Voltage-clamp and Hodgkin-Huxley models

Read:

Hille, Chapters 2-5 (best)
Koch, Chapters 6, 8, 9

See also

Clay, *J. Neurophysiol*. 80:903-913 (1998)
(for a recent version of the HH squid axon model)
Rothman and Manis, *J. Neurophysiol*. 89:3070, 3083 and 3097 (2003) for examples of separation of currents by voltage clamp.

Ion channel properties:

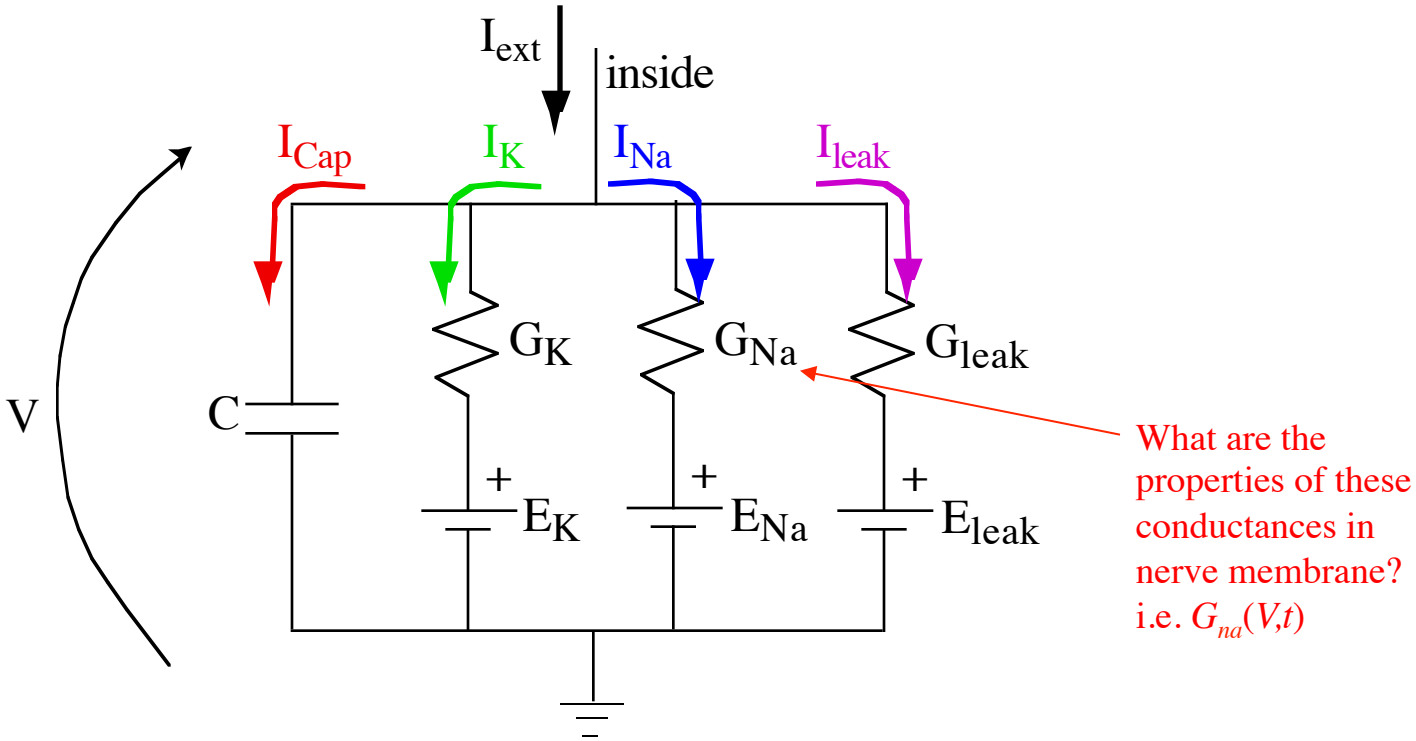
- Selectivity
- Rectification
- Saturation and block by toxins and other ions
- Gating
  - voltage-gating (Hille chapts. 3-5)
  - ligand-gating (Hille chapt. 6-7)
  - sensory (Hille chapt. 8)

today

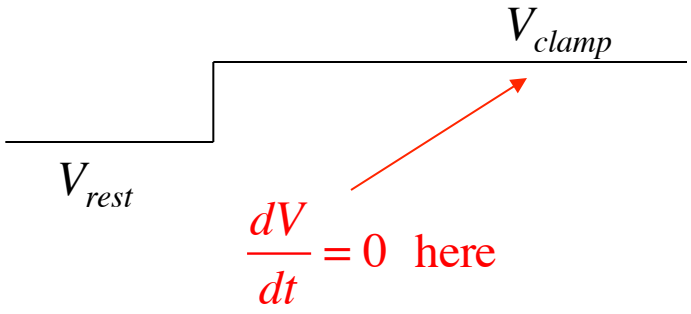
The membrane model (parallel currents through all the channels present):

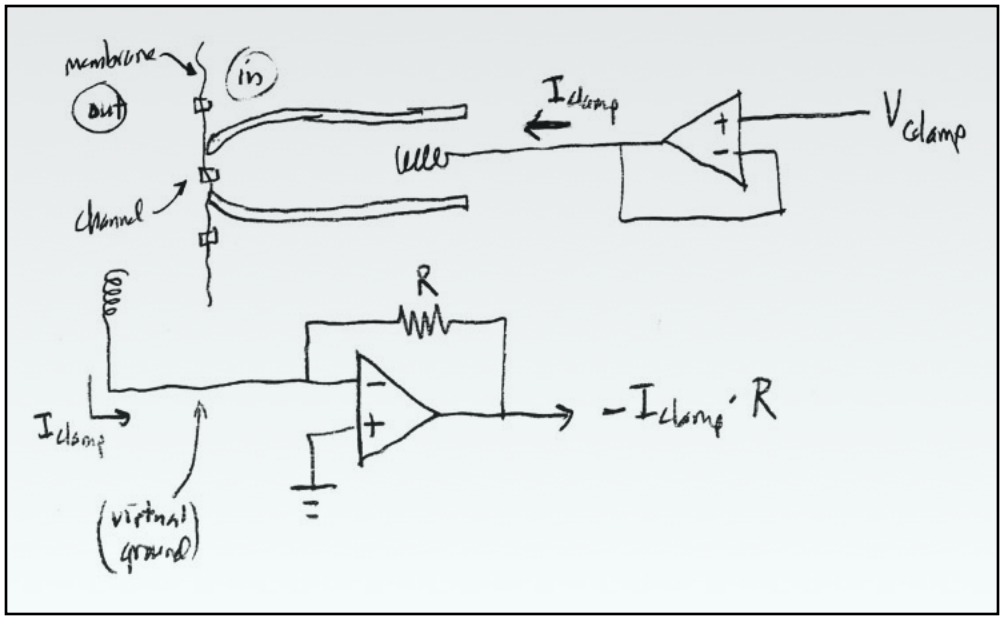
$$I_{cap} + I_K + I_{Na} + I_{leak} = I_{ext}$$

$$C\frac{dV}{dt} = I_{ext} - G_K(V - E_K) - G_{Na}(V - E_{Na}) - G_{leak}(V - E_{leak})$$



