ELEC ENG 3BB3:

Cellular Bioelectricity

Notes for Lecture 28

Thursday, March 20, 2014

Nerve excitation:

To evaluate the pattern of nerve activation that is produced by a particular electrode configuration, we must consider:

- the geometry of the electrode(s) and nerve fibers,
- the conductivities of the medium in which the electrode(s) and nerve fibers lie, and
- the properties of the nerve fiber membrane, either subthreshold (i.e., linear) or suprathreshold (i.e., nonlinear).

Nerve excitation (cont.):

Consider the linear-core-conductor model of a myelinated fiber being stimulated by a *bipolar* electrode pair (i.e., delivering equal and opposite current).

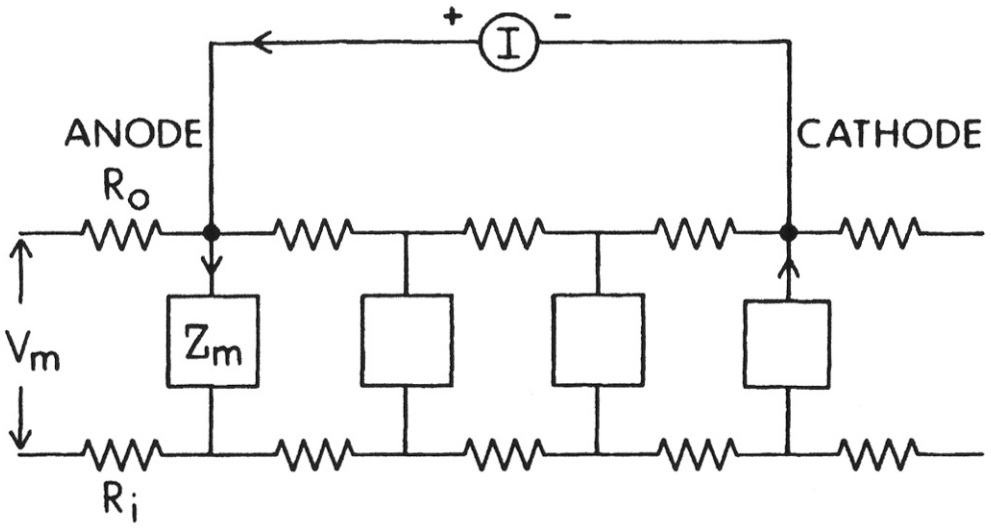

Figure 12.7. The linear-core-conductor model of a myelinated fiber. Since transmembrane current is assumed to flow only at the nodes, the axial resistances R_o, R_i are finite (and not infinitesimal) and represent the axial resistances in the internode. The figure describes the condition where subthreshold stimulating current is introduced at two separated nodes.

Nerve excitation (cont.):

For this configuration, excitation will occur *below the cathode* if the stimulating current is large enough.

The strength-duration behaviour can be described as:

$$I_{\text{th}} = \frac{I_R}{\left(1 - \mathrm{e}^{-Kt}\right)}, \qquad (12.7)$$

where I_R is the *rheobase* current and K is an experimentally-determined constant that depends on the electrode geometry, medium conductivities, etc., as well as the membrane properties.

Nerve excitation (cont.):

A result of this strength-duration behaviour is that charge is wasted in stimulating a nerve fiber if the duration of the pulse is much larger than the *chronaxie*, which is defined in this case as:

$$t_c = \frac{\ln 2}{K}\,. \qquad (12.13)$$

Recall that we wish to minimize the total charge delivered in order to avoid electrochemical reactions at the electrode-electrolyte interface.

Nerve excitation (cont.):

Thus, short pulse durations are highly desirable based on this criterion.

