane current; v_m is given in mV and i_m in μA/cm.

Propagation velocity constraint for uniform (unmyelinated) fiber:

For uniform propagation, the space-time behaviour of $V_m(x,t)$ must satisfy the wave equation:

$$V_m(x,t) = V_m(x - \theta t)\,, \qquad (6.37)$$

where θ is the *propagation velocity*.

(Note that propagation of the action potential waveform without dissipation requires an active membrane, i.e., voltage-gated ion channels.)

Propagation velocity constraint for uniform (unmyelinated) fiber (cont.):

Differentiating Eqn. (6.37) once with respect to x, utilizing the chain rule, gives:

$$\frac{\partial V_m}{\partial x} = -(1/\theta)\frac{\partial V_m}{\partial t}, \qquad (6.38)$$

and again results in:

$$\frac{\partial^2 V_m}{\partial x^2} = \left(1/\theta^2\right)\frac{\partial^2 V_m}{\partial t^2}. \qquad (6.39)$$

Propagation velocity constraint for uniform (unmyelinated) fiber (cont.):

Substituting Eqn. (6.39) into (6.31), with $I_0 = 0$, gives:

$$\frac{a}{2R_i\theta^2}\frac{\mathrm{d}^2V_m}{\mathrm{d}t^2} = C_m\frac{\mathrm{d}V_m}{\mathrm{d}t} + g_{\mathrm{K}}(V_m - E_{\mathrm{K}}) + g_{\mathrm{Na}}(V_m - E_{\mathrm{Na}}) + g_L(V_m - E_L) \qquad (6.41)$$

With an appropriate value for θ the solution to this ODE exhibits an action potential; the solution diverges with an incorrect θ.

Propagation velocity constraint for uniform (unmyelinated) fiber (cont.):

An important property of the propagation velocity can be obtained with inspection of Eqn. (6.41) without solving it explicitly.

Note that all the terms on the right-hand side (6.41) are independent of the fiber radius a, as is $\mathrm{d}^2V_m/\mathrm{d}t^2$, and thus the coefficient must be a constant independent of a, that is:

$$\frac{a}{2R_i\theta^2} = \text{constant} = \frac{1}{K}. \qquad (6.42)$$

Propagation velocity constraint for uniform (unmyelinated) fiber (cont.):

Consequently:

$$\theta = \sqrt{\frac{aK}{2R_i}} \, . \qquad (6.43)$$

Since K is unknown, it must be determined experimentally.

An empirically obtained relationship is:

$$\theta = \sqrt{d} \quad \text{m/s}, \qquad (6.44)$$

where d is the fiber diameter in μm.

Propagation in myelinated nerve fibers:

In vertebrates, Schwann cells produce myelin which wraps around an axon to produce an insulating sheath. The regularly-space breaks in the myelin are called *nodes of Ranvier*, and the axon segments between nodes are referred to as *internodes*.

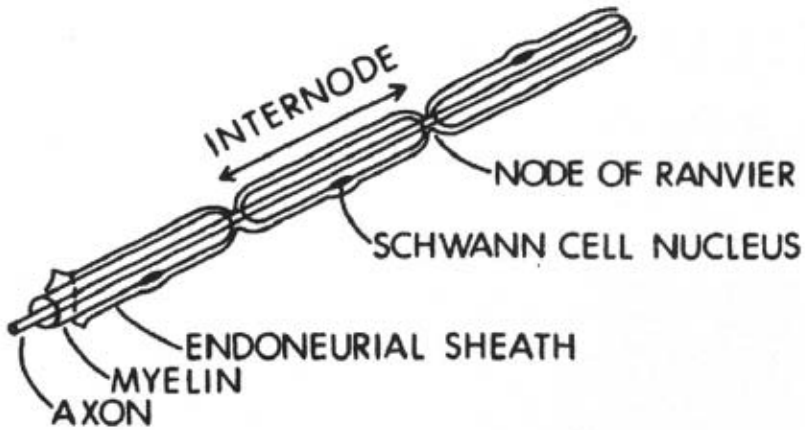


Figure 6.6. Diagram showing the structure of a myelinated nerve fiber. (Reprinted with permission from D. J. Aidley, *The Physiology of Excitable Cells*, Cambridge University Press, Cambridge, 1978.)

Propagation in myelinated nerve fibers (cont.):

The myelin is wrapped in layers around the axon, often on the order of 10s or even 100s of layers.

