Systems Biology II: Neural Systems (580.422)

Lecture 6, Neural Excitability: Calcium and Bursting

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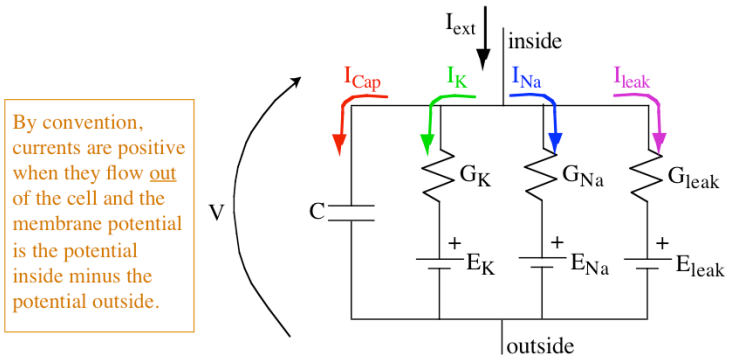
Reading:

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

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.

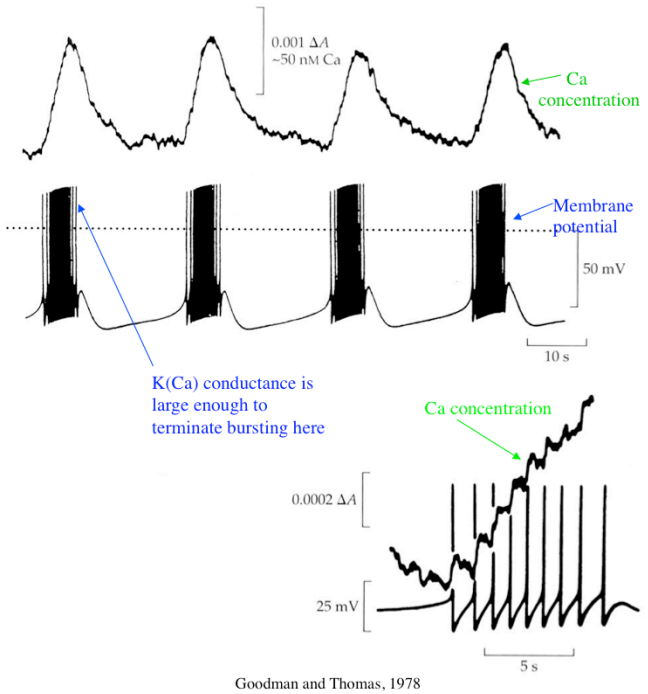
In the membrane model, each ion channel is represented by a battery in series with a resistor (e.g. Gna and Ena for sodium channels). The current through the resistor (Ina) is the current carried by a particular ion through the ensemble of channels of a particular type in the membrane. The battery/resistor 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 Ena = RT/F ln(Na(out)/Na(in)). The voltage difference across the resistor (e.g. V-Ena) 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, Ena. 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

Some neurons show bursting activity, meaning a short period of high-rate firing with intervals of no spiking.

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. Sometimes Ca-inactivation of Ca channels also contributes.



Goodman and Thomas, 1978

The slide shows the spike train of a bursting neuron, one that fires a burst of action potentials and is then silent for a period of time, followed by another burst, and so on. K(Ca) channels are often important in terminating such a burst. The top plot shows the calcium concentration in the bursting cell. Calcium builds up during the burst, because calcium is entering through voltage-gated calcium channels during each action potential. The inset at lower right shows a detail of the burst and the calcium concentration at a higher time resolution. Note the jumps in calcium concentration during each action potential. As the calcium concentration builds, the K(Ca) conductance increases (not shown), until the potassium conductance is sufficient to block further spiking.

The same effect can produce spike frequency adaptation, in which the spike discharge rate decreases during a steady response to some stimulus. In this case, the K(Ca) conductance is sufficient to slow down the spiking, but not large enough to block it.