To separate the currents for study, first the capacitive current is eliminated using *voltage clamp*. A step of current I_{clamp} is applied to force the membrane potential to adopt a constant value V_{clamp}.





$$C\frac{dV}{dt} = I_{clamp} - G_K(V - E_K) - G_{Na}(V - E_{Na}) - G_{leak}(V - E_{leak})$$

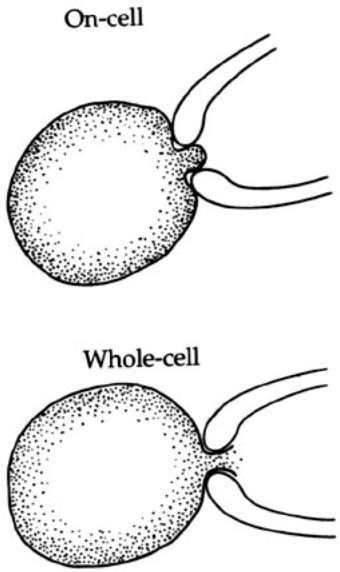
($\frac{dV}{dt} = 0$)

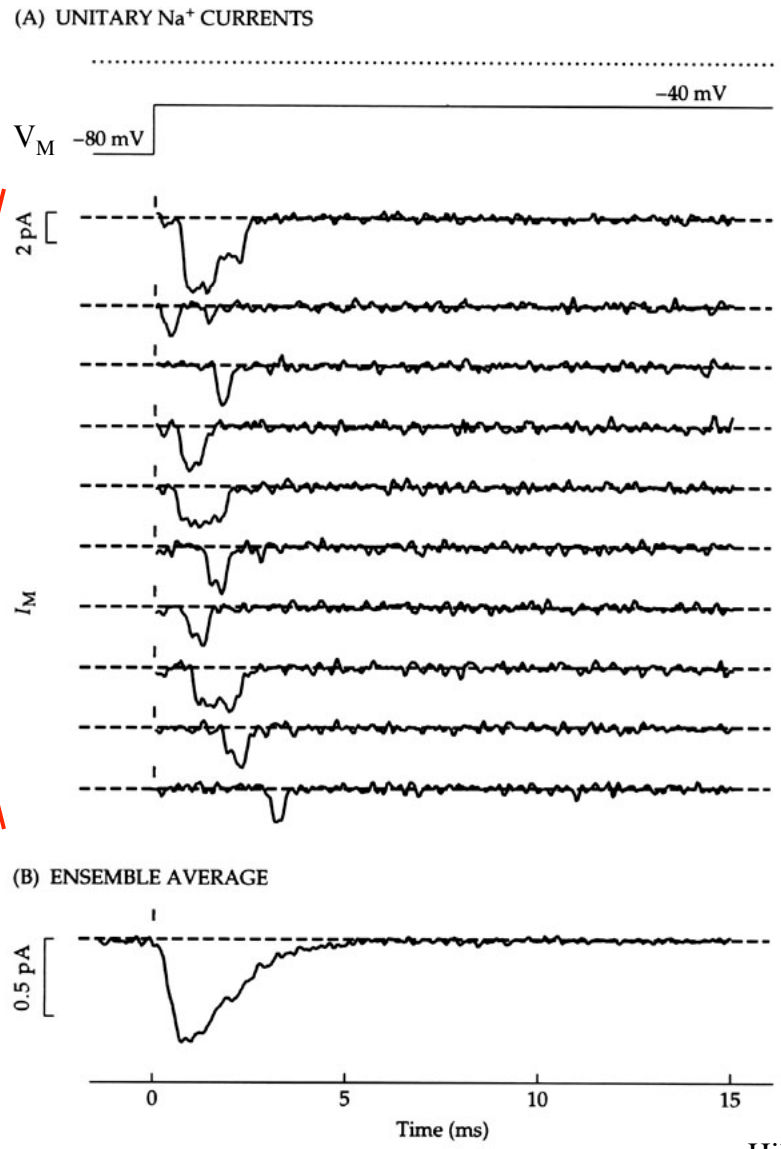
so $$I_{clamp} = G_K(V - E_K) + G_{Na}(V - E_{Na}) + G_{leak}(V - E_{leak})$$

Recording from single channels and ensembles of channels using voltage-clamp: single channels gate randomly, whole cell currents are the sum of the single-channel currents and behave smoothly.

$$I_{\text{whole cell}} = \sum_{j} i_{\text{jth channel}}$$

$$I_{\text{whole cell}} \approx N\, i_{\text{single channel}}\, P_{open}(V, t, \cdots)$$





(small capacitive transients at the time of the voltage step are subtracted out)

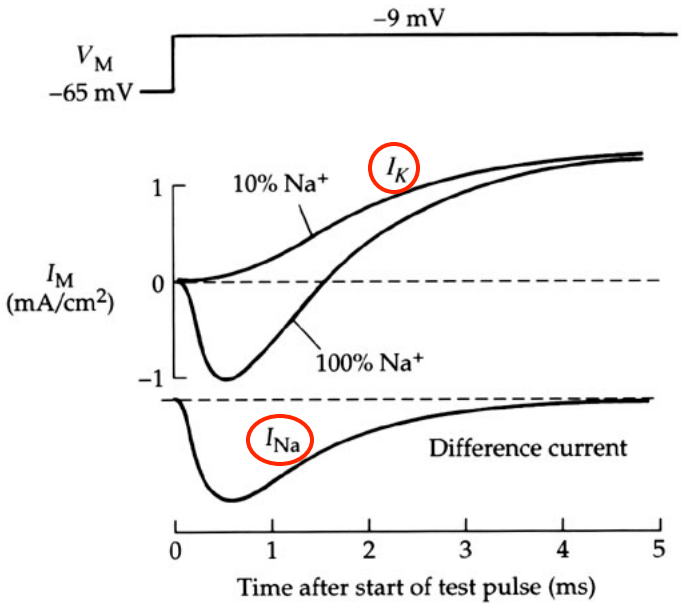
Hille, p. 90

Voltage clamp in the squid giant axon membrane from the original work of Hodgkin and Huxley.

The trace "100% Na^+" is the recording in normal solutions. This is a mixture of inward Na currents and outward K currents.

The currents are separated by setting the extracellular Na to 10% of its normal value, effectively eliminating the inward current and revealing the K current (I_K).

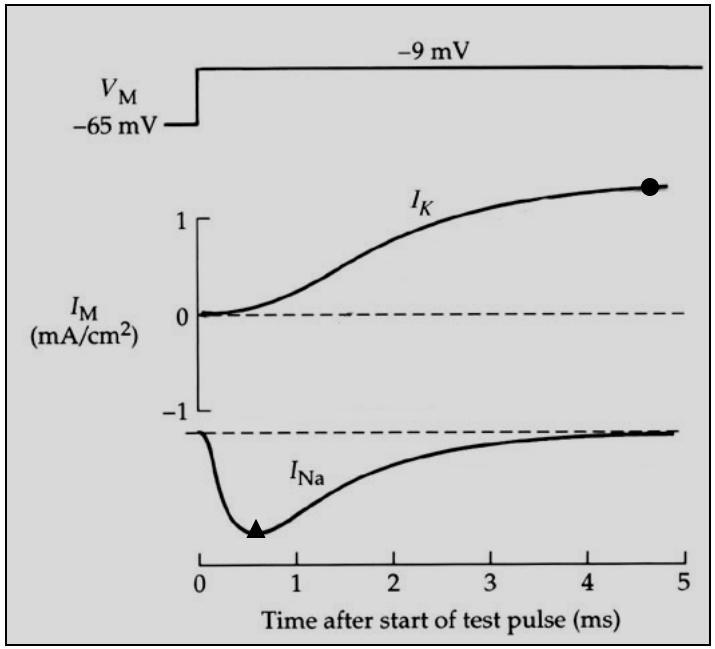
The difference of the 100% and 10% currents is the Na current (I_{Na}).