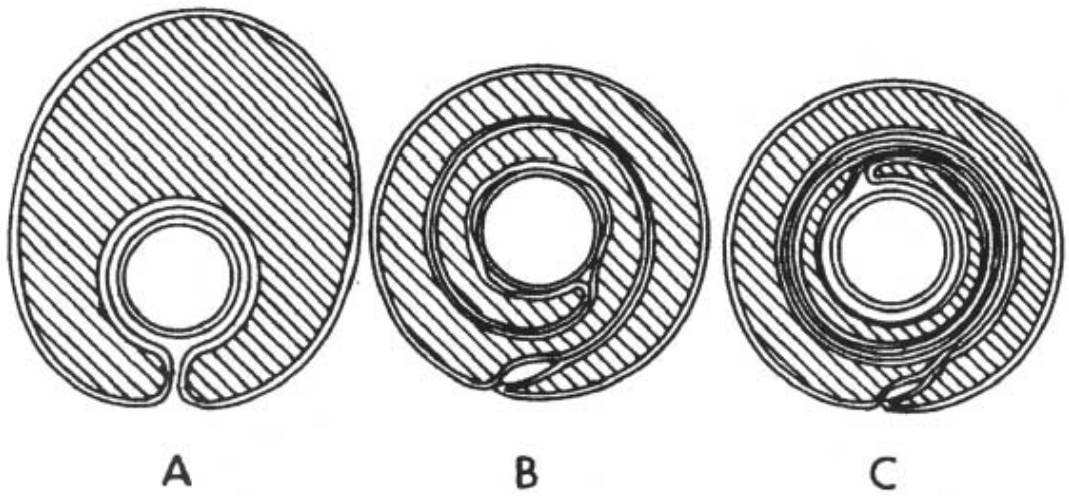


Figure 6.7. The development of the myelin sheath by vertebrate Schwann cells in the sequence A → B → C. [Reprinted with permission from J. V. Robertson, The molecular structure and contact relationships of the cell membrane, *Prog. Biophys.* **10**:343–417 (1960). Copyright 1960, Pergamon Journals, Ltd.]

Propagation in myelinated nerve fibers (cont.):

