RECALL - Four first order ODEs can get you a spiking neuron!

Start with the general equation for dV/dt. Add to this, the two (m and n) activation ODEs and one inactivation (h) ODE.

$$C * dV/dt = -I_{Na} - I_K - I_{leak} + I_{inject}$$

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

where $G_{Na} = Asoma * \bar{g}_{Na} * m^3 h$, $G_K = Asoma * \bar{g}_K n^4$, and .....

m, h and n are described by first order ODEs! .... as follows :

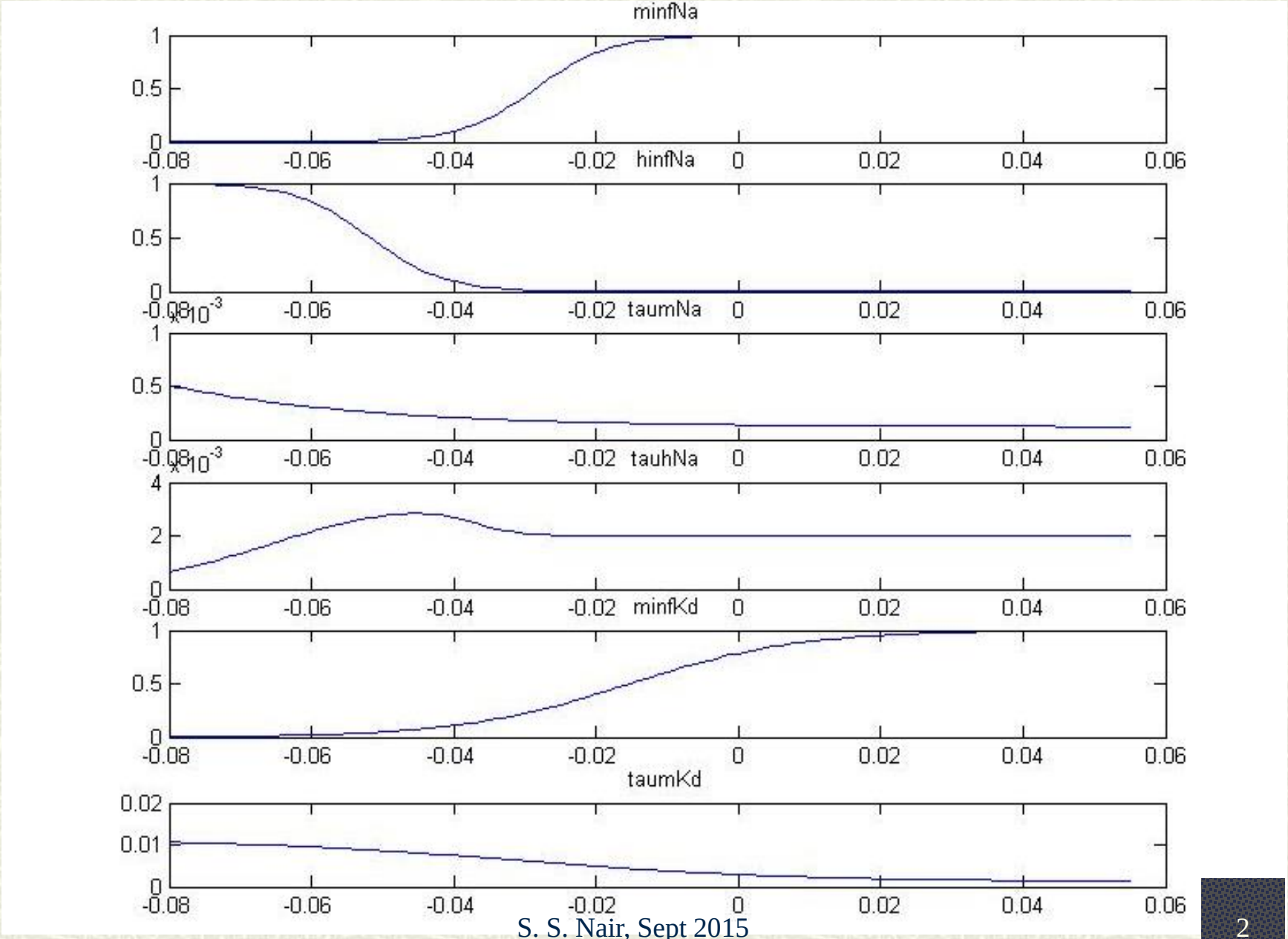
$$\tau_m(V) * dm/dt + m(V) = m_\infty(V) \quad \text{(ODE for } Na^+ \text{ activation)}$$

$$\tau_h(V) * dh/dt + h(V) = h_\infty(V) \text{ for } Na^+ \quad \text{(ODE for } Na^+ \text{ inactivation)}$$

$$\tau_n(V) * dn/dt + n(V) = n_\infty(V) \text{ for } K^+ \quad \text{(ODE for } K^+\text{)}$$

Remember that the algebraic eqns. $m_\infty(V)$ and $\tau_m(V)$ .... and the other activation functions depend on V – you just plotted them.

y-axis: activation functions or τ; x-axis:V in volts



Let's try to understand the 'activation' curve (m-curve)

First, plot the m curve completely and label it.

How does m differ from m_∞?

