ELEC ENG 3BB3:

Cellular Bioelectricity

Notes for Lecture 10

Friday, January 24, 2014

Notation for potentials:

- Transmembrane potential:

$$V_m = \Phi_i - \Phi_e$$

- Membrane potential relative to rest:

$$v_m = V_m - V_{\text{rest}}$$

- Intra- and extra-cellular potentials relative to their respective baseline values:

$$\phi_i = \Phi_i - \Phi_{i,\text{rest}}$$
$$\phi_e = \Phi_e - \Phi_{e,\text{rest}}$$

Voltage and space clamp:

- Hodgkin and Huxley used a *voltage* and *space clamp* apparatus to measure and quantify ionic currents in the squid giant axon.
- By applying a *voltage clamp* and making discrete steps in transmembrane voltage, the capacitive current is absent, and consequently only the ionic currents are recorded.
- By inserting a conducting wire along the inside of the axon, a *space clamp* is applied, i.e., the intracellular potential is the same along the entire length of the axon. Consequently, the ionic current from a large number of ion channels is recorded.

Voltage and space clamp (cont.):

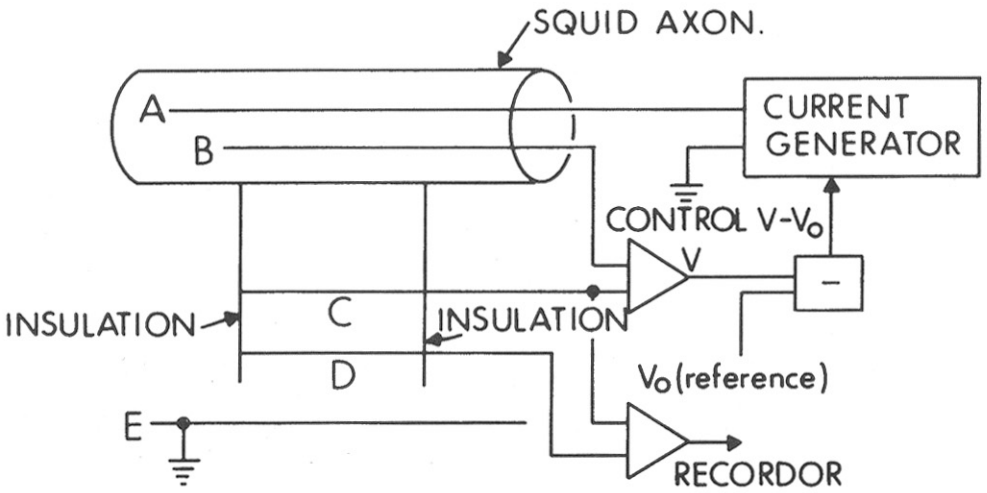

Figure 5.7. Schematic diagram showing the voltage and space clamp apparatus as developed by Hodgkin, Huxley, and Katz [6]. Current electrodes are (A) and (E); potential sensing electrodes are (B) and(C). Transmembrane current is determined from the potential between (C) and (D) and the total resistance between these electrodes. (Since the membrane current is uniform and in the radial direction only, the resistance can be calculated if the electrode end-effects are neglected.) Transmembrane voltage V is compared with the desired clamp V_0, and the difference causes a proportional transmembrane current of proper sign so that $(V - V_0) \rightarrow 0$.

Voltage and space clamp (cont'd)

