

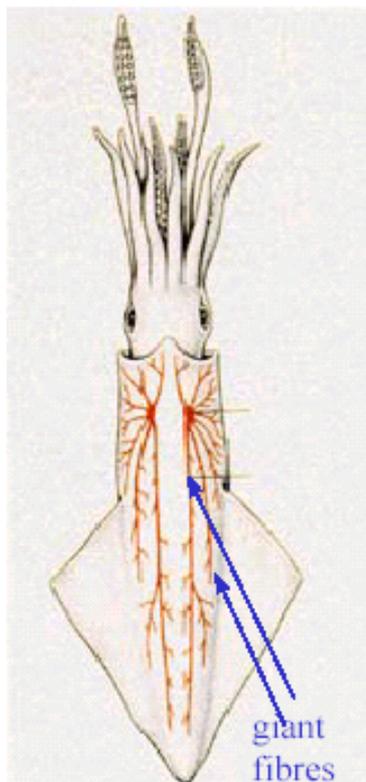
Model neurons

Hodgkin and Huxley models

Suggested reading:

Chapter 5.5-5.6 in Dayan, P. & Abbott, L., *Theoretical Neuroscience*, MIT Press, 2001.

Model neurons: Hodgkin and Huxley models



Contents:

- The giant axon of the squid
- Voltage clamp method
- Electrical circuit of the Hodgkin-Huxley M.
- Potassium current
- Sodium current
- Voltage dependency of the gating particles
- The full Hodgkin-Huxley model

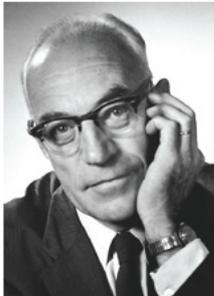


The Nobel Prize in Physiology or Medicine 1963

"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

Nowadays, much more details are known, but

the basic principles are still valid and used.