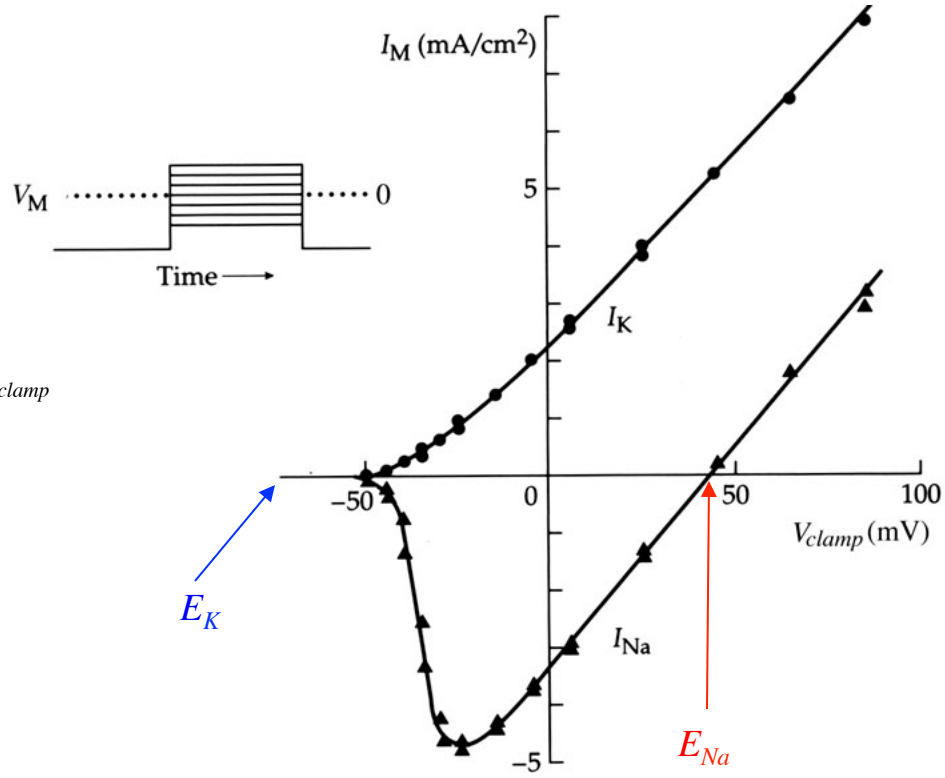


Current-voltage relationships for the HH sodium and potassium channels.

$$I_K = G_K(V,t)\cdot(V - E_K) \quad \text{and} \quad I_{Na} = G_{Na}(V,t)\cdot(V - E_{Na})$$

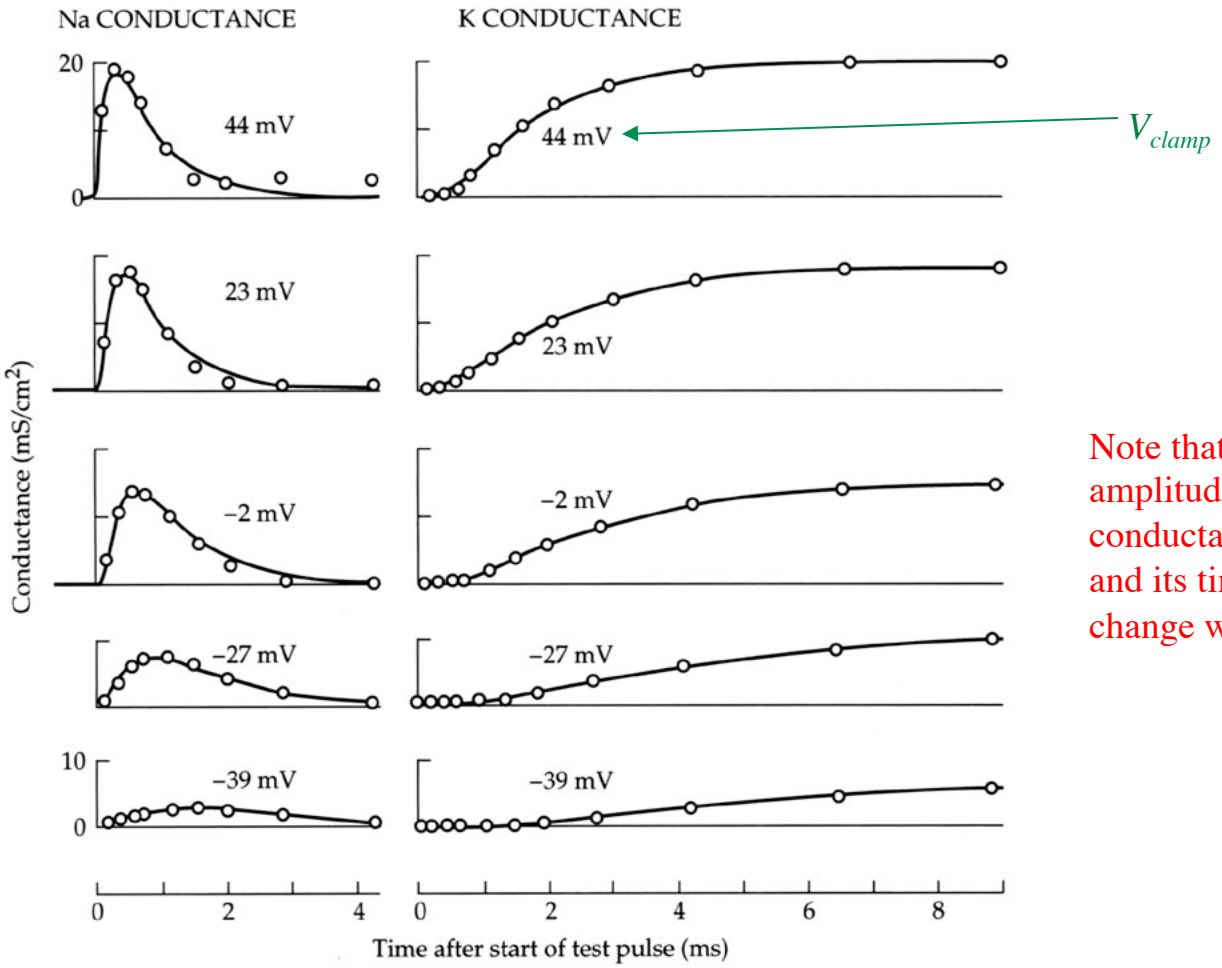
From these data, the conductances G_K and G_{Na} can be computed . . .