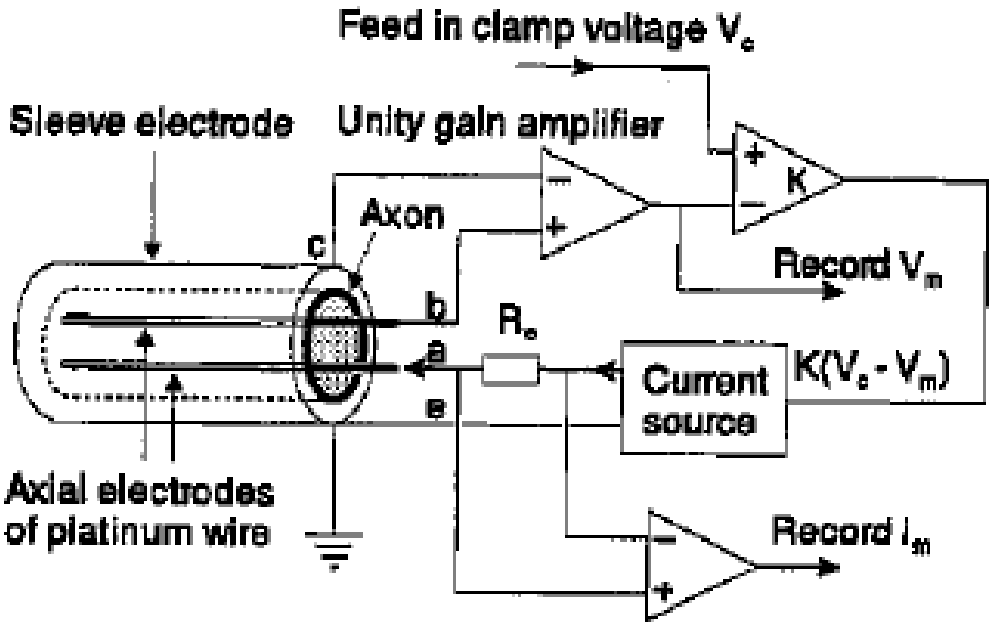

Fig. 4.4 Realistic voltage clamp measurement circuit. Current is applied through electrodes (a) and (e), while the transmembrane voltage, V_m, is measured with electrodes (b) and (c). The current source is controlled to maintain the membrane voltage at some preselected value V_c.

Example net ionic current to a voltage step:

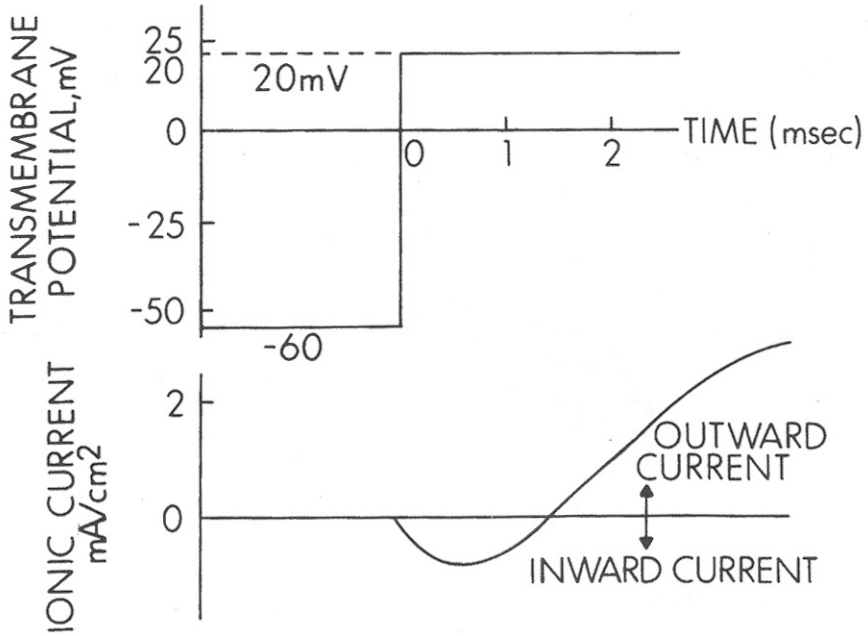

Figure 5.8. Illustrative example of the ionic current for a squid axon assuming the application of a voltage clamp of V_m = 20 mV at t = 0 sec. The assumed parameters are: resting potential of $V_m = V_{rest} = -60$ mV; sodium and potassium Nernst potentials $E_K = -70$ mV and $E_{Na} = 57$ mV.