Sir John Carew Eccles

🕒 1/3 of the prize

Australia

University College
London, United Kingdom

b. 1903
d. 1997



Alan Lloyd Hodgkin

🕒 1/3 of the prize

United Kingdom

University of Cambridge
Cambridge, United Kingdom

b. 1914
d. 1998



Andrew Fielding Huxley

🕒 1/3 of the prize

United Kingdom

University College
London, United Kingdom

b. 1917

The giant axon of the squid

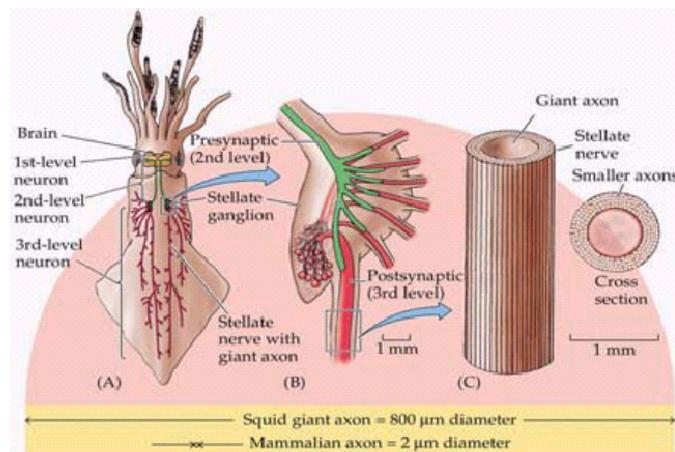
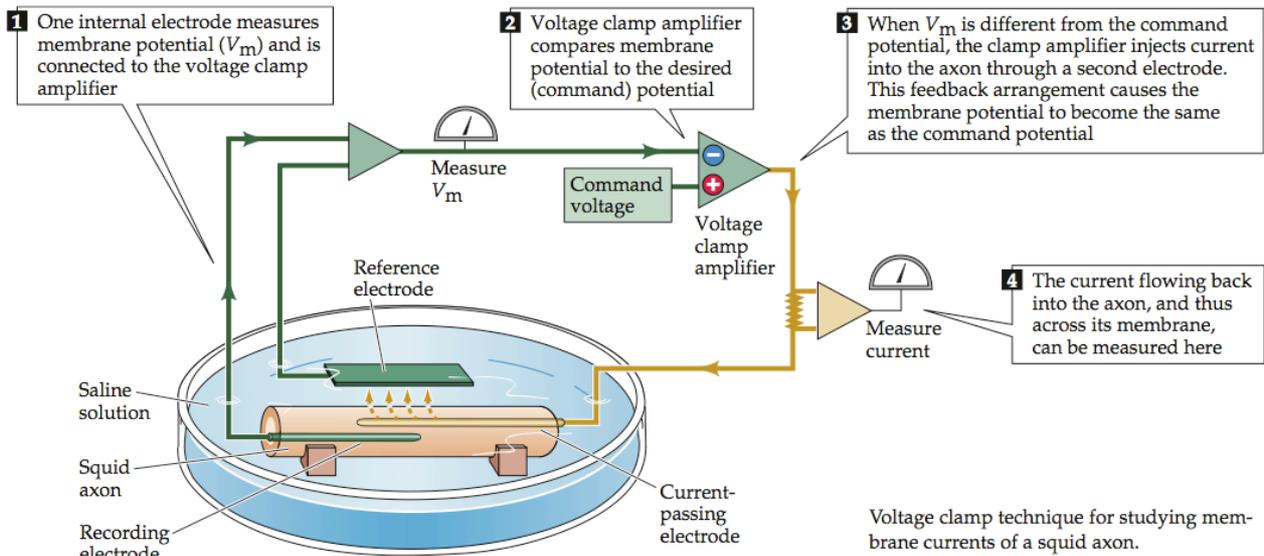


Diagram of squid, showing location of its giant nerve cells. Different colors indicate the neuronal components of the escape circuitry. The first- and second level neurons originate in the brain, while the third-level neurons are in the stellate ganglion and innervate muscle cells of the mantle.

(B) Giant synapses within the stellate ganglion. The second-level neuron forms a series of fingerlike processes, each of which makes an extraordinarily large synapse with a single third-level neuron.

(C) Structure of a giant axon of a third-level neuron lying within its nerve. The difference in the diameters of a squid giant axon and a mammalian axon are shown below. However, note that some mammalian motor neurons are as large as 20 μm in diameter.

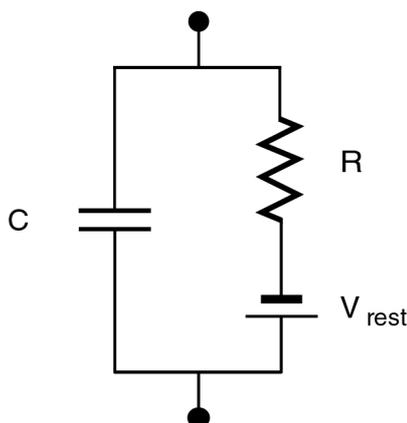
The voltage clamp method



Problems: during recordings all variables are changing
 Solution: hold one variable steady, measure a second and calculate the third

Remember !

Electrical circuit of the membrane potential:



Membrane equation:

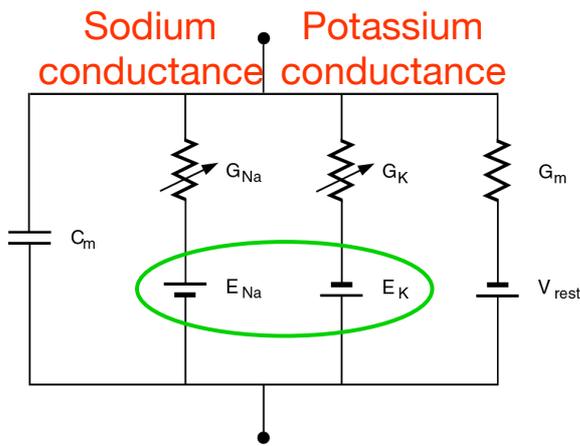
$$\tau \frac{dV(t)}{dt} = -V(t) + V_{rest} + RI_e(t)$$