Plot below a membrane with lots of pores

'Connect' this to the activation curve

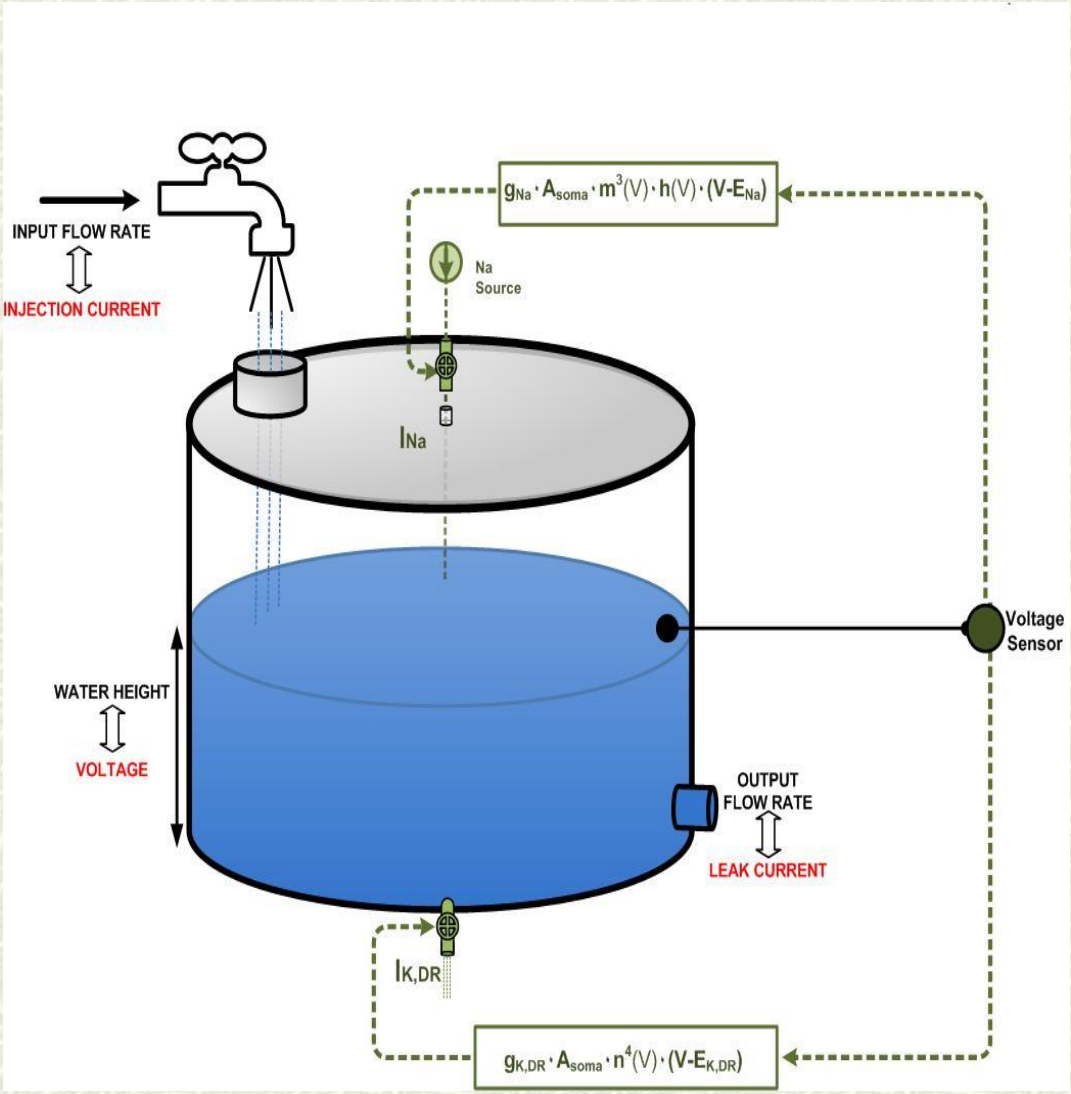
Now consider a voltage transition from V1 to V2.

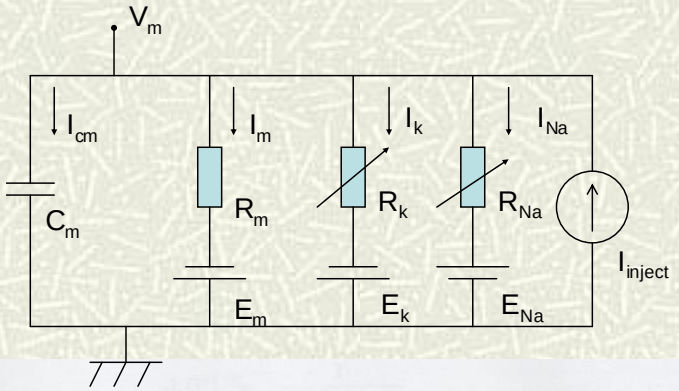
Plot this change v/s time below.

Plot two membrane schematics for the V1 and V2 (at steady state) below

How do we characterize the time course of this change, i.e., what happens as a function of time going from V1 to V2. What is the equation governing this transition?