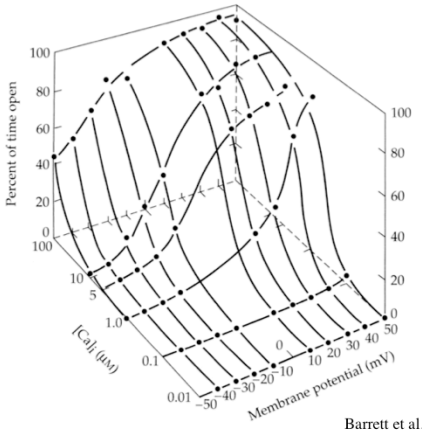
A *calcium-dependent potassium* or K(Ca) channel is activated by calcium concentration and sometimes also by membrane potential. The plot at right shows the open probability

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

for such a channel. A possible 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

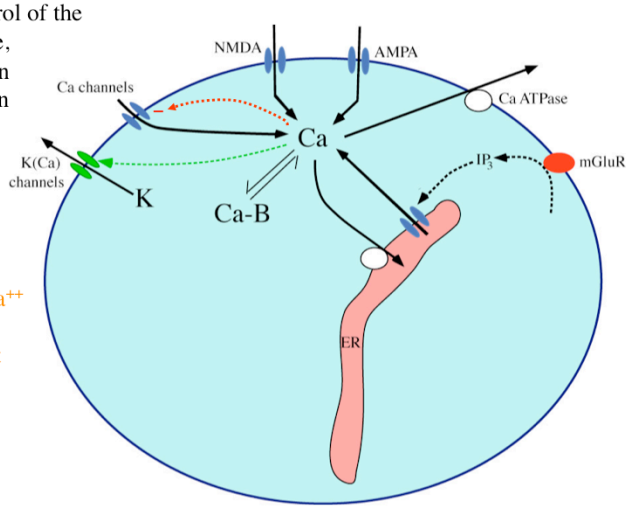
Note that this channel behaves like a HH potassium channel with its n_∞ function shifted along the V axis by the Ca^{++} concentration.

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

An important way that calcium affects membrane excitability is through calcium-dependent potassium channels. There are two families of such channels: the so-called BK channels and the SK channels. BK channels have large conductances and are gated by both calcium and membrane potential, as in the figure. One can think of these channels as delayed rectifiers whose n∞ functions are functions of calcium concentration also, so that the open probability of the channel is increased by either depolarization or increased calcium concentration. The SK channels are gated only by calcium.

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 some Ca channels.
2. Short-term control of such processes as neurotransmitter release (later)
3. Longer-term control of the cellular steady state, protein modification and gene expression (also later).

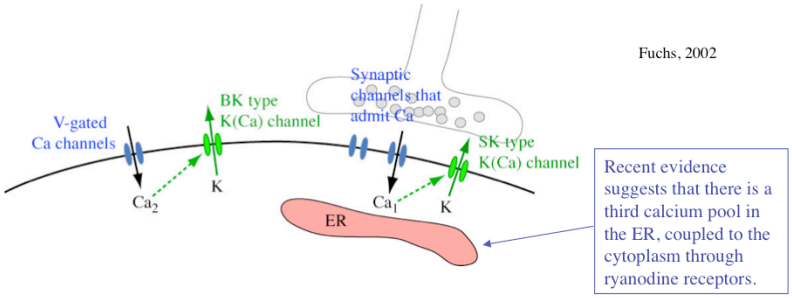


Of course, the ubiquitous role of Ca^{++} in control of cell functions means that models have to keep track of $[Ca^{++}]$.

Calcium channels are an essential component of neuron's excitability. Calcium currents are usually a relatively small part of the total membrane current, but calcium serves as an intracellular signal that controls many processes. Unlike other ions, the calcium concentration in the cytoplasm is a control variable. Normally the intracellular calcium concentration is quite low, typically 200 nM (compared to 10 mM for sodium and 150 mM for potassium). The calcium concentration is kept low by calcium pumps which move calcium out of the cell or into the ER and calcium buffering. During action potentials, calcium enters the cytoplasm through voltage-gated calcium channels; during synaptic activity, calcium enters through some synaptic channels (mainly NMDA channels, but some AMPA channels). Either source causes the calcium concentration to rise. An increase in calcium can close calcium channels (Ca-dependent inactivation) or open potassium channels (K(Ca) channels). It can also initiate a variety of processes including neurotransmitter release and activation of protein kinases.

Like the inactivation gate of the A channel in the previous slides, the calcium concentration in the cytoplasm serves as a short-term memory for the amount of excitability or excitatory synaptic input that the cell has experienced recently. The length of this memory is the time it takes the calcium to be transported out of the cytoplasm.

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.



The two potassium currents can be separated because they are blocked by different antagonists:

The BK type channels are driven only by calcium entry through voltage-gated channels (Ca_2 above).

