Systems Biology II: Neural Systems (580.422)

Lectures 5 and 6, Neural Excitability

Eric Young 5-3164 eyoung@jhu.edu

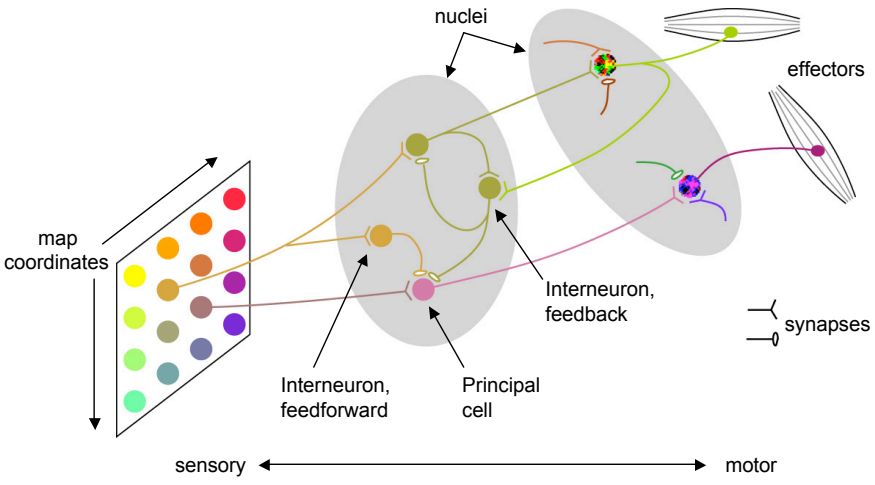
Reading:

D. Johnston and S.M. Wu *Foundations of Cellular Neurophysiology* (MIT Press, 1995). Chapters 6 and 7 (review)

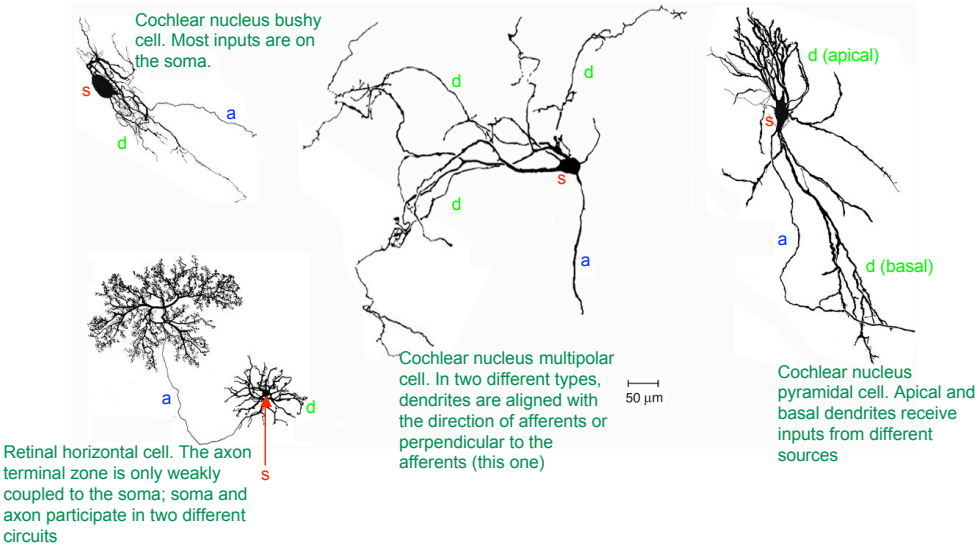
G.M. Shepherd *Synaptic Organization of the Brain* (Oxford Press, 2004). Chapters 1, 2, and 3. (general orientation to neurons and neural circuits)

J. Rinzel and B. Ermentrout "Analysis of neural excitability and oscillations." In: C. Koch and I. Segev *Methods in Neuronal Modeling* (MIT Press, 1998). (Supplementary reading for a more in-depth look at excitability)

Neural integration occurs through networks, in which neurons interact via synapses. Neurons can be *principal cells* (projection neurons) or *interneurons* or both. The diagram below shows a general schema in which information from a sensory map (e.g. the vestibular endorgans sensing head motion) is used to control some effectors (e.g. the eye muscles, countermoving the eyes to hold the visual world stable on the retina as the head moves).

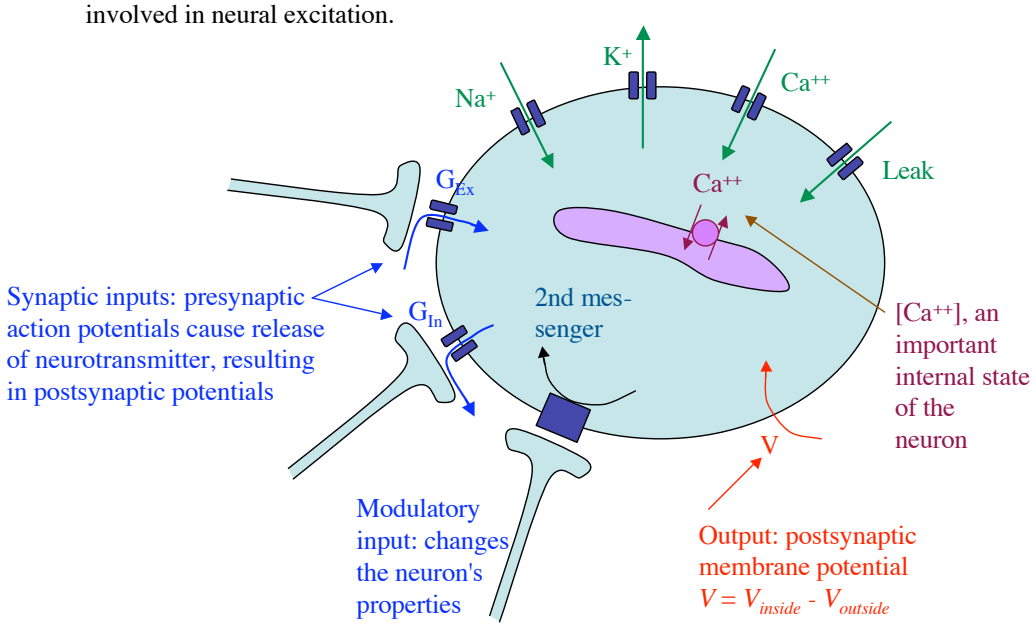


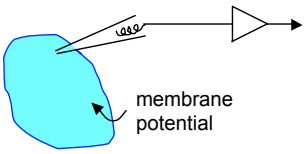
Neurons come in all shapes and sizes, depending on the orientation of input axons, the functional arrangement of inputs on the dendrites and soma, and the destinations of the outputs. For the cells below, "a" means axon, "s" means soma, and "d" means dendrites. The top three neurons are principal cells, the one at bottom left is an interneuron.