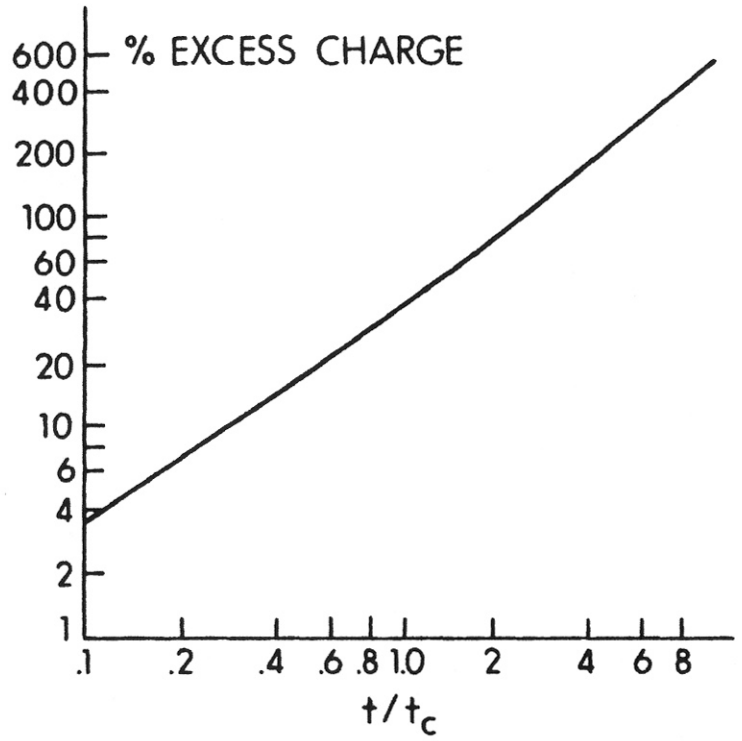

Figure 12.8. Charge injected to reach membrane threshold in excess of theoretical minimum as function of pulse duration.Pulse duration (t) has been normalized to the chronaxie value (t_c). See Eq. (12.5), where percent excess charge is a function of t/t_c and equals $[0.693\ (t/t_c)/(1-2^{-t/t_c}) - 1]100\%$.

Nerve excitation (cont.):

The injected *primary* current pulse is designed to achieve nerve activation.

The *secondary* pulse in a biphasic current waveform is introduced solely to achieve reversibility in the electrode-electrolyte interface.

However, this secondary pulse will be *hyperpolarizing*, and consequently it may suppress action potential generation. Adding an inter-phase delay can avoid this problem.

Nerve excitation (cont.):

The effect of inter-phase delay on action potential generation is illustrated below.

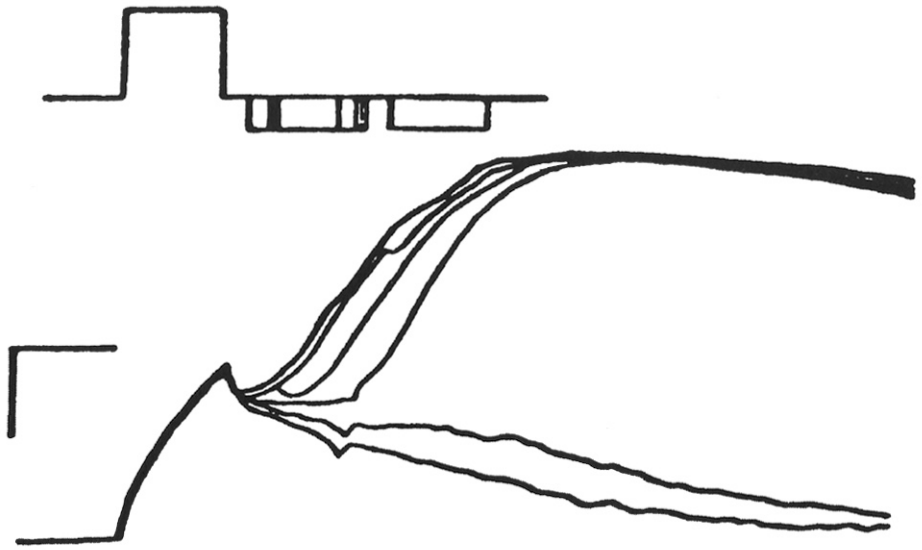

Figure 12.9. Transmembrane voltage response of myelinated nerve to short pulse stimuli. Shown is the effect of an increasing delay between primary and secondary pulses. Vertical calibration bar is 20 mV and horizontal bar is 50 μsec. [Reprinted with permission from C. van den Honert and J. T. Mortimer, The response of the myelinated nerve fiber to short duration biphasic stimulating currents, *Ann. Biomed. Eng.* **7**:117–125 (1979), copyright 1979, Biomedical Engineering Society.]

Nerve excitation (cont.):

Another important factor is the electrode-fiber geometry.

Consider stimulation of the peripheral nerve via a cuff electrode as shown below.