The SK-type channels are driven only by calcium entry through the synaptic channels (Ca_1 above).

An important question when considering calcium driven processes is which calcium pools are relevant? Because of buffering, calcium does not diffuse very far in the cytoplasm. Thus the calcium admitted by a voltage-gated or synaptic channel is only available to calcium-dependent elements that are near the entry point. The slide shows an example from the hair cell in the auditory and vestibular systems. Voltage-gated calcium currents affect a population of BK type channels, whereas synaptic calcium currents affect SK channels. There is very little crosstalk between the two. There is increasing evidence that the locations of channels in the membrane is controlled by structural proteins so as to maintain relationships between specific populations of channels.

When modeling calcium effects in cells, an additional differential equation is necessary for each calcium pool.

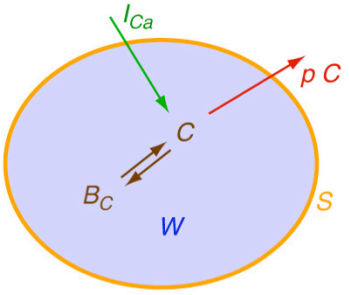
For each Ca^{++} pool, a model for calcium like the following is needed:

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

calcium flux through Ca channels

active transport of Ca^{++}

calcium buffering



C = calcium concentration

I_{Ca} = Ca current through voltage gated or synaptic channels

F = charge/mole of ions

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

When modeling calcium effects in cells, an additional differential equation like the one shown is necessary for each calcium pool. The equation models the time rate of change of calcium concentration C in the pool (the l.h.s.) as the sum of calcium entry through voltage-gated or synaptic channels (Ica), pumping of calcium out of the pool (p(C,V), and buffering. This is the simplest possible equation; more complex equations are needed if the effects of diffusion of calcium are to be included in the model. For examples of the latter, see C. Koch, Biophysics of Computation (1999) chapter 11.

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

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

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

The basic MLE model.

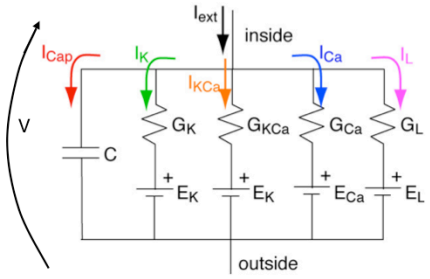
$$\frac{dCa}{dt} = A\left(-\frac{I_{Ca}}{2F} - B\,Ca\right) \qquad G_{KCa} = \bar{G}_{KCa}\frac{Ca}{Ca+1}$$

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.

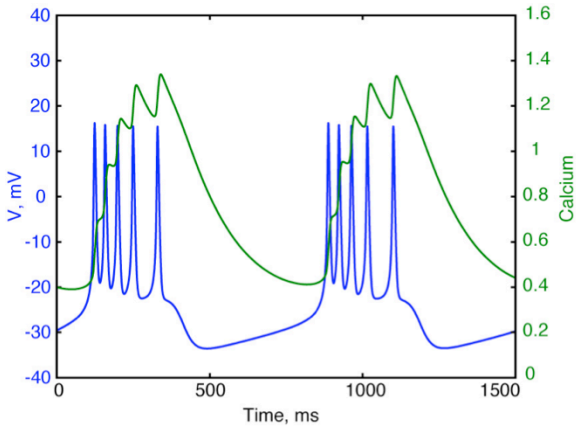
G_{Ca} is governed only by the m_∞ function.



Rinzel and Ermentrout 1998

To model bursting, it is necessary to add an additional channel to the model (for a K-Ca channel) and a differential equation to keep track of calcium. For the simplest model, the conductance of the K-Ca channel is just a function of the calcium concentration. Note that the usual Na channel has been replaced by a Ca channel in this model, so there is a source of Ca. Real bursting cells are more complex, discussed later.

Bursting produced by the model.



