Excitability (Ch. 5 Intro)

- Regulation of membrane potential by control of the ionic channels is one of the most important cellular functions.
- Many cells, such as neurons and muscle cells use the membrane potential as a signal, and thus the operation of the nervous system and muscle contraction are both dependent on the generation and propagation of electrical signals.
- Two types of cells: excitable and nonexcitable cells
- Nonexcitable cells are the epithelial cells that line the walls of the gut. Photoreceptors are also nonexcitable. Membrane potentials are important, but no action potentials.
- Excitable cells include cardiac cells, smooth and skeletal muscle cells, most neurons. They produce action potentials.
- The most important of the past 100 years, Hodgkin and Huxley developed the first quantitative model of the propagation of an electrical signal, the most important landmark.
- The most important model in all of the physiological literature.

History of the Hodgkin-Huxley Equations (Ch. 5.1.1)

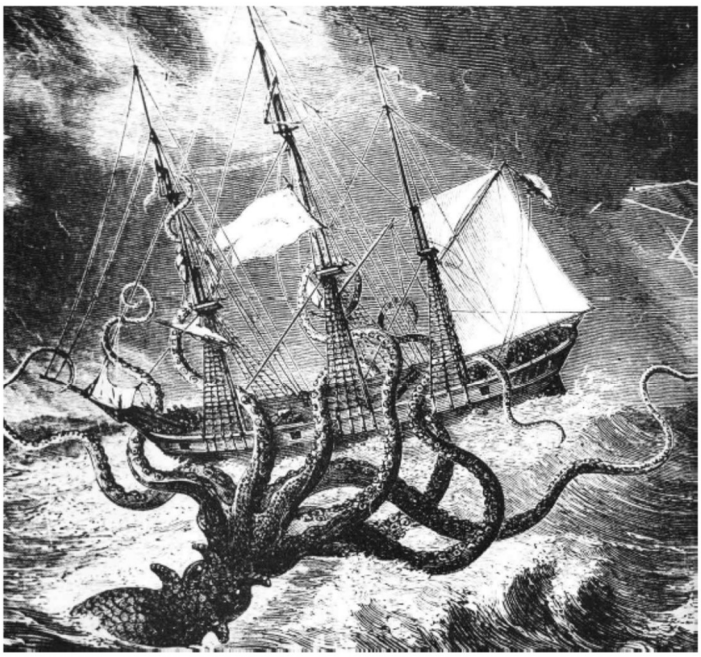


Figure 5.1 The infamous giant squid (or even octopus, if you wish to be pedantic), having nothing to do with the work of Hodgkin and Huxley on squid giant axon. From *Dangerous Sea Creatures*, © 1976, 1977 Time-Life Films, Inc.

The Hodgkin-Huxley Model (5.1)

Starts with

$$C_m \frac{dV}{dt} + I_{ion}(V,t) = 0$$

$$\mathbf{V} = \boldsymbol{V_i}\text{-}\boldsymbol{V_o}$$

- In many neural cells, the principle ionic currents are sodium and potassium currents
- The chloride current and other ionic current lumped into the leakage current

$$C_m \frac{dV}{dt} = -g_{Na}(V - V_{Na}) - g_K(V - V_K) - g_L(V - V_L) + I_{app}$$

I_{app}: applied current

- Rewrite

$$C_m \frac{dV}{dt} = -g_{eff}(V - V_{eq}) + I_{app}$$

$$g_{eff} = g_{Na} + g_K + g_L$$

$V_{eq} = (g_{Na}V_{Na} + g_K V_K + g_L V_L)/g_{eff}$, membrane resting potential