Analogy – AP generation





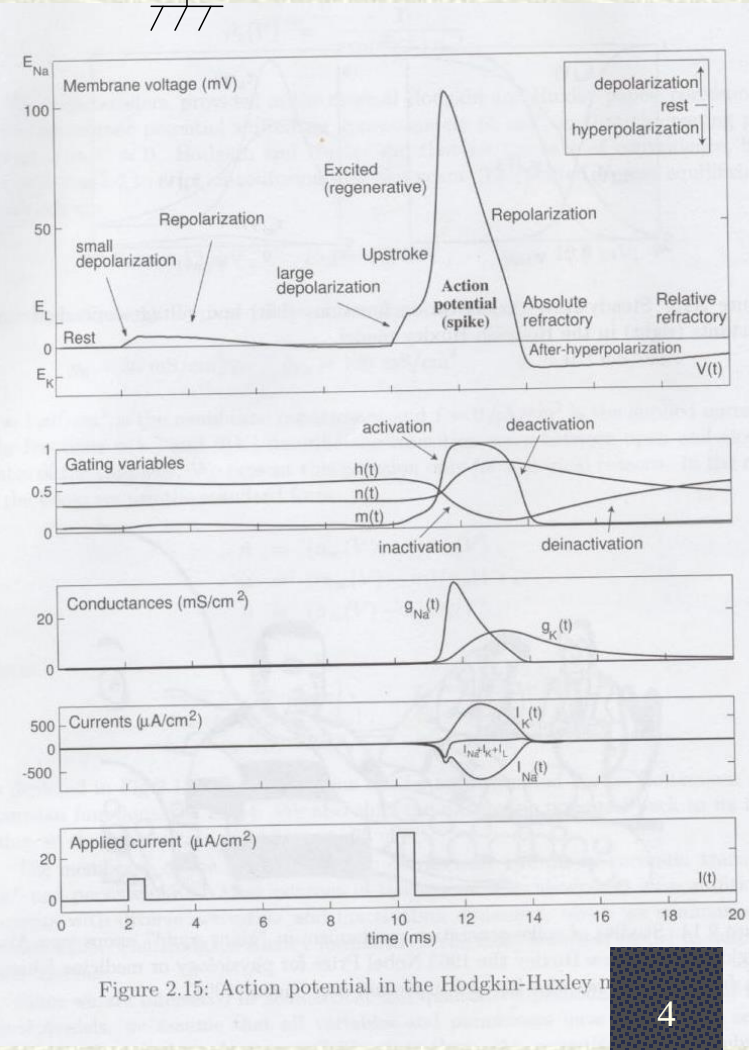


Figure 2.15: Action potential in the Hodgkin-Huxley m

NEXT STEP – you need a mechanism to reduce the spike rate and maybe even make the cell silent - this phenomenon is termed ADAPTATION

First of all, why might this be useful?

How can this be accomplished?

Cast this in the Function/Biology/Model/Math framework

ADAPTATION …continued

Neural adaptation or **sensory adaptation** is a change over time in the responsiveness of the sensory system to a constant stimulus. It is usually experienced as a change in the stimulus. For example, if one rests one's hand on a table, one immediately feels the table's surface on one's skin. Within a few seconds, however, one ceases to feel the table's surface. The sensory neurons stimulated by the table's surface respond immediately, but then respond less and less until they may not respond at all; this is neural adaptation…….

While large mechanosensory neurons such as type I/group Aβ will display adaptation, smaller type IV/group C nociceptive neurons do not. As a result, pain does not usually subside rapidly but persists for long periods of time; in contrast, one quickly stops receiving touch or other sensory information if surroundings remain constant. - Wikipedia

ADAPTATION IN CELLS

Assume the injection current is above the rheobase value. For such a case, the firing frequency decreases with time in some types of cells, and goes to a steady lower frequency, or can result in the cell becoming quiescent.

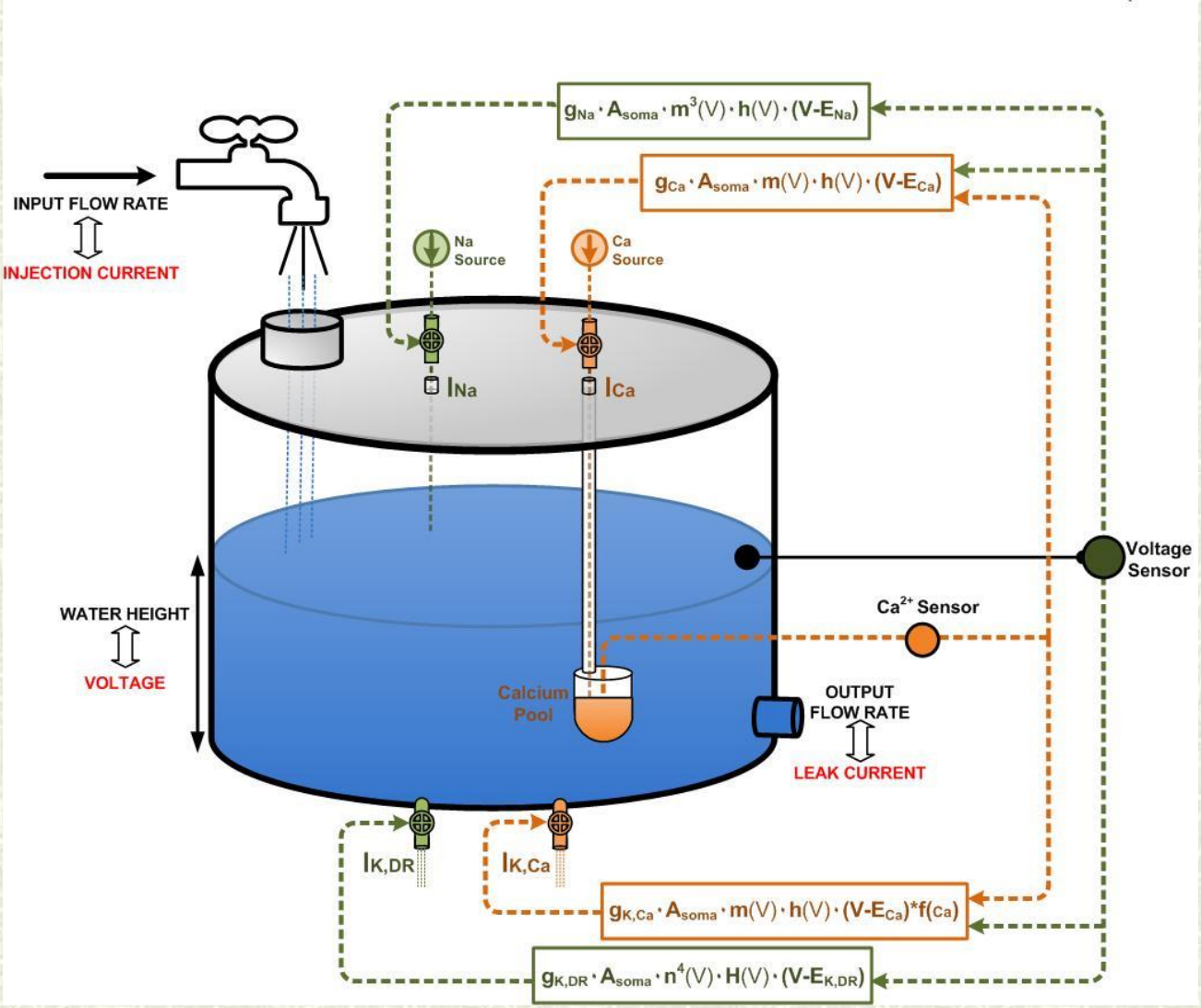
Mechanism of spike frequency adaptation

- **When the cell is at rest, the Ca^{2+} channels are closed. What about the other channels?**
- **The Ca^{2+} channel is a high-threshold channel, i.e., they activate only at high thresholds. This means that they will activate with action potentials.**
- **So, every action potential results in an influx of Ca^{2+} into the cell, increasing the concentration of the Ca-pool. This Ca-pool concentration is sensed by an as-yet-unknown sensor and this signal is used to activate a calcium-activated potassium (Kca) channel, i.e., the current I _KCa is controlled by the Ca-pool concentration; the larger the concentration, the larger the current.**
- **This current I_KCa increases the inter spike interval (spike frequency adaptation) and this can even shut down spiking completely.**
- **There are other channels similar to I_KCa that cause spike frequency adaptation – so, we have discussed only one possibility here.**