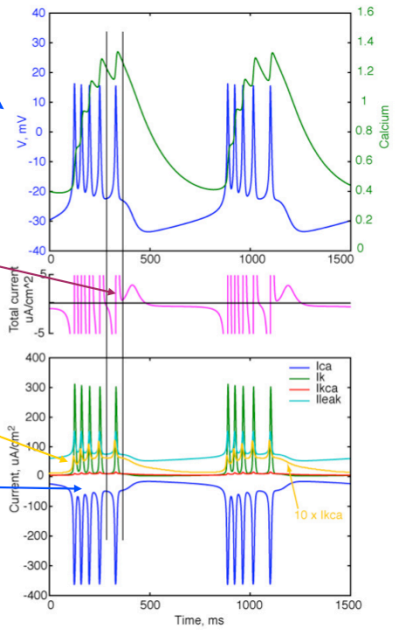
Solution to the bursting model in the previous slide. As in the data shown previously, the model fires a burst of action potentials (blue trace). The parameters of the model are adjusted so that it does not have a stable resting potential, but continuously produces bursts of spikes as shown. On each action potential, there is a step increase in Ca++ concentration (green trace) due to opening of voltage-gated Ca++ channels. The Ca++ decreases between spikes, but the increase is larger than the decrease during rapid spiking and the Ca++ builds up. As the Ca++ increases, the KCa conductance increases, eventually stopping the action potentials and forcing a repolarization of the membrane potential. Then the Ca++ concentration decreases back down towards its resting value Kca is small enough to allow the spiking to begin again, starting another cycle.

Bursting produced by the model.

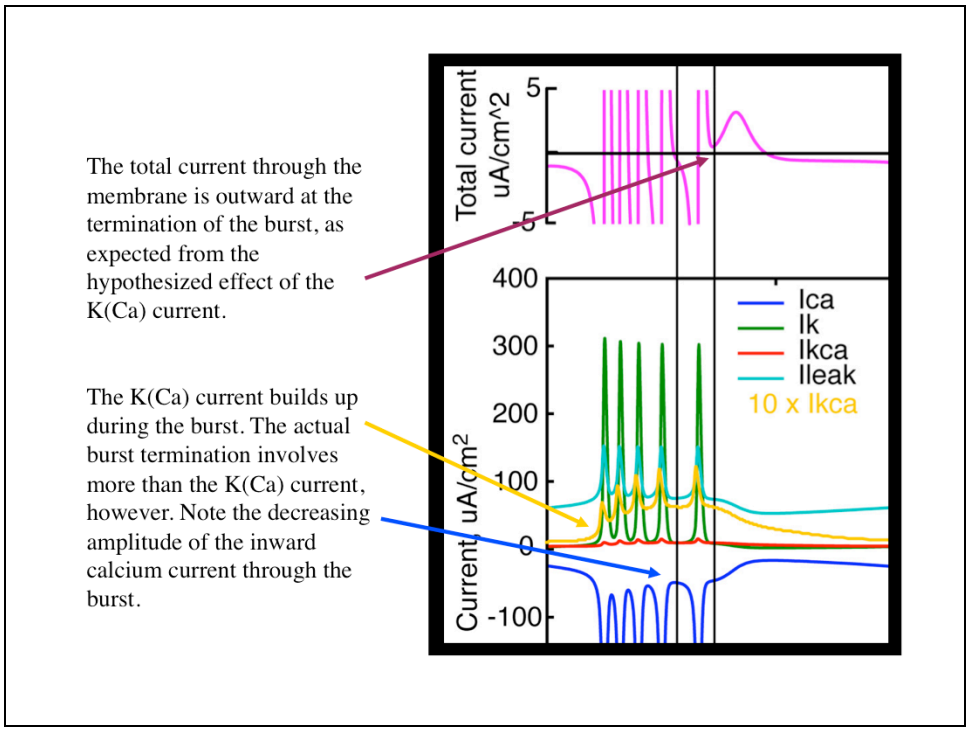
The total current through the membrane is outward (hyperpolarizing) at the termination of the burst, as expected from the hypothesized effect of the K(Ca) current.

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.

Note how small the K(Ca) current is.



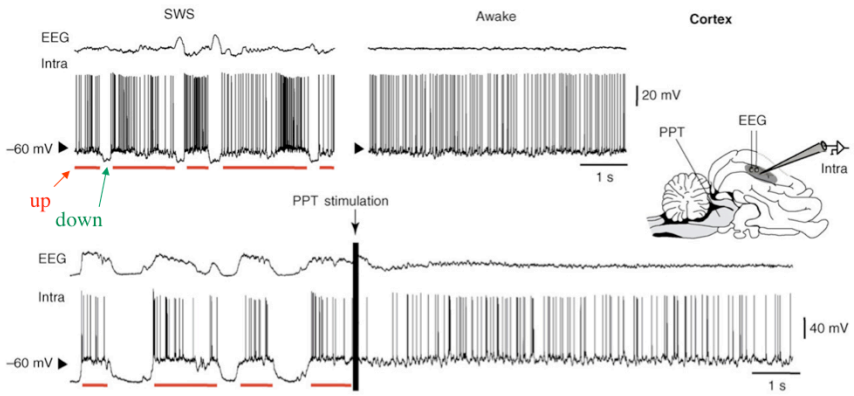
Detailed examination of the summation of currents. The K(Ca) current is very small (red trace) but is large enough to produce the bursting. Its behavior can be seen in the yellow trace, which shows 10*Ikca. Note that Ikca builds up during the burst, decreasing the membrane potential in between action potentials, which decreases Ica. Eventually, Ica is smaller than the sum of the K currents and the bursting stops.