Measured ionic current for different voltage steps:

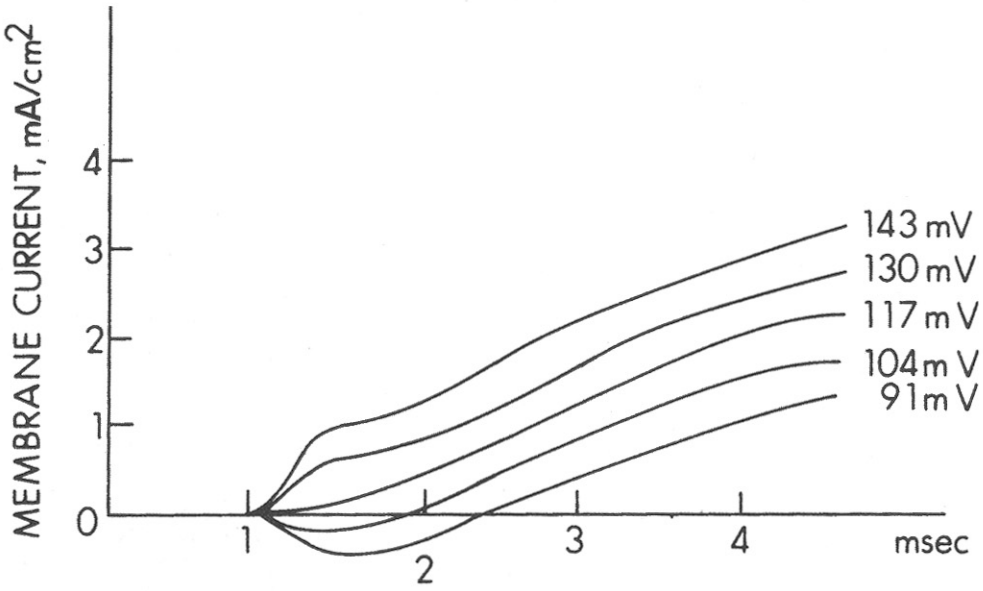

Figure 5.9. Measured ionic current for the squid axon following the application of a voltage clamp of the value indicated. The sodium Nernst potential is reached with a step change of 117 mV (since the resting potential is –60 mV and E_{Na} = 57 mV). [From A. L. Hodgkin, Ionic movements and electrical activity in giant nerve fibers, *Proc. R. Soc.* **148**:1–37 (1958). After A. L. Hodgkin, A. F. Huxley, and B. Katz, Measurement of current voltage relations in the membrane of the giant axon of *Loligo*, *J. Physiol.* **116**:424–448 (1952).]

Current-voltage curves:

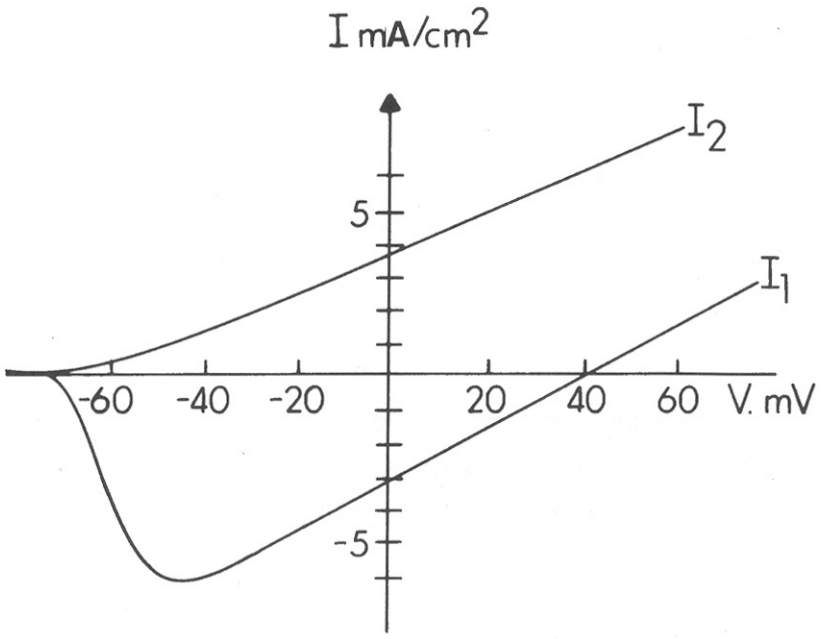

Figure 5.10. A typical current–voltage relation for squid axon. Curve I_1 shows the peak inward current versus clamped transmembrane voltage V_m after holding at rest. Curve I_2 plots the steady-state outward current versus the clamped voltage V_m. The voltage clamp value of V_m is plotted on the abscissa. Note that $I_1 = 0$ at $V_m = V_{rev} \approx E_{Na}$.

