ELEC ENG 3BB3:

Cellular Bioelectricity

Notes for Lecture 11

Tuesday, January 28, 2013

Simulation of membrane action potential:

The complete Hodgkin–Huxley model is a parallel-conductance model incorporating:

- nonlinear (active) potassium and sodium currents:

$$I_{\mathrm{K}} = \bar{g}_{\mathrm{K}} n^4 \left(V_m - E_{\mathrm{K}}\right)$$

$$I_{\mathrm{Na}} = \bar{g}_{\mathrm{Na}} m^3 h \left(V_m - E_{\mathrm{Na}}\right),$$

- a linear (passive) "leakage" current:

$$I_L = g_L \left(V_m - E_L\right), \qquad (5.44)$$

- and a capacitive current: $I_C = C \dfrac{\mathrm{d}V_m}{\mathrm{d}t}.$

Simulation of action potential (cont.):

The total transmembrane current for the Hodgkin–Huxley model is then:

$$I_m = I_{\mathrm{K}} + I_{\mathrm{Na}} + I_L + I_C. \qquad (5.45)$$

With the equations describing the gating particle dynamics, we have one first-order nonlinear differential equation coupled with three first-order linear differential equations.

Analytical solutions are not very tractable, so in most cases it is necessary to find numerical solutions.

Simulation of action potential (cont.):

Eq. (5.45) can be illustrated schematically as:

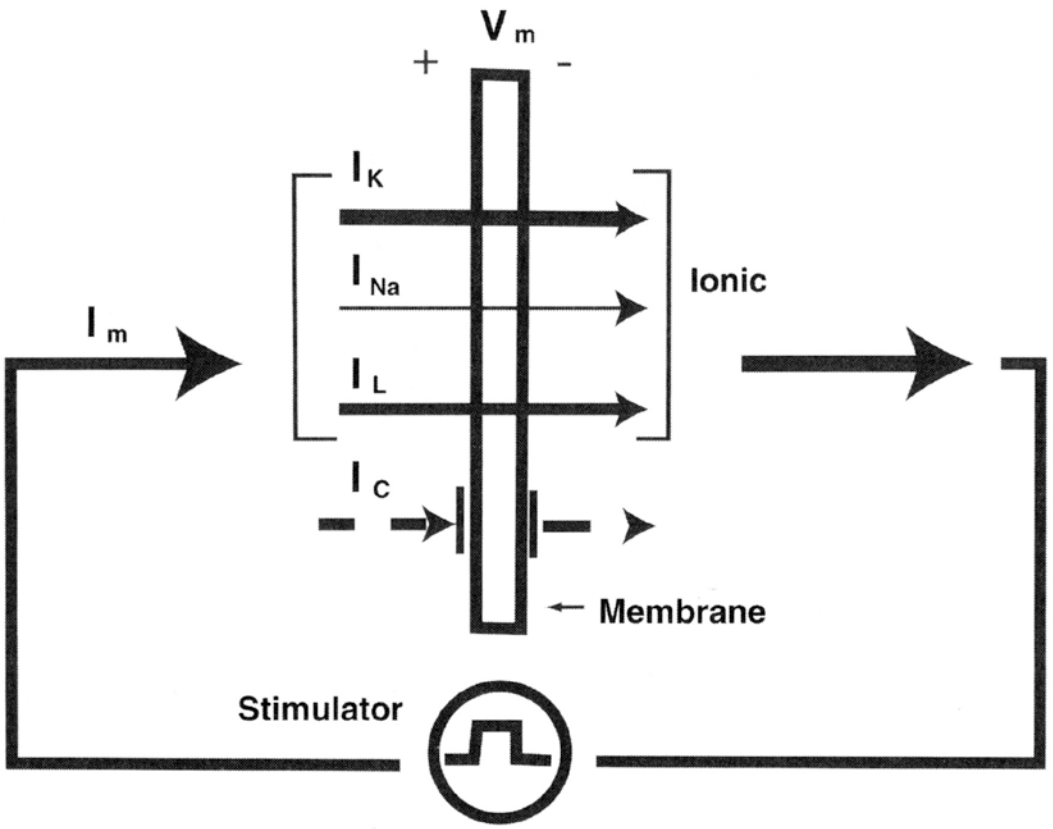


Figure 5.14. Membrane Voltage Change Due to Stimulus. The Figure shows a cartoon of a stimulator as it imposes total current I_m across a membrane (rectangle). The current from the stimulator divides into the components given by Eq. (5.47), including the ionic currents I_{K}, I_{Na}, and I_L. The remaining current is capacitive current I_C, shown as a dashed line. As I_C charges the membrane capacitance it modifies the transmembrane voltage V_m.

Simulation of action potential (cont.):

- Hodgkin and Huxley had assistants doing numerical solutions by hand – not much fun!
- Matlab has a set of numerical ODE solvers.
- Software packages for simulating neurons include:
  - HHsim: Graphical Hodgkin–Huxley Simulator
  - NEURON: For computer simulations of neurons and neural networks
  - The GEneral NEural SImulation System (GENESIS)

Simulation of action potential (cont.):

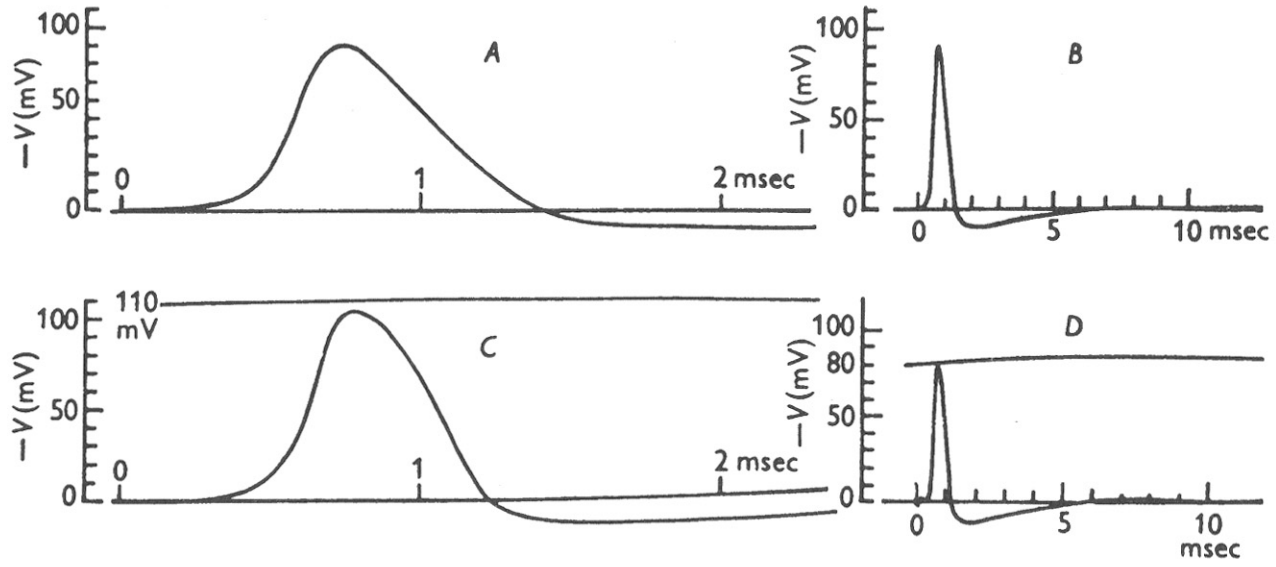


Figure 5.14. Curve A is the computed (propagated) action potential. Curve B is the same result to a slower time scale. Curves C and D are measured from different axons. [From A. L. Hodgkin and A. F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve, *J. Physiol.* **117**:500–544 (1952).]