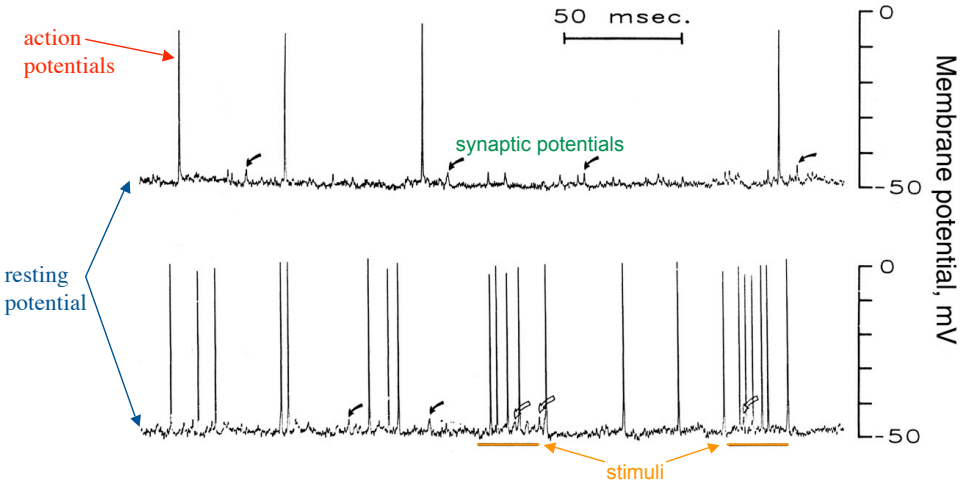
Shepherd (2004), Synaptic Organization of the Brain

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 the components of a neuron that are involved in neural excitation.

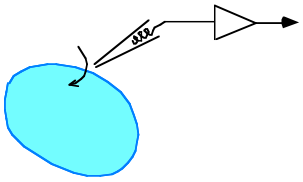




Membrane potential can be recorded intracellularly, in which case the resting potential, synaptic potentials, and action potentials can be seen . . .

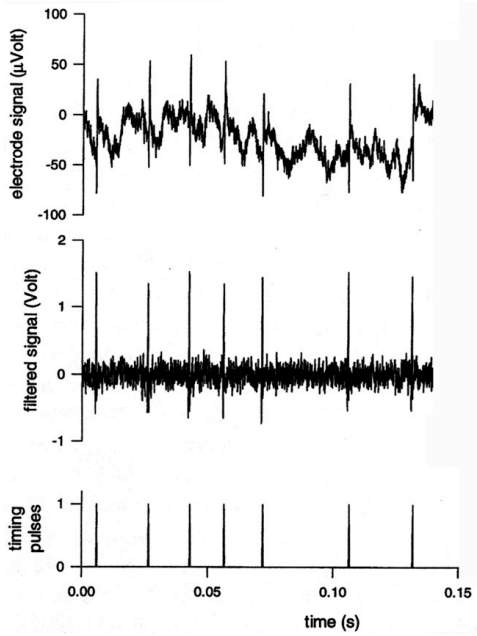


Smith and Rhode, 1987



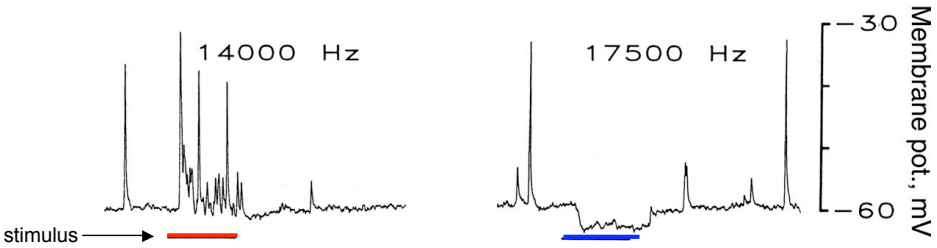
. . . or they can be recorded extracellularly, in which case only the action potentials (spikes) can be seen.

This mode is used to study information processing under the assumption that neurons convey information only by the times of occurrence of spikes.



Rieke et al., 1997

Excitation and inhibition correspond to depolarization and hyperpolarization of the membrane



Excitation:
depolarization
EPSPs (excitatory post-synaptic potentials)
Increased spike rate

Inhibition:
hyperpolarization
IPSPs (inhibitory post-synaptic potentials)
Decreased spike rate

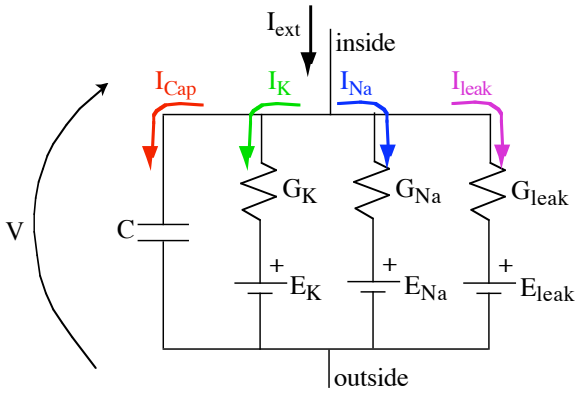
Smith and Rhode, 1987

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:

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

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

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



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

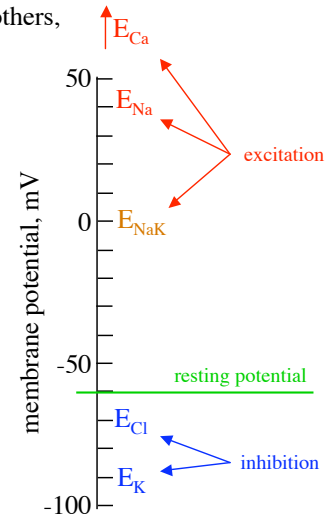
$$V_{rest} = \frac{G_K E_K + G_{Na} E_{Na} + G_{leak} E_{leak}}{G_K + G_{Na} + G_{leak}}$$

As one conductance becomes large compared to the others,

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

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 by a *mixed cation conductance* (E_{NaK}).
Action potentials are produced by Na and Ca conductances.