Separation of sodium and potassium currents:

Hodgkin and Huxley utilized two approaches to separating the contributions of sodium and potassium currents to the net ionic current:

1. Assuming $I_K = 0$ for $0 \cdot t \cdot T/3$, where T is the time of peak inward current.
2. Varying the extracellular sodium concentration while keeping the extracellular potassium concentration fixed.

Effects of varying extracellular sodium concentration:

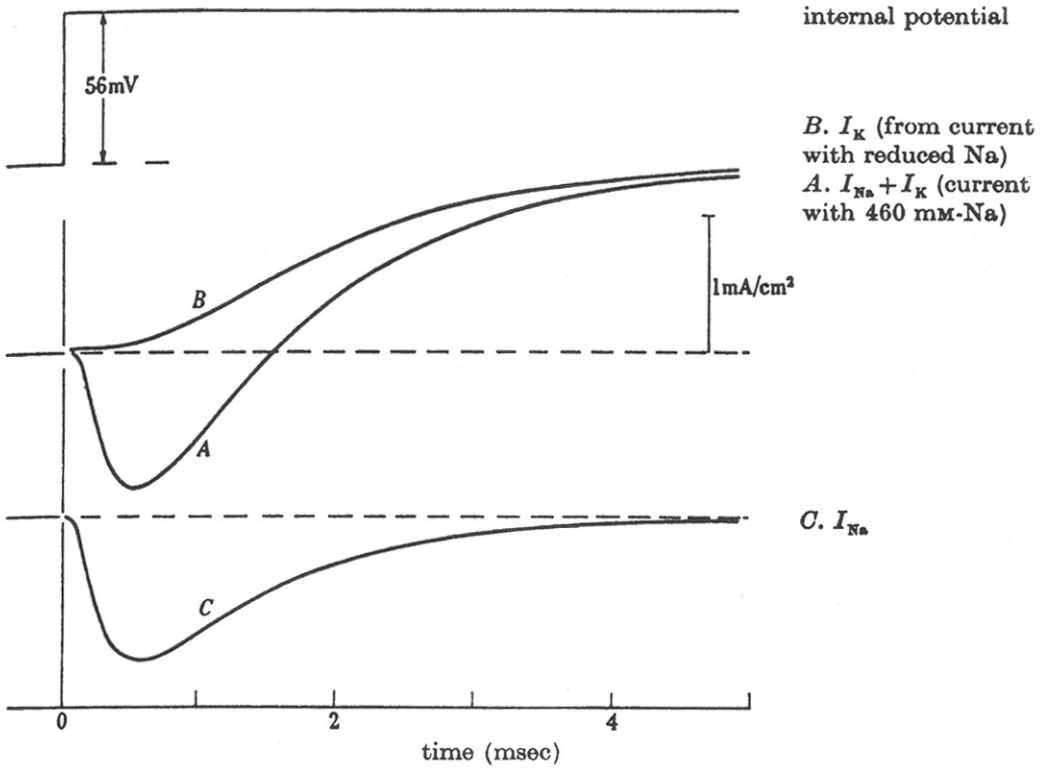

Figure 5.11. Analysis of the ionic current in a *Loligo* axon during a voltage clamp. Trace A shows the response to a depolarization of 56 mV with the axon in seawater. Trace B is the response with the axon in a solution comprising 10% seawater and 90% isotonic choline chloride solution. Trace C is the difference between traces A and B. Normal E_{Na} = 57 mV and in the reduced seawater E_{Na} = −1 mV. [From A. L. Hodgkin, Ionic movements and electrical activity in giant nerve fibers, *Proc. R. Soc.* **148**:1–37 (1958). After A. L. Hodgkin, A. F. Huxley, and B. Katz, Measurement of current voltage relations in the membrane of the giant axon of *Loligo*, *J. Physiol.* **116**:424–448 (1952).]