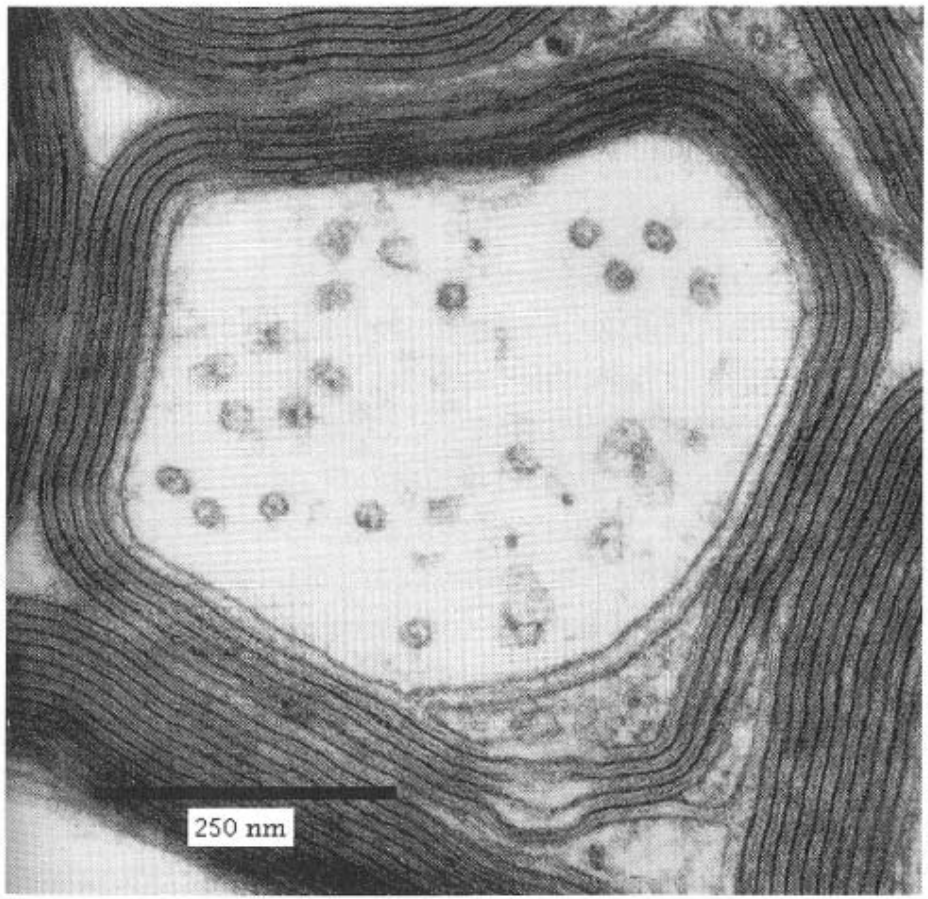


Fig. 6.14 MYELINATED AXONS Electron micrograph of a cross section through a portion of the optic fiber in an adult rat. The complete transverse section through a single myelinated axon is shown in close neighborhood to other axons. About four wrappings of myelin insulation are visible. The circular structures inside the axonal cytoplasm are transverse sections through microtubules. Reprinted by permission from Peters, Palay, and Webster (1976).

(from Koch)

Propagation in myelinated nerve fibers (cont.):

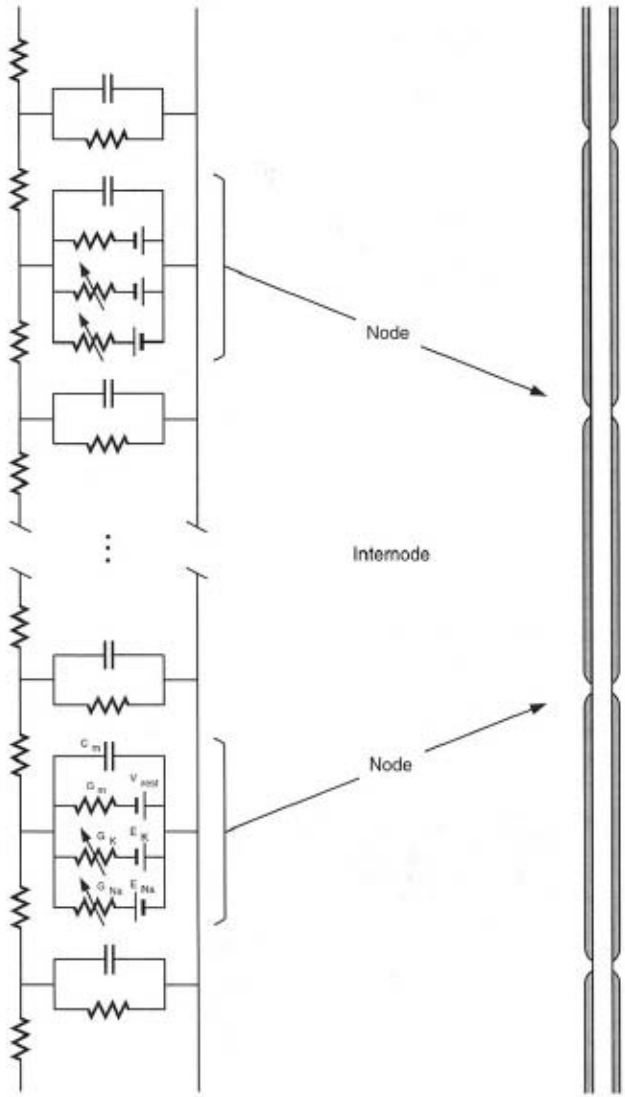


Fig. 6.15 Electrical Circuit for a Myelinated Axon Geometrical and electrical layout of the myelinated axon from the frog sciatic nerve (Frankenhaeuser and Huxley, 1964; Rogart and Ritchie, 1977). The diameter of the axon and its myelin sheath is 15 μm, the diameter of the axon itself 10.5 μm, the difference being made up by 250 wrappings of myelin. The myelin is interrupted every 1.38 mm by a *node of Ranvier* that is 2.5 μm wide. The total distributed capacitance for the internode (2.2 pF) is only slightly larger than the capacitance of the much smaller node (1.6 pF). The same is also true of the distributed resistance. At each node, the spike is reamplified by a fast sodium current and is repolarized by a potassium current. Little or no potassium current is found at the nodes of Ranvier in mammalian myelinated axons. There, repolarization is accomplished by rapid sodium inactivation in conjunction with a large effective "leak" current.

(from Koch)

Propagation in myelinated nerve fibers (cont.):

The specific leakage resistances and specific capacitances of the myelin sheath and cell membrane shown below are consistent with the myelin sheath being equivalent to around 100 layers of cell membrane.