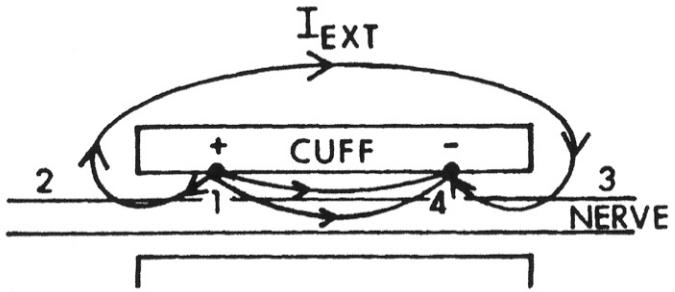

Figure 12.15. External paths 1 and 2 illustrate current which flows from anode to cathode around the outside of the cuff. Components will also enter the nerve and result in a virtual cathode and anode. External path 3 describes current from anode to cathode within the cuff but which does not enter the nerve; it will be greater for cuffs which fit loosely. The internal current illustrates the component lying within the cuff that links with the nerve; this is the desired depolarizing or hyperpolarizing pathway.

Nerve excitation (cont.):

Modelling cuff-electrode stimulation using the equivalent circuit illustrated below gives rise to the activation pattern shown on the next slide.

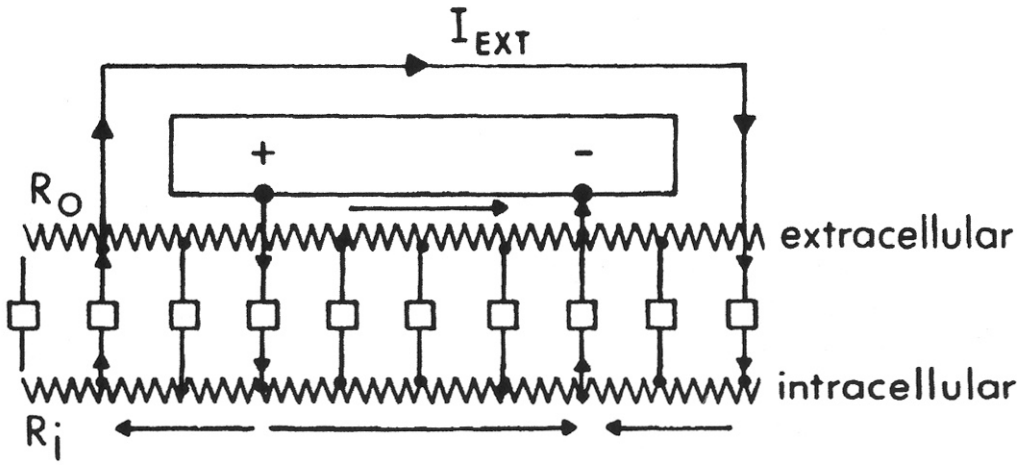

Figure 12.16. Ladder network model of the system including current pathways external to electrode cuff. A quantitative analysis of nerve response to current stimulation can be obtained from this approximating model (which lumps the internal and external paths into the two shown).

Nerve excitation (cont.):