Hille, p. 39

. . . yielding the following dependence of conductance on time and V_{clamp}



Note that both the amplitude of the conductance change and its time constant change with V_{clamp}

With the data shown in previous slides in hand, Hodgkin and Huxley modeled the conductances by assuming them to be proportional to one or two *activation* and *inactivation* variables, representing the fraction of gates that are open. In the case of the K conductance, only activation n is needed.

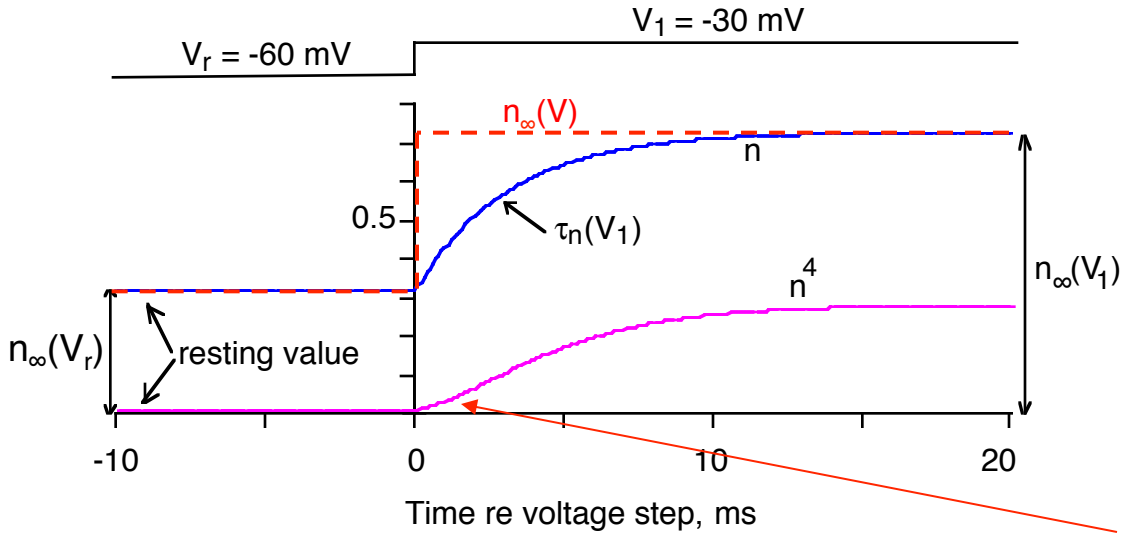
$$G_K = \bar{G}_K\, n^4(V,t)$$

$$\frac{dn}{dt} = \frac{n_\infty(V_1) - n}{\tau_n(V_1)}$$

assuming that $\quad n(0) = n_\infty(V_r)$

$$n(t) = n_\infty(V_r) + \left[n_\infty(V_1) - n_\infty(V_r)\right]\left[1 - \exp\left(-t/\tau_n(V_1)\right)\right]$$

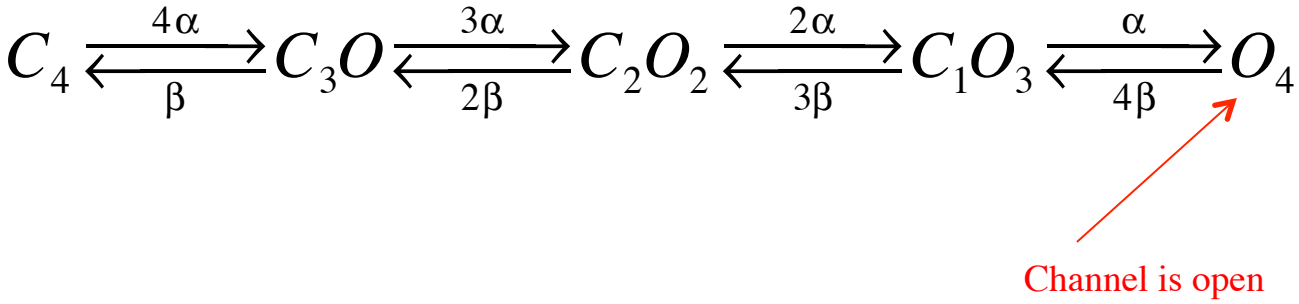
The behavior of G_K is determined by functions $n_\infty(V)$ and $\mathtt{t}_n(V)$.



The exponent 4 is chosen to make the rise of G_K sigmoidal.

An interpretation of the HH potassium channel model:

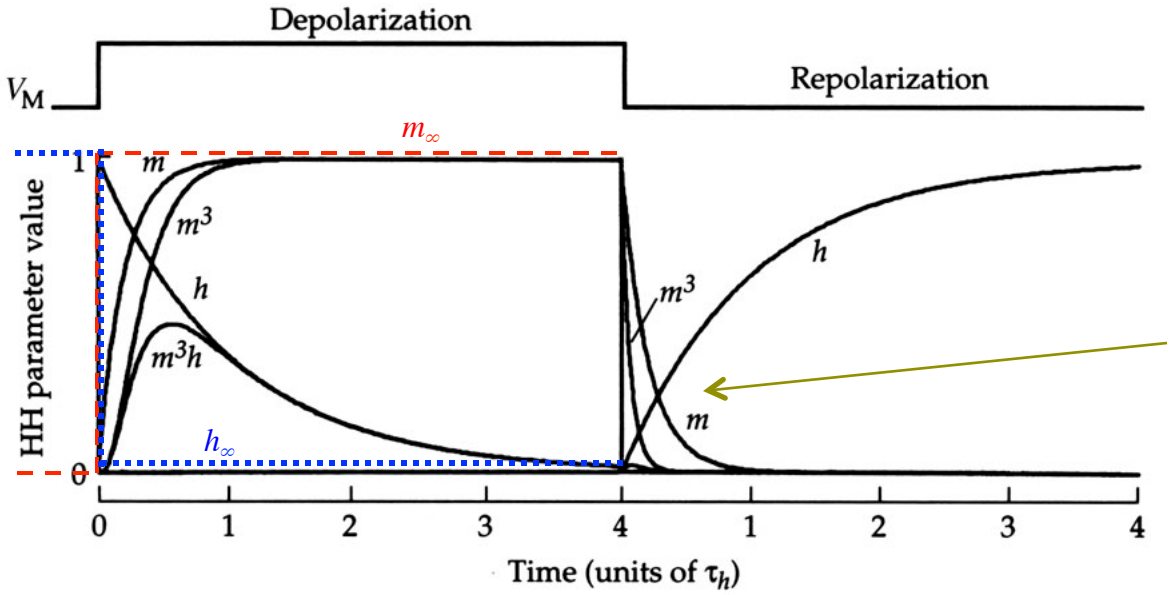
Recall that the potassium channel has 4 subunits. If each subunit has an independent gate and the probability that any one gate is open is n then the probability that all 4 gates are open (i.e. the channel is open) is n^4.



