ELEC ENG 3BB3:

Cellular Bioelectricity

Notes for Lecture 16

Friday, February 7, 2014

6. ELECTRICAL STIMULATION OF EXCITABLE TISSUE

We will look at:

- Linear (subthreshold) response of a single spherical cell
- Linear (subthreshold) response of a cylindrical fiber

Electrical stimulation of excitable tissue:

In order to study how action potentials are initiated in spherical cells and cylindrical fibers, we will make the assumption that the membrane is linear (passive) up to the threshold potential.

In the case of spherical cells, our aim is to understand how threshold is reached as a function of stimulus amplitude and duration.

In the case of cylindrical fibers, we wish to understand the space-time characteristics of subthreshold membrane potentials, such as those generated by electric stimulation or synaptic input, and again to determine how threshold is reached.

Spherical cell response to current step:

If R_m (Ω cm^2) and C_m (μF/cm^2) are the *specific resistance* and the *specific capacitance*, respectively, of the membrane, then for a spherical cell with surface area A (cm^2) the *membrane resistance* is:

$$R = \frac{R_m}{A} \quad \Omega, \tag{7.1}$$

and the *membrane capacitance* is:

$$C = C_m A \quad \mu\text{F}. \tag{7.2}$$

Spherical cell response to current step (cont.):

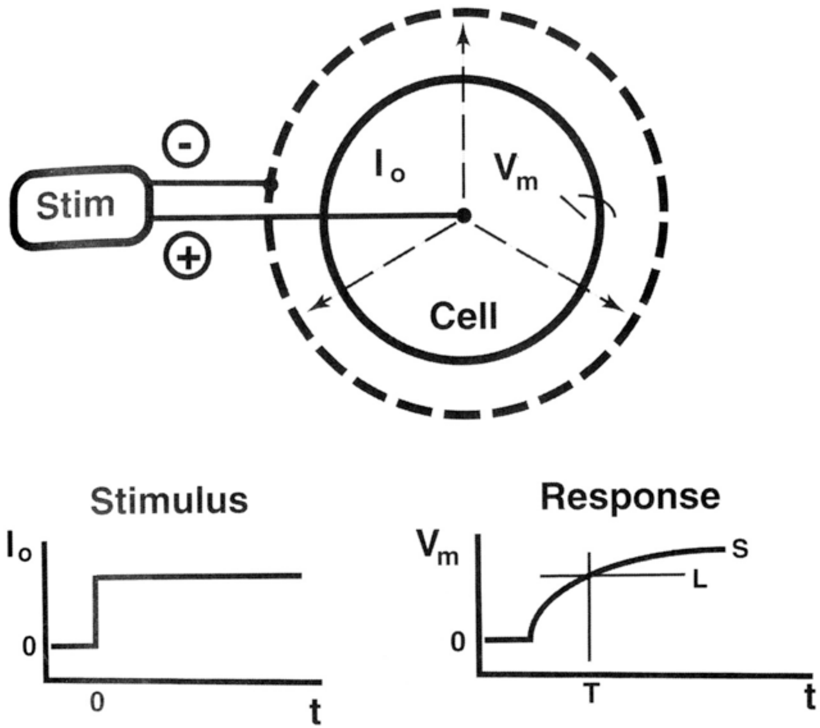


Figure 7.1. Top: A stimulator (left) applies a current I_0 to the center of a spherical cell. Current flows symmetrically outward (arrows) through the membrane (solid circle). Current is collected symmetrically at the periphery of the surrounding extracellular bath (dashed sphere). Bottom: A current step of magnitude I_o is applied (lower left) by the stimulator between the intracellular and extracellular electrodes. The stimulus current continues indefinitely during time t. The current produces a rising transmembrane voltage, v_m (solid curve), that does not have the step waveform of I_0. Even though the stimulus current I_0 continues on, the rise of v_m approaches limiting level $v_m = S$. Level S is called the "strength" of the stimulus. Of particular interest is the time T required to reach a "threshold" voltage level $V_T = L$ (short lines crossing v_m curve at lower right). The v_m curve is sketched as the response if membrane resistance R_m is constant. Furthermore, the concept of this simplified view of stimulation is that R_m will change abruptly once v_m reaches threshold voltage level L, as an active membrane response will occur thereafter.