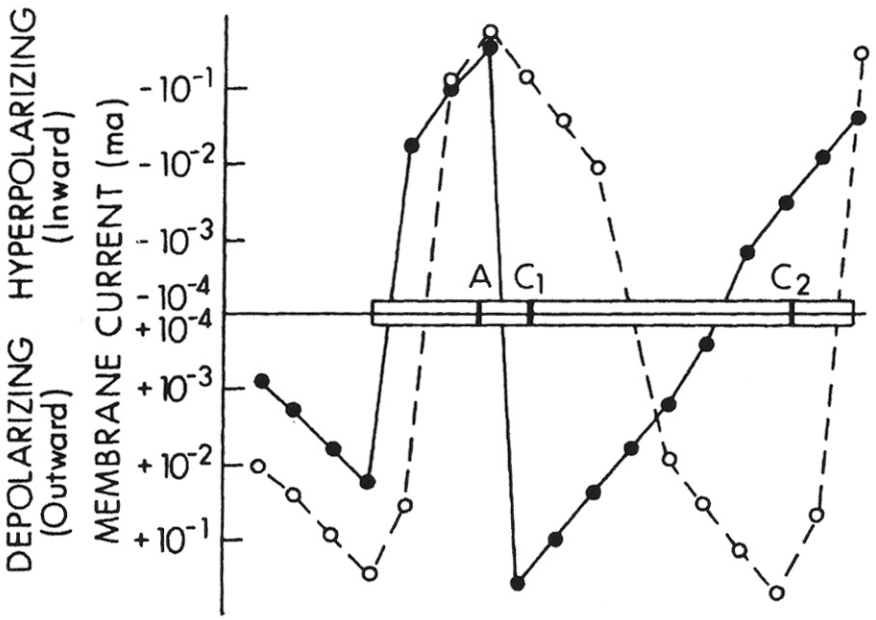

Figure 12.17. Transmembrane current distribution for axon in a cuff-type electrode. Outward current results in local depolarization of axon. The rectangular region represents the insulator portion of the electrode with axon located along the horizontal axis of the graph. Nodes of Ranvier are located at dot marks along the horizontal axis. Node separation in the model is 2.5 mm. The anode is located at the point indicated by A, and for the closely spaced case the cathode is located at point C_1, a distance of 2.5 mm. The cathode is located at C_2 for the 20 mm separation case. The solid line is the transmembrane current distribution for case C_1. The dashed line is the current distribution for case C_2.(Adapted from M. Karkar, Nerve excitation with a cuff electrode—a model, MS Thesis, Case Western Reserve University, Cleveland, Ohio, 1975. Also J. T. Mortimer, Motor prostheses, in *Handbook of Physiology*, Sec. I: *The Nervous System*, Vol. II, *Motor Control*, Part I, American Physiological Society, Bethesda, Maryland, 1981, pp. 155–187.)

Nerve excitation (cont.):

Stimulation using a surface electrode produces the activation pattern shown on the next slide if the neuron is normal to the surface.

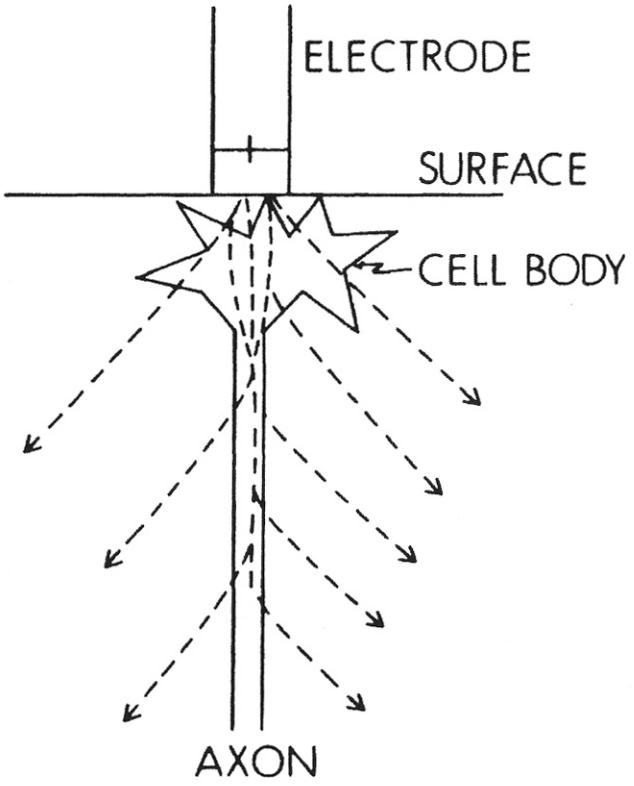

Figure 12.20. Current path for a surface electrode (anode) relative to a remote reference, in the vicinity of a neuron oriented normal to the surface.

Nerve excitation (cont.):