(from Plonsey and Barr, 2nd Edition)

Action potential characteristics:

The characteristics of action potentials can be interpreted in terms of:

- how the ionic and capacitive currents vary as a function of time, membrane potential and injected current,

The behaviour of the ionic currents is understood in terms of:

- voltage-dependent channel gating, i.e., the dynamics of activation and inactivation particles.

Action potential characteristics (cont.):

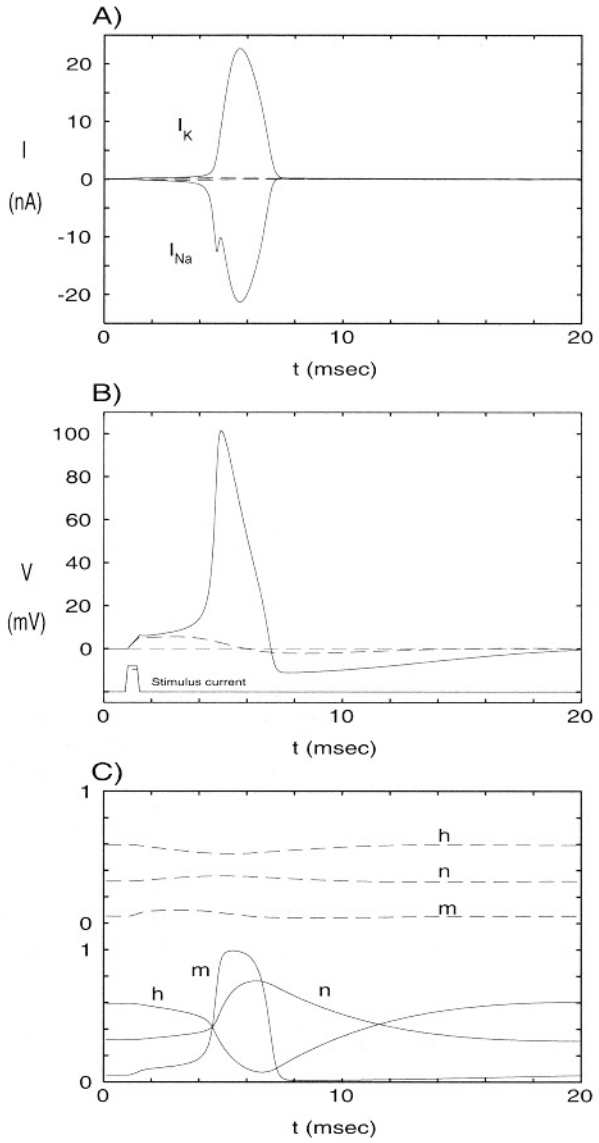


Fig. 6.5 HODGKIN-HUXLEY ACTION POTENTIAL Computed action potential in response to a 0.5-msec current pulse of 0.4-nA amplitude (solid lines) compared to a subthreshold response following a 0.35-nA current pulse (dashed lines). **(A)** Time course of the two ionic currents. Note their large sizes compared to the stimulating current. **(B)** Membrane potential in response to threshold and subthreshold stimuli. The injected current charges up the membrane capacity (with an effective membrane time constant $\tau = 0.85$ msec), enabling sufficient I_{Na} to be recruited to outweigh the increase in I_K (due to the increase in driving potential). The smaller current pulse fails to trigger an action potential, but causes a depolarization followed by a small hyperpolarization due to activation of I_K. **(C)** Dynamics of the gating particles. Sodium activation m changes much more rapidly than either h or n. The long time course of potassium activation n explains why the membrane potential takes 12 msec after the potential has first dipped below the resting potential to return to baseline level.

(from Koch)

Strength-duration behaviour:

For a finite-duration current pulse, the strength of the stimulating current required to just elicit one action potential is characterized by a *strength-duration curve*.