LIVE DEMO

Spiking Crew

Adaptation Crew

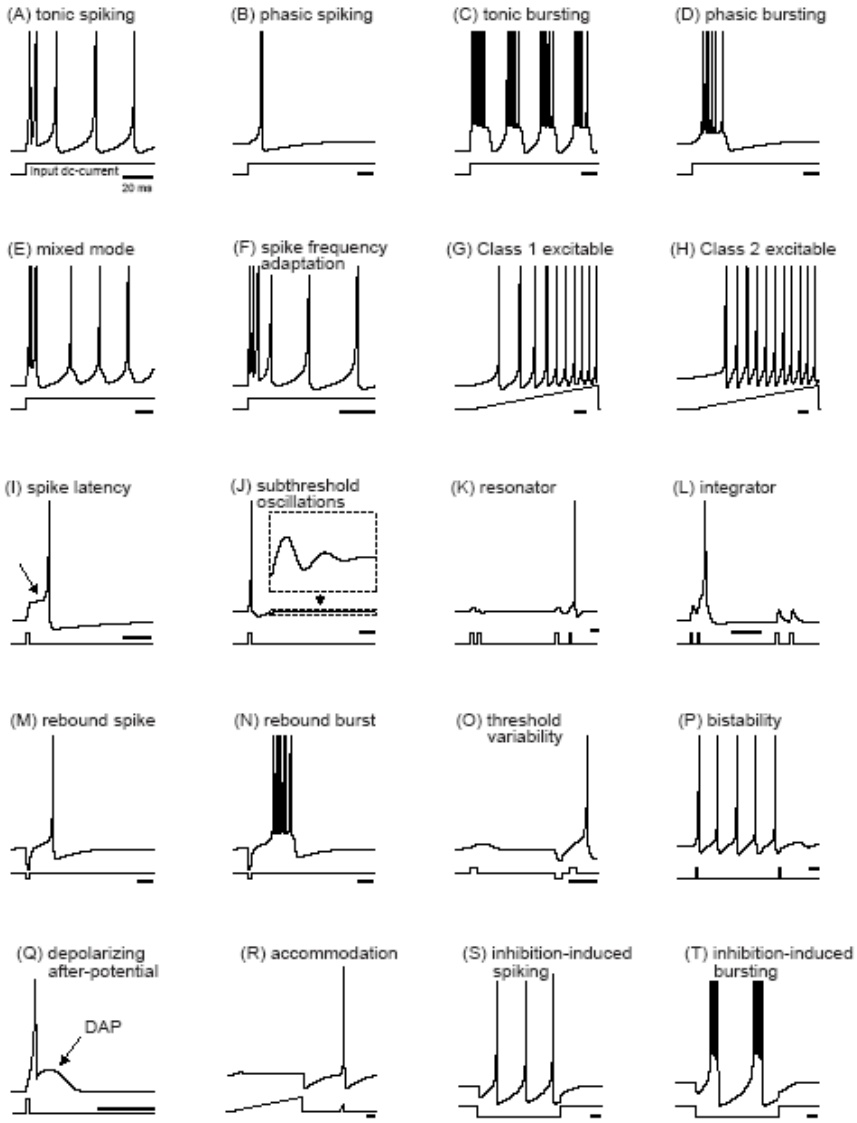


ADAPTATION IN CELLS – Assume the injection current is above the rheobase value. For such a case, the firing frequency decreases with time in some types of cells, and goes to a steady lower frequency, or can result in the cell becoming quiescent.

HOW CAN WE MAKE A TONIC SPIKER EXHIBIT SPIKE FREQUENCY ADAPTATION?

ADAPTATING cells are more complex than the ones that just firing repetitive action potentials. Cells exhibit a variety of firing patterns as shown alongside (original figure can be downloaded from www.izhikevich.com)

The next level of complexity we will consider is exhibited by **BURSTING** cells.



NEXT STEP – you need a mechanism to generate several spikes together in a short time, i.e., a BURST

Again, why might this be useful?

How can this be accomplished?

Cast this in the Function/Biology/Model/Math framework

There are many hypotheses on the importance of bursting activity in neural computation.

Bursts are more reliable than single spikes in evoking responses in postsynaptic cells. Indeed, excitatory post-synaptic potentials (EPSP) from each spike in a burst add up and may result in a superthreshold EPSP.

Bursts overcome synaptic transmission failure. Indeed, postsynaptic responses to a single presynaptic spike may fail (release does not occur), however in response to a bombardment of spikes, i.e., a burst, synaptic release is more likely (Lisman 1997).

Bursts facilitate transmitter release whereas single spikes do not (Lisman 1997). Indeed, a synapse with strong short-term facilitation would be insensitive to single spikes or even short bursts, but not to longer bursts. Each spike in the longer burst facilitates the synapse so the effect of the last few spikes may be quite strong.

Bursts evoke long-term potentiation and hence affect synaptic plasticity much greater, or differently than single spikes (Lisman 1997).

Bursts have higher signal-to-noise ratio than single spikes (Sherman 2001). Indeed, burst threshold is higher than spike threshold, i.e., generation of bursts requires stronger inputs.