Ionic conductances from ionic currents:

Rearranging Eqns. (3.26) and (3.27) gives:

$$g_{\mathsf{K}}(t) = \frac{I_{\mathsf{K}}(t)}{(V_m - E_{\mathsf{K}})}, \qquad (5.16)$$

$$g_{\mathsf{Na}}(t) = \frac{I_{\mathsf{Na}}(t)}{(V_m - E_{\mathsf{Na}})}. \qquad (5.17)$$

In the voltage clamp experiments, the denominators of Eqns. (5.16) and (5.17) are constant)

$$g_{\mathsf{K}}(t) \propto I_{\mathsf{K}}(t)\,, \quad g_{\mathsf{Na}}(t) \propto I_{\mathsf{Na}}(t)\,.$$

Ionic conductances from ionic currents (cont.):

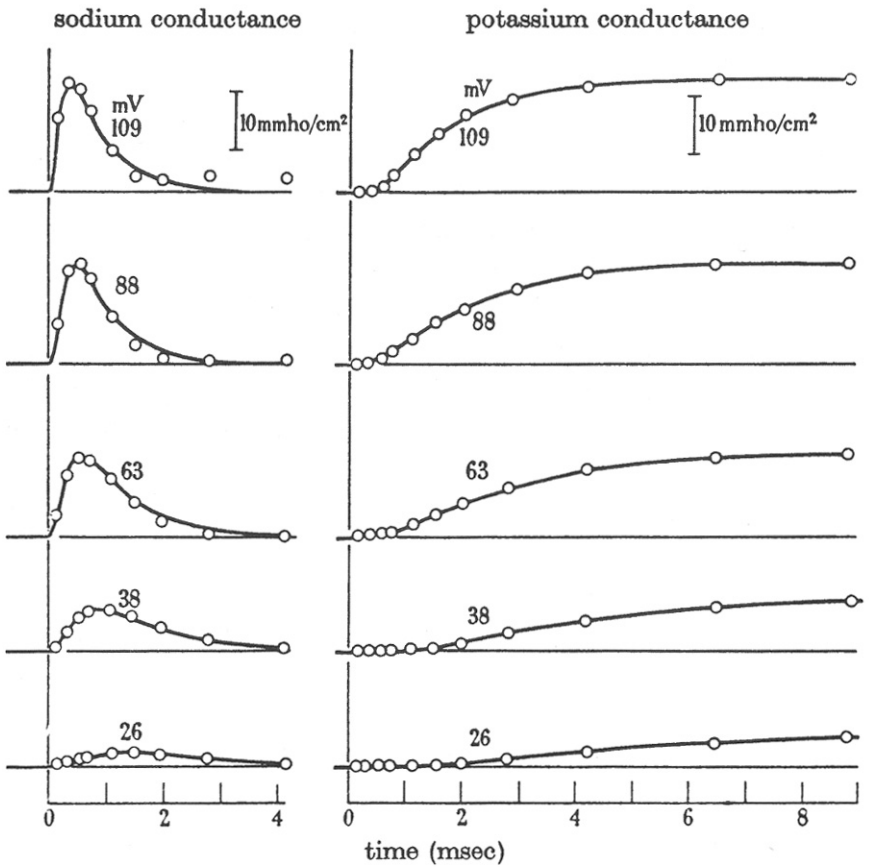

Figure 5.12. Conductance changes brought about by clamped depolarizations of different magnitudes. The circles represent values derived from the experimental measurements of ionic current, and the curves are drawn according to methods described in the text. The voltage clamp transmembrane potential values are in millivolts and are described relative to the resting value (i.e., v_m). [From A. L. Hodgkin, Ionic movements and electrical activity in giant nerve fibers, *Proc. R. Soc.* **148**:1–37 (1958). After A. L. Hodgkin and A. F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**:500–544 (1952).]