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

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

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

where the conductances are given by

$$G_K = \bar{G}_K n^4 \qquad G_{Na} = \bar{G}_{Na} m^3 h$$

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

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.

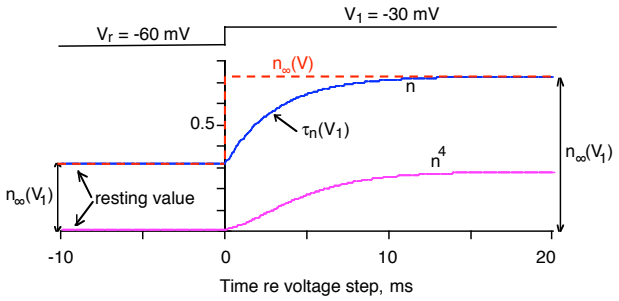
The sodium channel has two independent gates, one represented by m and the other by h. In fact, there are 4 activation (m) gates and one inactivation (h) gate in each sodium channel.

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

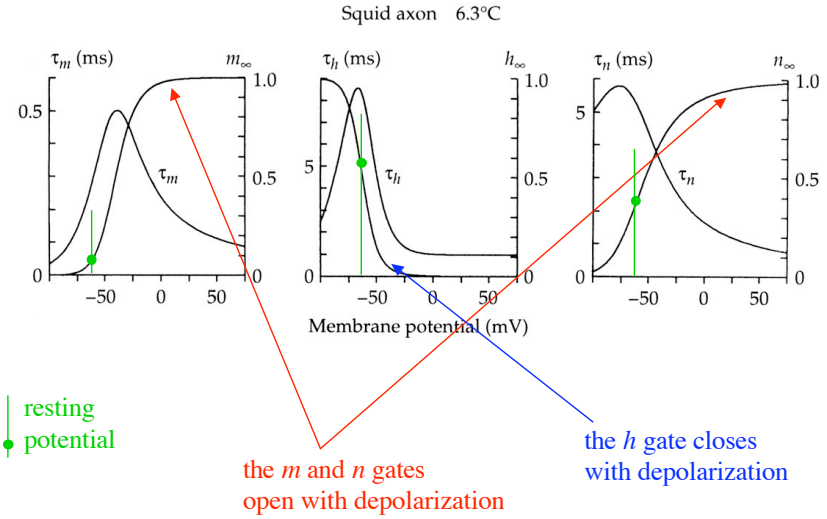
$$\frac{dn}{dt} = \frac{n_\infty(V_1) - n}{\tau_n(V_1)} \quad \text{and} \quad n(0) = n_\infty(V_r)$$

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

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



The 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

Reconstruction of the action potential by the HH model :

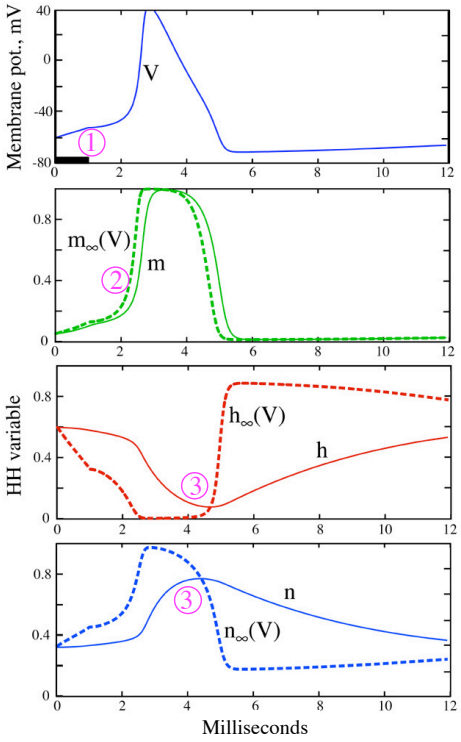
① Depolarization of the cell (by an injected current in this case) leads to

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

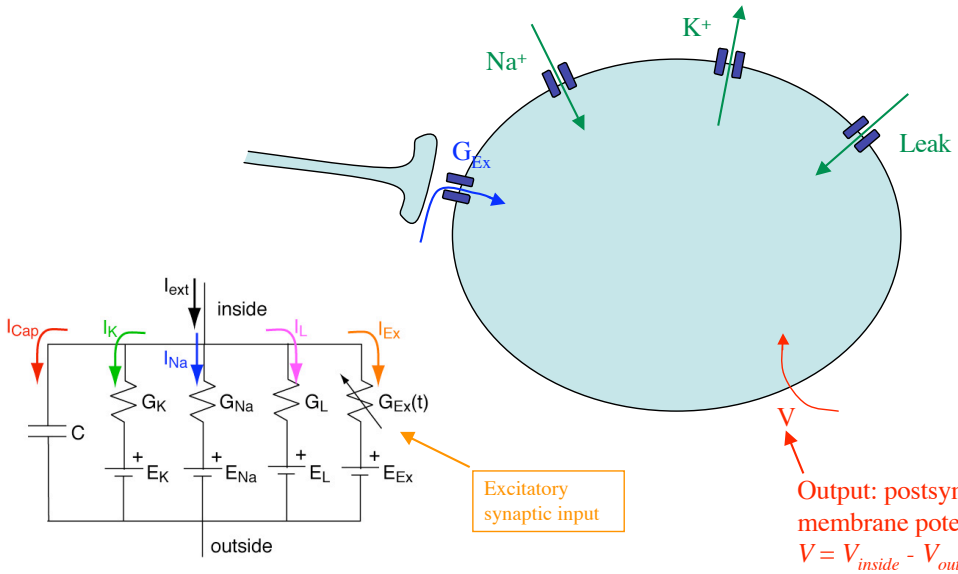
③ a decrease in $h_\infty(V)$ and an increase in $n_\infty(V)$. The resulting decrease in h and increase in n terminate the action potential and repolarize the membrane.