$\boldsymbol{R_m} = \mathbf{1}/g_{eff}$, membrane resistance

- Steady state

$$0 = -\frac{1}{\boldsymbol{R_m}}(V - V_{eq}) + I_{app}$$

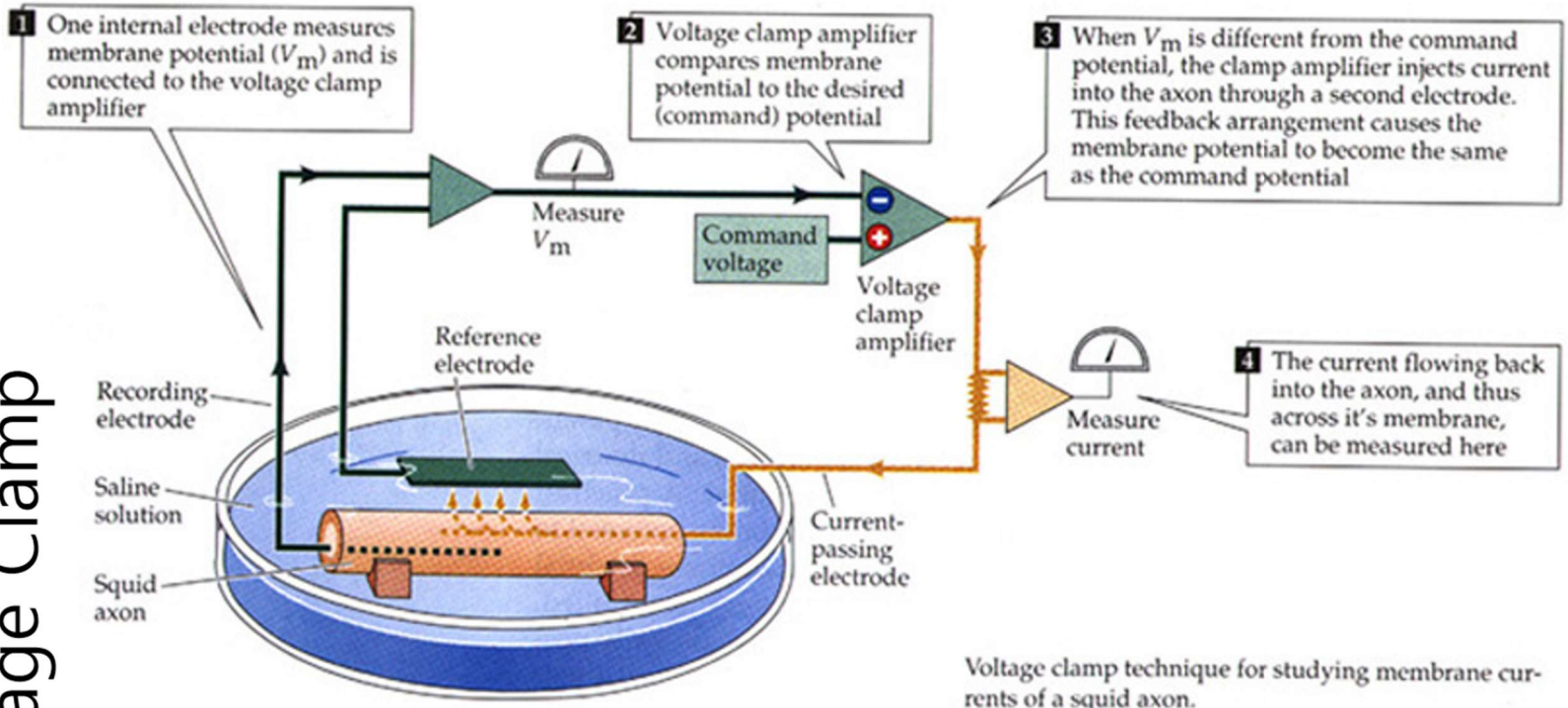
$$\frac{\boldsymbol{V}}{\boldsymbol{R_m}} = \frac{V_{eq}}{\boldsymbol{R_m}} + \ I_{app}$$

$$\mathbf{V} = V_{eq} + \boldsymbol{R_m} I_{app}$$

- Key to determine conductance was being able to measure individual ionic current. From this to deduce the changes in conductance.

- Voltage clamp techniques

Voltage Clamp



Voltage clamp technique for studying membrane currents of a squid axon.

- The **voltage clamp** is an experimental method used by electrophysiologists to measure the ion currents through the membranes of excitable cells, such as neurons, while holding the membrane voltage at a set level. A basic voltage clamp will iteratively measure the membrane potential, and then change the membrane potential (voltage) to a desired value by adding the necessary current. This "clamps" the cell membrane at a desired constant voltage, allowing the voltage clamp to record what currents are delivered. Because the currents applied to the cell must be equal to (and opposite in charge to) the current going across the cell membrane at the set voltage, the recorded currents indicate how the cell reacts to changes in membrane potential. Cell membranes of excitable cells contain many different kinds of ion channels, some of which are voltage-gated. The voltage clamp allows the membrane voltage to be manipulated independently of the ionic currents, allowing the current-voltage relationships of membrane channels to be studied. - Wikipedia

