Neural excitability, Hodgkin-Huxley models

Eric D. Young

References:


For an elegant program that simulates the Hodgkin-Huxley model, see http://www-2.cs.cmu.edu/~dst/HHsim (David Touretzky).

The goal of this lecture is to discuss neural excitability in the context of Hodgkin-Huxley style models of the action potential. Chapter 7 of Johnston and Wu provides a nice introduction to this topic, assuming that the material in chapters 2-6 has been mastered.
Neurons represent information by changes in their membrane potential $V$, produced either by synaptic inputs or by autonomous properties of the collection of ion channels in the cell membrane. Ion channels differ in the ion that flows through them.

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 the next lecture. These provide depolarization and hyperpolarization of the membrane potential. 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?
Excitability differs among neurons. Five examples to illustrate differences in response to a simple step depolarization of the membrane. The differences among these are produced by differences in the ensemble of ion channels in the membrane.

Neurons spike trains are (“spike trains” is jargon for the train of action potentials produced either spontaneously or in response to some stimulus). The examples above are all taken from a part of the auditory system, but there is nothing special about this patterns for hearing. In each case, the main plot shows membrane potential in response to a depolarizing (positive) current injected into the cell. Membrane potential is recorded intracellularly and the waveform of the injected current is plotted below the spike trains. In two cases (left column), responses to hyperpolarizing (negative) currents are also shown.

The neuron at upper left (“steady spiking”) responds to steady depolarization just as the Hodgkin-Huxley model would, with a steady train of action potentials. The neuron at lower left (“strong rectification”) produces only a spike at stimulus onset or a spike at the offset of hyperpolarization (an “anode break” spike). This behavior is produced by a potassium channel like the HH delayed rectifier, except that it is activated at the resting potential. It is thus able to block spikes after the first one or two. The two examples in the middle column show delayed spiking after the onset of depolarization. This behavior will be discussed later in this lecture. The example at right shows complex spiking, meaning that the action potentials are produced by a mixture of sodium and calcium channels. This behavior will also be discussed.
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.

\[ I_{\text{cap}} + I_K + I_{\text{Na}} + I_{\text{leak}} = I_{\text{ext}} \]

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

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.

In the membrane model, each ion channel is represented by a battery in series with a resistor (e.g. G_{\text{Na}} and E_{\text{Na}} for sodium channels). The current through the resistor (I_{\text{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 \( E_{\text{Na}} = \frac{RT}{F} \ln(\text{Na}(\text{out})/\text{Na}(\text{in})) \). The voltage difference across the resistor (e.g. V-\( E_{\text{Na}} \)) 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 \( E_{\text{Na}} \). 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 a statement of Kirchoff’s current law for the circuit model. Usually additional differential equations are necessary to model the conductances. The Hodgkin-Huxley model is an example.
At the resting potential, $dV/dt = 0$, so the resting potential is given by

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

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 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 (next lecture) 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 Thèvenin 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 critical property of ion channels for excitability is *gating*, illustrated below for single Na channels and for an ensemble of channels. The latter is the current that flows through all the channels of a particular type in the cell.

In the case of the Na channel, the gates are closed at the resting potential and open in response to depolarization. However, the opening is transient. This behavior reflects the presence of two gates:
- Activation - opens with depolarization
- Inactivation - open at rest, closes with depolarization

The ensemble or whole-cell sodium current. As predicted by the battery-resistor model of a previous slide, this is a negative or inward current.

Models for ion-channel conductances have to account for voltage-gating of ion channels. Ion channels have a gate which is either closed or open and channels snap back and forth between these two states. The probability of being open varies with the membrane potential. The single-channel data above show the behavior of a sodium channel. It is closed at -80 mV and opens transiently when the membrane is depolarized to -30 mV. To model action potentials, we deal with the sum of the currents through all the channels in a membrane. This is shown by the bottom trace in the slide. Essentially it is a smoothed version of the individual channel traces, showing an increase in current when the depolarization occurs and a decay to zero current. This corresponds to the probability that channels are open, inferred from the single channel records.