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

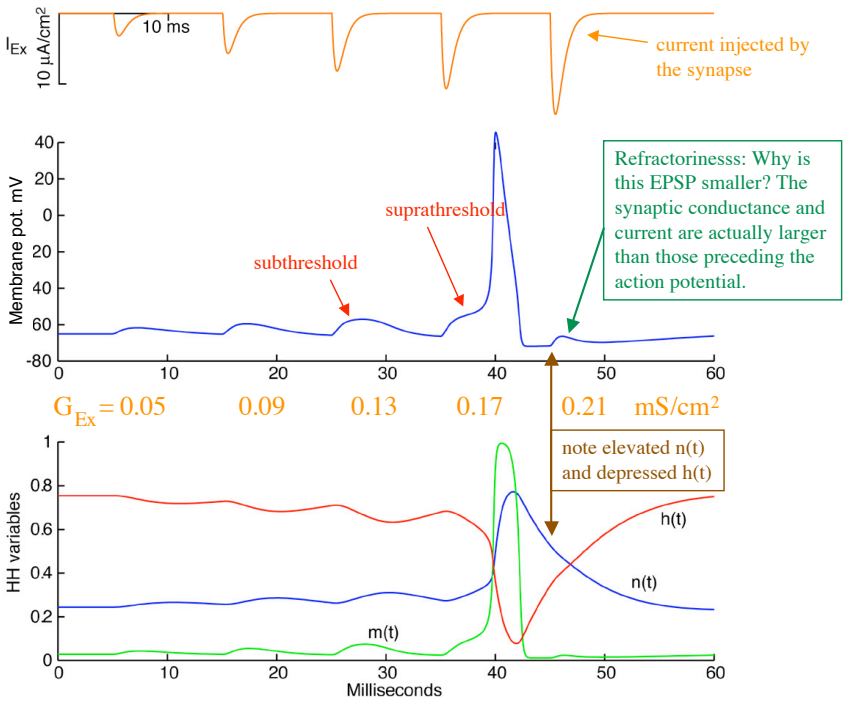
(AP produced by a 1 ms, 9 µA current pulse at the heavy bar in the V plot)



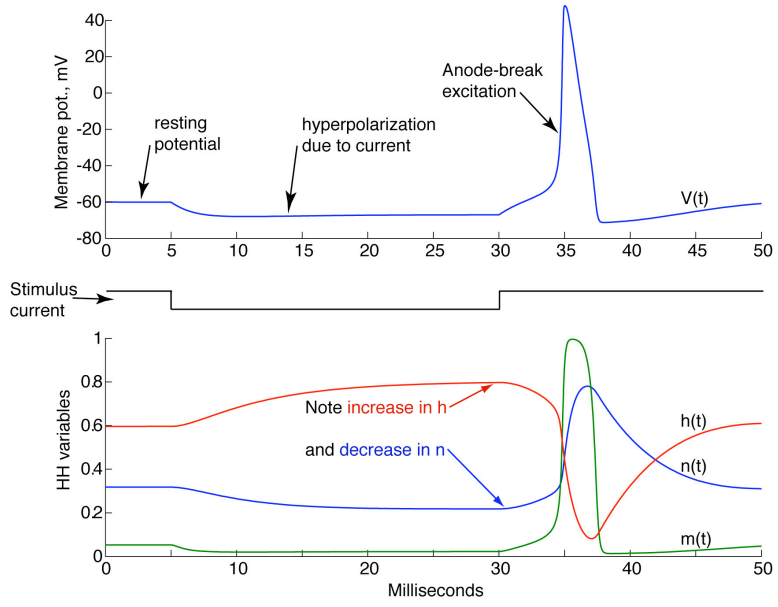
Consider a cell with HH-style channels in its membrane and an excitatory synaptic input, G_{Ex}. The properties of synaptic channels are discussed in a later lecture; for now, the synapse injects depolarizing current to excite the neuron.



The HH model shows *threshold* and *refractoriness*, similar to the phenomena in real neurons.



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.



The entire HH model is not needed to produce excitation. A *minimal model* with one excitatory channel (Na or Ca) and one stabilizing channel (K) suffices, as in the *Morris-Lecar* model. Note there are only two differential equations, as opposed to four in the HH model.

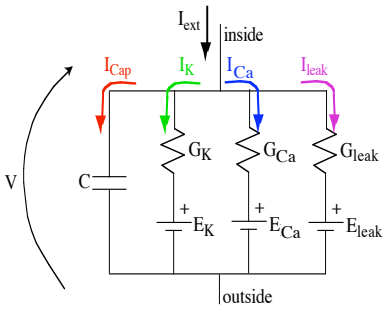
$$I_{cap} + I_K + I_{Ca} + I_{leak} = I_{ext}$$

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

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

Now we have assumed that:

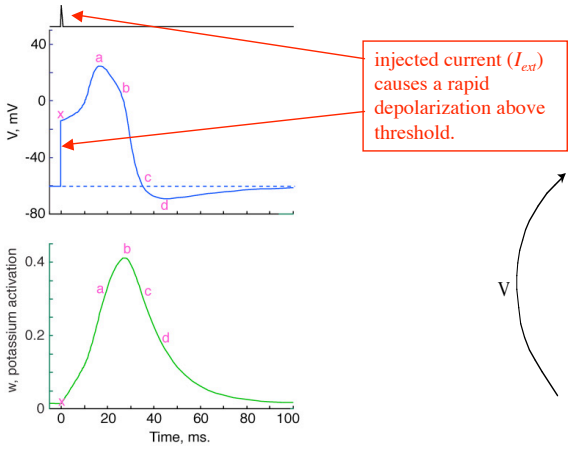
1. $m = m_\infty(V)$, no differential eqn.
2. there is no h, again no diff. eqn.
3. instead of n^4, we use w



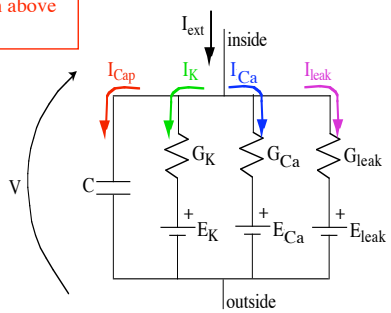
An action potential produced by this model is plotted below.

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).

