

Systems Biology II: Neural Systems (580.422)

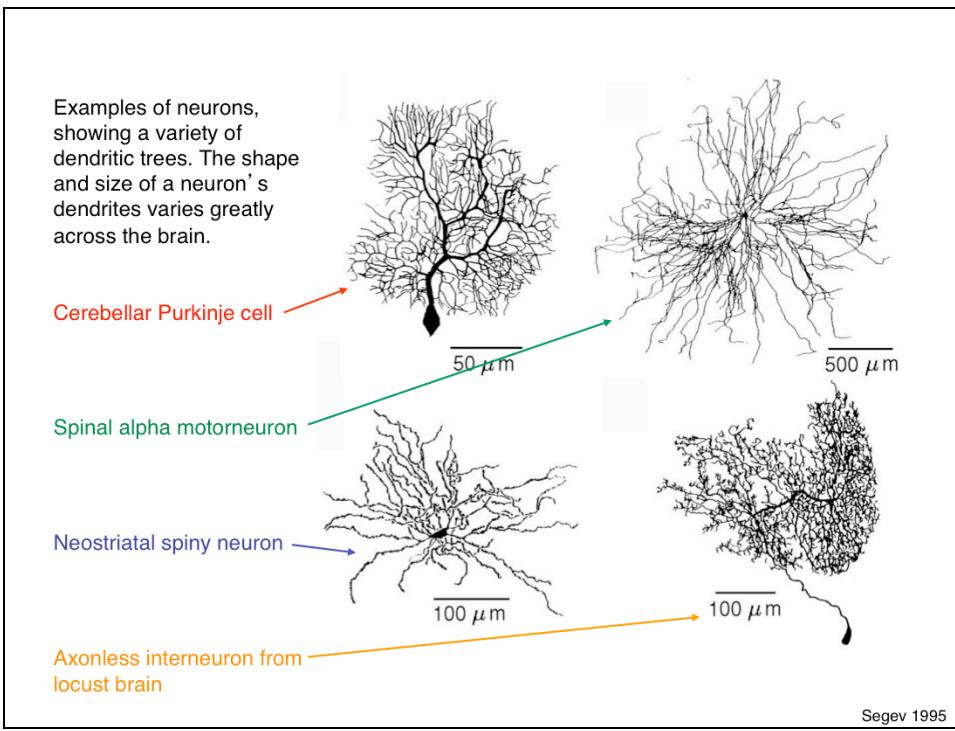
Lecture 5, Neural Excitability

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Reading:

Purves et al. *Neuroscience* (Sinauer Assoc. 2008). Unit 1, Chapters 2-4.

P. Dayan and L. Abbott *Theoretical Neuroscience* (MIT Press, 2001).
Chapters 5 and 6 on model neurons.



Some more details about neural structure:

Dendrites of many neurons are *spiny*. The spines are the sites of excitatory synaptic inputs.

These figures show the reconstruction of a cell that has been filled with a dye.