Voltage and Time Dependence of Conductance (5.1.2)

- Voltage clamp technique enables to investigate the dynamics of the conductance.
- Fig. 5.2: Experimental results of the total membrane currents
- HH used a clever trick to separate the total ionic current into its constituent ionic parts.
- Tetrodotoxin (TTX): to block sodium currents
- Tetraethylammonium (TEA): to block potassium currents
- Fig. 5.3: Samples of HH's data

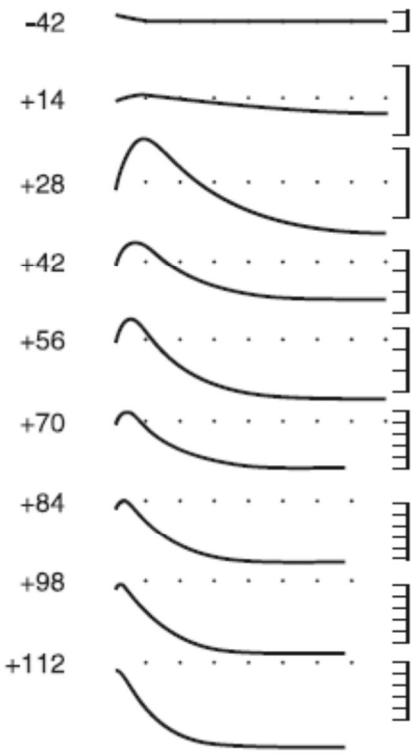


Figure 5.2 Experimental results describing the total membrane current in response to a step depolarization. The numbers on the left give the final value of the membrane potential, in mV. The interval between dots on the horizontal scale is 1 ms, while one division on the vertical scale represents 0.5 mA/cm^2. (Hodgkin and Huxley, 1952a, Fig. 2a.)

The Potassium Conductance

- Based on Fig. 5.3A and B, assume that g_k obeys some differential equation,

$$\frac{dg_k}{dt} = f(v,t)$$

v = V − V_{eq} =the membrane potential – the resting potential

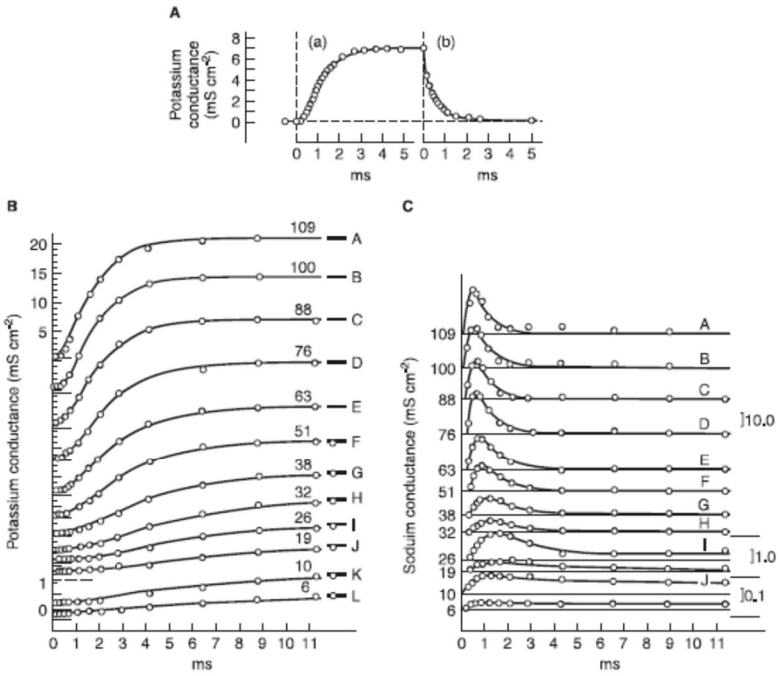


Figure 5.3 Conductance changes as a function of time at different voltage clamps. A: The response of g_K to a step increase in V and then a step decrease. B: Responses of g_K to step increases in V of varying magnitudes. The number on each curve gives the depolarization in mV, and the smooth curves are calculated from solution of (5.11) and (5.12), with the initial condition $g_K(t = 0) = 0.24$ mS/cm^2. The vertical scale is the same in curves A–J, but is increased by a factor of four in the lower two curves. For clarity, the baseline of each curve has been shifted up. C: Responses of g_{Na} to step increases in V of magnitudes given by the numbers on the left, in mV. The smooth curves are the model solutions. The vertical scales on the right are in units of mS/cm^2. (Hodgkin and Huxley, 1952d, Figs. 2, 3, and 6.)