If you don’t understand this kind of voltage-clamp experiment, refer to the notes from first semester or Johnston and Wu, chapters 6 and 8.
The Hodgkin-Huxley model represents ensemble currents. It represents currents using the linear model consistent with the battery-resistor representation

\[ I_k = G_k (V - E_k) \]

and so on for \( I_{\text{leak}} \) and \( I_{\text{out}} \).

where the conductances are given by

\[
\begin{align*}
G_k &= g_k n^4 \\
G_{\text{leak}} &= g_m m^3 h
\end{align*}
\]

\[
\begin{align*}
\frac{dn}{dt} &= \frac{n_m(V) - n}{\tau_n(V)} \\
\frac{dm}{dt} &= \frac{m_m(V) - m}{\tau_m(V)} \\
\frac{dh}{dt} &= \frac{h_m(V) - h}{\tau_h(V)}
\end{align*}
\]

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 appropriate, but the power of \( m \) is not. In fact, the gating of sodium channels is more complex and the HH model is an approximation.
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

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

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

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 $n(V)$, $m(V)$, and $h(V)$ determine whether gates serve to activate channels (conventionally, open the channel with depolarization) or inactivate the channel (close the channel with depolarization).

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 \( m_\infty(V) \), \( m \), \( I_{Na} \), 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 \( \mu \)A 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.
What would be the effect of adding an H-channel to the Hodgkin-Huxley model? This is a channel with an inactivation gate only, so that

\[ I_H = \overline{g}_H h(V - E_H) \quad \text{where} \quad E_H = -20 \text{ mV} \]

This channel should be excitatory, because its reversal potential is substantially above the resting potential, but it will only be active with the membrane potential in the vicinity of the resting potential. Such a channel is a pacemaker.

H-channels are mixed-cation channels that have only an inactivation gate. The HH model of the channel is given in the graph. Note that for most of the range of action potentials, the steady-state value of the channels gate is closed. The gate will open only near the rest potential. Think about the effect of a channel which is depolarizing (because it is a mixed-cation channel and therefore produces an inward current) but is activated only near the rest potential. Such a channel might make the rest state unstable by depolarizing the channel when it is at rest. In fact, H channels often serve this pacemaker role.
The H-channel will be rapidly inactivated during the action potential. Following the spike, the H-channel will activate slowly. Because $E_H$ is substantially above resting potential (-20 mV), the H current will be inward (depolarizing) with V near rest. Thus the H channel will have an excitatory effect. If the excitatory effect is sufficient, it will drive the cell above threshold, giving continuous spiking, pacemaker activity.

A qualitative explanation of the behavior of an H channel during an action potential. The plot at top right repeats the HH model of the channel. The plot at bottom right shows an action potential waveform with the same membrane potential axis as the HH model and with time running vertically. The green and red arrows show the $h_{\infty}$ values that would drive the h channel gate during the peak of the action potential (red, closing the h channel gate) and immediately after the action potential (green, opening the h channel gate).
Pacemaker activity produced in the HH model by the addition of an H-channel with the properties in the previous slide. (Without the H-channel, the membrane potential is stable at the rest potential.)

The behavior of the $h$ gate is similar to what was predicted.

The inward current during the interstimulus interval depolarizes the cell and produces the next AP.

Results of a simulation of the HH model with an added H channel. The model without the channel would be stable at the rest potential; the pacemaker effect of the channel is evident.
Note that the H-conductance and the current through the H channel are very small compared to the currents associated with the action potential. (The same is true of the leak current, green).

This is a general motif: the currents that control cell excitability near threshold are small compared to the currents evoked once threshold is exceeded. Often the most important ion channels for information processing are the small ones that are active near rest potential.