$$\tau = RC$$

with units

$$\Omega F = \text{sec}$$

Electrical circuit of the Hodgkin and Huxley model



voltage-dependent ionic conductances

Sodium current is inward directed

Membrane current

$$I_m(t) = I_{ionic}(t) + C \frac{dV(t)}{dt}$$

Ionic current

$$I_{ionic} = I_{Na} + I_K + I_{leak}$$

$$I_i = g_i(V(t), t)(V(t) - E_i)$$

$$g_i = \bar{g}_i P_i$$

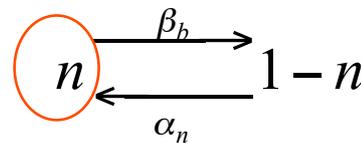
Probability of the channel being open

Potassium current

$$P_K = n^4$$

$$0 \leq n \leq 1$$

$$I_K = \bar{g}_K n^4 (V - E_K)$$



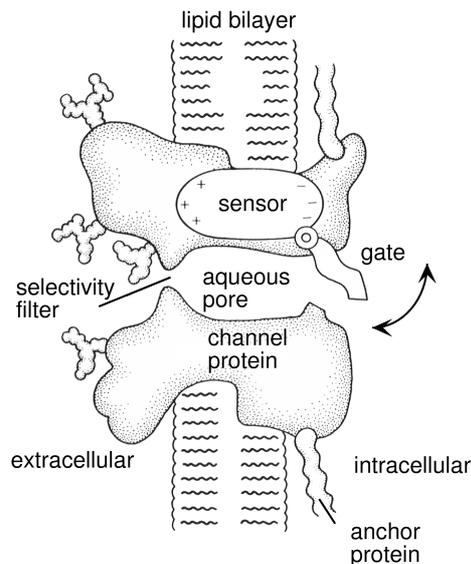
Probability of gating particle in the open state

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$$\tau_n(V) \frac{dn}{dt} = n_\infty(V) - n$$

$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)} \quad n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

Persistent conductances



The delayed rectifier K^+ conductance is responsible for repolarizing a neuron after an action potential

It is constructed from four identical subunits that all must undergo a structural change for the channel to open

$$P_K = n^4$$

A selectivity filter ensures that only K^+ ions pass through the channel

Experimental findings:

$$\alpha_n = \frac{.01(V + 55)}{1 - \exp(-.1(V + 55))} \quad \text{and} \quad \beta_n = 0.125 \exp(-0.0125(V + 65))$$

Sodium current

$$P_{Na} = m^3 h$$

$$0 \leq m, h \leq 1$$

m : activation particle

h : inactivation particle

$$I_{Na} = \bar{g}_{Na} m^3 h (V - E_{Na})$$

$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m$$

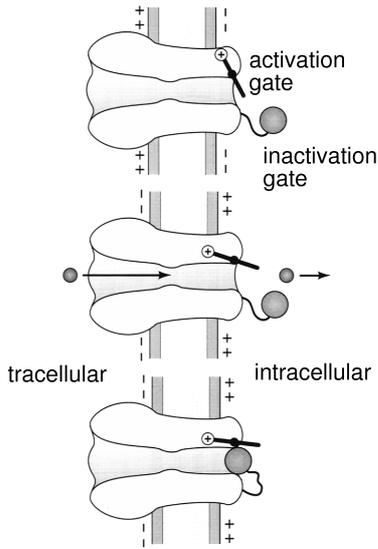
$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h$$

Sodium current is negative

for $V < E_{Na}$

$$E_{Na} = 115mV$$

Transient conductances



The sodium current rapidly depolarizes the membrane.