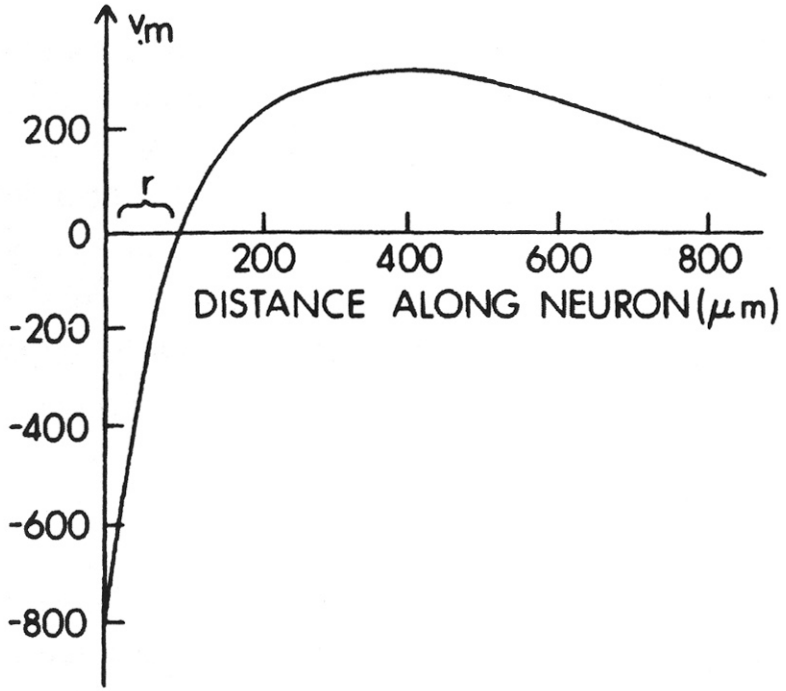

Figure 12.21. Transmembrane potential along nerve cell with geometry as described in Fig. 12.20. Stimulating electrode is located at zero, and indifferent electrode is located a great distance to the right. Note that the change in transmembrane potential reverses sign at distance *r* to the right of the stimulating electrode. (Adapted from W. B. Marks, Polarization changes of stimulated cortical neurons caused by electrical stimulation at the cortical surface, in *Functional Electrical Stimulation*, J. B. Reswick and F. T. Hambrecht, eds., Marcel Dekker, New York, 1977, described in J. T. Mortimer, Motor prostheses, in *Handbook of Physiology*, Sec. I: *The Nervous System*, Vol. II, *Motor Control*, Part I, American Physiological Society, Bethesda, Maryland, 1981, pp. 155–187.)

Nerve excitation (cont.):

In contrast, the activation pattern is quite different if the electrode is adjacent to the fiber.

In this case, the flanking hyperpolarized regions may block action potential generation.

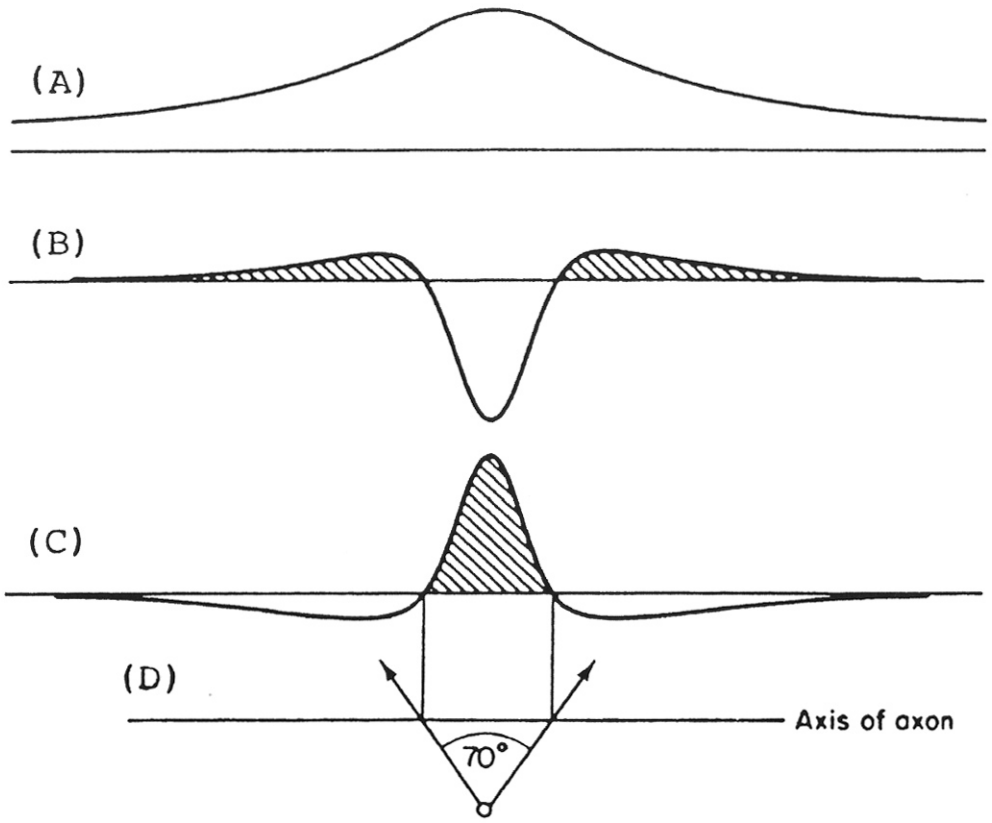

Figure 12.23. Induced transmembrane potential with a point source electrode for (b) anodal and (c) cathodal stimulation. The depolarized regions are shaded. (a) describes the applied field over the surface of the axon with anodal stimulation (the field would have the opposite sign for cathodal stimulation). The electrode position is shown in (d). The border between hyperpolarizing and depolarizing regions of 70.5° is independent of fiber parameters or extracellular conductivity. The reader can generate this figure using (7.86). [From F. Rattay, Ways to approximate current–distance relations for electrically stimulated fibers, *J. Theor. Biol.* **125**:339–349 (1987).]

Nerve excitation (cont.):

Comparison of neural response to intracellular and extracellular electrical stimulation.