Hodgkin-Huxley equations:

Potassium channel model:

- Potassium conductance:

$$g_{\mathrm{K}}(t, v_m) = \bar{g}_{\mathrm{K}} n^4(t, v_m) \qquad (5.18)$$

- Potassium *activation* particle dynamics:

$$\frac{\mathrm{d}n(t, v_m)}{\mathrm{d}t} = \alpha_n(v_m)\,(1-n) - \beta_n(v_m)\,n \qquad (5.19)$$

or:

$$\frac{\mathrm{d}n(t, v_m)}{\mathrm{d}t} = \frac{n_\infty - n}{\tau_n} \qquad (5.22)$$

Hodgkin-Huxley equations (cont.):

- Potassium *activation* transition rates:

$$\alpha_n(v_m) = \frac{0.01\,(10 - v_m)}{\exp\left(\frac{10 - v_m}{10}\right) - 1} \qquad (5.24)$$

$$\beta_n(v_m) = 0.125 \exp\left(\frac{-v_m}{80}\right) \qquad (5.25)$$

Hodgkin-Huxley equations:

Sodium channel model:

- Sodium conductance:

$$g_{\mathrm{Na}}(t, v_m) = \bar{g}_{\mathrm{Na}} m^3(t, v_m)\, h(t, v_m) \quad (5.26)$$

- Sodium *activation* particle dynamics:

$$\frac{\mathrm{d}m(t, v_m)}{\mathrm{d}t} = \alpha_m(v_m)\,(1-m) - \beta_m(v_m)\, m \quad (5.27)$$

- Sodium *inactivation* particle dynamics:

$$\frac{\mathrm{d}h(t, v_m)}{\mathrm{d}t} = \alpha_h(v_m)\,(1-h) - \beta_h(v_m)\, h \quad (5.28)$$

Hodgkin-Huxley equations (cont.):

- Sodium *activation* transition rates:

$$\alpha_m(v_m) = \frac{0.1\,(25 - v_m)}{\exp\left(\frac{25 - v_m}{10}\right) - 1};$$

$$\beta_m(v_m) = 4\exp\left(\frac{-v_m}{18}\right) \qquad (5.36)$$

- Sodium *inactivation* transition rates:

$$\alpha_h(v_m) = 0.07\exp\left(\frac{-v_m}{20}\right);$$

$$\beta_h(v_m) = \left\{\exp\left(\frac{30 - v_m}{10}\right) + 1\right\}^{-1} \qquad (5.37)$$

Hodgkin-Huxley equations (cont.):