Two processes control the sodium conductance: **activation** that rapidly increases g_{Na} , and the slower **inactivation**

that reduces g_{Na} upon depolarization

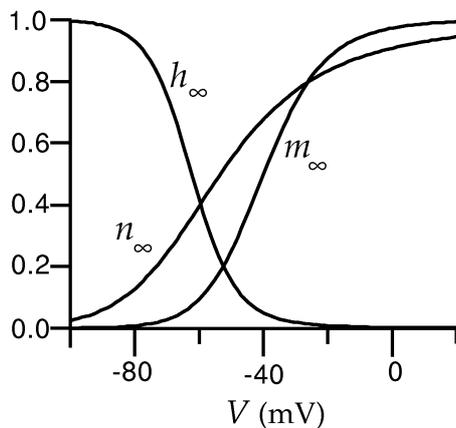
Experimental findings ($[V] = mV$):

$$\alpha_m = \frac{.1(V + 40)}{1 - \exp(-.1(V + 40))} \quad \beta_m = 4 \exp(-.0556(V + 65))$$

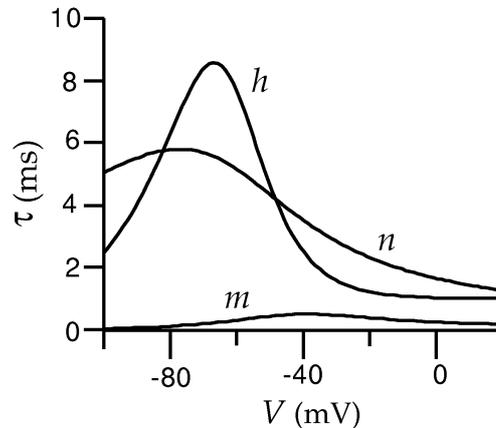
$$\alpha_h = .07 \exp(-.05(V + 65)) \quad \beta_h = 1 / (1 + \exp(-.1(V + 35)))$$

Voltage dependency of the gating particles

Steady state activation and inactivation

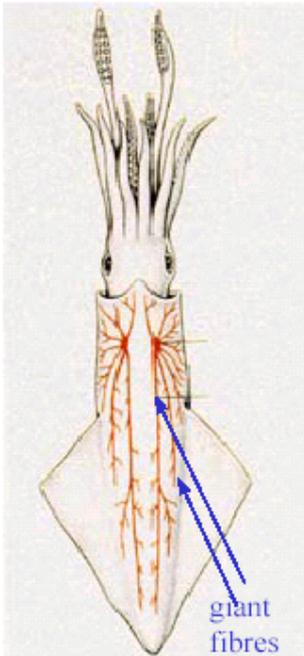


Time constants



At values of the membrane close to the resting potential h takes on a value close to 1. When a sudden depolarizing voltage step is imposed, the sodium activation m changes within a fraction of a millisecond to its new value close to 1, while the sodium inactivation h takes longer to relax to zero. In addition the potassium activation n will turn on, causing the membrane potential to dip down from its peak.

The Hodgkin-Huxley Model



Model of the squid giant axon

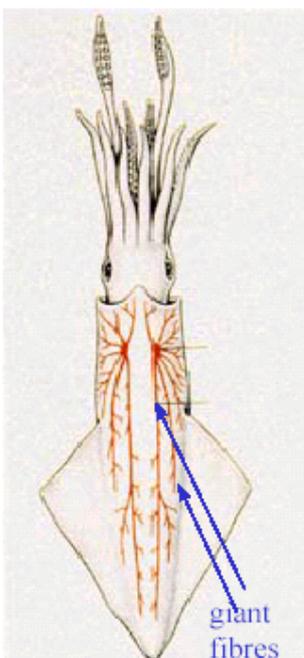
$$\tau \frac{dV_m(t)}{dt} = \text{Leak current} \\ + \text{Potassium current} \\ + \text{Sodium current}$$