Table 6.1. Electrical Properties of Myelin Sheath and Cell Membrane

	Specific leakage resistance ($\Omega\ cm^2$)	Specific capacitance (F/cm^2)
Myelin sheath	10^5	10^{-8}
Cell membrane	10^3	10^{-6}

Propagation in myelinated nerve fibers (cont.):

Considering the Frankenhaeuser-Huxley model under subthreshold (i.e., linear/passive) conditions, the nodes of Ranvier have a specific membrane resistance and specific membrane capacitance of:

$$R_m = 20\ \Omega\ \mathrm{cm}^2$$

and (6.45)

$$C_m = 3\ \mu\mathrm{F}/\mathrm{cm}^2,$$

respectively.

Propagation in myelinated nerve fibers (cont.):

Note:-

- Nodes of Ranvier are around $1\ \mu\mathrm{m}$ in length.
- Internodal distances are on the order of 1 to 2 mm. (A rough empirical rule is that the internodal length equals $100 \times d$, where d is the fiber diameter.)

Although internodes are much longer than nodes, the much smaller specific capacitance of the former means that an internode and a node have approximately the same capacitance.

Propagation in myelinated nerve fibers (cont.):

The purpose of the myelin is clearly to:

1. reduce the capacitance of long stretches of membrane, the *internodes*, such that they do not need to be charged up for action potential propagation, and
2. increase the membrane leakage resistance so that there is less leakage across the membrane of the intracellular longitudinal current.

Consequently, the "local circuit currents" extend over much longer lengths of the fiber.

Propagation in myelinated nerve fibers (cont.):

Because the local circuit currents extend from node to node, action potentials effectively jump or skip from node to node, which is referred to as *saltatory propagation*.

Saltatory propagation produces:

1. faster propagation of action potentials, and
2. a "failsafe" mechanism – if one node is blocked, the action potential will skip over it to the next.

Propagation in myelinated nerve fibers (cont.):

In contrast to Eqn. (6.44), for myelinated fibers:

$$\theta = 6d \quad \text{m/s}, \tag{6.46}$$

where d is the fiber diameter in μm.

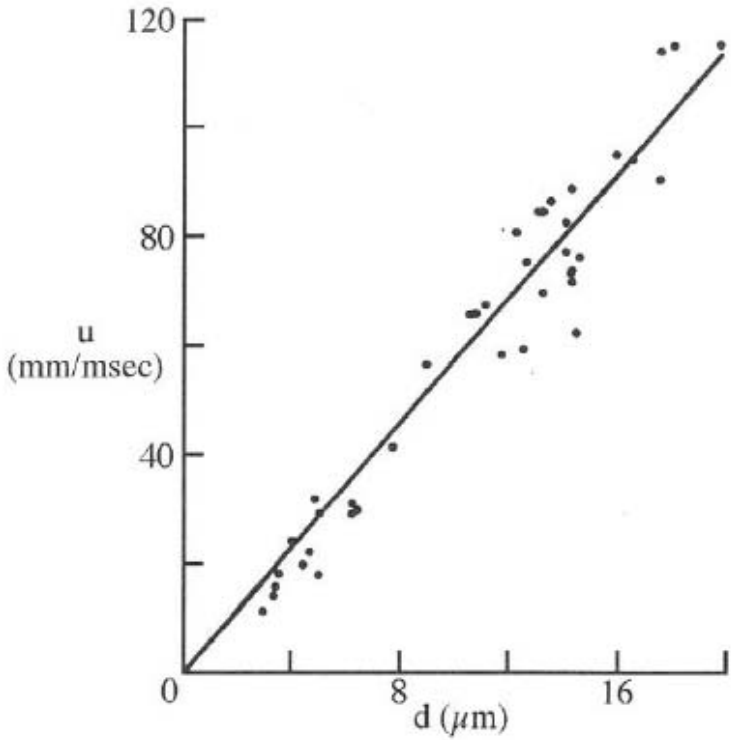


Fig. 6.16 DIAMETER AND PROPAGATION VELOCITY Relationship between (internal) diameter d of adult cat peripheral myelinated fibers and propagation velocity u of the action potential. The data are shown as dots (Hursh, 1939) and the least-square fit as a line. Peripheral myelinated fibers are bigger than 1 μm, while myelinated fibers in the central nervous system can be as thin as 0.2 μm, with an expected velocity in the 1-mm/msec range. Reprinted by permission from Ritchie (1982).

(from Koch)