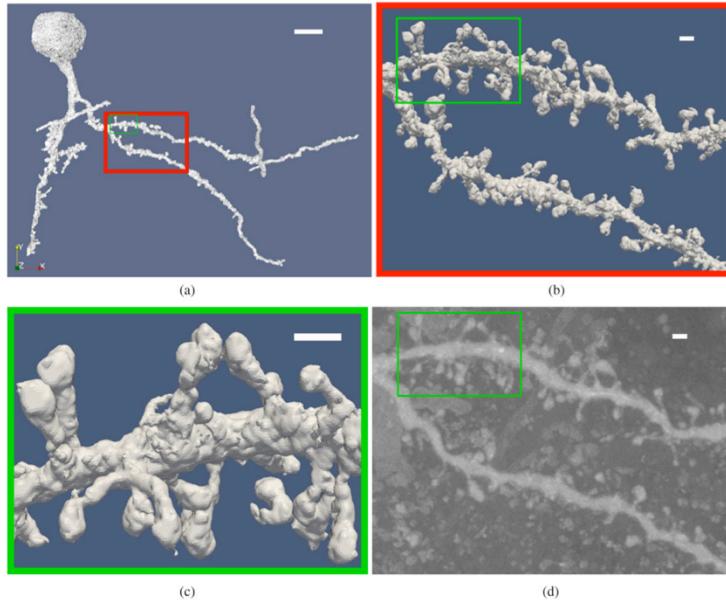
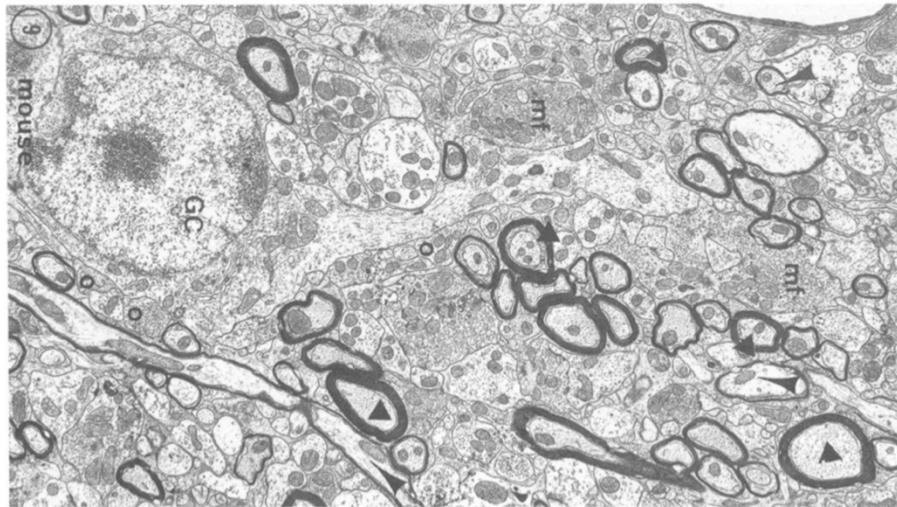


Fig. 9 Surface reconstruction of a spiny L4 cell from Dataset II: (a) soma with dendrites. (b) details of the dendritic branch complex and spines in direct comparison with (d) a projection of

the experimental data. (c) zoom of a spiny dendrite section. The area shown corresponds to the region that is marked green in (b). White length bars are 10 μm in (a), 1 μm otherwise

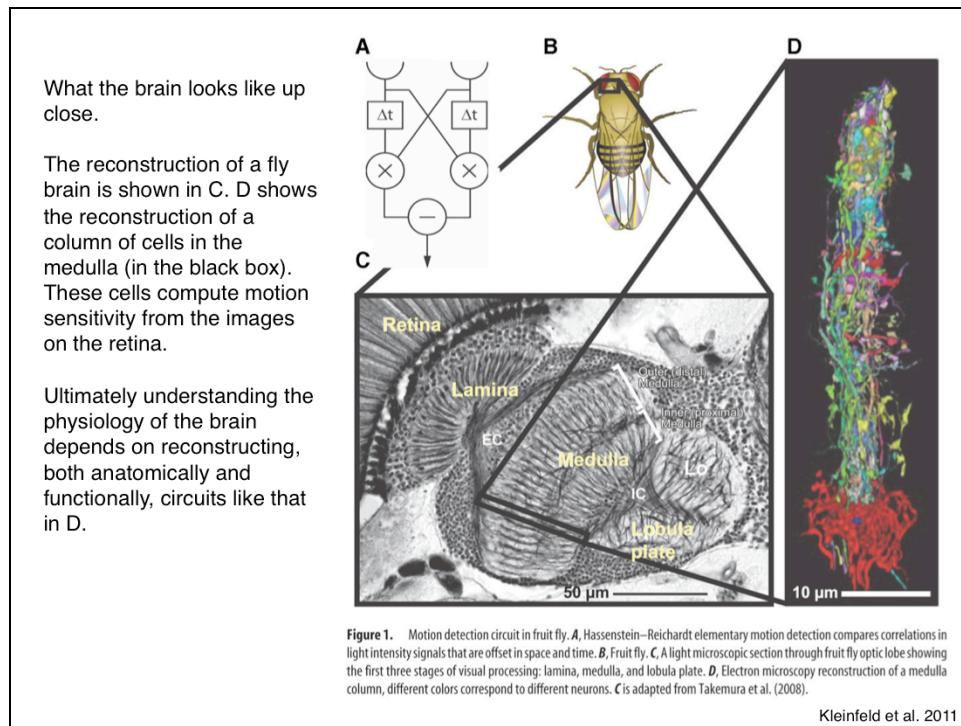
Lang et al. J. Comput. Neurosci. (2011) DOI 10.1007/s10827-011-0316-1

What the brain really looks like up close. An electron micrograph showing a neuron (GC) with part of its primary dendrite and the associated neuropil. In the neuropil can be seen axons, the dendrites of other neurons, and synapses.