Spherical cell response to current step (cont.):

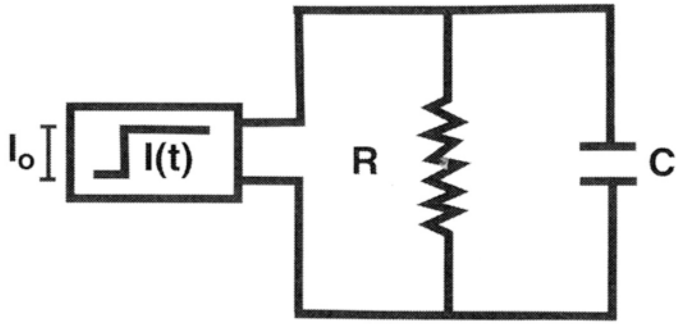


Figure 7.2. Equivalent Electrical Circuit for the Ppreparation of Figure 7.1. The membrane resistance of the cell as a whole is R, and the capacitance of the cell is C. The stimulator (box on left) creates a stimulus current $I(t)$ that is a function of time. In particular, the stimulus current is a current step of magnitude I_0 starting at time zero. Analysis is done for R and C constant. (However, in a real cell R will change when the cell becomes active and ion channels open.) The spherical symmetry of the cell in Figure 7.1 allows this simple electrical equivalent.

Spherical cell response to current step (cont.):

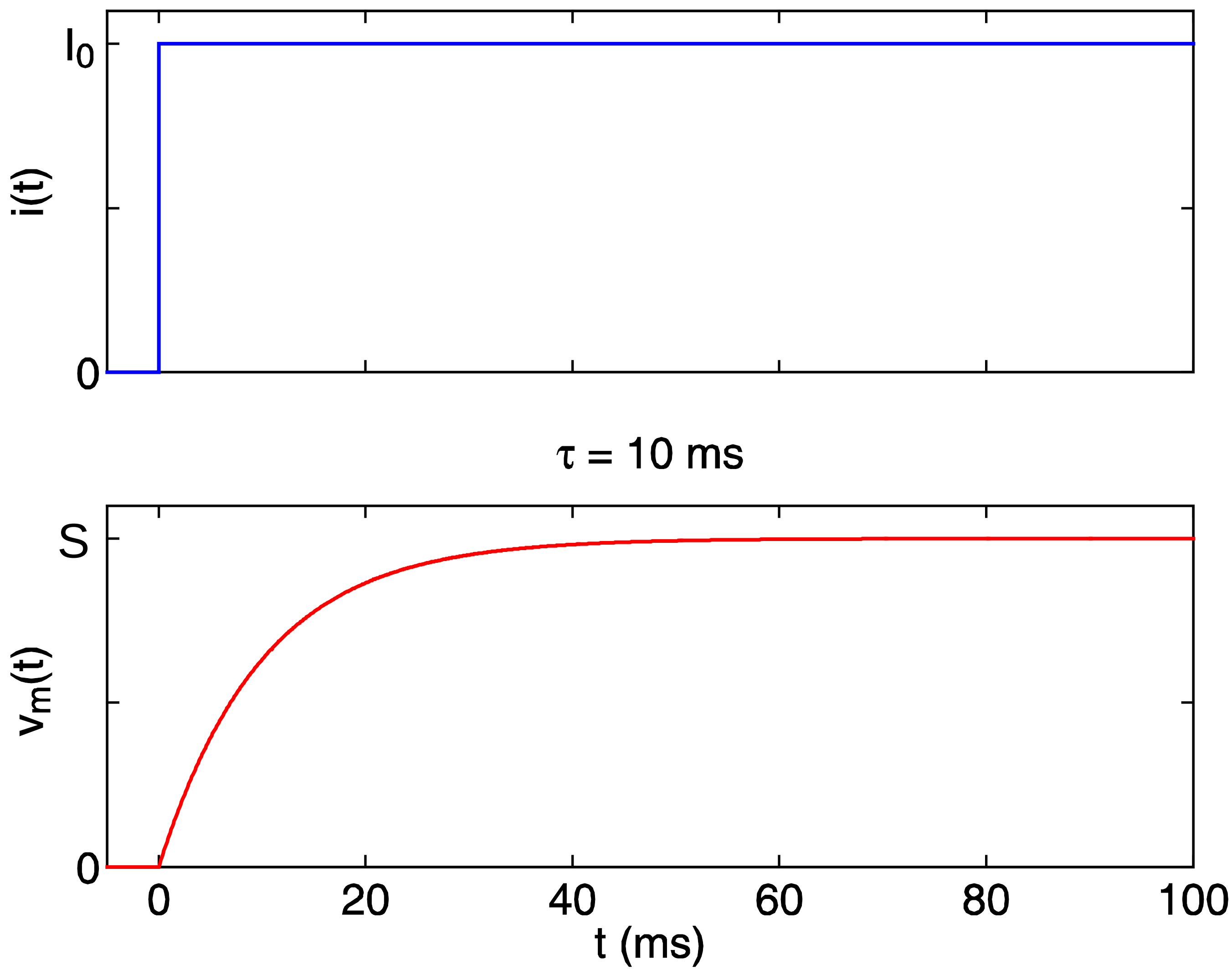
The response of the relative transmembrane potential v_m of a spherical cell subjected to an intracellularly-injected current step of amplitude I_0 is:

$$v_m = I_0 R \left(1 - \mathrm{e}^{-t/\tau}\right) \quad (7.3)$$

$$= S \left(1 - \mathrm{e}^{-t/\tau}\right), \quad (7.4)$$

where $\tau = RC$ and $S = I_0 R = v_m(t!1)$.

Spherical cell response to current step (cont.):



Strength-duration relationship:

Suppose that a relative transmembrane potential of V_T (< S) is the "threshold" potential for eliciting an action potential.

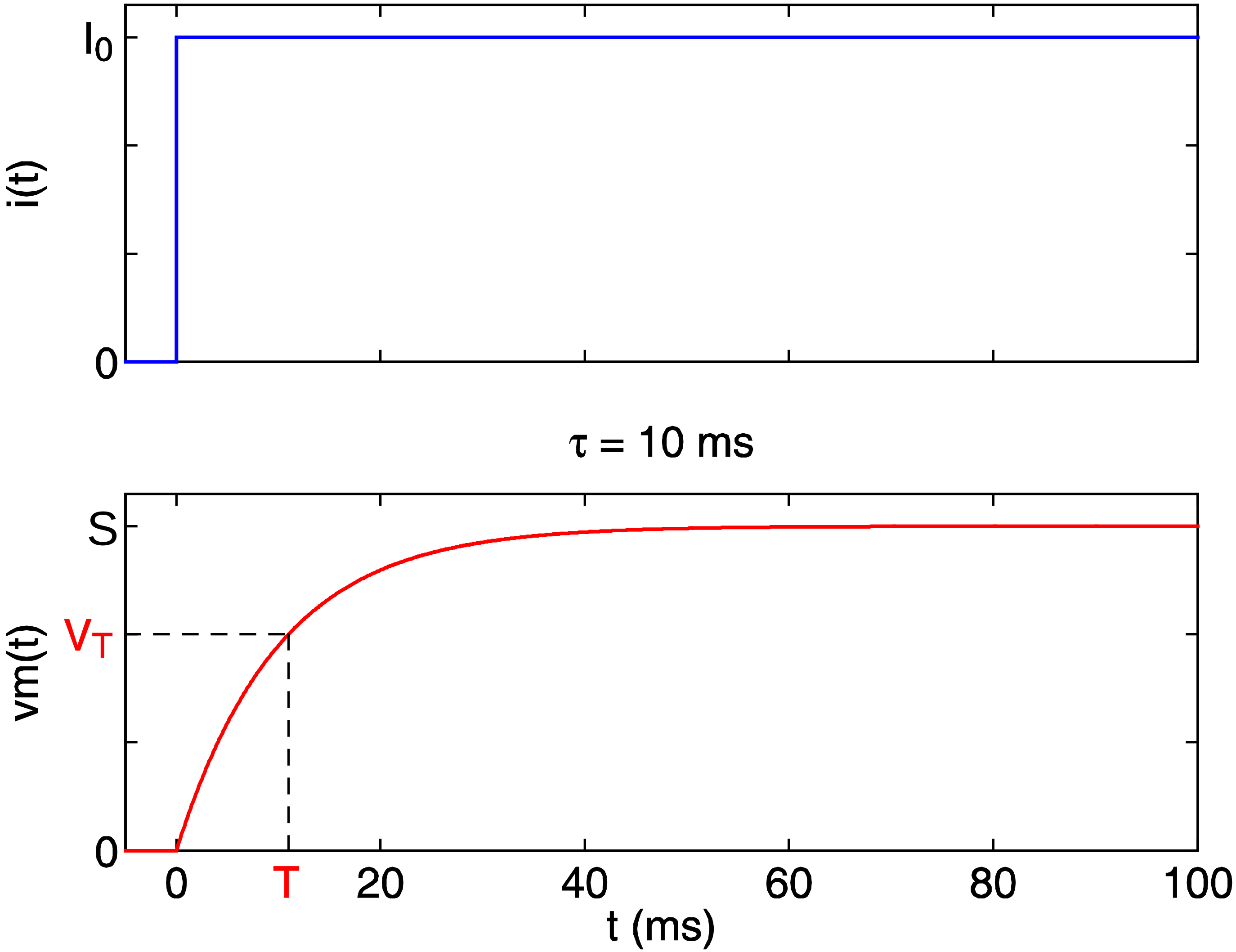
From Eqn. (7.4), the membrane potential will reach V_T at time T (following the onset of the current pulse) according to the equation:

$$V_T = S\left(1 - \mathrm{e}^{-T/\tau}\right). \qquad (7.4)$$

Solving for T gives:

$$T = \tau \ln\left(\frac{1}{1 - V_T/S}\right) = \tau \ln\left(\frac{S}{S - V_T}\right). \qquad (7.6)$$

Strength-duration relationship (cont.):



Strength-duration relationship (cont.):

Eqn. (7.4) can also be rearranged to provide a relationship between the stimulus strength and threshold voltage:

$$S = V_T / \left(1 - \mathrm{e}^{-T/\tau}\right). \tag{7.7}$$

Division of both sides of (7.7) by the membrane resistance R gives the strength-duration relationship (plotted on the next slide) according to the equation:

$$I_{\mathrm{th}} = I_R / \left(1 - \mathrm{e}^{-T/\tau}\right), \tag{7.8}$$

where I_{th} is the threshold current for a pulse of duration T and I_R is the rheobase current.

Strength-duration relationship (cont.):

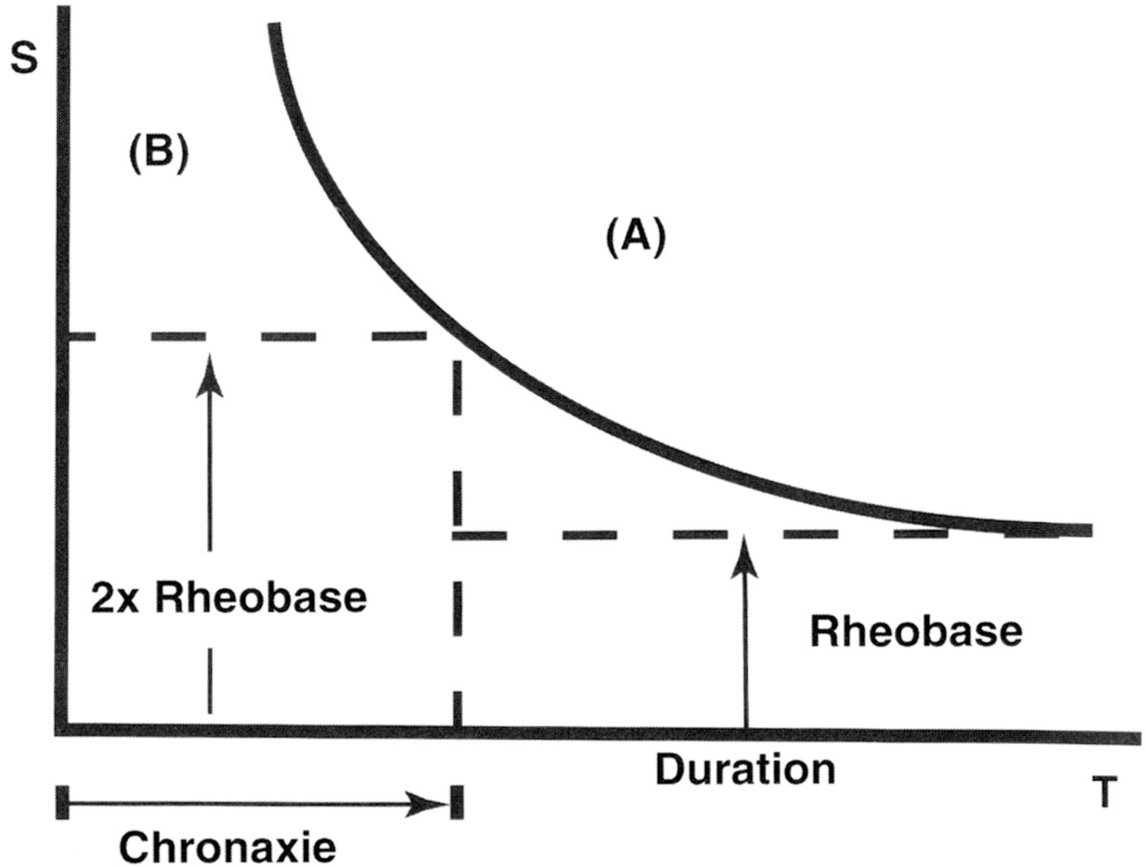


Figure 7.3. Strength–Duration Curve. Line $V_T = L$ shows the combinations of stimulus strength S (on the vertical axis) and stimulus duration T (on the horizontal axis) that are just sufficient to reach the threshold level. Combinations on side A of line L are above threshold and may lead to action potentials, while combinations on side B are below threshold. *Rheobase* is the value of stimulus current that is just sufficient to reach L with a long stimulus duration T. *Chronaxie* is the stimulus duration required to reach L if the stimulus current is set to twice rheobase.

Strength-duration relationship (cont.):

- *Rheobase* (I_R) is the minimum excitation required to just reach threshold as T ! 1, i.e., S = V_T.
- *Chronaxie* is the pulse duration T_c required to reach threshold when the stimulus is twice rheobase, which can be calculated according to:

$$T_c = \tau \ln 2 = 0.693\tau. \tag{7.11}$$

Chronaxie is significant as a nominal time period required to reach the threshold voltage.

Comparison to experimental findings:

1. We assumed that the membrane is linear (passive) up to V_T, while from Fig. 5.6 we know that it is only linear up to around 50% of V_T.