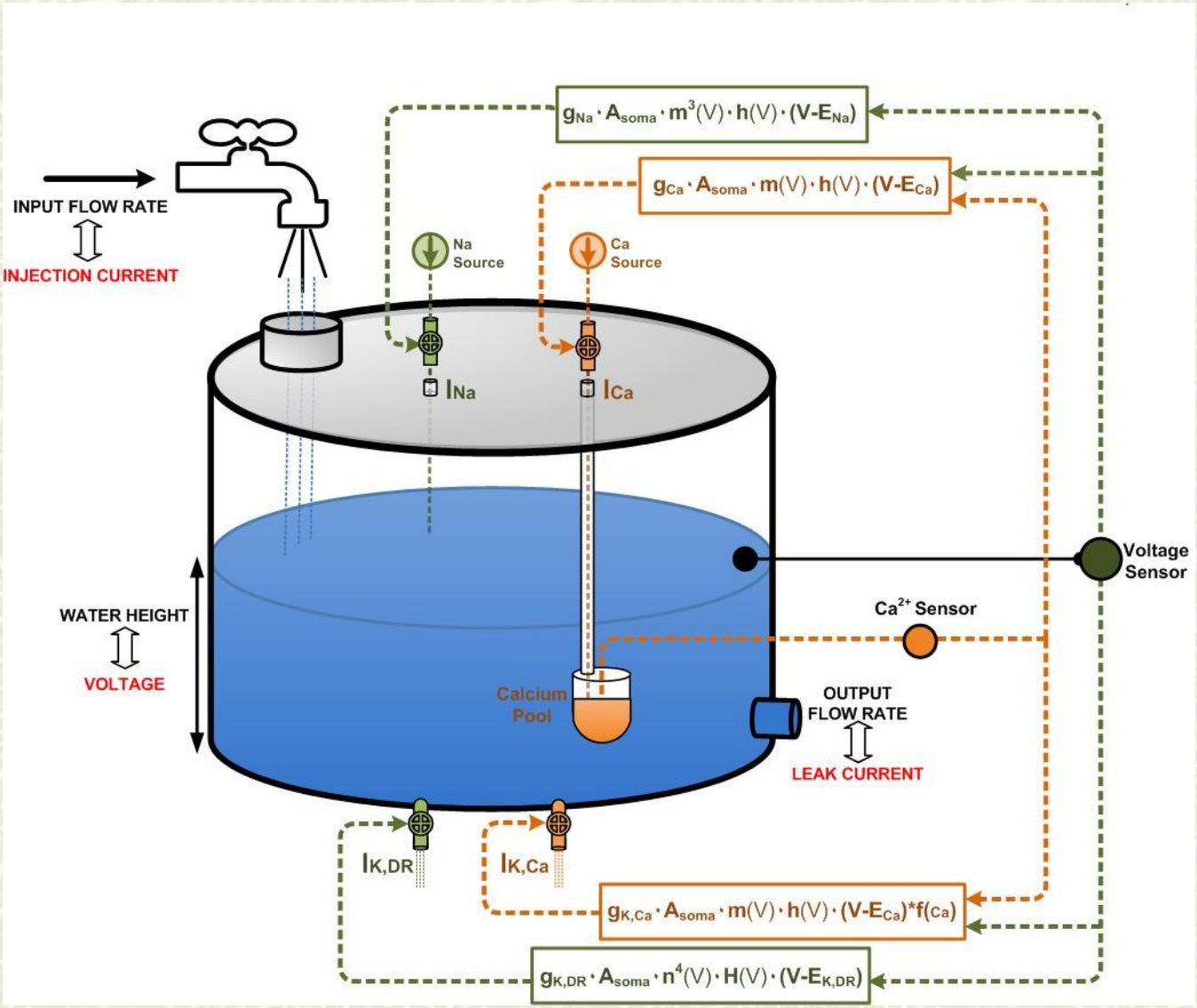
Bursts can be used for selective communication if the postsynaptic cells have subthreshold oscillations of membrane potential. Such cells are sensitive to the frequency content of the input. Some bursts resonate with oscillations and elicit a response, others do not, depending on the interburst frequency (Izhikevich et al. 2003).

Bursts can resonate with short-term synaptic plasticity making a synapse a band-pass filter (Izhikevich et al. 2003). A synapse having short-term facilitation and depression is most sensitive to a burst having certain resonant interspike frequency. Such a burst evokes just enough facilitation, but not too much synaptic depression, so its effect on the postsynaptic target is maximal.

Bursts encode different features of sensory input than single spikes (Gabbiani et al. 1996, Oswald et al. 2004). For example, neurons in the electrosensory lateral-line lobe (ELL) of weakly electric fish fire network induced-bursts in response to communication signals and single spikes in response to prey signals (Doiron et al. 2003). In the thalamus of the visual system bursts from pyramidal neurons encode stimuli that inhibit the neuron for a period of time and then rapidly excite the neuron (Lesica and Stanely, 2004). Natural scenes are often composed of such events.

Bursts have more informational content than single spikes when analyzed as unitary events (Reinagel et al. 1999). This information may be encoded into the burst duration or in the fine temporal structure of interspike intervals within a burst.

In summary, burst input is more likely to have a stronger impact on the postsynaptic cell than single spike input, so some believe that **bursts are all-or-none events, whereas single spikes may be noise**.



To a spiking cell, add another MODULE consisting of both low and high threshold Ca^{2+} channels an a Ca-activated potassium current, KCa.