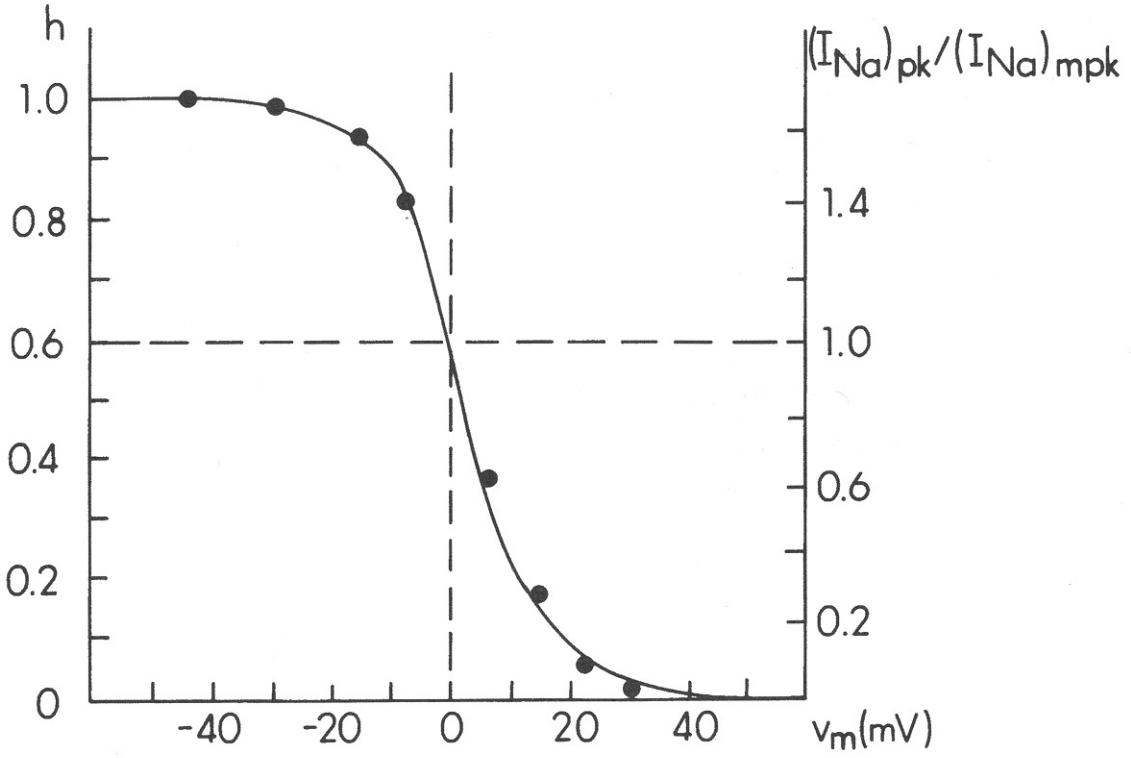

Figure 5.13. Sodium inactivation curve. Abscissa is the deviation from the resting potential (i.e., v_m). Dots are experimental points, and the smooth curve satisfies (5.33) for v_{mh} = 2.5 mV. [From A. L. Hodgkin and A. F. Huxley, The dual effect of membrane potential on sodium conductance in the giant axon of *Loligo*. *J. Physiol.* **116**:497–506 (1952).]

Hodgkin-Huxley equations (cont.):

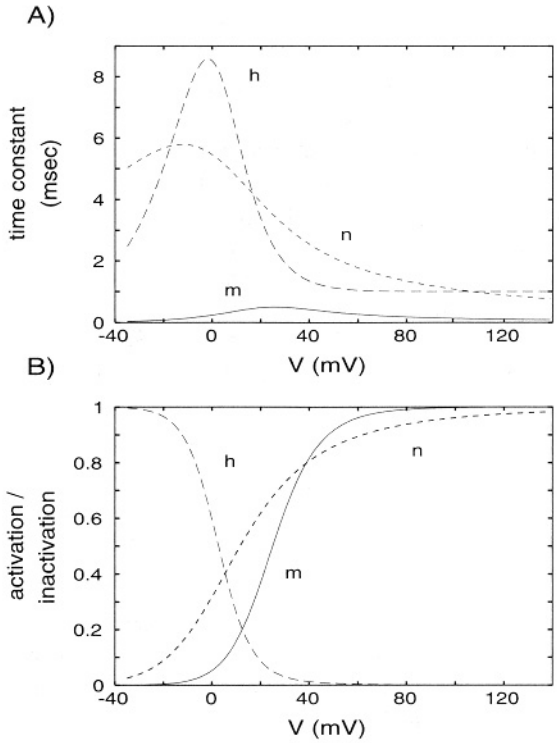

Fig. 6.3 VOLTAGE DEPENDENCY OF THE GATING PARTICLES Time constants **(A)** and steady-state activation and inactivation **(B)** as a function of the relative membrane potential V for sodium activation m (solid line) and inactivation h (long dashed line) and potassium activation n (short, dashed line). The steady-state sodium inactivation h_∞ is a monotonically decreasing function of V, while the activation variables n_∞ and m_∞ increase with the membrane voltage. Activation of the sodium and potassium conductances is a much steeper function of the voltage, due to the power-law relationship between the activation variables and the conductances. Around rest, G_{Na} increases e-fold for every 3.9 mV and G_K for every 4.8 mV. Activating the sodium conductance occurs approximately 10 times faster than inactivating sodium or activating the potassium conductance. The time constants are slowest around the resting potential.

(from Koch)