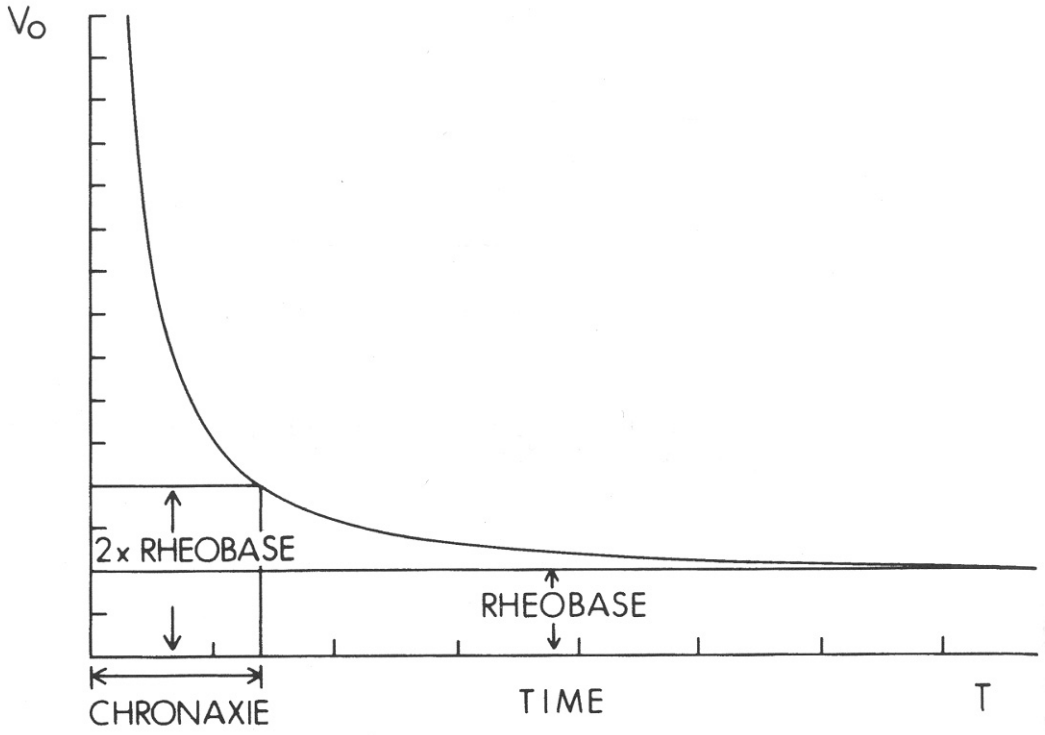


Figure 7.3. Strength–duration curve [from Eq. 7.5)].