For Na, an activation variable *m* and an inactivation variable *h* are needed. The former is a gate that opens with depolarization and the latter is a gate that closes with depolarization.

$$G_{Na} = \bar{G}_{Na} m^3 h$$

$$\frac{dm}{dt} = \frac{m_\infty(V) - m}{\tau_m(V)} \quad \text{and} \quad \frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)}$$

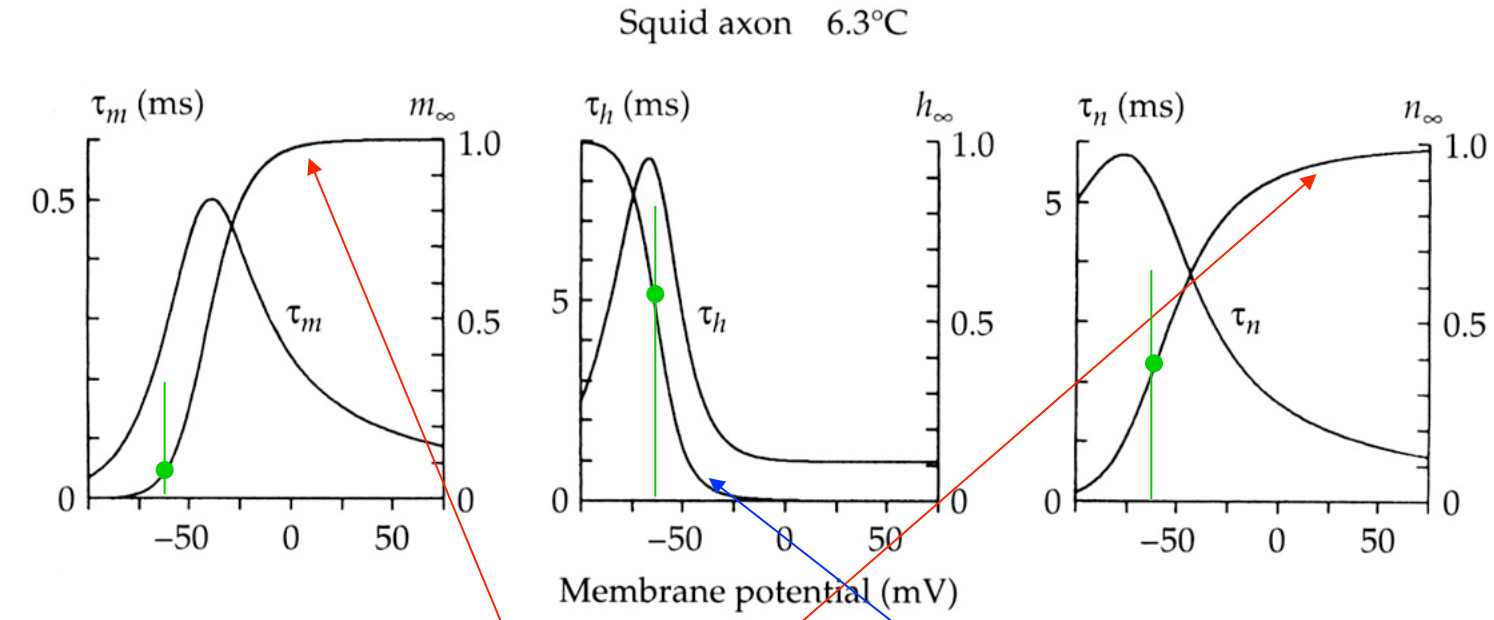


tail current

9/21/2011
#10

Hille, p. 48

The functions $n_\infty(V)$, $m_\infty(V)$, and $h_\infty(V)$ determine whether gates serve to activate channels (conventionally, open the channel with depolarization) or inactivate the channel (close the channel with depolarization). τ_m, τ_h, and τ_n are the time constants. These shapes are expected from a barrier model of gating (see Homework).



resting potential

the *m* and *n* gates open with depolarization

the *h* gate closes with depolarization

Reconstruction of the action potential by the HH model :

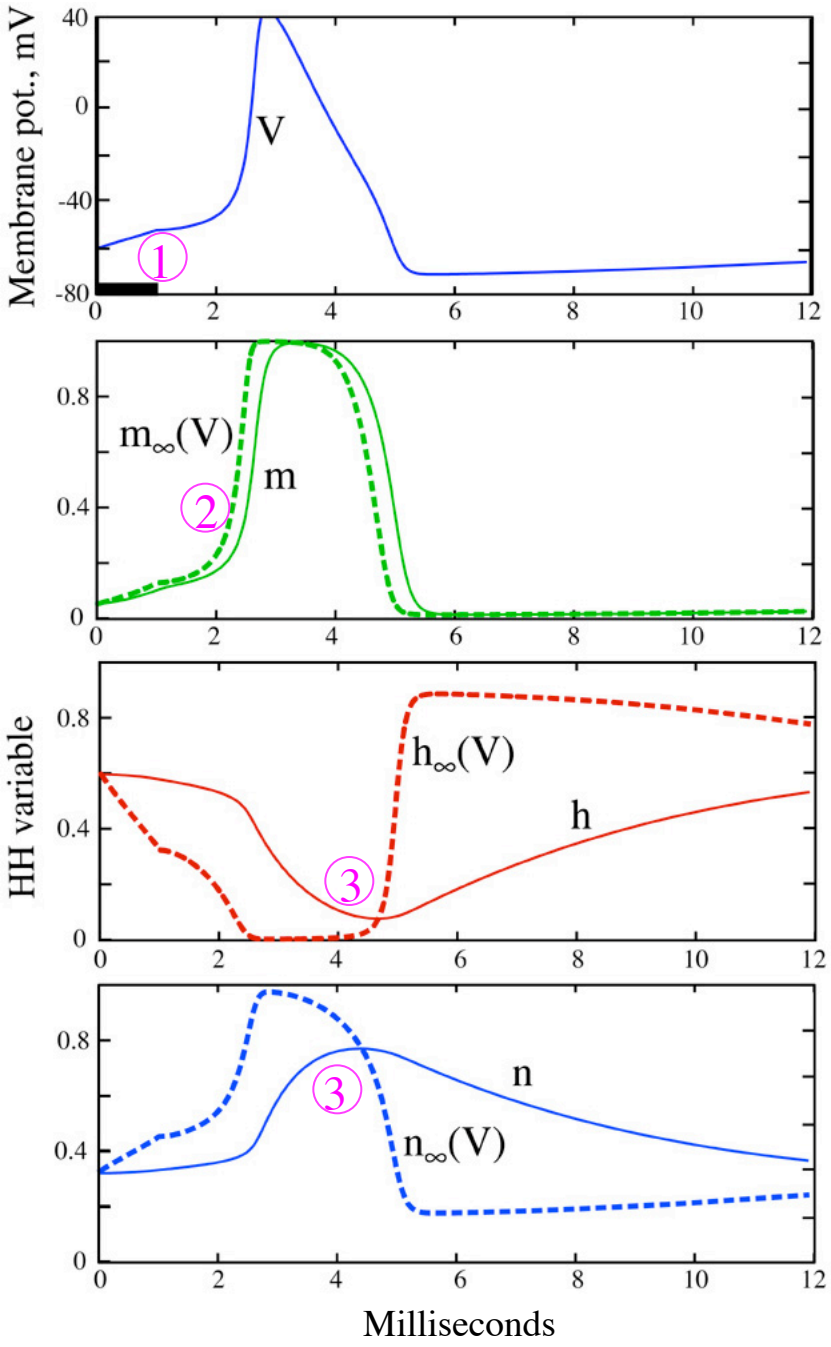
① Depolarization of the cell (by an injected current in this case) leads to