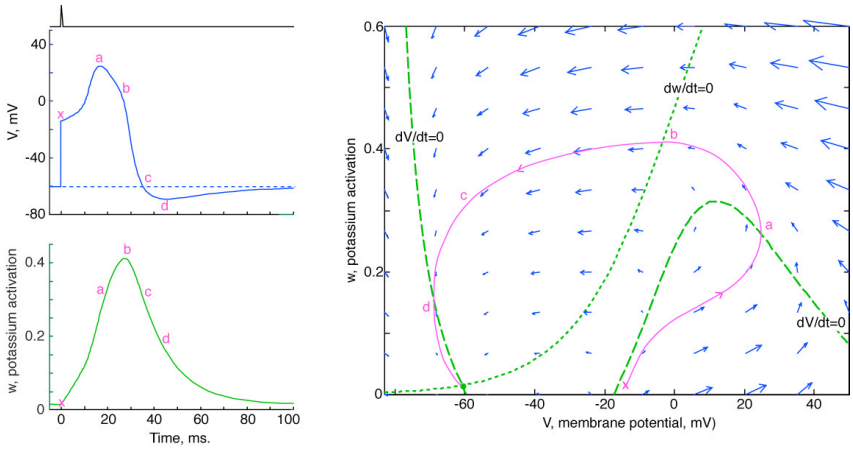


injected current (I_{ext}) causes a rapid depolarization above threshold.



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

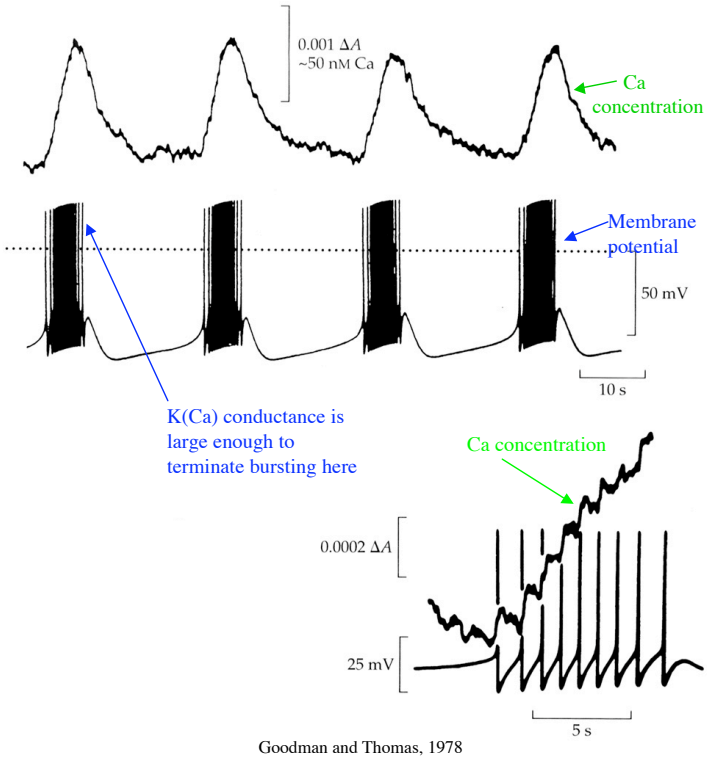
The resting potential is the point V =-60 mV, w = 0.04, where both dV/dt=0 and dw/dt=0 (the green dashed lines).



Some neurons show bursting activity, meaning a short period of high-rate firing with intervals of silence.

Often this is accompanied by Ca^{++} accumulation in the cytoplasm.

The burst is terminated by a *calcium-dependent potassium conductance* K(Ca) whose conductance increases as the [Ca^{++}] increases, until it is large enough to stop the burst.



Goodman and Thomas, 1978

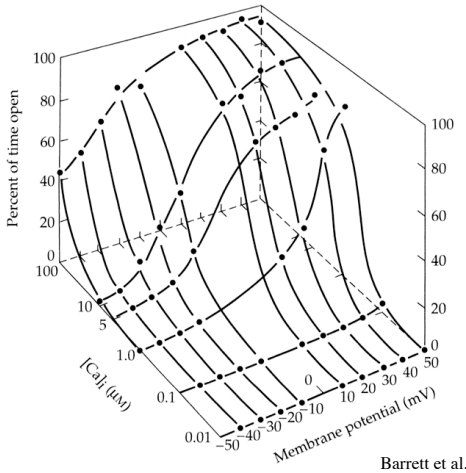
A *calcium-dependent potassium* or K(Ca) channel is activated by calcium concentration and sometimes also by membrane potential. The plot at right shows the open probability

$$n_{\infty KCa}(V, Ca)$$

for such a channel. The HH model for the channel's current $I_{K(Ca)}$ is as follows:

$$I_{K(Ca)} = \bar{G}_{K(Ca)}\, n_{KCa}\, (V - E_k) \quad \text{and}$$

$$\frac{dn_{KCa}}{dt} = \frac{n_{\infty KCa}(V,Ca) - n_{KCa}}{\tau_{KCa}}$$



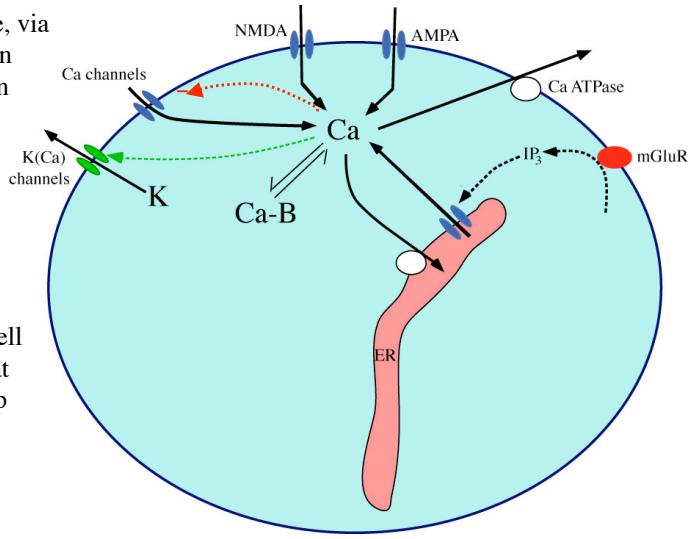
Barrett et al. 1982

This model is appropriate for so-called *BK* channels. Another group of K(Ca) channels, the *SK*s, are gated only by Ca (i.e. not by membrane potential).

Note that this channel behaves like a HH potassium channel with its n_∞ function shifted along the V axis by the Ca^{++} concentration.