$$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

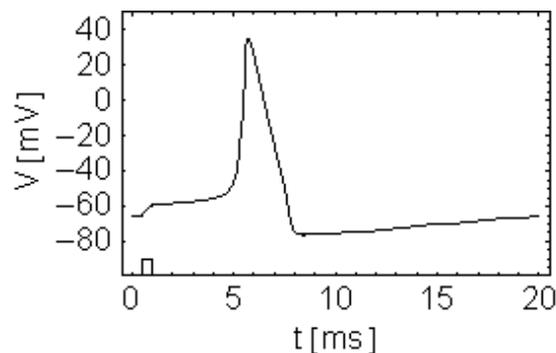
$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$

The Hodgkin-Huxley Model



Model of the squid giant axon

$$\tau \frac{dV_m(t)}{dt} = \bar{g}_L(V_m - E_L) \\ + \bar{g}_K n^4(V_m - E_K) \\ + \bar{g}_{Na} m^3 h(V_m - E_{Na})$$



H-H model links the microscopic level of ion channels to the macroscopic level of currents and action potentials

Complete Hodgkin-Huxley model

$$c_m \frac{dV(t)}{dt} = -i_m + \frac{I_e(t)}{A}$$

$$i_m = \bar{g}_L(V - E_L) + \bar{g}_K n^4 (V - E_K) + \bar{g}_{Na} m^3 h (V - E_{Na})$$

$$\frac{dn}{dt} = \alpha_n(V)(1 - n) - \beta_n(V)n$$

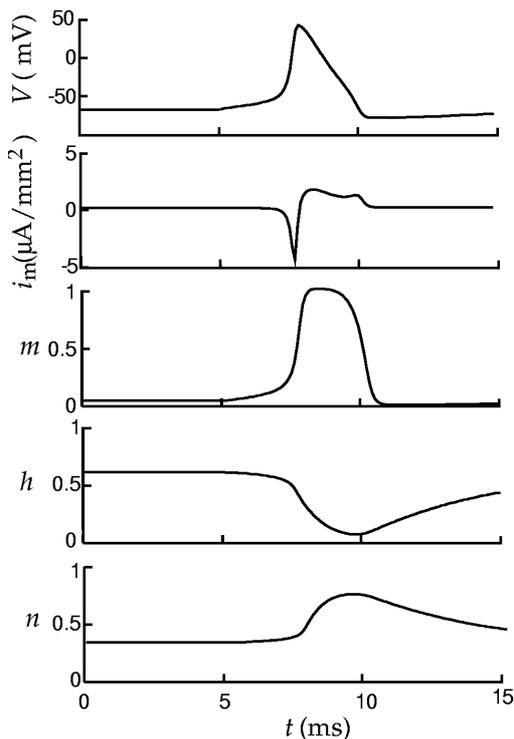
$$\frac{dm}{dt} = \alpha_m(V)(1 - m) - \beta_m(V)m$$

$$\frac{dh}{dt} = \alpha_h(V)(1 - h) - \beta_h(V)h$$

Note, if the leakage current is the result of several channels you can calculate it with:

$$i_L = \bar{g}_L(V - E_L) = \bar{g}_K^L(V - E_K) + \bar{g}_{Na}^L(V - E_{Na}) + \bar{g}_{Cl}^L(V - E_{Cl})$$