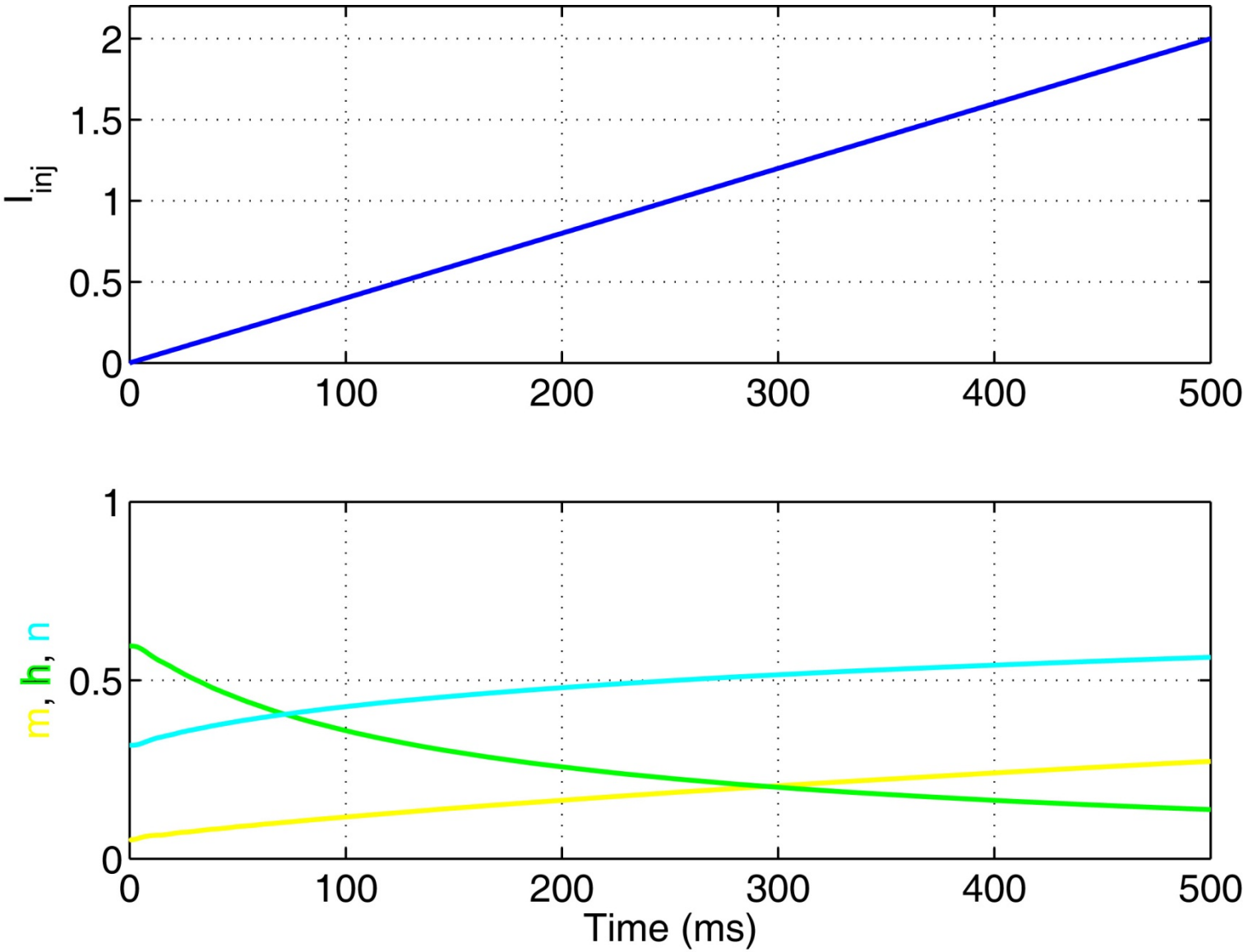
Accommodation:

Very slow changes in the membrane potential allow sodium inactivation and potassium activation to overcome sodium activation.

Consequently, the cell may not spike, even though the nominal threshold potential (i.e., in the case of a rapid depolarization) has been reached.

Any definition of a “threshold potential” is therefore restricted to a particular stimulus.

Accommodation (cont.):



Anode break excitation:

Sodium deinactivation and potassium deactivation can give rise to an action potential at the offset of a hyperpolarizing pulse. This is referred to as "*anode break*" *excitation*.