The K(Ca) channel is one of many cellular processes that depend on the calcium concentration in some part of the cell. Calcium has three kinds of effects:

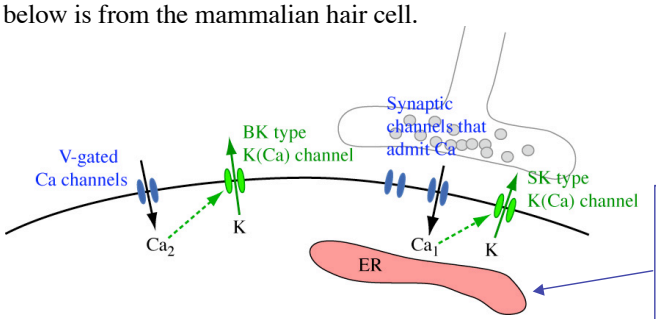
1. Immediate control of channel gating, as for the K(Ca) channel, or inactivation as for the Ca channel.
2. Short-term control of such processes as neurotransmitter release (not shown)
3. Longer-term control of the cellular steady state, via protein modification and gene expression (also not shown).



Of course, the ubiquitous role of Ca^{++} in control of cell functions means that models have to keep track of [Ca^{++}].

Neurons have multiple calcium pools which are segregated from one another. Sometimes these interact with different groups of calcium-dependent channels. The example below is from the mammalian hair cell.

Fuchs, 2002



Recent evidence suggests that there is a third calcium pool in the ER, coupled to the cytoplasm through ryanodine receptors.

For each Ca^{++} pool, a minimal model like the following is needed:

$$W\frac{dC}{dt} = S\left[-\frac{I_{Ca}(V,t)}{2F} - p(C,V)C\right] + k_1 B_C - k_2 C B$$

calcium current

active transport of Ca^{++}

calcium buffering

C = calcium concentration
I_{Ca} = Ca current through voltage gated or synaptic channels
B_C, B = bound and free Ca buffer

W = pool volume
S = pool surface area
$p(C,V)$ = active transport rate
k_1, k_2 = buffering rate constants

A *minimal model for bursting* can be obtained by adding a calcium pool and a K(Ca) channel to the MLE above.

$$C\frac{dV}{dt} = I_{ext} - G_K(V-E_K) - G_{KCa}(V-E_{KCa}) - \bar{G}_{Ca}\, m_\infty(V)(V-E_{Ca}) - G_L(V-E_L)$$

$$\frac{dw}{dt} = \frac{w_\infty(V)-w}{\tau_w(V)} \qquad G_K = \bar{G}_K w$$

The basic MLE model.

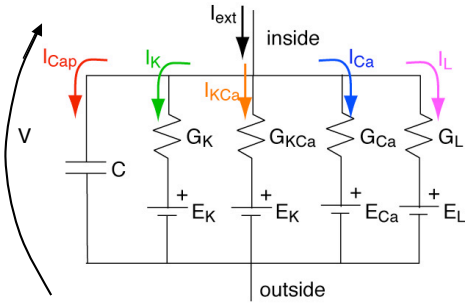
$$\frac{dCa}{dt} = A\left(-\frac{I_{Ca}}{F} - B\,Ca\right) \qquad G_{KCa} = \bar{G}_{KCa}\frac{Ca}{Ca+1}$$

New equations for the KCa channel dependent on Ca concentration.

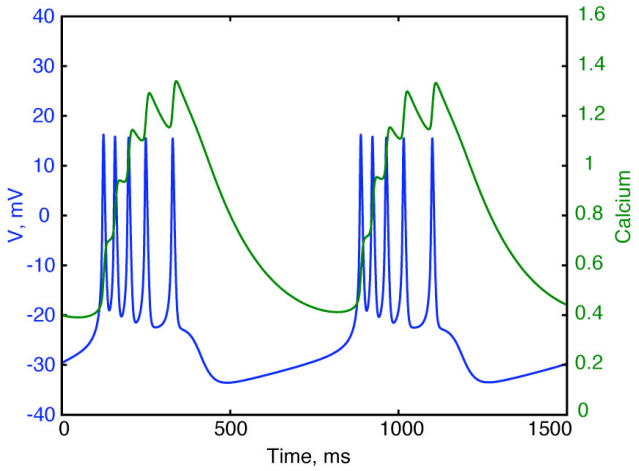
There are three differential equations, for V, w, and the calcium concentration Ca.

G_{KCa} is a function of Ca only.

G_{Ca} is governed only by the m_∞ function.



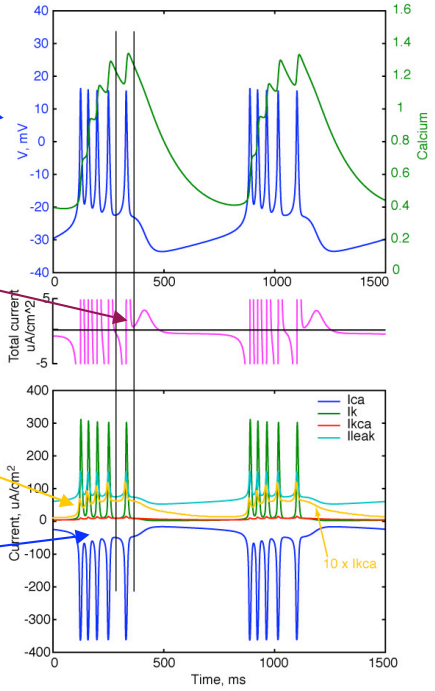
Bursting produced by the model.



Bursting produced by the model. Membrane potential and calcium behave as shown in a previous data slide.

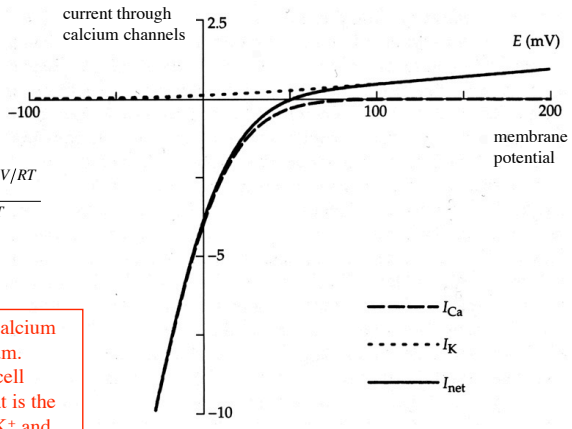
The total current through the membrane is outward at the termination of the burst, as expected from the hypothesized effect of the K(Ca) current.