View of the currents at the termination of the burst. During a spike, the total membrane current is initially inward (negative, depolarizing) from the Ca current (blue), but then outward (positive, hyperpolarizing) from the sum of the K currents, giving repolarization. The next spike begins when the potassium currents decrease enough that the residual Ca current makes the total current negative again. This is seen at the left-hand vertical black line for the last spike in the burst. After the last spike, however, the Ca current is not sufficient to produce a net inward current because of the (small) increase in KCa current and the decrease in the Ca current. This terminates the burst at the right hand vertical black line.

Neurons in cortex show two modes of activity, correlated with the wake/sleep state. Slow-wave sleep (SWS) shows switches between up and down states. When awake, the brain seems to be permanently in the up state.

Top: intracellular recordings in vivo showing natural sleep and waking states.



Bottom: transition from SWS pattern of up and down states to an activated pattern by stimulating in the pedunculopontine tegmentum (PPT), part of the reticular activating system. This is in a cat anesthetized with ketamine/xylazine.

Destexhe et al. 2007

Up states and down states in thelamocortical neurons.

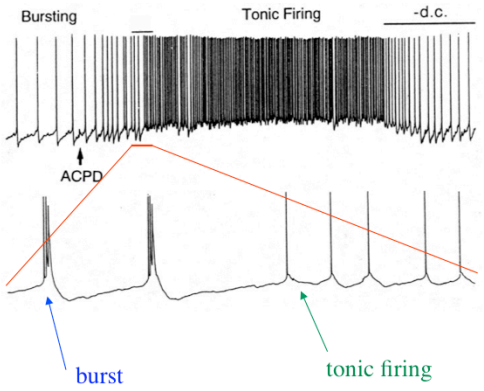
Neurons generally express a number of different channels. The example below is from the mammalian cortex, where neurons can produce spikes in bursts (during down state) or in a tonic-firing (during up state) mode. The cells switch modes under the control of metabotropic neurotransmitters (later lecture), 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.)

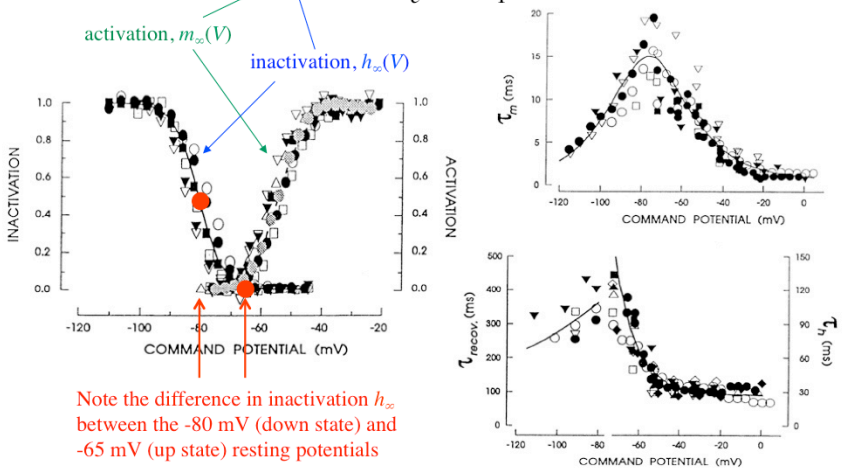
Wang & McCormick, 1993

An example of a neuron typical of the mammalian thalamus and cortex. This neuron displays two modes of spiking, bursts and tonic firing, defined in the slide. The cell shifts from one mode to the other when the resting potential of the cell changes from up to down state. In this case the resting potential is changed by adding a drug (ACPD), which opens channels that depolarize the membrane. In the brain, the switch would occur by releasing glutamate at a certain kind of synapse that produces a metabotropic effect.