② a self-sustaining increase in $m_\infty(V)$, m, I_{Na}, and V, which leads to

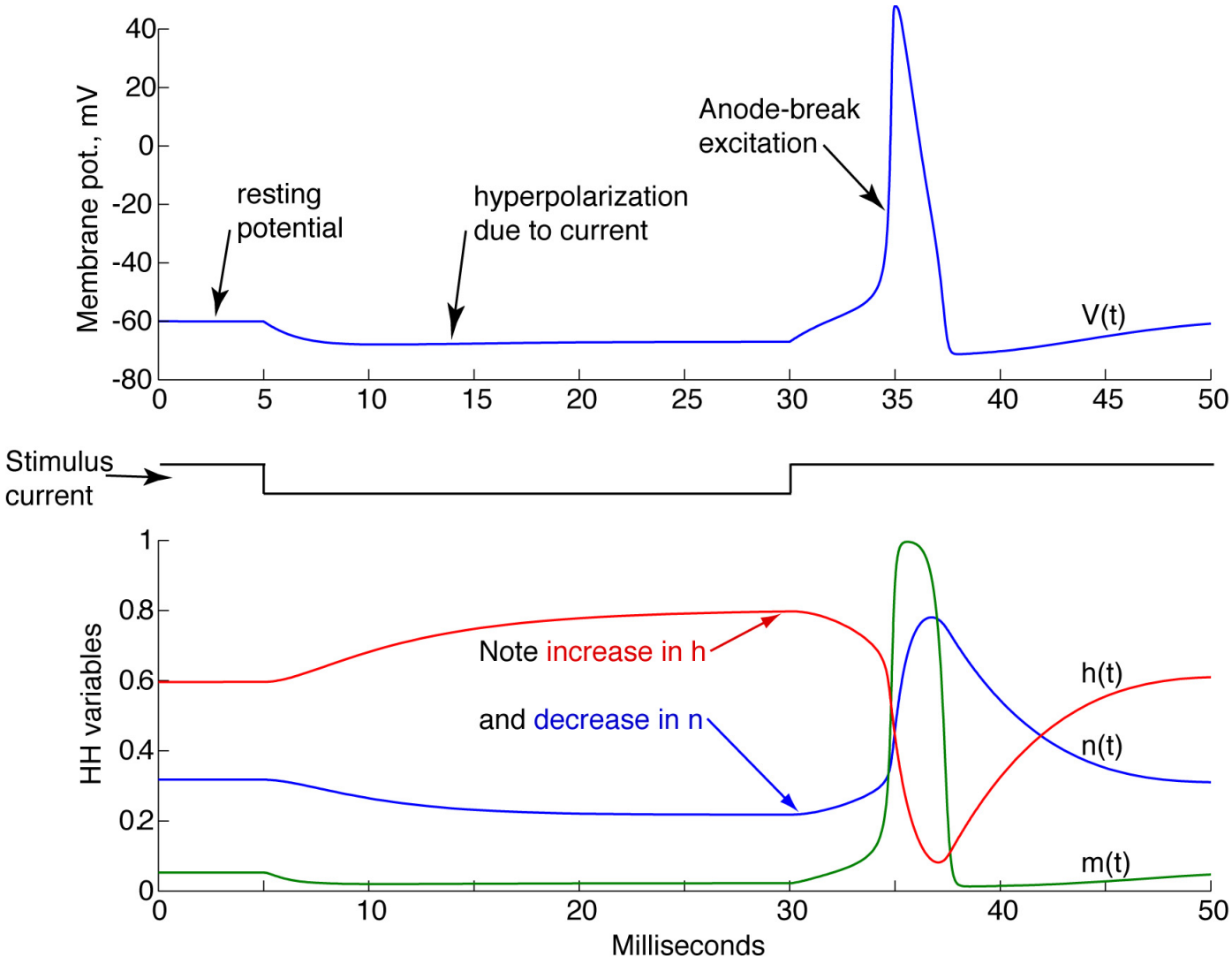
③ a decrease in $h_\infty(V)$ and an increase in $n_\infty(V)$. The resulting decrease in h and increase in n terminate the action potential and repolarize the membrane.

Note the difference in the response times of m (fast) versus n and h (slow).

(AP produced by a 1 ms, 9 mA current pulse at the heavy bar in the V plot)



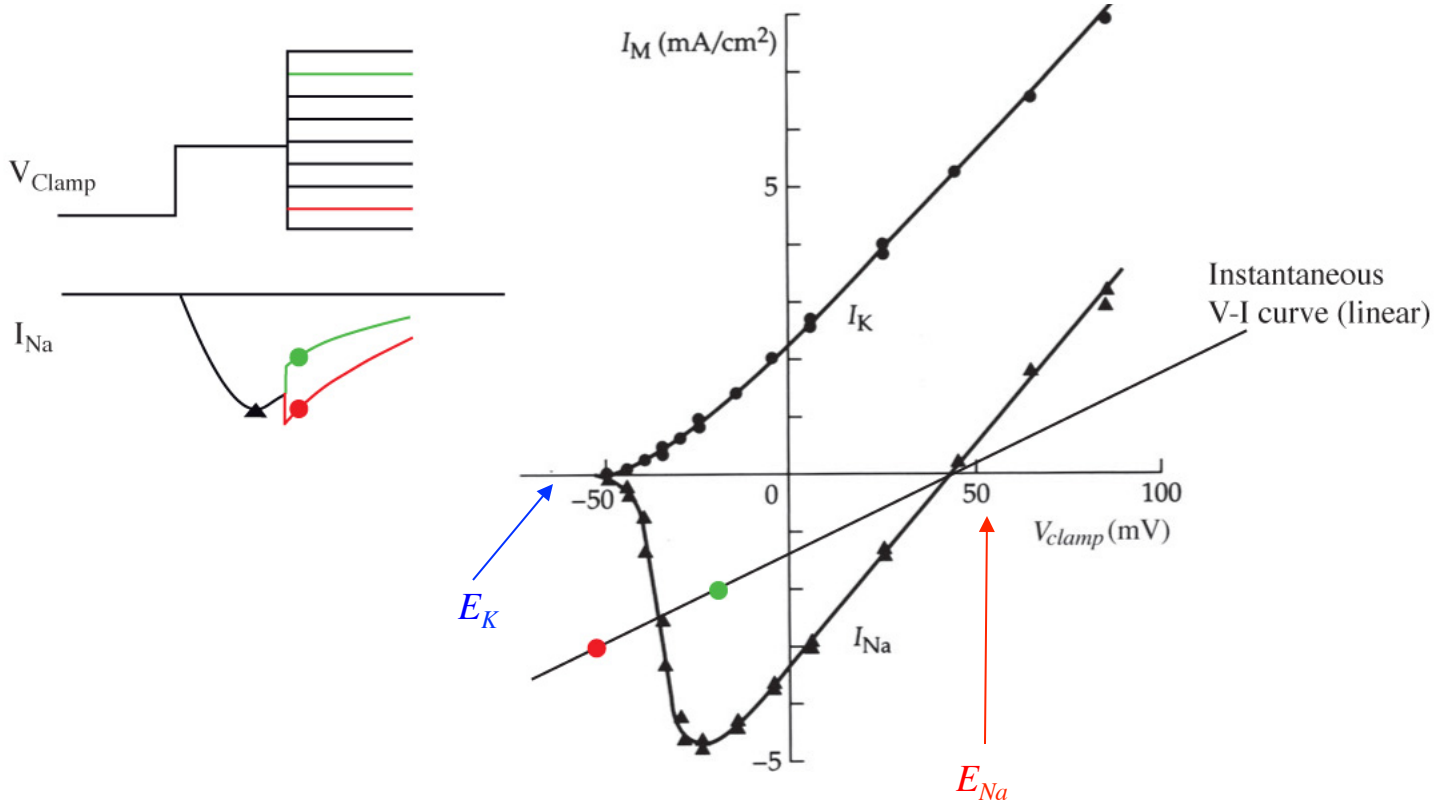
An explanation for anode break excitation. During a hyperpolarization, membrane excitability is increased by decreases in K channel activation and Na channel inactivation.