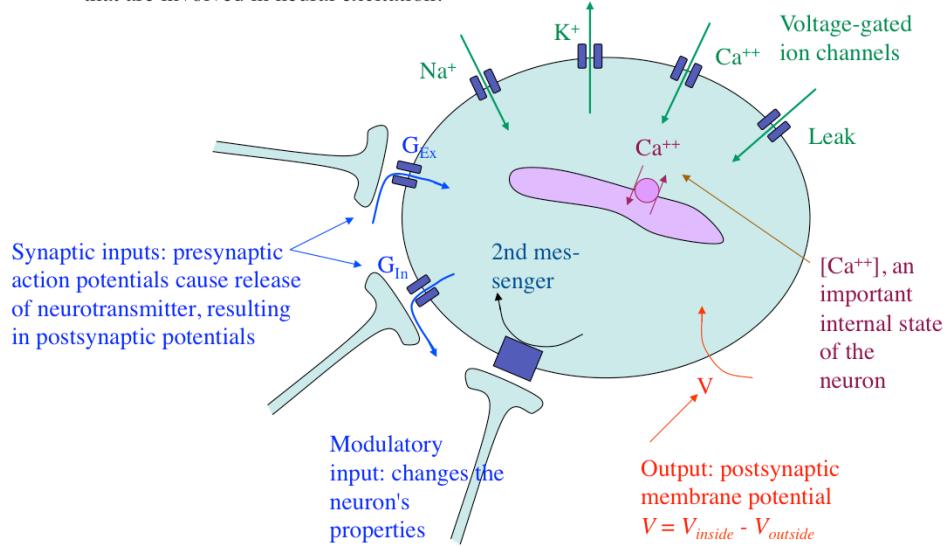
Mugnaini et al. 1980

In brain, neurons and the processes of neurons are packed densely, with little empty space. In this slide, 'GC' is the nucleus of a neuron. The heavy black circles are myelinated axons of other neurons. 'mf' are synaptic terminals of a special large type. The usual assumption, of a neuron in a pool of extracellular fluid, seems to be at odds with this reality. In fact it is an approximation which is probably accurate enough, as long as the processes that surround a cell don't have activity correlated with that of the cell.



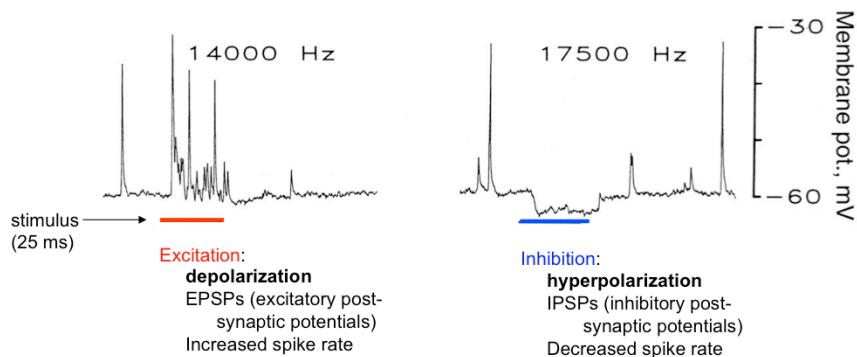
An idea of the complexity of neural circuits is shown by the reconstruction in D. This shows the cell bodies, processes, and synapses of many neurons forming a column in the fly brain.

Neurons represent information by changes in their **membrane potential V** , produced by **synaptic inputs** and controlled by the collection of **ion channels** in the cell membrane. The drawing below shows some of the components of a neuron that are involved in neural excitation.



Consider the problem of neural excitability in the input/output terms described in the figure. The inputs to neurons are synaptic currents, to be discussed in a later lecture. These provide depolarization and hyperpolarization of the membrane potential V . The actual membrane potential is produced by the collective action of the synaptic inputs and the population of ion channels present in the membrane. When the membrane potential is sufficiently depolarized, an action potential or a train of action potentials will be produced. This lecture focuses on the ion channel part of this system. How is the electrical activity of the neuron affected by the particular ion channels present in its membrane?