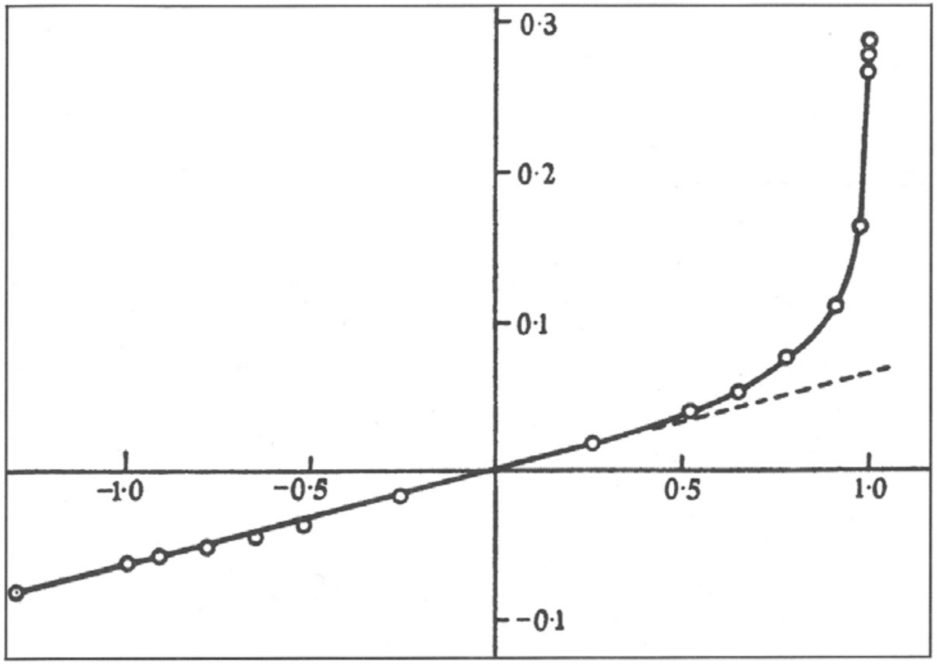


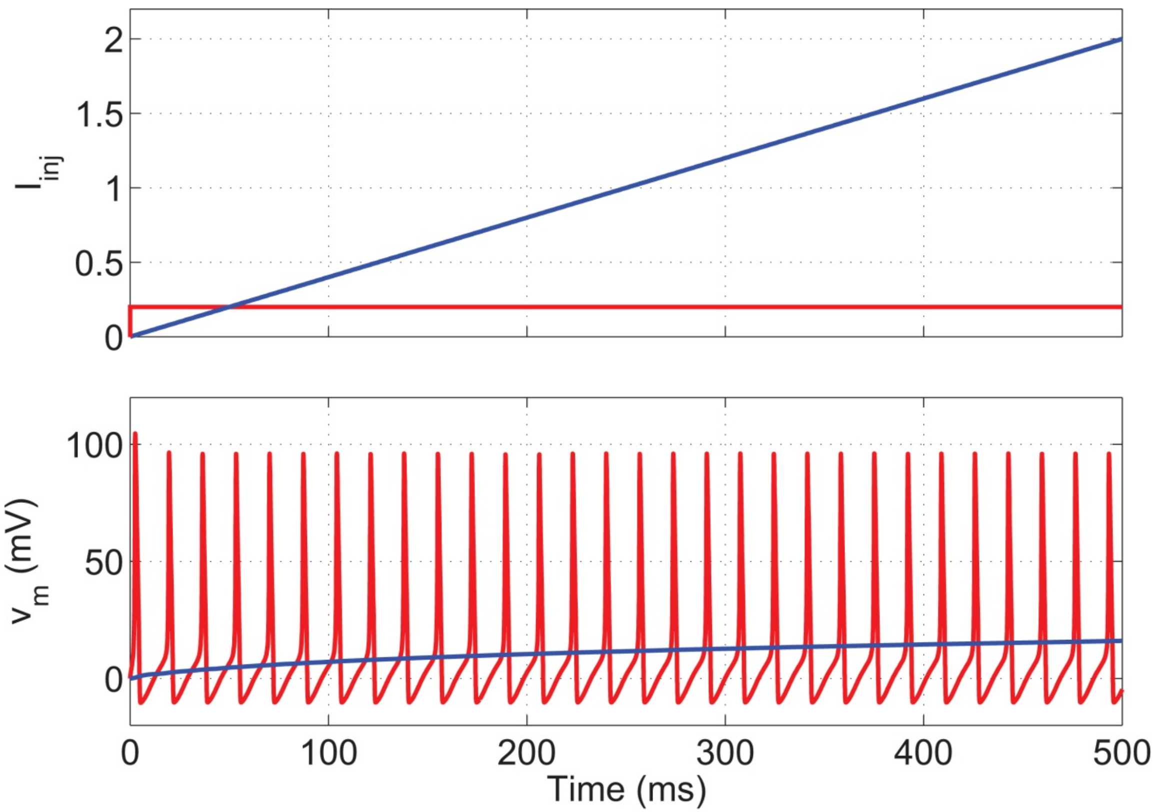
Figure 5.6. The relation between stimulus and response in a crab axon. This figure was derived from Fig. 5.5. The abscissa shows the stimulus intensity, measured as a fraction of the threshold stimulus. The ordinate shows the recorded potential 0.29 msec after the stimulus, measured as a fraction of the action potential peak. [Reprinted with permission from A. L. Hodgkin, The subthreshold potentials in a crustacean nerve fibre, *Proc. R Soc. London, Ser. B* **126**:87–121 (1938).]

Comparison to experimental findings (cont.):

2. A spherical cell with an intracellular electrode is a fairly artificial case.
   In general, stimulating electrodes are extracellular and produce a response that depends on the electrode-cell geometry.
   We will look at a particular example later.

Comparison to experimental findings (cont.):

3. A fixed threshold fails to account for "accommodation", where the time-course of activation is important because of sodium inactivation and potassium activation.



Comparison to experimental findings (cont.):

4. For stimuli with durations shorter than the sodium activation time constant τ_m, the positive-feedback loop of:

depolarization

sodium channel opening

may not be initiated, even if the nominal threshold voltage has been exceeded.