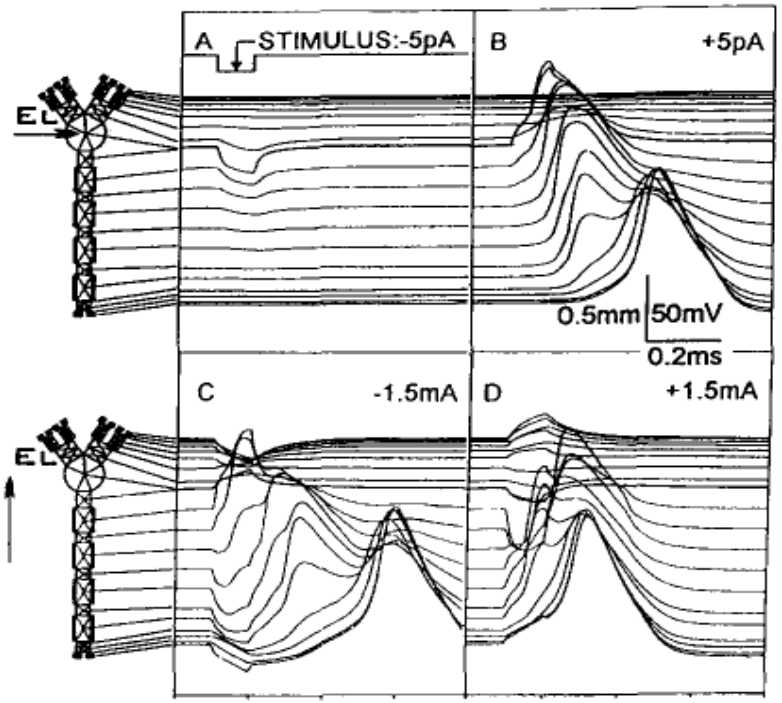

Fig. 1. Computed reactions of a simple model neuron stimulated internally (upper traces) and externally (lower traces). The neuron consists of the following subunits: dendritic tree, soma, initial segment, and the axonal segments consisting of internode, node and terminal partition (cf. Fig. 2). Stimulation with negative and positive 0.1-ms current impulses at the inside of the cell body (A, B) and by an extracellular microelectrode 0.5 mm away from the center of the cell body (C, D), as indicated by the tips of the arrows. Every line has a position according to the real location along the neuron (pictures of the neuron on the left side are not to scale), showing the membrane voltage of a single compartment as a function of time. (A) Local hyperpolarization. (B) An action potential propagates towards the axonal branching terminal region. Current injection causes a situation at the soma that is rather similar to that of the "space clamp" experiment of Hodgkin and Huxley: when the impulse is applied, the strongest reaction is at the soma, but some of the injected current flows along the neuron and therefore the voltages in all compartments have the same sign in the initial stimulating phase (A, B). Extracellular stimulation generates stimulated and hyperpolarized zones within the neuron (C, D). The strongest reaction is within the axon, at a position which is rather far away from the electrode, especially in D.

(Rattay, *Neurosci.* 1999)

Nerve excitation (cont.):