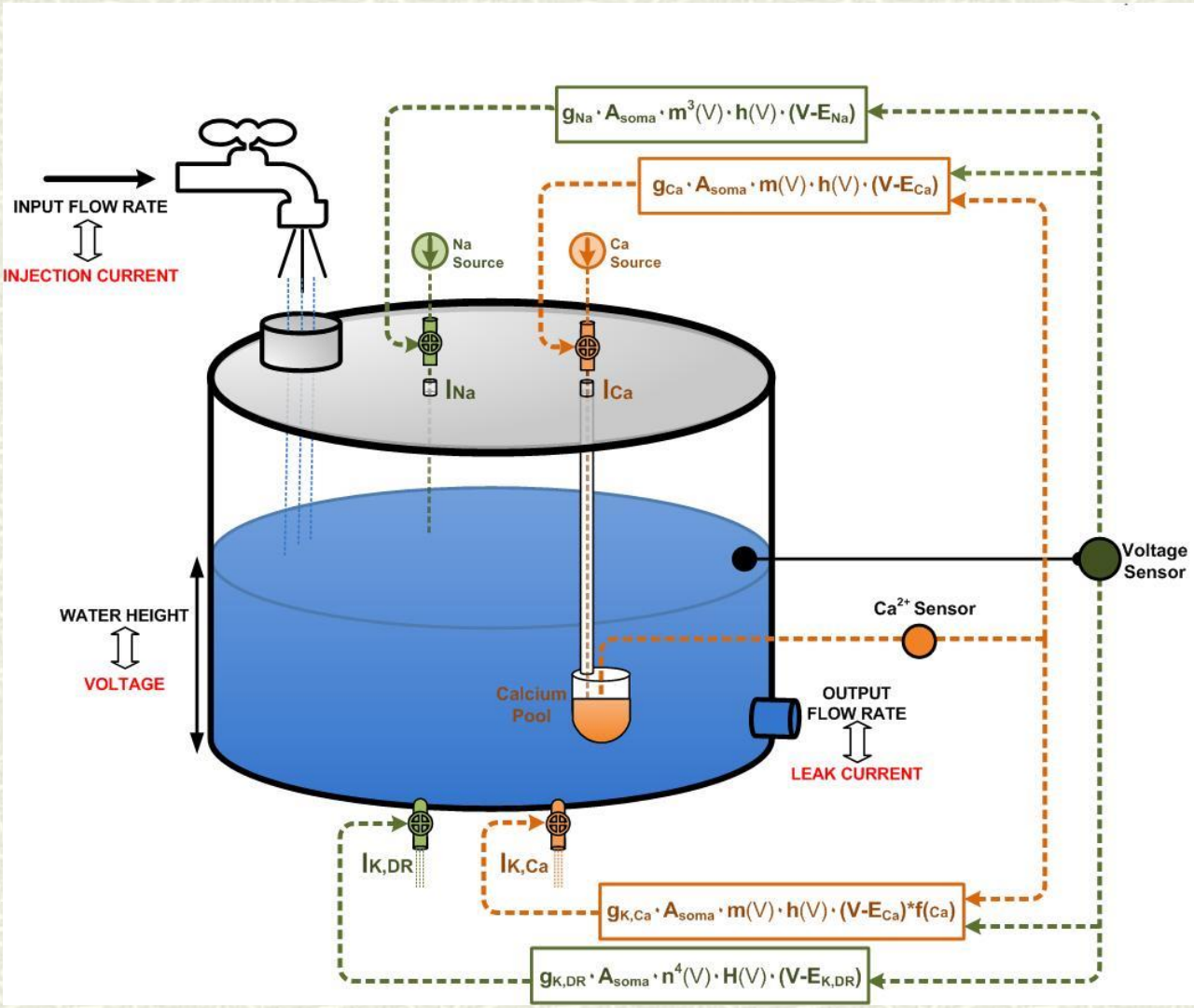
How does this module work?

Ca^{2+} enters thro' the calcium channels and depolarizes the cell leading to action potential 'bursts'. Also, Ca^{2+} accumulates near the cell membrane.

Concentration of this Ca^{2+} pool is sensed and this modulates the KCa channel that hyperpolarizes the cell, terminating the bursts

Bursting is nothing but sustained spiking for short durations of time followed by periods of quiescence – can you visualize this scenario in the water tank abo

BURSTING – "**Bursting** is a dynamic state where a neuron repeatedly fires discrete groups or bursts of spikes. Each such burst is followed by a period of quiescence before the next burst occurs. A burst of two spikes is called a *doublet*, of three spikes is called a *triplet*, four - *quadruplet*, etc. Neuronal bursting can play important roles in communication between neurons. In particular, bursting neurons are important for motor pattern generation and synchronization ."
(Izhikevich, Scholarpedia)

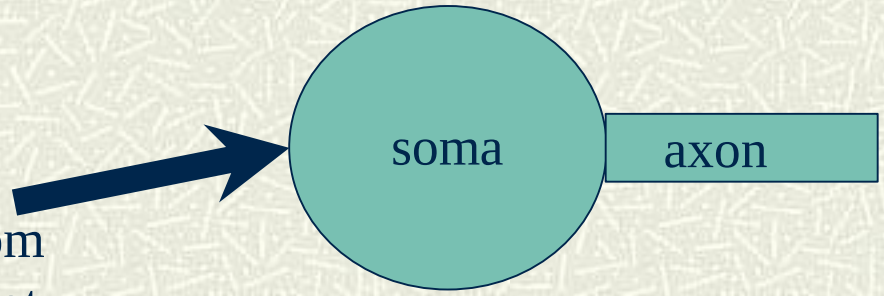


Bursting in a water tank?

http://www.scholarpedia.org/article/Bursting

Now, a more realistic (i) NEURONAL MORPHOLOGY, and (ii) INPUT (synaptic rather than current injection)

•Soma and axon are distinct compartments in most neurons with typically different sets of currents. A two-compartmental model of a neuron is shown below (neuronal model with over 1000 compartments have been reported)

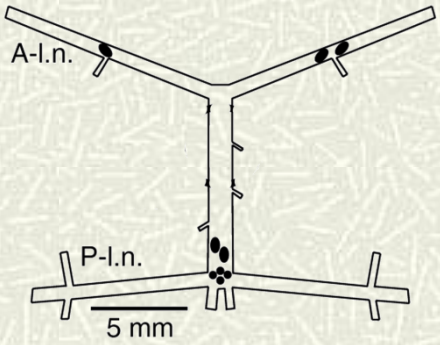


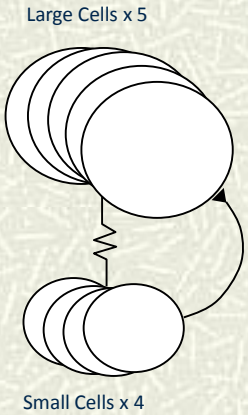
Synaptic input from another neuron (not needed for endogenous burster of Soft. Lab 3!)