The difference between instantaneous I-V curves and those dependent on gating. Consider the sodium channel:

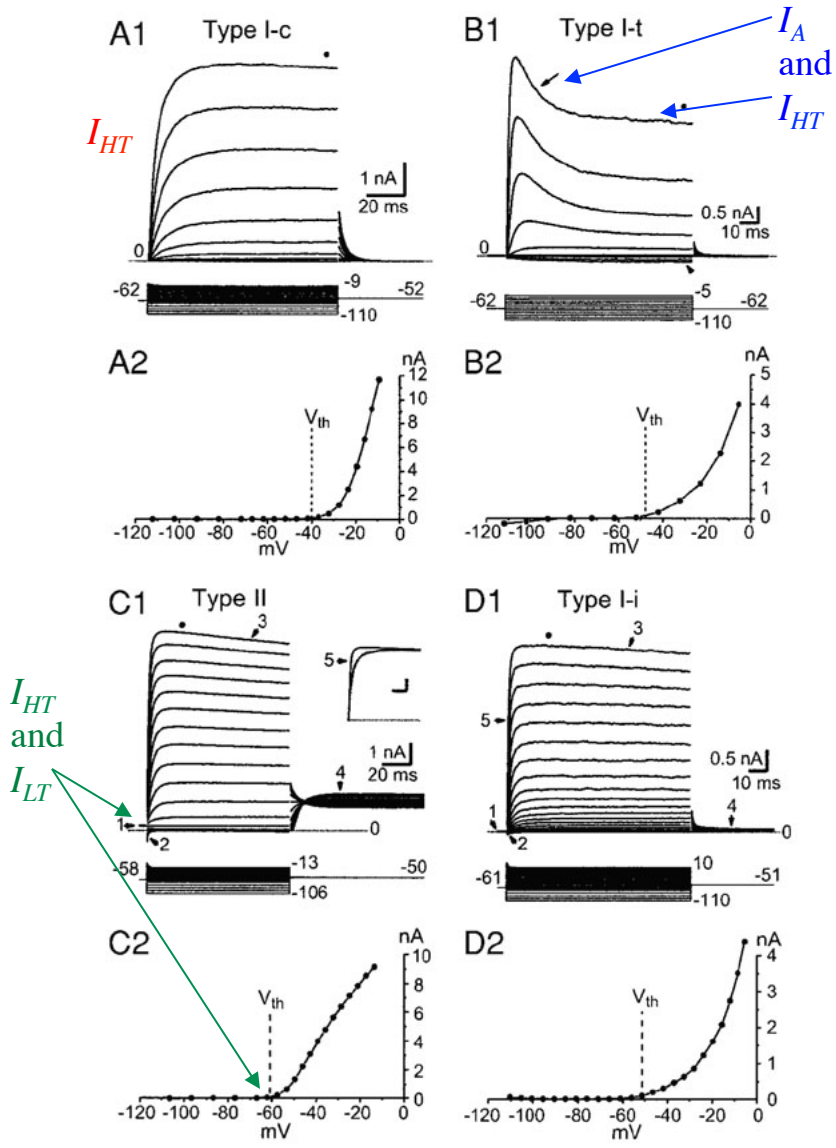
$$I_{Na} = G_{Na}(V,t)\cdot(V - E_{Na})$$

This equation applies instantaneously after a voltage clamp with a constant conductance, as well as over time as gating proceeds.



In neuron cell bodies, there are often many more types of channels. The voltage-clamp data at right are from four types of cells in the cochlear nucleus. The Na^+ and Ca^{++} currents were blocked using tetrodotoxin and Cd^{++}, respectively, so only K^+ currents are present. These records were decomposed into three different K^+ channels:

- I_{HT} - like the HH K^+ channel, actually carried by two different channels.
- I_{LT} - also like the HH K^+ channel, but with a low activation threshold. Specifically blocked by dendrotoxin
- I_A - a K^+ channel with inactivation.



Rothman and Manis, 2003

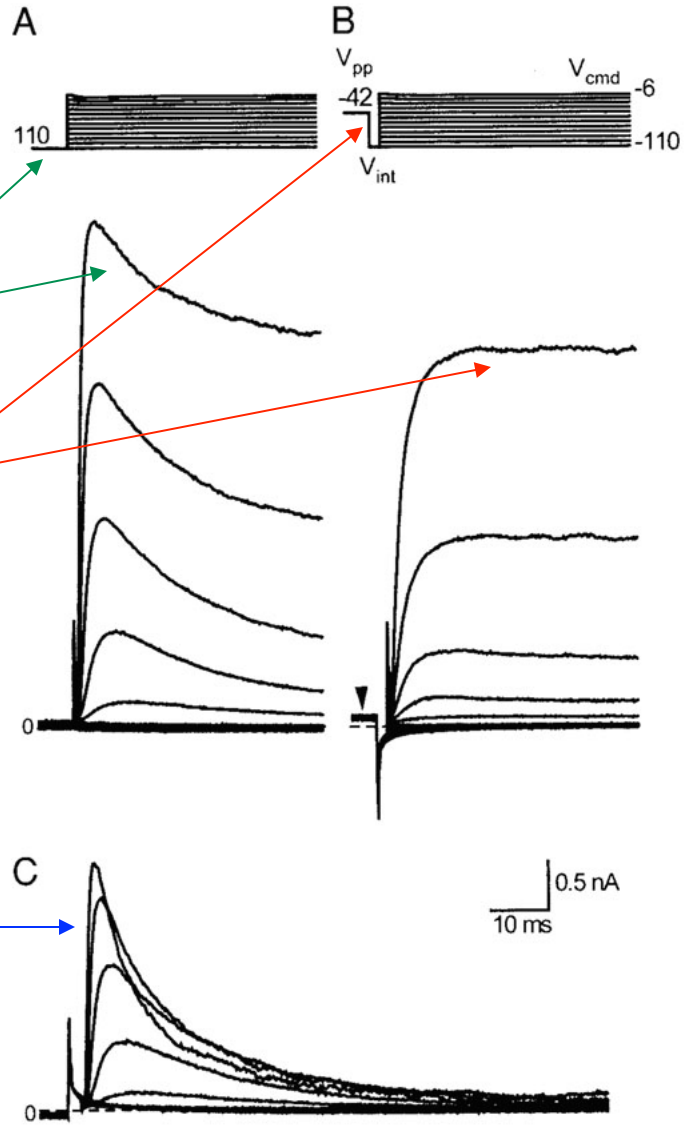
To see how the separation proceeds, consider the case of I_A. No pharmacological blockers were available.