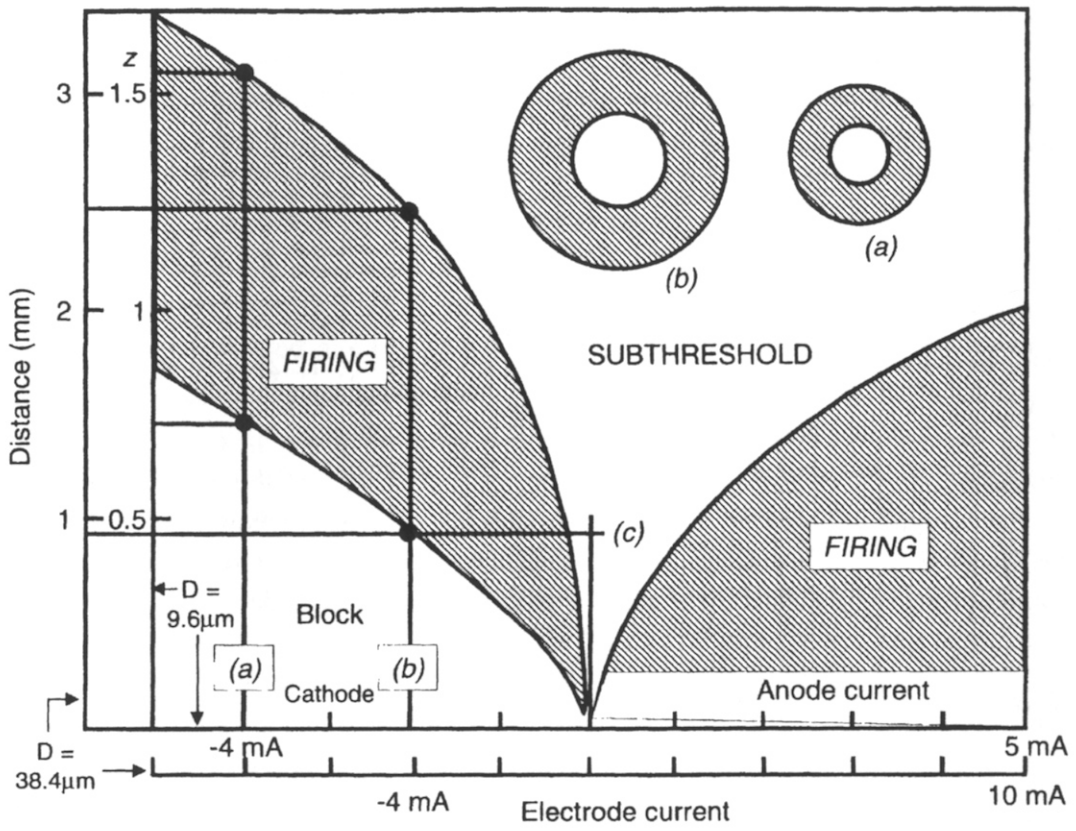

Figure 12.24. Stimulation with a monopolar electrode arises for points lying in the shaded areas. The inner scales are for a fiber diameter of 9.6 μm while the outer are for a diameter of 38.4 μm. For a stimulus of −4.0 mA and $d = 9.6$ μm [line (*a*)], the lower and upper limit of electrode–fiber distance while still achieving excitation is roughly 0.75–1.6 mm. For the same stimulus with $d = 38.4$ μm [line (*b*)] the interval is roughly 0.9–2.5 mm, hence more distant fibers are reached. Line (*c*), for a fixed distance, shows the upper and lower stimulus current magnitude for excitation. Computation was conducted with the Hodgkin–Huxley membrane model, $T = 27$ °C, $\rho_e = 300$ Ω cm, and a square pulse of 100 msec duration was chosen. [From F. Rattay, Ways to approximate current–distance relations for electrically stimulated fibers, *J. Theor. Biol.* **125**:339–349 (1987).]

Nerve excitation (cont.):

When modelling the response of *myelinated fibers*, it may be sufficient to just included active (nonlinear) membrane properties in the node closest to the electrode.