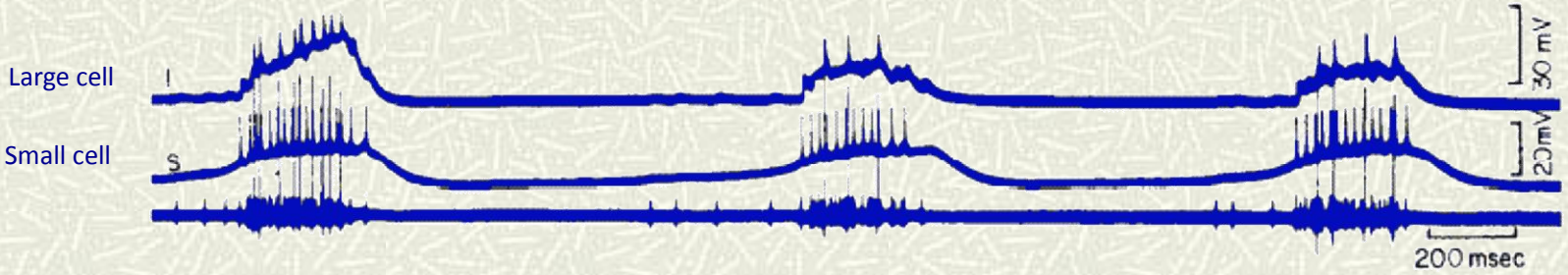
•How might the synaptic input (stimulus) in the form of spikes from another neuron make the 2-compartmental neuron above fire? Note that this is a more realistic input in vivo where current injection is not possible!

Consider the case of the Crustacean Cardiac Ganglion

4 small pacemaker cells + 5 large cells that activate the crab heart



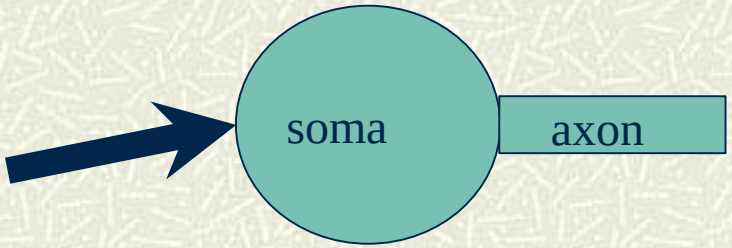




Author: Dr. David Schulz

Recordings courtesy of Tazaki and Cooke (1979a,b)

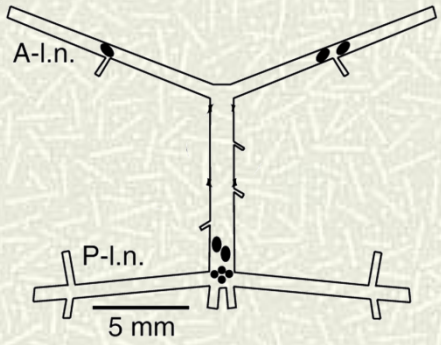
List the sequence of steps involved in endogenous AB cell burster (Software Lab 3) that has a soma and axon, with the following channels:



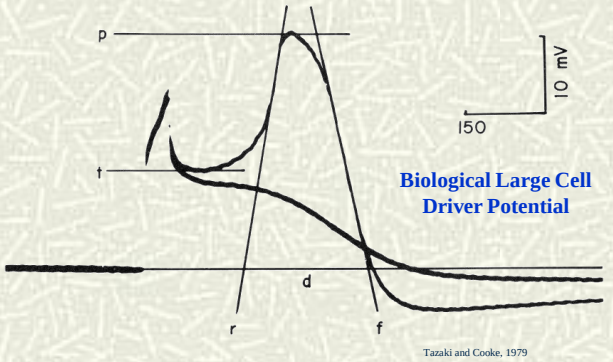
SOMA: CaS, CaT, A, Kd, Leak

Dendrite: Na, Kd, Leak

What happens with a pulsed stimulation, i.e., forced bursting case?



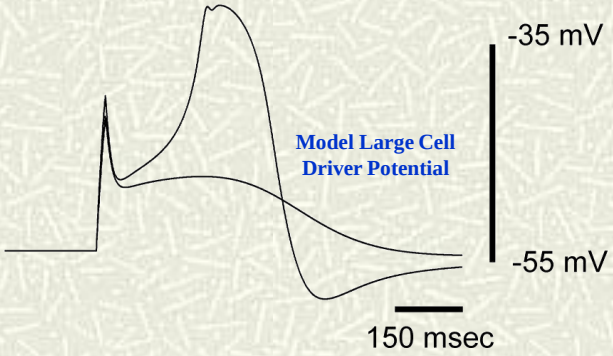
(cardiac ganglion)