Analysis of the conductance and current through the channels in this model.
One potassium channel type, the transient or A channel, has relatively rapid inactivation.

\[ I_A = g_A m^4 h (V - E_K) \]

The \( m \) and \( h \) functions are shown at right. For the channel modeled here, \( \tau_m \approx 1 \text{ ms} \) and \( \tau_h \approx 11 \text{ ms} \).

Note that the channel is inactivated for typical resting membrane potentials and the action potential is de-inactivated only in response to hyperpolarizing potentials (like the IPSPs shown).

A second example of a channel that changes the properties of membrane excitability. Many potassium channels have inactivation gates, so that a full model of such channels is similar to the HH sodium channel model. The so-called potassium A channel has \( h^\infty \) and \( n^\infty \) functions like those drawn above. Notice that this channel is inactivated at the resting potential (-60 mV). Thus it can only produce current if excitation is preceded by inhibition.

The graph at bottom right shows a train of action potentials preceded by a hyperpolarization which might be caused by an inhibitory synaptic input. Whereas the inactivation gate is closed at the resting potential (red arrow), it is partly opened by the hyperpolarization (green arrow). The effect is to add potassium current when the cell is depolarized, which opens the A channels’ \( m \) gates, blocking action potentials for a brief time after depolarization.
Cells with transient potassium channels often show **pausing**, a delay in response to depolarizing currents.

The pause is longer if the depolarizing current is preceded by a hyperpolarizing current. This occurs because the hyperpolarization gives the channel time to de-inactivate.

No hyperpolarization, no pause

Hyperpolarization is followed by a pause

An example of a neuron that displays pausing or delayed spiking behavior when a depolarization is preceded by a hyperpolarization. The neuron is stimulated by current injection, as shown by the waveform at the bottom of the slide. A hyperpolarization or slight depolarization precedes the main depolarization. With slight depolarization, the neuron spikes immediately following depolarization (top trace). With hyperpolarization, there is a significant delay before spiking begins (third trace). This effect can be reproduced by adding an A channel to the model (next slide).

The behavior of this example is slightly different from that of the previous slide, in that the neuron requires less hyperpolarization to create the delay. Presumably this behavior reflects the threshold of the inactivation function $h_{\infty}(V)$ which is higher (more positive) than in the example in the previous slide.
A HH model with a transient potassium current like that described above shows pausing behavior. The A channel’s current peaks during the pause, stabilizing the membrane and blocking action potentials.

Note that the transient potassium channel is a sort of memory for recent hyperpolarizing events, like IPSPs.

Showing the responses of a HH-like model with an A current added. The stimulus is the hyperpolarizing current followed by depolarizing current shown in the bottom trace. The membrane potential is shown in the middle and the A current is shown at top.
The calcium concentration in the cell is an additional important variable generating and controlling cell excitability. 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 (not shown).

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. 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.
Calcium currents cannot be modeled by the usual Hodgkin-Huxley linear equation. 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, in some cases, like the one shown here, the outward current through the Ca$^{2+}$ channel is actually carried by K$. The GHK equation usually provides a sufficiently accurate model.

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

Hille, 2001

Suppose the outward current through a Ca channel is half calcium and half potassium. Given the usual concentrations inside a cell ($[K^+] = 150$ mM, $[Ca^{2+}] = 100$ nM), what is the relative permeability of the channel for K$^+$ and Ca$^{2+}$?

Calcium currents show extreme rectification because of the large difference concentration difference between the inside and outside of the cell (200 nM versus 1-2 mM). The GHK formalism for current-voltage relationships can be used to model calcium currents. Recall (from 1st semester) that the GHK current-voltage relationship approaches straight lines at large negative and large positive membrane potentials. The slopes of these lines are proportional to the calcium concentration outside and inside the cell, respectively. The predicted current for a calcium channel using this model is the dashed line in the graph. The solid line is the actual current measured for a calcium channel. The difference between the two is actually potassium current leaking through the channel.