Excitation and inhibition correspond to depolarization and hyperpolarization of the membrane



Smith and Rhode, 1987

The responses of neurons can be excitatory or inhibitory, with the properties listed in the figure. Excitation means an increased rate of firing of action potentials; it results from depolarization of the cell, usually produced by EPSPs (excitatory post synaptic potentials) produced by activation of an excitatory synapse.

Inhibition means a decreased rate of firing of the cell; it results from hyperpolarization of the cell, produced by IPSPs (inhibitory post synaptic potentials) produced by activation of an inhibitory synapse. In actual fact, inhibition does not require actual hyperpolarization, as in the example above. It is sufficient to simply block depolarization; many inhibitory synapses work this way. This point will be discussed later.

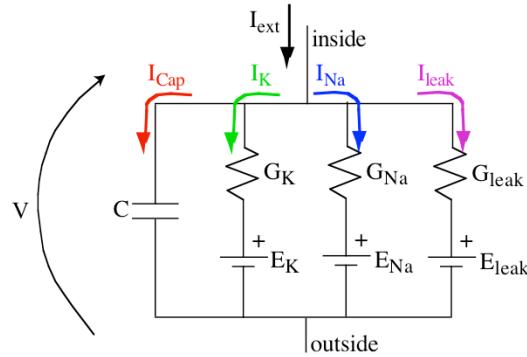
The net activity of a neuron is always determined by a balance of excitatory and inhibitory effects.

Membrane dynamics: the electrical model of the membrane consists of a capacitance in parallel with battery-resistor models for current flow through each of the ion channels. In the Hodgkin-Huxley analysis of squid giant axon:

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

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

By convention, currents are positive when they flow out of the cell and the membrane potential is the potential inside minus the potential outside.



In the membrane model, each ion channel is represented by a battery in series with a resistor (e.g. G_{Na} and E_{Na} for sodium channels). The current through the resistor (I_{Na}) is the current carried by a particular ion through the ensemble of channels of a particular type in the membrane. The battery/resistor circuits are in parallel for a piece of membrane, just as the ion channels are in real membrane. That is, the total ionic current through the membrane is the sum of the currents through the individual ion channels. The membrane capacitance completes the circuit. The voltage across the membrane V is the voltage across the capacitance and each ion channel's battery-resistor model.

Each battery is the equilibrium potential of the ion flowing through the corresponding ion channel. The value of the battery is given by the Nernst equation, for example $E_{Na} = RT/F \ln(Na(out)/Na(in))$. The voltage difference across the resistor (e.g. $V-E_{Na}$) is the electrochemical driving force for that ion through the membrane and represents the difference between the electrical potential V and the “potential” produced by the concentration gradient of the ion, E_{Na} . The resistors represent the conductance state of the ion channel. The resistances (actually conductances) are generally functions of the membrane potential V as well as other signals, like the calcium concentration near the channel or the phosphorylation state of the ion channel. The membrane potential is the solution to the differential equation given on the slide, which is

At the resting potential, $dV/dt = 0$, so the resting potential is given by (for $I_{ext}=0$)

$$V_{rest} = \frac{G_K E_K + G_{Na} E_{Na} + G_{leak} E_{leak}}{G_K + G_{Na} + G_{leak}}$$

As one conductance becomes large compared to the others,

$$\lim_{G_{Na} \rightarrow \infty} \left[\frac{G_K E_K + G_{Na} E_{Na} + G_{leak} E_{leak}}{G_K + G_{Na} + G_{leak}} \right] = E_{Na}$$

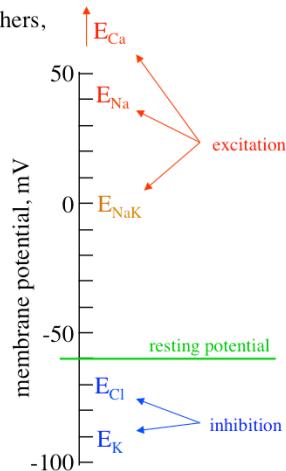
Thus the effect, excitatory or inhibitory, of an ion is determined by its **equilibrium potential**.

The resting potential is maintained by K conductances, in balance with other ions.