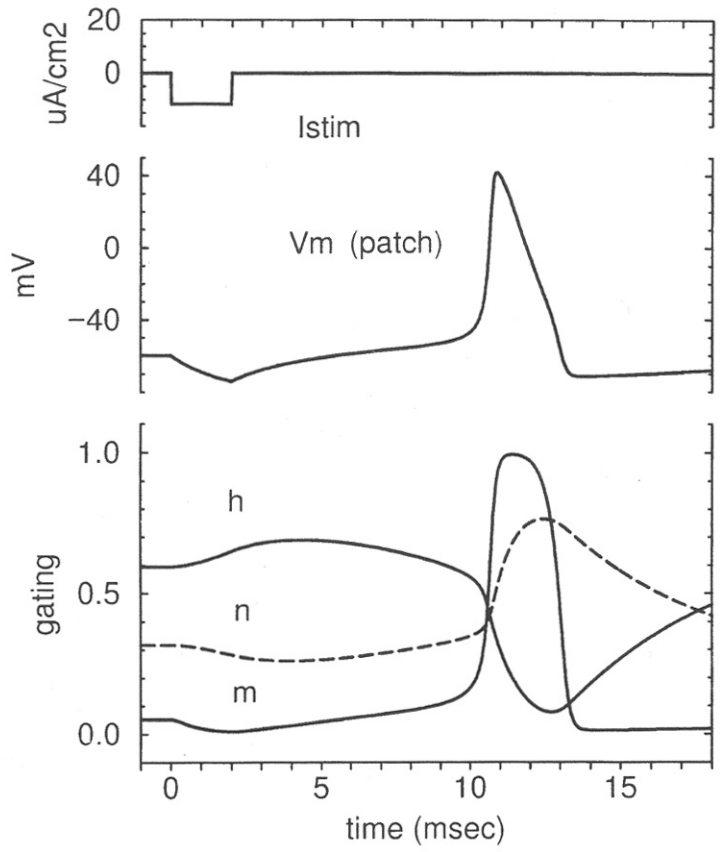


Figure 5.17. Anode break excitation. Computed values of m, n, h, and V_m from Hodgkin–Huxley equations. Space-clamped conditions. Values are computed during and after a 2 msec–11.7 μa/cm^2 hyperpolarizing pulse which starts at $t = 0$. The resting potential is –60 mV and the temperature is T = 6.3°C.

Repetitive firing:

Injection of a sustained suprathreshold current gives rise to repetitive firing, illustrating the regenerative nature of spiking.

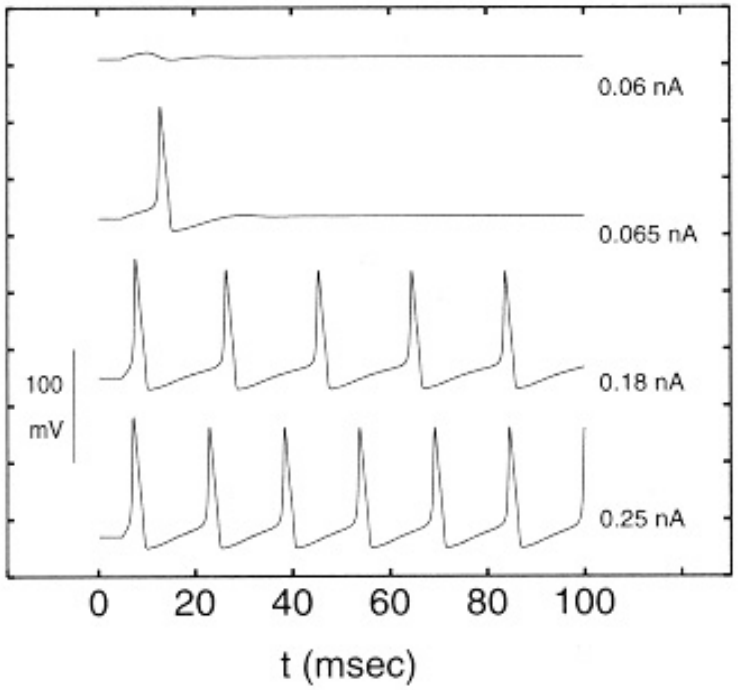


Fig. 6.8 REPETITIVE SPIKING Voltage trajectories in response to current steps of various amplitudes in the standard patch of squid axonal membrane. The minimum sustained current necessary to initiate a spike, termed *rheobase*, is 0.065 nA. In order for the membrane to spike indefinitely, larger currents must be used. Experimentally, the squid axon usually stops firing after a few seconds due to secondary inactivation processes not modeled by the Hodgkin–Huxley equations (1952d).

(from Koch)

Refractory effects:

- After the generation of an action potential it is impossible to generate another action potential with injected current of feasible magnitude within a certain time period. This is referred to as the *absolute refractory period*.
- For some time following the absolute refractory period the injected current required to reach threshold is greater than is necessary when the membrane is at rest. This is referred to as the *relative refractory period*.