- Assume g_k follows the sigmoidal increase and exponential decrease which can be expressed as some power of a different variable, thus

$$g_k = \overline{g_k} n^4$$

where $\overline{g_k}$ is a constant.

- The fourth power was chosen not for physiological reasons, but because it was the smallest exponent that gave acceptable agreement.
- Now the secondary variable n now obeys the differential equation

$$\tau_n(v)\frac{dn}{dt} = n_\infty(v) - n \qquad (*)$$

where $\tau_n(v)$ and $n_\infty(v)$ to be determined from the experimental data (by fitting)

- Rewrite the equation (*)

$$\frac{dn}{dt} = \alpha_n(v)(1-n) - \beta_n(v)n$$

where

$$n_\infty(v) = \frac{\alpha_n(v)}{\alpha_n(v) + \beta_n(v)}$$

$$\tau_n(v) = \frac{1}{\alpha_n(v) + \beta_n(v)}$$

- n(t) is called potassium activation.
- As v changes from 0 to v_0, solution for (*) becomes

$$\mathrm{n(t)} = n_\infty(v_0)[1 - \exp\left(\frac{-t}{\tau_n(v_0)}\right)]$$

  It is an increasing curve to the maximum $n_\infty(v_0)$. n^4 provides a sigmoidally increasing curve for g_k.
- By fitting this equation, obtain $\tau_n(v)$ and $n_\infty(v)$. See Fig. 5.4.
- As v changes form v_0 to 0 (step decrease of v), the solution is

$$\mathrm{n(t)} = n_\infty(v_0)\exp(\frac{-t}{\tau_n(v_0)})$$

  now raising to the fourth power gives exponential decrease.

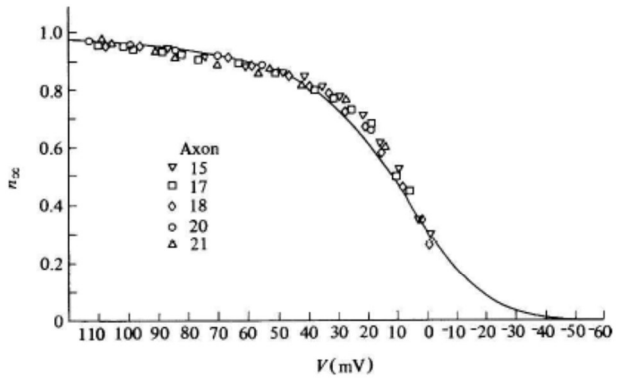


Figure 5.4 Data points (symbols) of n_∞, determined by fitting (5.16) to the experimental time courses. The smooth curve through the symbols provides a continuous description of n_∞, and its functional form has no physiological significance. In the original plot (Hodgkin and Huxley, 1952d, Fig. 5) V was calculated with a reverse sign, which has here been changed to agree with modern conventions. Thus, the horizontal axis appears reversed.

The Sodium Conductance

- The sodium conductance is in a form of

$$g_{Na}(v) = \overline{g_{Na}} m^3 h$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

where *m* is small at rest and first increases, it is called the sodium activation.
h shuts down or inactivates the sodium current. It is called the sodium inactivation.

- The unknowns α_m , β_h , α_h 및 β_h are determined by fitting to the experimental activation.
- m=sodium activation
- h=sodium inactivation

- Therefore

$$C_m \frac{dv}{dt} = -\bar{g}_k n^4 (v - v_k) - \bar{g}_{Na} m^3 h (v - v_{Na}) - \bar{g}_L (v - v_k) + I_{app}$$

$$\frac{dm}{dt} = \alpha_m(1-m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h(1-h) - \beta_h h$$

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n$$

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

$$\beta_m = 4\exp(\frac{-v}{18})$$

$$\alpha_h = 0.07\exp(\frac{-v}{20})$$

$$\beta_h = \frac{1}{\exp\left(\frac{30 - v}{10}\right) + 1}$$

$$\alpha_n = 0.01 \frac{10 - v}{\exp\left(\frac{10 - v}{10}\right) - 1}$$

$$\beta_n = 0.125\exp(\frac{-v}{80})$$

$$\bar{g}_{Na} = 120$$
$$\bar{g}_{k} = 36$$
$$\bar{g}_{L} = 0.3$$

- Now assume the sodium channel has three m gages and one h gate.
- The potassium channel has four n gates.
- Look at Fig. 5.5, 5.6.