This current is only activated when its inactivation is removed by hyperpolarizing.

Hyperpolarizing prepulse, I_A is present

No hyperpolarizing prepulse, I_A is not seen. The current is entirely I_{HT}.

I_A derived from the difference between A and B.

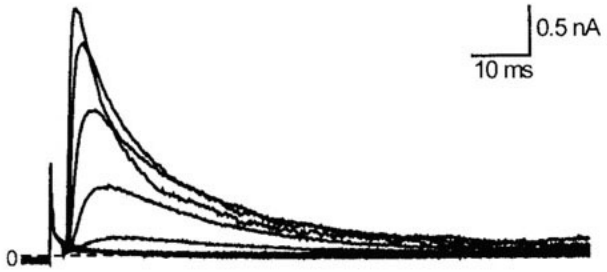


Rothman and Manis, 2003

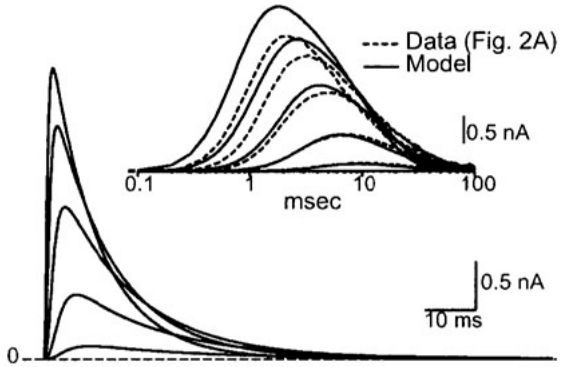
The A-channel is fit by an HH model with activation a and two inactivations b and c.

$$I_A = \bar{G}_A a^4 b c (V - E_K)$$

Data

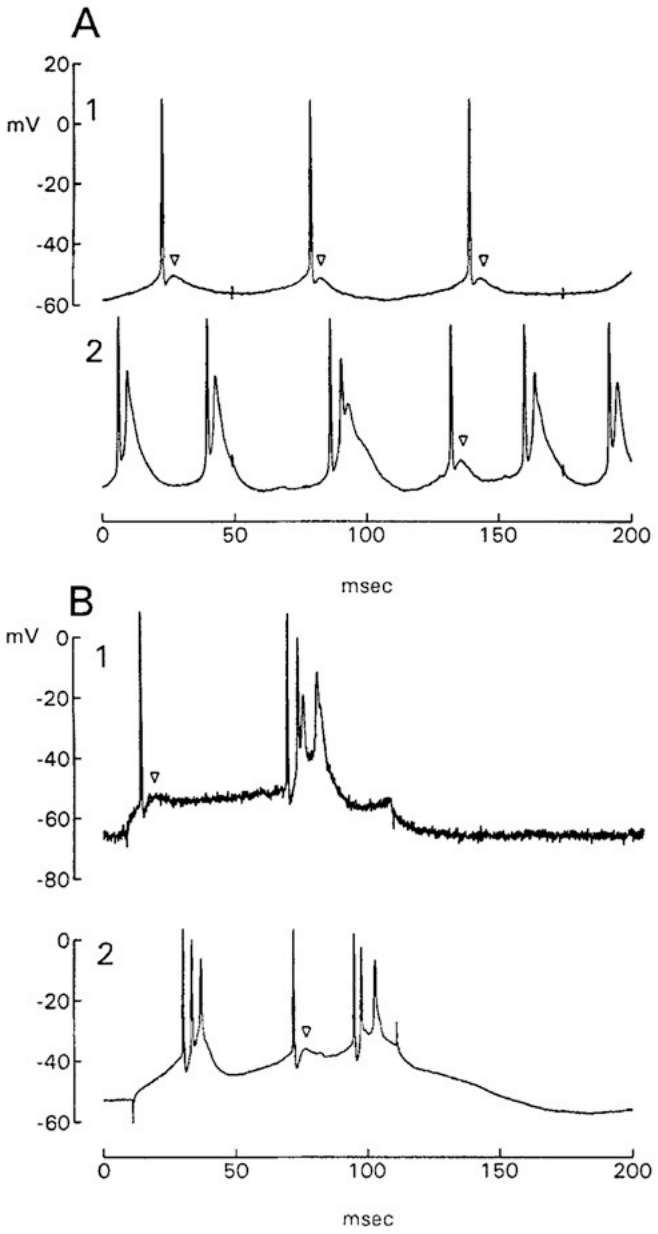


Model



Rothman and Manis, 2003

Action potentials are not always so simple. Many neurons fire complex spikes, often accompanied by simple spikes. This requires additional (Ca^{++}) channels, not included in HH.



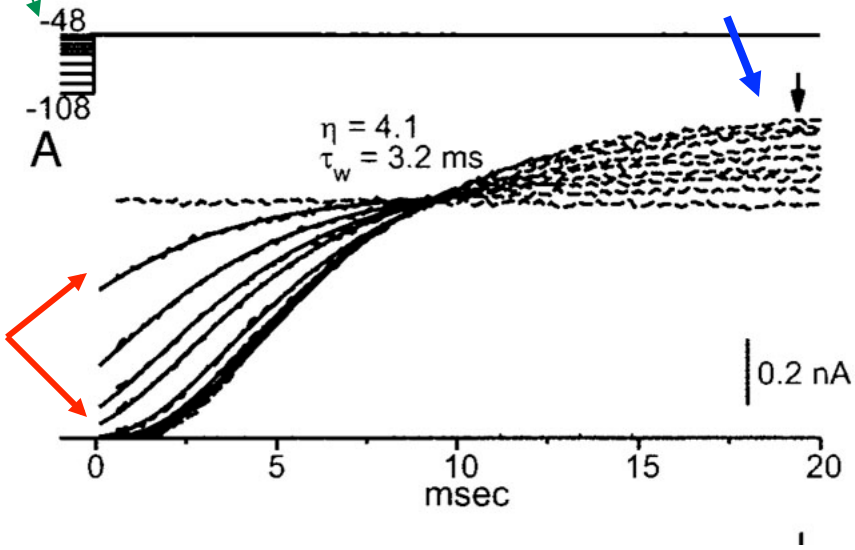
Manis et al. 1994

Some detail on the sigmoidal (as opposed to exponential) rise of I_A.

Voltage clamps start with a hyperpolarized prepulse of various levels. Then the clamp is taken to a fixed depolarized level (-48 mV) which activates the channel.

Two things happen during the prepulse:

1. Inactivation of the channel is relieved, giving larger currents after activation.
2. Activation of the channel is delayed, giving activation waveforms that vary from exponential (after -48 mV prepulses) to sigmoidal (after -108 mV prepulses). This delay determines the exponent of 4 in the model.



Rothman and Manis, 2003