The practical consequence of the extreme rectification of calcium channels is that the GHK equation has to be used for calcium currents, as opposed to the simple resistor model used for most channels, e.g. $G(V-E)$. An example is given in the slide. Not that HH variables, m and h, are used to modulate the current and model gating as usual.
A calcium-dependent potassium or K(Ca) channel is activated by calcium concentration and perhaps also membrane potential. The plot at right shows the HH activation function

\[ m_{\infty}(V, Ca) \]

for such a channel. The HH model for such a channel is as follows:

\[ I_{K(Ca)} = \sigma_{K(Ca)} m(V - E_k) \quad \text{and} \quad \frac{dm}{dt} = \frac{m_{\infty}(V, Ca) - m}{\tau_{KCa}} \]

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

Ca also gates some chloride channels and inactivates some Ca channels.

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 or slo 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 \( n_{\infty} \) functions are functions of calcium concentration also, so that the open probability of the channel is increased by either depolarization or calcium concentration. The SK channels are gated only by calcium.
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.

For each pool, equations like the following are needed:

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

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

$C = \text{calcium concentration}$
$I_{ca} = \text{Ca current through voltage-gated or synaptic channels}$
$B_c, B = \text{bound and free Ca buffer}$

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 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 channels ($I_{ca}$), 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, chapter 11 (1999).
Calcium accumulation is often used to terminate bursting in neurons. During a burst of spikes, Ca builds up inside the cell (figure at lower right). As $[\text{Ca}]_\text{m}$ rises, the $K(\text{Ca})$ conductance increases, ultimately stopping spiking and terminating the burst.

(In many cases Ca-dependent inactivation of Ca channels is also important)

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. $K(\text{Ca})$ 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 $K(\text{Ca})$ conductance increases, 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 $K(\text{Ca})$ conductance is sufficient to slow down the spiking, but not large enough to block it.
Neurons generally express a number of different channels. This gives them the ability to show a variety of different patterns of discharge. The example below is from the mammalian cortex and thalamus, where neurons can produce spikes in **burst**s 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.

<table>
<thead>
<tr>
<th>Channel Type</th>
<th>Function</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na - HH type</td>
<td>Persistent</td>
<td>Bursting</td>
</tr>
<tr>
<td>Ca - T-type</td>
<td></td>
<td>Tonic Firing</td>
</tr>
<tr>
<td>L-type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed cation - H channel</td>
<td>Leak</td>
<td></td>
</tr>
<tr>
<td>K - delayed rectifier (HH type)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K(Ca) (coupled to L channels)</td>
<td>Transient (A-type)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>burst</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>tonic firing</strong></td>
<td></td>
</tr>
</tbody>
</table>

Wang & McCormick, 1993

(ACPD blocks metabotropic glu channels; in this case, the effect is to change the resting potential of the cell, which causes a switch from burst to simple-spike encoding.)

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 is changed, as in the example. In this case the resting potential is changed by adding a drug. In the brain, the switch would occur by releasing glutamate at a certain kind of synapse that produces a metabotropic effect. These effects will be discussed later. What is important for now is the change in resting potential.

The next few slides show a model that accounts for this behavior. The model has the nine channels listed at left. 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 behavior is the T-type calcium channel. It’s HH model is shown below.

\[ I_T = m^2 h (\text{const}) \frac{C_m e^{FV/RT} - C_{out}}{e^{FV/RT} - 1} \]

activation, \( m_\infty(V) \)
inactivation, \( h_\infty(V) \)

Note the difference in inactivation between the -80 mV and -60 mV resting potentials

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 \( m_\infty \) and \( h_\infty \) 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; however for a -80 mV resting potential, the T channels’ inactivation gates are about 50% open. This is the important difference between the two modes of operation of the cell.
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.

The slide shows the results of simulations of the model containing the nine 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. 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.

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. The large T-type current 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 action potentials as in the real cells.