Dynamics in the Hodgkin-Huxley model



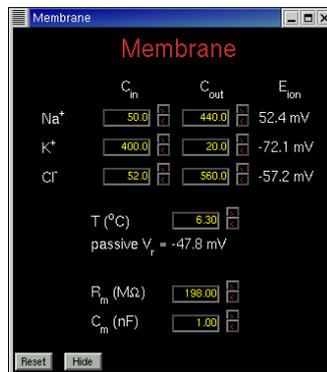
The membrane potential initially rises due to the injection of a current at $t=5$ ms. When this current drives the membrane potential up to about -50 mV the sodium activation m suddenly jumps from nearly 0 to 1. Since the sodium inactivation h is around 0.6, m and h are sufficiently different from zero to allow a large influx of Na^+ ions producing a strong inward (neg.) current. The inward current pulse causes the membrane potential to rise rapidly to around 50mV. Since m increases with V and V with m , positive feedback occurred. The rise in the membrane potential causes the Na^+ conductance to inactivate by driving h towards 0. In addition, the rise in V activates the K^+ conductance by driving n towards 1. This increases the K^+ current, which drives the membrane potential back down to negative values. Since the potassium current persists longer than the sodium current, the membrane potential is depressed to below its resting potential - it hyperpolarizes.

HHsim: Graphical Hodgkin-Huxley Simulator for MATLAB

(David S. Touretzky, Mark V. Albert, Nathaniel D. Daw, and Alok Ladsariya)

HHsim is free software distributed under the GNU General Public License.

Example: Nernst and Goldman-Hodgkin-Katz equations



Model neurons

Beyond Hodgkin and Huxley

Suggested reading:

Chapter 6.1-6.3 in Dayan, P. & Abbott, L., Theoretical Neuroscience, MIT Press, 2001.

Even more currents

The cornerstone of modern biophysics is the analysis by Hodgkin and Huxley. Their model considers two currents: a fast sodium (*Na*) current and a delayed potassium (*K*) current.

Following research using other cells has shown **more than several dozen membrane conductances**. Among those are calcium currents. Many different genes have been discovered for each type of voltage-gated ion channel. An example is the identification of **10 human Na^+ channel genes**.

Calcium currents

Calcium Ca^{2+} currents seem to be important even beyond merely generating action potentials. Calcium currents are always

- inward directed
- activated by depolarization

They vary in their sensitivity to depolarization. They appear to be largely absent in axons, but can be found throughout the dendritic tree, the cell body, and at presynaptic sites.

High-threshold calcium current (L)

$I_{\text{Ca(L)}}$ is only activated at very depolarized levels. Its inactivation is not dependent on the membrane potential but on the intracellular calcium concentration.

$$I_{\text{Ca(L)}} = m(V)^k h([\text{Ca}^{2+}]_i) I_{\text{Ca}}$$

I_{Ca} - Goldman-Hodgkin-Katz current equation (e.g., Koch, 1999)

Low-threshold transient calcium current (T)

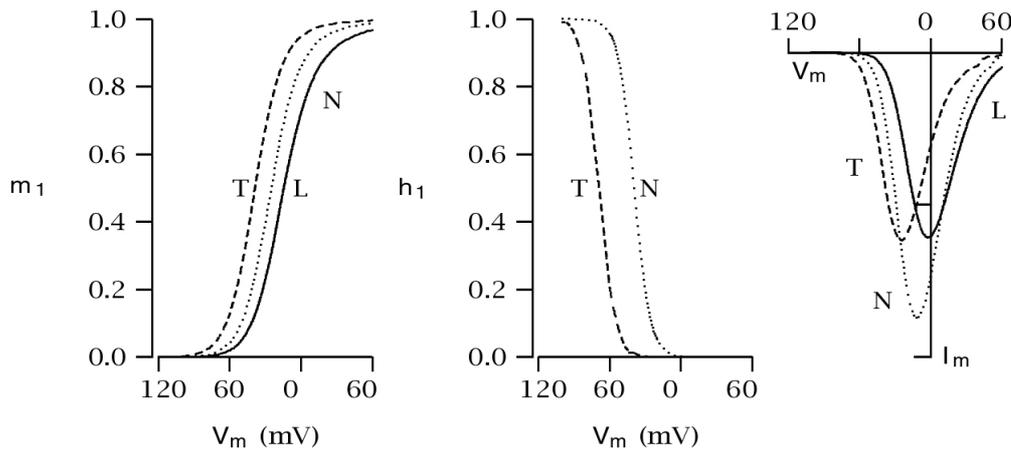
$I_{\text{Ca(T)}}$ is activated at lower voltages than the L current. Under physiological conditions, the T current can be triggered by hyperpolarizing the membrane potential, which completely removes inactivation. A subsequent synaptic input activates a broad action potential, on top of which sodium spikes (*Na*) can ride.