The next few slides show a model that accounts for this behavior. The model has the nine channels listed at left, plus a leak channel. Many of these have already been discussed: leak channels regulate the resting potential; the HH-type Na channel and the three types of K channels produce the action potentials; the L-type calcium channels and the K(Ca) channel terminate spiking during the bursts; and the H channel is a pacemaker that depolarizes the cell between bursts or spikes. The persistent Na channel is a small sodium conductance that does not have an inactivation gate. When present, it increases the excitability of the cell, serving to amplify depolarizing potentials of all types. The channel that is most important for the bursting-tonic firing switch is the T-type calcium channel.

The most important channel for this kind of bursting is the T-type calcium channel. Its HH model is shown below; it is similar to the Na channel, except that the *h* gating is at lower potentials.

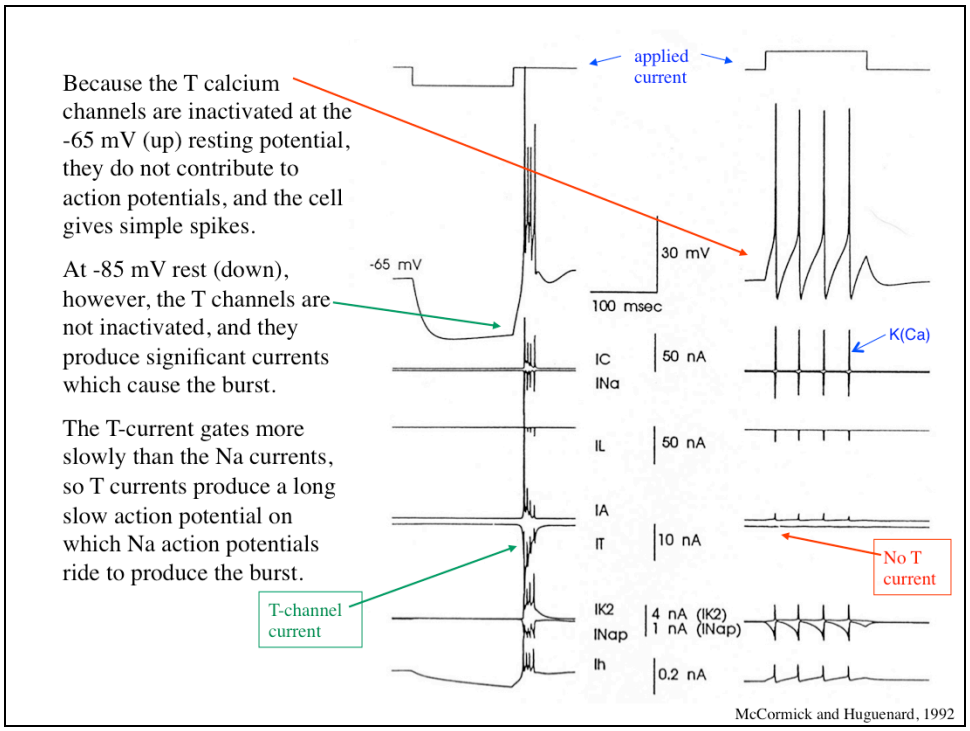
$$I_T = m^2 h(const)\frac{C_{in}e^{zFV/RT} - C_{out}}{e^{zFV/RT} - 1}$$



Note the difference in inactivation h_∞ between the -80 mV (down state) and -65 mV (up state) resting potentials

Huguenard and McCormick, 1992

This slide shows the HH model of the T-type calcium channel. It is similar to the HH sodium channel in that it has an activation gate and an inactivation gate. The HH variables m and h are similar to those for the HH sodium channel. The m∞ and h∞ functions are shown at left below. Notice that the T channels are inactivated when the cell is depolarized to a resting potential of -60 mV (up state); however for a -80 mV resting potential, the T channels' inactivation gates are about 50% open (down state). This is the important difference between the two modes of operation of the cell.