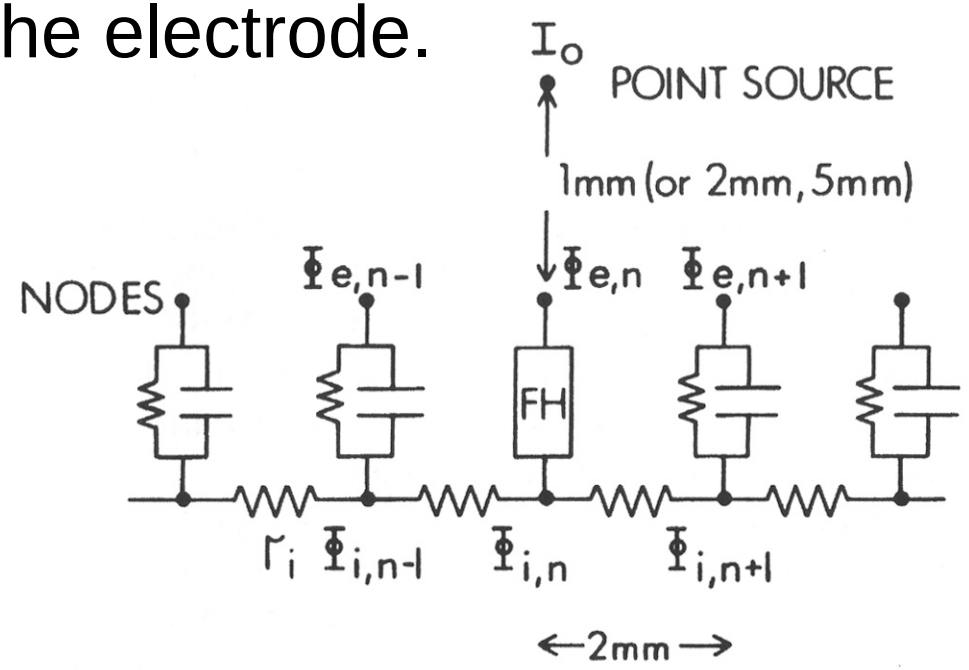

Figure 12.10. Model to study response of myelinated nerve fiber to a point-source stimulus. Source is 1, 2, or 5 mm from nerve [10]. The central node is described by Frankenhauser–Huxley equations, while lateral nodes are assumed to remain subthreshold and to be adequately described by *RC* elements. [Based on D. McNeal, Analysis of model for excitation of myelinated nerve, *IEEE Trans. Biomed. Eng.* **BME-23**:329–377 (1978), copyright 1978, IEEE.]

Nerve excitation (cont.):

However, if the electrode is more distant from the fiber, or close to the soma or dendrites, then more complicated excitation patterns can result.

(Rattay, *IEEE Trans. Biomed. Eng.* 1998)

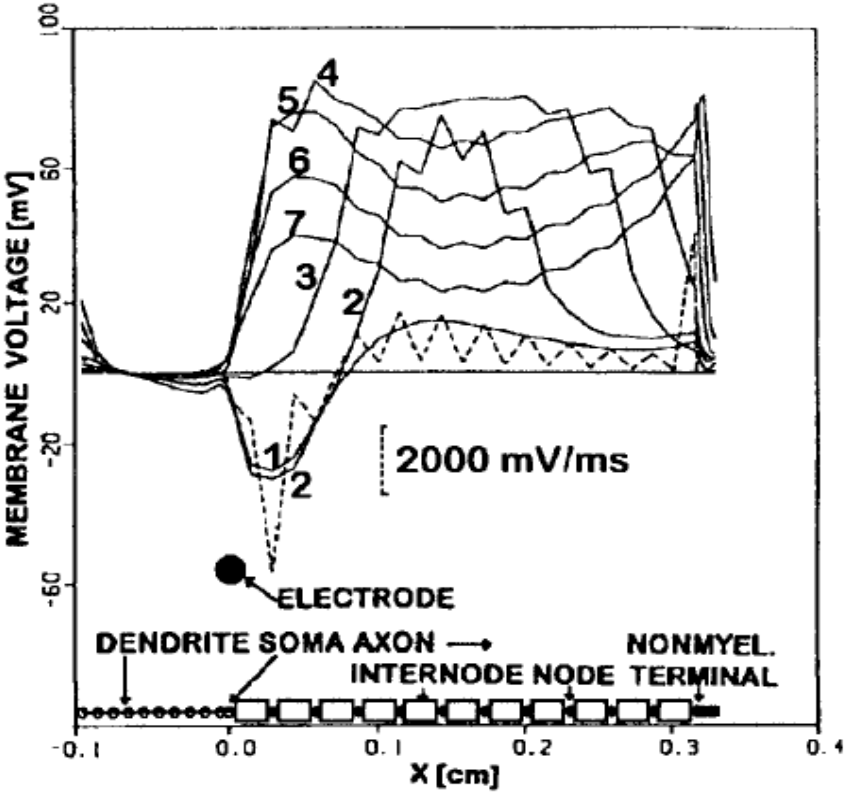

Fig. 3. Voltage distribution of model neuron 1 evoked by a positive 100 μs/5 mA stimulating pulse. The lower picture indicates the positions of the center points of the 40 compartments where membrane voltages are calculated. The positions of the soma and the initial segment coincident in the graph. The electrode is 1 mm just above the soma. The voltage change along the neuron generated by a positive stimulating pulse as predicted by the activating function f is shown as a dashed line. Note that the part of the neuron nearest to the electrode is the soma, but there is neither the maximum nor the minimum of f. The strongest negative value of f is at the first node, the strongest positive value of f is at the first element of the unmyelinated part of the axon. Full lines show snapshots of the computed membrane voltage in intervals of 50 μs, marked by numbers 1–7. Line 1 ($t = 50$ μs) is similar in shape to the activating function. Scale bar is for the activating function.

Nerve excitation (cont.):

Note that in the previous figures the activating function is not smooth.

This is because in the case of *myelinated fibers* the transmembrane current is only non-zero at the nodes of Ranvier, and thus the activating function is effectively discretized to:

$$\frac{\partial^2 \Phi_e}{\partial z^2} \Rightarrow \frac{\Phi_{e,n-1} - 2\Phi_{e,n} + \Phi_{e,n+1}}{\Delta z^2},$$

where n indicates the index to the n^{th} node of Ranvier and ¢ z is the distance between nodes.