Inhibitory synaptic potentials are produced by Cl conductance.

Excitatory synaptic potentials are produced by a mixed cation conductance (E_{NaK}).

Action potentials are produced by Na and Ca conductances.



Inward currents carry charge into the cell and depolarize it. Current flows inward when the membrane potential V is more negative than the equilibrium potential of the ion. Thus sodium and calcium channels usually carry inward currents and potassium channels carry outward (hyperpolarizing) currents.

Synaptic channels can be chloride channels, in which case they are hyperpolarizing like potassium channels, or mixed cation channels. Mixed cation channels admit both sodium and potassium so are properly modeled by two battery-resistor circuits in parallel. These can be converted to a single battery and resistor (a Thévenin equivalent). For mixed cation channels, the resulting battery usually has a potential somewhere near 0 mV. Synaptic channels that are mixed cation channels are depolarizing, inward currents.

Make sure you understand why chloride currents are outward currents, even though chloride ions are flowing into the cell.

The Hodgkin-Huxley model represents the whole-cell currents of ion channels in a membrane. Currents are modeled as a battery-resistor representation

$$I_K = G_K(V - E_K) \text{ and so on for } I_{Na} \text{ and } I_{leak}$$

where the conductances are given by

Later, we will see that this model is inadequate for Ca^{++} currents.

$$\begin{aligned} G_K &= \bar{G}_K n^4 & G_{Na} &= \bar{G}_{Na} m^3 h \\ \frac{dn}{dt} &= \frac{n_\infty(V) - n}{\tau_n(V)} & \frac{dm}{dt} &= \frac{m_\infty(V) - m}{\tau_m(V)} \text{ and } \frac{dh}{dt} = \frac{h_\infty(V) - h}{\tau_h(V)} \end{aligned}$$

The variables n , m , and h are called *activation* (n , m) and *inactivation* (h) variables. They represent the probability of a channel's gate being open.

For the potassium channel, the 4th power corresponds (fortuitously) to the fact that the channel has four subunits, each with a gate, and all four must be open to open the channel.

The sodium channel has two independent gates, one represented by m and the other by h . In fact, there are 4 activation (m) gates and one inactivation (h) gate in each sodium channel.

A review of the Hodgkin-Huxley model for gating. The probability of a gate being open is given by gating variables n , m , and h . The gating variables are described by the differential equations given in the slide. The model is completed by specifying the functions $n^\infty(V)$, $m^\infty(V)$, $h^\infty(V)$, $\tau_n(V)$, $\tau_m(V)$, and $\tau_h(V)$.

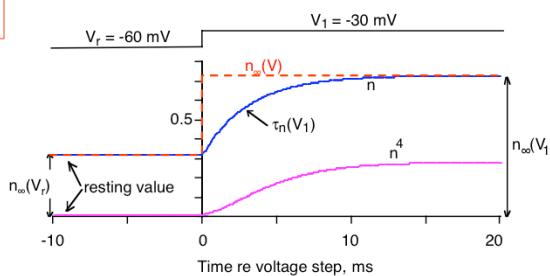
The Hodgkin-Huxley model is a curve-fit to voltage-clamp data obtained in the squid giant axon. Parts of the model turn out to correspond rather well to the microscopic gating properties of voltage-gated ion channels. For example, voltage-gated channels consist of four subunits. Each subunit has its own gate, so the n gating variable of potassium channels can be thought of as the probability that a subunit gate is open. The probability that the whole channel is open is then n^4 , because all subunit gates must be open for the whole channel to open.

For the sodium channel, the model is not fully accurate, but it is accurate in that the sodium channel has two independent gating mechanisms, called activation, modeled by m , and inactivation, modeled by h . These are two separate parts of the ion channel molecule. The channel has four activation gates, one in each subunit, and one inactivation gate. Thus the power of h is

The HH differential equations cause the activation and inactivation variables n , m , and h to follow the fluctuations of the voltage-dependent steady-state functions $n_\infty(V)$, $m_\infty(V)$, and $h_\infty(V)$ with a certain time constant. For example, during the voltage-clamp experiment drawn below the HH equation for n can be written as

$$\frac{dn}{dt} = \frac{n_\infty(V_1) - n}{\tau_n(V_1)} \quad \text{and} \quad n(0) = n_\infty(V_r)$$