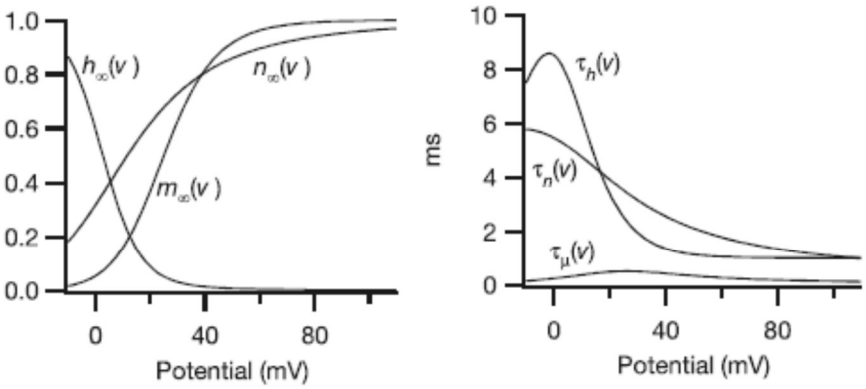


Figure 5.5 In the left panel are the steady-state functions, and in the right panel are the time constants of the Hodgkin–Huxley equations (5.20)–(5.23).

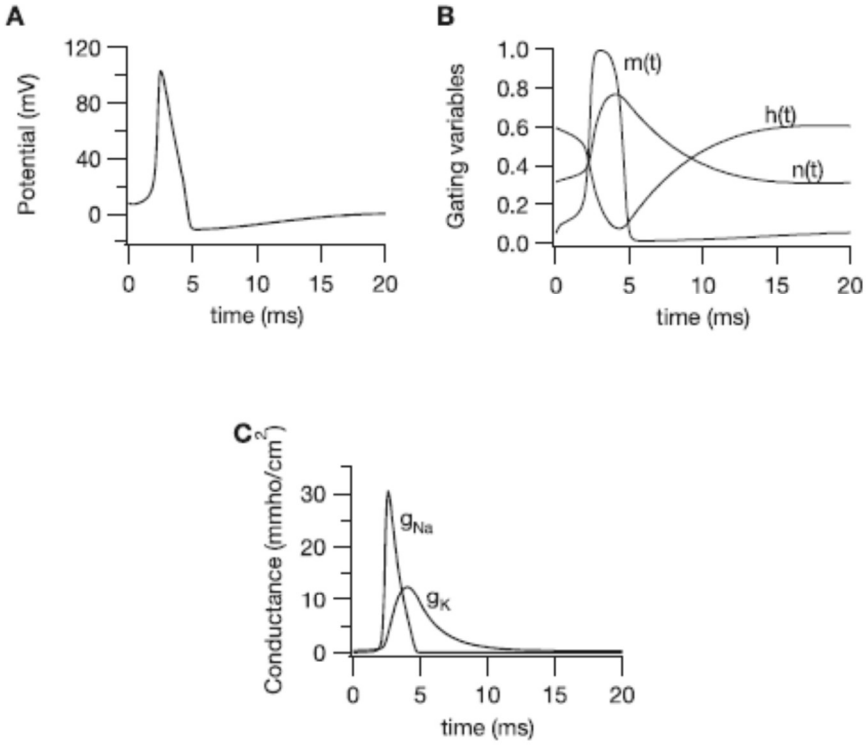


Figure 5.6 An action potential in the Hodgkin–Huxley equations. A: The action potential; B: the gating variables during an action potential, and C: the conductances during an action potential.

How to compute (summary)

1. Get $\tau_n(v)$ and $n_\infty(v)$.
   $\tau_m(v)$ and $m_\infty(v)$.
   $\tau_h(v)$ and $h_\infty(v)$. (see their shapes).

2. Compute $\mathrm{n(t)}$, $\mathrm{m(t)}$, and $\mathrm{h(t)}$ (check out the shapes).
3. Compute $g_k(t)$ and $g_{Na}(t)$ (check out the shapes.)
4. Compute $V(t)$, action potential