Refractory effects (cont.):

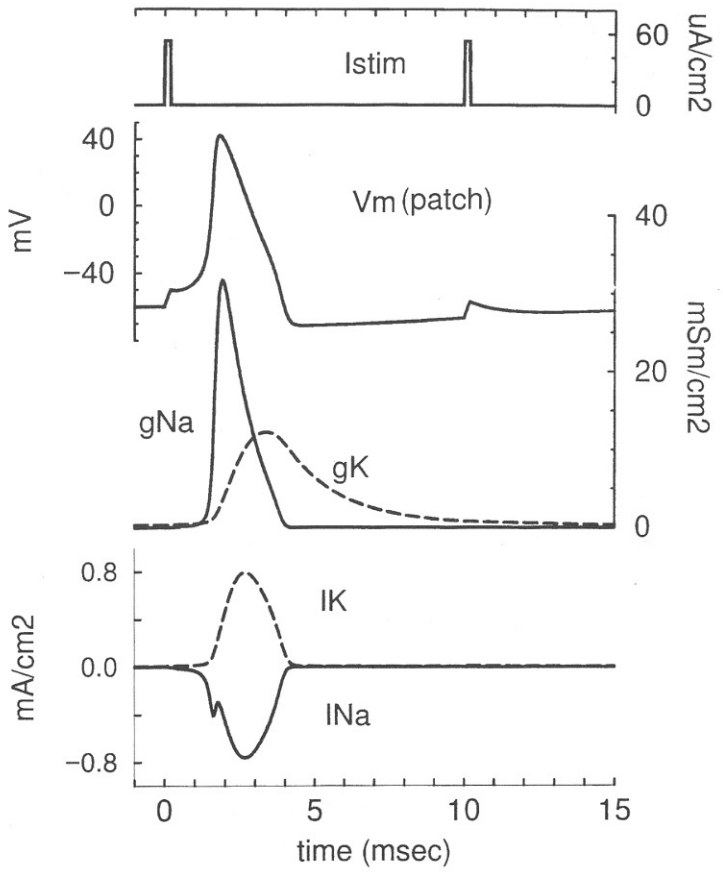


Figure 5.15. Calculated changes in membrane potential (upper curve), sodium and potassium conductances (middle curves), and sodium and potassium currents; all curves are for a squid giant axon membrane patch. The second stimulus is seen to elicit essentially no response even though it is of the same size and duration as the first (for which an action potential results, as is seen). It therefore identifies the condition as refractory. Since a larger stimulus would generate an action potential this is a *relatively refractory* period. The stimulus amplitude is 53 μa/cm^2 and its duration is 0.2 msec. The second stimulus is similar in amplitude and duration and occurs after a delay of 15 msec. The resting potential is –60 mV while $T = 6.3°C$. Calculations were based on the Hodgkin–Huxley equations.

Refractory effects (cont.):