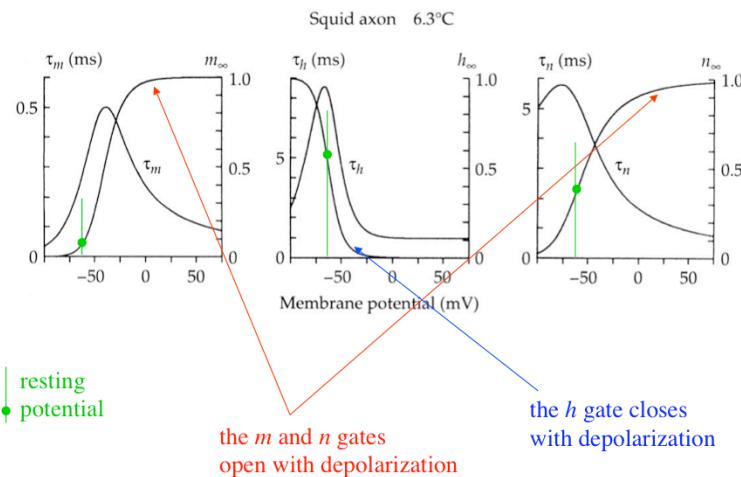
This solution can only be written because V_r and V_1 are constants.
Normally both n_∞ and τ_n vary with time.



The differential equations describing gating express the fact that the gating variables track the value of $n^\infty(V)$ (or $m^\infty(V)$ or $h^\infty(V)$) as membrane potential changes. The tracking follows with time constant $\tau_n(V)$ (etc.). For the voltage-clamp shown above, $n^\infty(V)$ changes as a step function when the membrane potential changes (red dashed line) and the value of n (blue) follows, but more slowly as determined by the time constant $\tau_n(V)$.

The example above shows the behavior during a voltage-clamp, where the membrane potential is constant except at the voltage step. Of course in a real membrane, voltage is changing continuously and is not constant (except at the resting potential). Still, the important feature of the model is that n (m , h) tracks $n^\infty(V)$ ($m^\infty(V)$, $h^\infty(V)$) with some delay.

The functions $n_\infty(V)$, $m_\infty(V)$, and $h_\infty(V)$ determine whether gates serve to **activate** the channel (conventionally **open the channel with depolarization**) or **inactivate** the channel (**close the channel with depolarization**).



Hille, 2001

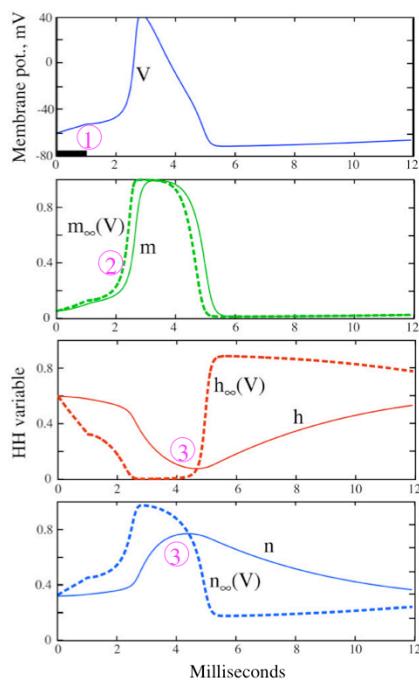
Plots of the functions underlying n , m , and h for the Hodgkin-Huxley model. Make sure you understand why the activation gates (n and m) are different in function from the inactivation gate (h).

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 , G_{Na} , 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.

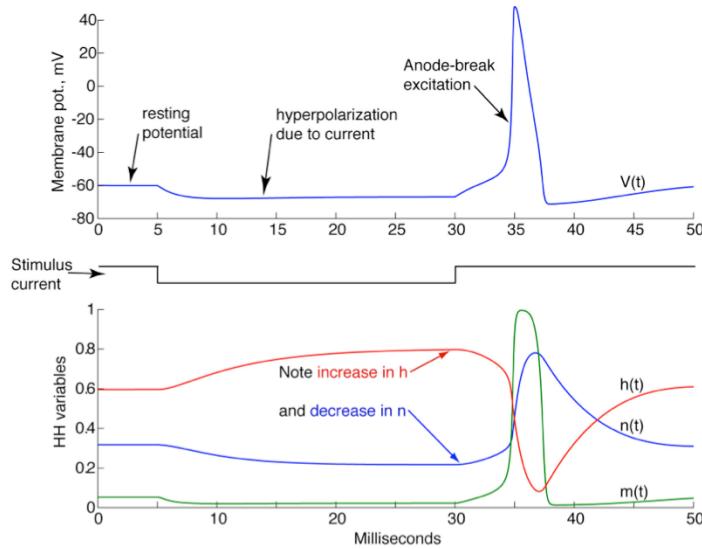
Note the difference in the response times of m (fast) versus n and h (slow).