Biological Large Cell Driver Potential

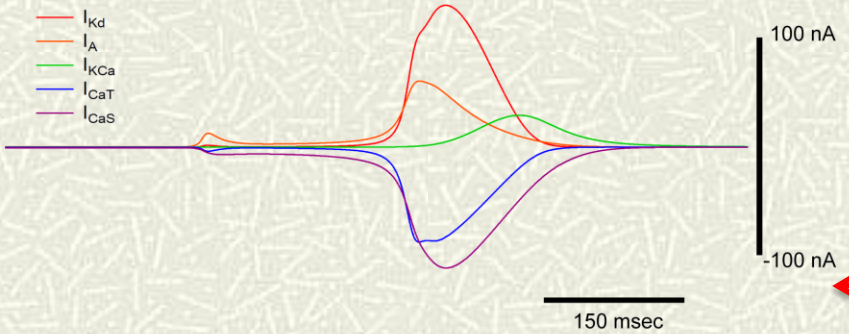
V_{LC}

Tazaki and Cooke, 1979



Model Large Cell Driver Potential

Input - single pulse



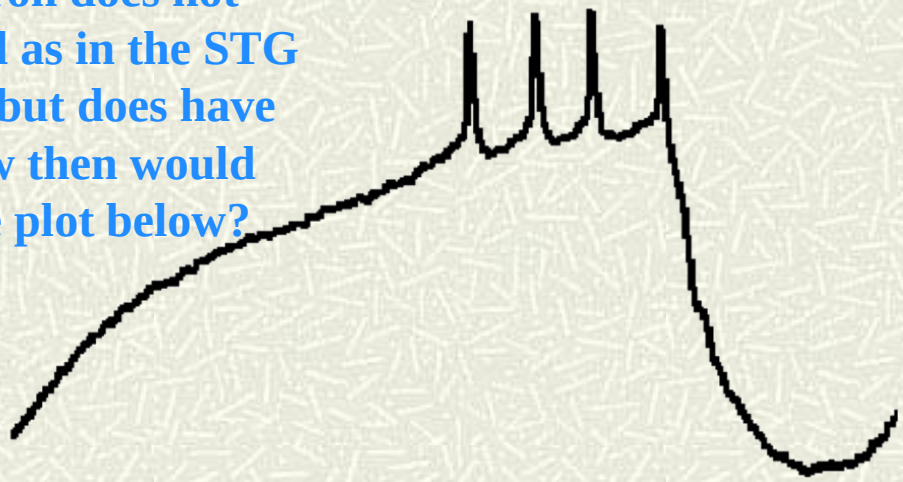
$$C_m \frac{dV}{dt} = -I_{CaS} - I_{CaT} - I_{Kd} - I_A - I_{KCa} - I_{leak} + I_{inj}$$

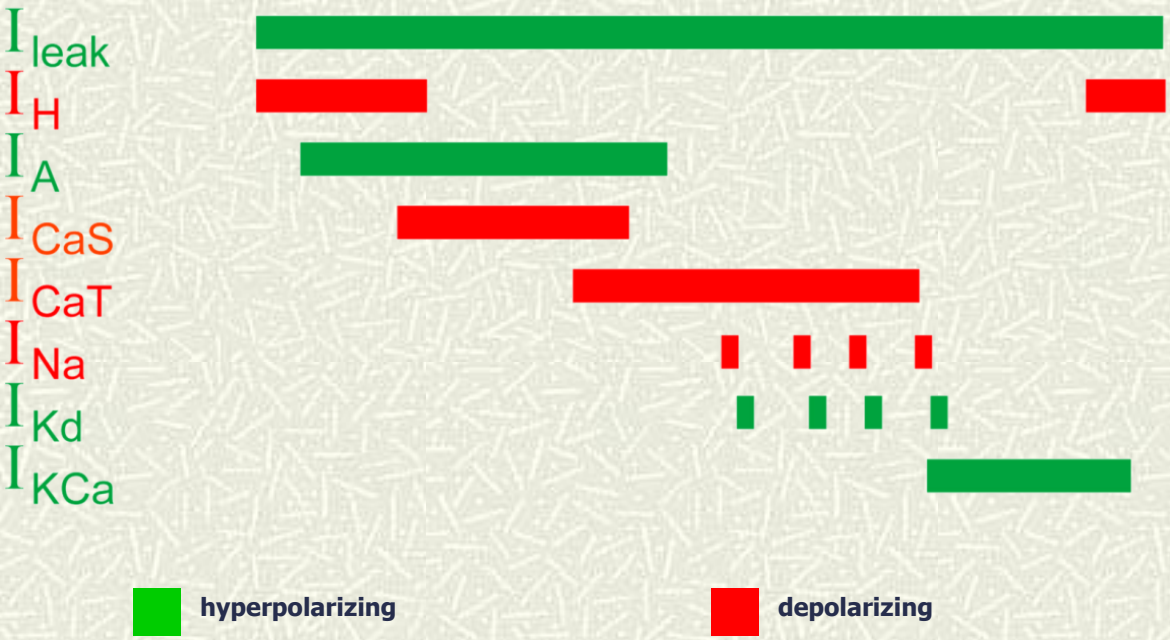
Author: Dr. David Schulz

What happens in the axon?

Ball et al., *J Neuroscience* (2009)

Note: Our neuron does not have H channel as in the STG burster below, but does have the others. How then would you redraw the plot below?





PY neuron in STG; Author: Dr. David Schulz

STG Burster in the Schulz lab

Bursting can be either forced or intrinsic – H (or equivalent) or a strong CaS are needed for the spontaneous case. Voltage gated channels have overlapping ranges of activation. Na is present in the axon only, while Kd is present in axon and soma for CG cells. H is not present in CG cells, or in the AB cell studied in the S3 Lab.

- Sequence of 'domino' events with currents?
1. …
2. ….

Consider the case of forced bursting. Draw the activations/ currents as a function of time

- Now consider the spontaneous bursting case and sketch the activations/currents

LIVE DEMO

Spiking Crew **Adaptation Crew** **Bursting Crew**

SOFTWARE LAB 3

What is spike frequency adaptation? What is bursting?

The AB cell modeled in S-Lab 3 is an endogenous burster, i.e., it bursts continuously without any input, i.e., with I_{inject} = 0. Run S3 Burster…..
Some of the model features are as follows:

- **Two compartments, soma and axon, with different sets of currents, i.e., a more realistic model of the neuron**
- **SOMA currents: I_CaS, I_A (potassium current), I_CaT, I_KCa, I_Kd, I_leak**
- **Axon currents: I_Na, I_Kd, I_leak**
- **I_CaS and I_A oppose each other and their relative ratio decides whether the cell would be an endogenous or forced burster (see problem related to this). I_CaS is a regenerative current – what does this mean? I_A can control it.**
- **The fact that axon has the action potential currents makes the spikes look small in the soma. Why?**
- **SLOW WAVE OSCILLATION? Note that the membrane potential plots show both fast (which one?) and slow (which one?) oscillations. Try to explain how this works……**
- **DEMO – two compartment bursting**

How does the H current work? What are its specs?

- The current I_H used to be called the 'funny' currents because it's dynamics were opposite to the conventional channels such as Na, Kd, etc. which activate with increasing depolarization and inactivate with hyperpolarization. It was discovered in human heart neurons - http://en.wikipedia.org/wiki/HCN_channel
- It was later renamed as 'Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels
- I_H actually activates in a hyperpolarized state and inactivates when the cell membrane depolarizes!:
- What might the m and h curves for such a channel look like? Draw them below. Then write down the equation for the current thro' the H channel.