The K(Ca) current builds up during the burst. The actual burst termination involves more than the K(Ca) current, however. Note the decreasing amplitude of the inward calcium current through the burst.



Calcium currents cannot be accurately modeled by the usual linear conductance equation $G_{Ca}(V\text{-}E_{Ca})$, as in the previous models. Because of the dramatic difference in the calcium concentration inside and outside the cell (10^{-7} M versus 10^{-3} M), the outward current is very small compared to the inward current. In fact, often the outward current through the Ca^{++} channel is actually carried by K^+. The GHK equation usually provides a sufficiently accurate model.

$$I_{Ca} = m^a h\ (const)\ V \frac{C_{in} - C_{out} e^{-2FV/RT}}{1 - e^{-2FV/RT}}$$



Suppose the outward current through a calcium channel is half calcium and half potassium. Given the usual concentrations inside a cell ($[K^+]$ = 150 mM, $[Ca^{++}]$ = 100 nM), what is the relative permeability of the channel for K^+ and Ca^{++}?

Hille, 2001

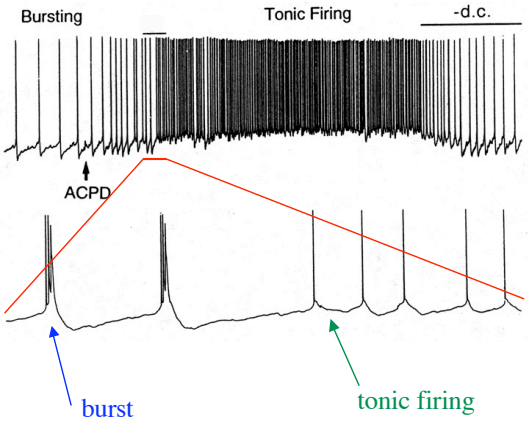
Neurons generally express a number of different channels. This gives them the ability to show a variety of patterns of discharge. The example below is from the mammalian cortex and thalamus, where neurons can produce spikes in bursts or in a tonic-firing mode. The cells switch modes under the control of metabotropic neurotransmitters (later lecture), often as part of the switch from sleeping to waking. A model containing the nine channel types at left can reproduce this activity.

Na - HH type
persistent (no inact.)

Ca - T-type (inact.)
L-type (no inact.)

Mixed cation - H channel
leak

K - delayed rectifier (HH type)
K(Ca) (coupled to L channels)
transient (A-type)



(ACPD activates metabotropic glutamate channels; in this case, the effect is to decrease a K^+ conductance, depolarizing the cell, which causes a switch from burst to simple-spike encoding.)

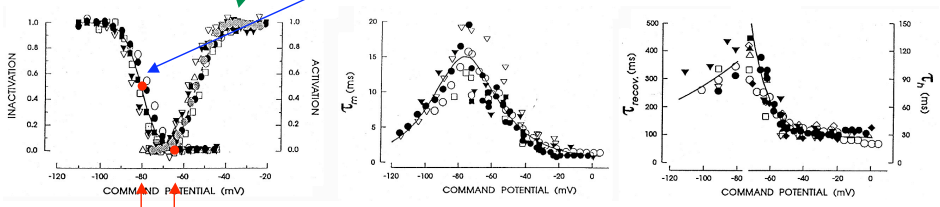
Wang & McCormick, 1993

The most important channel for this kind of bursting is the T-type calcium channel. It's HH model is shown below.

$$I_T = m^2 h(const)\frac{C_{in}e^{zFV/RT} - C_{out}}{e^{zFV/RT} - 1}$$

activation, $m_\infty(V)$

inactivation, $h_\infty(V)$



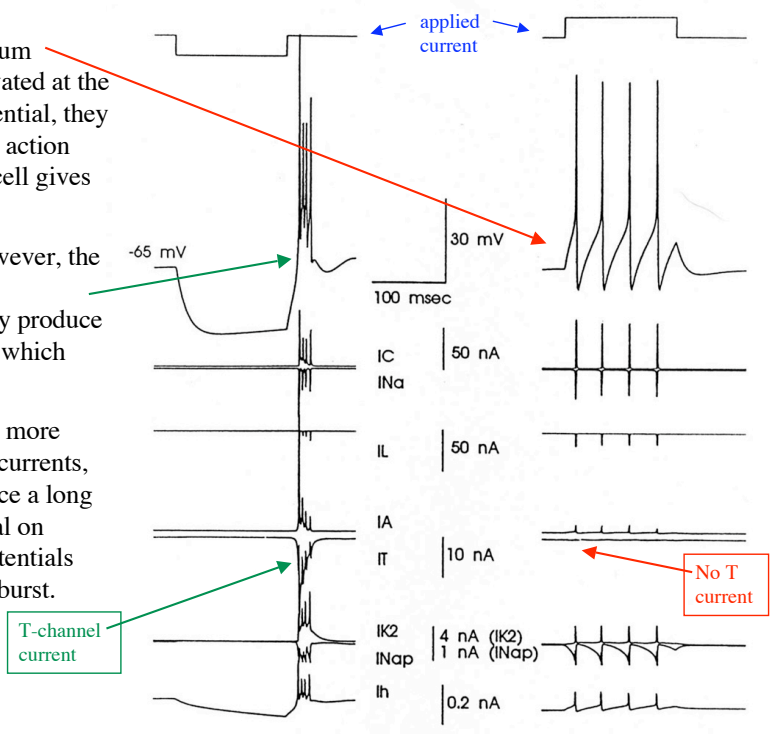
Note the difference in inactivation h_∞ between the -80 mV and -65 mV resting potentials

Huguenard and McCormick, 1992

Because the T calcium channels are inactivated at the -65 mV resting potential, they do not contribute to action potentials, and the cell gives simple spikes.

At -85 mV rest, however, the T channels are not inactivated, and they produce significant currents which cause the burst.

The T-current gates more slowly than the Na currents, so T currents produce a long slow action potential on which Na action potentials ride to produce the burst.



McCormick and Huguenard, 1992

This table lists a few types of Na and Ca channels that are important in producing various patterns of neural activity (see also Johnston & Wu, pp. 208-209) . . .