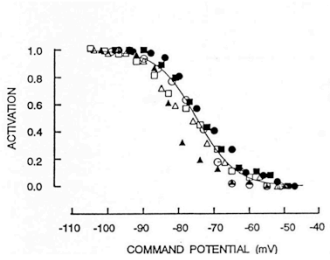
The slide shows the results of simulations of the model containing the conductances from the previous slide. The leak conductance is set so that the resting potential is about -65 mV, so that there is no T-type calcium current. The right-hand column of plots shows the membrane potential (2nd from the top) and the various ionic currents for this situation. In response to a depolarizing current (top trace) the cell fires tonically. The currents below show a standard HH-type behavior, only with more currents involved, but the basic physiology (Na depolarizes, K hyperpolarizes) is the same. Spikes are produced by the sodium current and perhaps the L-type calcium current and repolarized by the collection of potassium currents. The H current contributes to the depolarization between spikes. There is no T-type calcium current, because those channels are inactivated.

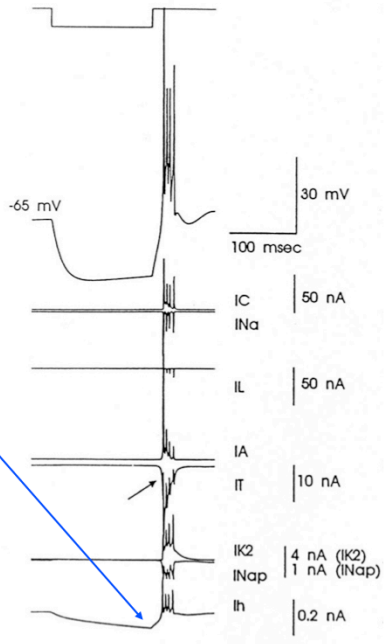
By contrast, if the cell is hyperpolarized by negative current (left column in the figure), the inactivation of the T-type channels is relieved and the cell fires a burst of spikes at the end of the hyperpolarization. The large T-type current in the left column is the difference between the burst and the tonic firing in the right column. If the leak conductance is changed in the model to make the resting potential -80 mV, then the model will fire trains of bursts as in the real cells shown in a previous slide.

A second important channel is the H-channel, so-called because it contains only an inactivation gate h, i.e.

$$I_H = \bar{G}_H h(V,t)(V - E_H)$$

Because H admits both potassium and sodium (E_H~-10 mV), it is a depolarizing mixed cation channel. It's role in the cell is to provide a pacemaker current when the cell is hyperpolarized.





The H channel serves as a pacemaker, depolarizing the cell during the hyperpolarizing current, or in between bursts for the model with a -80 mV rest potential.

This table lists a few types of Na and Ca channels that are important in producing various patterns of neural activity . . .

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

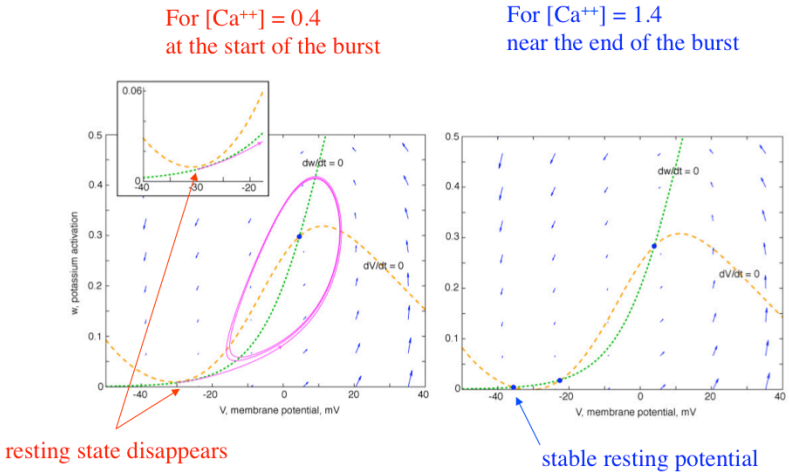
McCormick in Shepherd, 2004

. . . 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, 2004

An explanation for the burst initiation in the minimal bursting model can be found in the phase plane. The planes below are approximate, showing the 2-D system that remains when the calcium concentration is fixed and the corresponding differential equation is removed.



Phase planes for the system consisting of the V and w HH variables for two of the differential equations in the system. The third differential equation, for Ca, is deleted and Ca is held fixed at a low value (left plot) that starts bursting by eliminating the equilibrium point at -30 mV. This system will continue spiking forever, because Ca is not allowed to increase, thus preventing the increase in KCa conductance which would stop the spiking. At right, the Ca++ concentration is held at a higher value at which there is a stable equilibrium point at -35 mV. Note that the blue direction arrows change only very slightly between these two conditions.