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



Reconstruction of the action potential using the HH model. $n^\infty(V)$, $m^\infty(V)$, and $h^\infty(V)$ are plotted along with the gating variables to illustrate how the model works.

The model also shows *anode-break excitation*, a spike at the release of a hyperpolarizing current. Again, this can be understood qualitatively in terms of an elevated h and a depressed n at the end of the hyperpolarization.



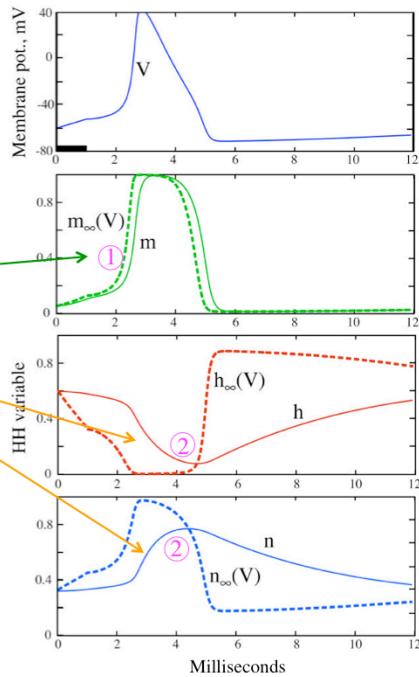
Explaining anode break excitation was one of the accomplishments of the HH model. As shown, during the hyperpolarization, the variables that repolarize the neuron, n and h change in the direction that increases the excitability of the cell (by decreasing G_k and decreasing sodium inactivation, allowing G_{Na} to increase more). The result is an anode break spike at the end of the hyperpolarization.

The entire HH model is not needed to produce excitation, as in the action potential. Potential simplifications are suggested by the waveforms for the full HH model:

Note that

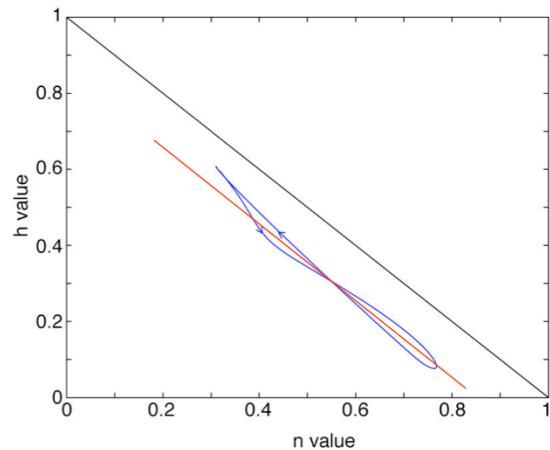
$$1. \quad m \approx m_\infty(V)$$

$$2. \quad h \text{ and } n \text{ behave similarly.}$$



Reconstruction of the action potential using the HH model. $n^\infty(V)$, $m^\infty(V)$, and $h^\infty(V)$ are plotted along with the gating variables to illustrate how the model works.

The blue trace shows a plot of n versus h during an action potential. These two HH variables are related approximately as $h \approx 0.85 - n$ (the red line). Thus it is not really necessary to include both variables in the model (although it does make the simulation more accurate).



A minimal model with one excitatory channel (Na or Ca) and one stabilizing channel (K) suffices, as in the *Morris-Lecar* model (MLE). Note there are only two differential equations, as opposed to four in the HH model.