Current	Description	Function
Na^+		
I_{Na} or $I_{Na,t}$	Transient; rapidly activating and inactivating	Action potentials
$I_{Na,p}$	Persistent; non-inactivating	Enhances depolarization; contributes to steady-state firing
Ca^{2+}		
I_T, low threshold	Transient; rapidly inactivating; threshold negative to −65 mV	Underlies rhythmic burst firing
I_L, high threshold	Long-lasting; slowly inactivating; threshold around −20 mV	Underlies Ca^{2+} spikes that are prominent in dendrites; involved in synaptic transmission
I_N	Neither; rapidly inactivating; threshold around −20 mV	Underlies Ca^{2+} spikes that are prominent in dendrites; involved in synaptic transmission
I_P	Purkinje; threshold around −50 mV	Underlies Ca^{2+} spikes that are prominent in dendrites

McCormick in Shepherd, 1998

. . . and similarly for K channels.

Current	Description	Function
K^+		
I_K	Activated by strong depolarization	Repolarization of action potential
I_C ← (I_{KCa})	Activated by increases in $[Ca^{2+}]_i$	Action potential repolarization and interspike interval
I_{AHP}	Slow afterhyperpolarization; sensitive to increases in $[Ca^{2+}]_i$	Slow adaptation of action potential discharge; the block of this current by neuromodulators enhances neuronal excitability
I_A	Transient; inactivating	Delayed onset of firing; lengthens interspike interval; action potential repolarization
I_M	Muscarine sensitive; activated by depolarization; non-inactivating	Contributes to spike frequency adaptation; the block of this current by neuromodulators enhances neuronal excitability
I_h	Depolarizing (mixed cation) current that is activated by hyperpolarization	Contributes to rhythmic burst firing and other rhythmic activities
$I_{K,leak}$	Contributes to neuronal resting membrane potential	The block of this current by neuromodulators can result in a sustained change in membrane potential

McCormick in Shepherd, 1998

Channels in the thalamic neuron model:

I_{Na}	m^3h	12 μS	+45 mV
I_{NaP}	m	7 nS	+45 mV
I_{CaT}	m^2h	$40x10^{-6}$ cm^3/s *	
I_{CaL}	m^2	$80x10^{-6}$ cm^3/s *	
I_H	h	9 nS	-43 mV
I_K	$m(V,Ca^{++})$	1 μS	-105 mV
I_A (2)	m^4h	0.8 μS	-105 mV
I_{K2} (2)	$mh + m^4h$	0.8 μS	-105 mV
I_{Kleak}	1	15 nS	-105 mV
I_{Naleak}	1	6 nS	+45 mV

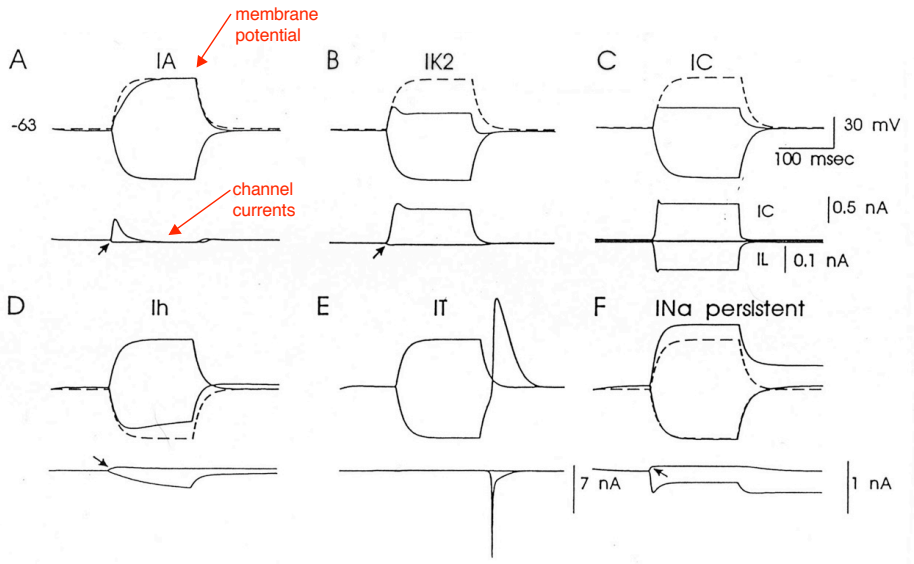
$$m_\infty(V,Ca) = \frac{250\,Ca\,e^{V/24}}{250\,Ca\,e^{V/24} + 0.1\,e - V/24}$$

Ca^{++} gating coupled to the L-type Ca^{++} channel only

These K^+ channels contain multiple components, with different HH models

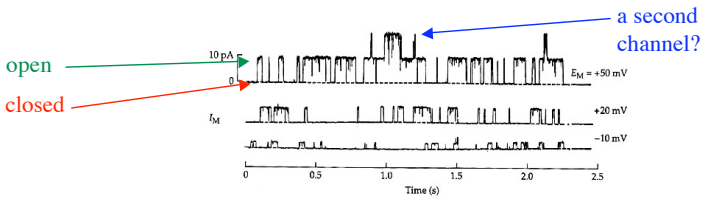
* Note the permeabilities given above translate into very large equivalent conductances (≈600 and 1200 μS) for the Ca^{++} channels.

Voltage responses to current pulses for a membrane containing capacitance, leak conductances and one or two other channels.

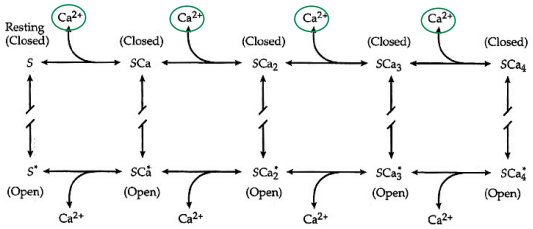


McCormick and Huguenard, 1993

Remember that the HH model is only an curve-fit to whole-cell data. Individual ion channels gate in a discrete process with a finite number of open and closed states. When recordings are made from a single BK channel using a patch electrode, the opening and closing of the channel can be seen as jumps in the current through the channel.



A more accurate model of the BK channel is shown at right. The channel binds Ca^{++} from left to right. Raising the membrane potential or binding Ca^{++} increases the probability of the open states. The HH model on a previous slide is an approximation to this. In fact, even this is a simplification.



$$A \underset{k_{BA}}{\overset{k_{AB}}{\rightleftharpoons}} B \qquad \frac{dB}{dt} = k_{AB}A - k_{BA}B$$