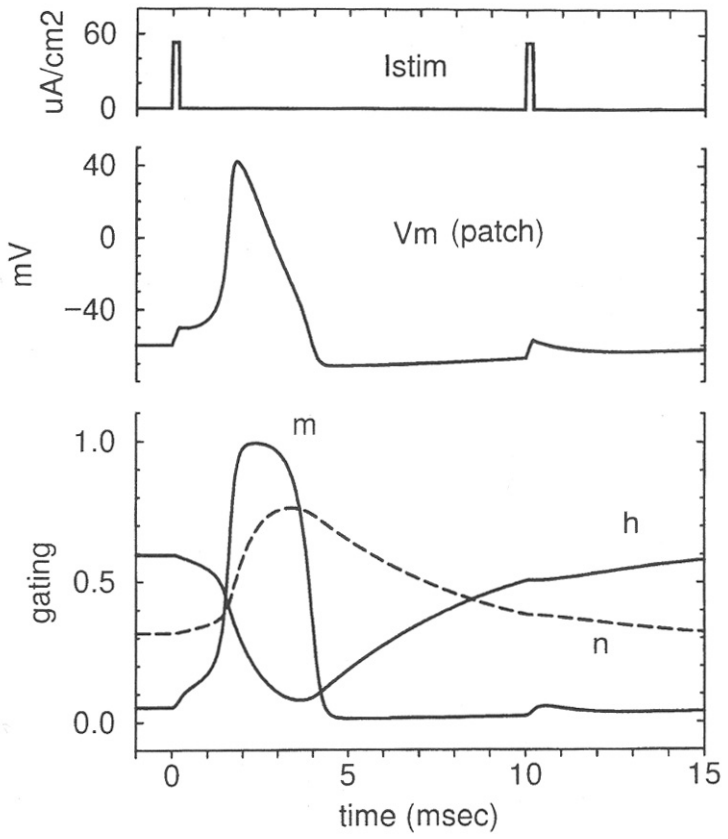


Figure 5.16. Computed membrane action potential using the Hodgkin–Huxley equations. In addition to the temporal variation of $V_m(t)$, the gating variables temporal behavior [i.e., $m(t), n(t), h(t)$] are shown. In this simulation resting $v_m = -60$ mV, while the stimulus current starting at $t = 0$ is 53 μa/cm^2 for 0.2 msec. The temperature is 6.3°C.

Refractory effects (cont.):

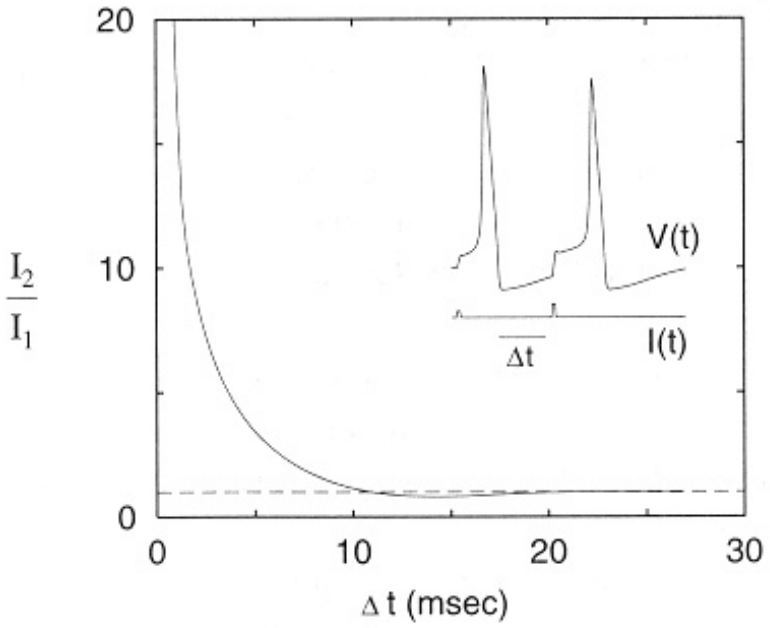


Fig. 6.7 Refractory Period A 0.5-msec brief current pulse of $I_1 = 0.4$ nA amplitude causes an action potential (Fig. 6.5). A second, equally brief pulse of amplitude I_2 is injected Δt msec after the membrane potential due to the first spike having reached $V = 0$ and is about to hyperpolarize the membrane. For each value of Δt, I_2 is increased until a second spike is generated (see the inset for $\Delta t = 10$ msec). The ratio I_2/I_1 of the two pulses is here plotted as a function of Δt. For several milliseconds following repolarization, the membrane is practically inexcitable since such large currents are unphysiological (*absolute refractory period*). Subsequently, a spike can be generated, but it requires a larger current input (*relative refractory period*). This is followed by a brief period of reduced threshold (hyperexcitability). No more interactions are observed beyond about $\Delta t = 18$ msec.

(from Koch)