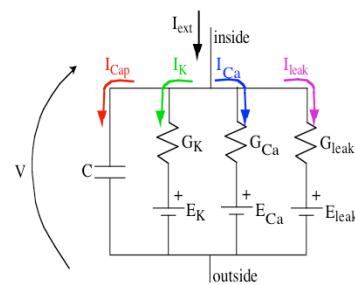
$$I_{cap} + I_K + I_{Ca} + I_{leak} = I_{ext}$$

$$C \frac{dV}{dt} = I_{ext} - \bar{G}_K w(V,t)(V - E_K) - \bar{G}_{Ca} m_\infty(V)(V - E_{Ca}) - G_{leak}(V - E_{leak})$$

$$\frac{dw}{dt} = \frac{w_\infty(V) - w}{\tau_w(V)}$$

We have assumed that:

1. $m = m_\infty(V)$, no differential eqn.
2. there is no h , again no diff. eqn.
3. instead of n^4 , we use w



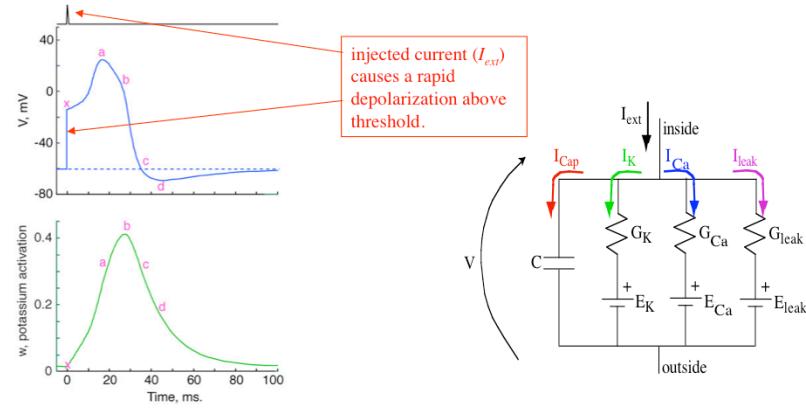
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An [action potential](#) produced by the MLE is plotted below.

The sequence of events in the action potential is similar to that in the full HH model:

1. Rapid depolarization with slower growth of w (**x** to **a**).
2. A plateau phase during which w continues to increase (**a** to **b**).
3. Repolarization occurs when w is large enough (**b** to **d**).
4. Afterhyperpolarization caused by the remaining elevation in w (**d**).



m increases as a function of V . From HH AP data shown earlier this is close to what happens in the full model.

there is no h , but h and n covary (again see HH AP data), so both are not needed.

Several other combinations are possible:

Leak channel plus sodium channel modeled as $G_{Na}^*m^\infty*h$ with no potassium channel (h substitutes for n or w above).

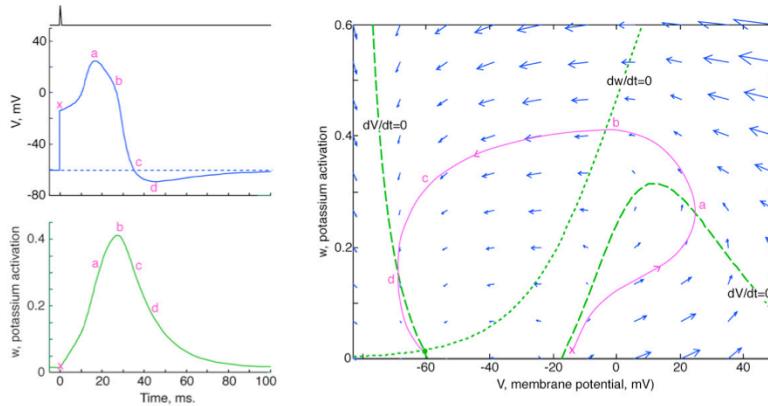
As above but with a rapidly-gated potassium channel $G_K^*n^\infty$

Leak plus sodium as $G_{Na}^*m_{inf}$ plus an "H" channel, like the potassium channel above except depolarizing. Used to study pacing

A way to better understand the action potential is to plot the MLE variables in a *phase-plane*, a plot of V versus w . The blue arrows show the time derivatives as a vector $(dV/dt, dw/dt)$. The solutions to the MLE must follow these blue arrows.

The trajectory followed by the action potential is the magenta line, marked to correspond to the voltage-time plot at left.

The resting potential is the point $V = -60$ mV, $w = 0.04$, where both $dV/dt=0$ and $dw/dt=0$ (the green dashed lines).



Rinzel and Ermentrout 1998

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