$$I_{\text{Ca(T)}} = m(V)^2 h(V) I_{\text{Ca}}$$

N-type calcium current (N)

$I_{Ca(N)}$ is activated at potentials intermediate between the L and T current. N channels appear to complement the locations of L channels, which are restricted to the cell bodies and the proximal dendrites of pyramidal cells.

$$I_{Ca(N)} = m(V)^3 h(V) I_{Ca}$$



Transient potassium current and the Connor-Stevens model:

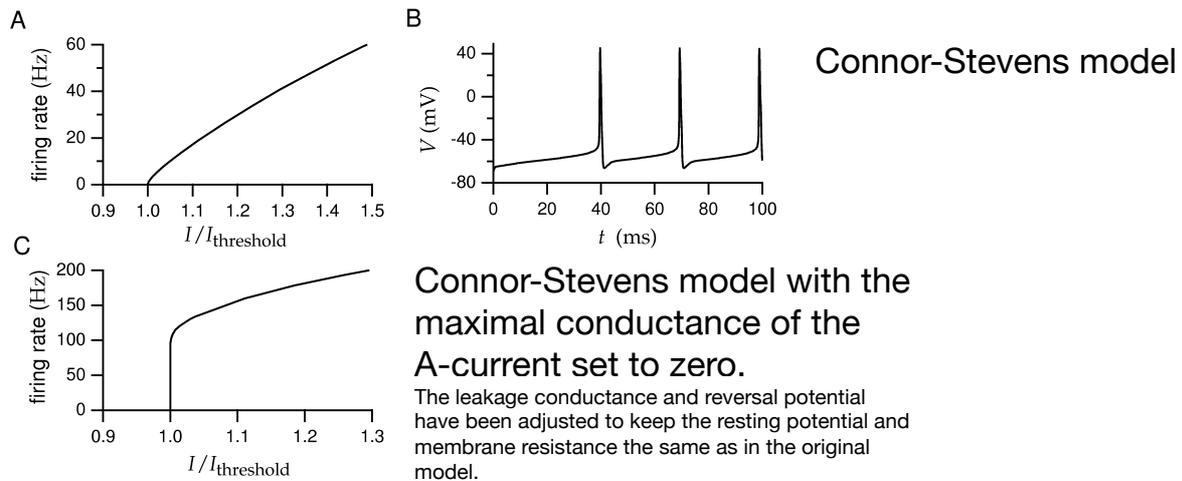
Another important potassium current is transient inactivating Potassium current, known as I_A .

$$C_m \frac{dV(t)}{dt} = -i_m + \frac{I_e(t)}{A}$$

$$i_m = \bar{g}_L (V - E_L) + \bar{g}_{Na} m^3 h (V - E_{Na}) + \bar{g}_K n^4 (V - E_K) + \bar{g}_A a^3 b (V - E_A)$$

The gating variables are determined similar to the Hodgkin and Huxley model, but with different parameters, such that the kinetics are faster and the action potentials are briefer.

What is the role of the additional A-current?

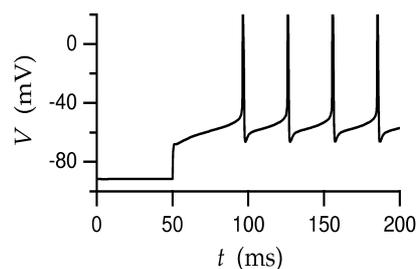


The firing rate is clearly much higher with the A-current turned off. This is because the deinactivation rate of the A-current limits the rise time of the membrane potential between action potentials.

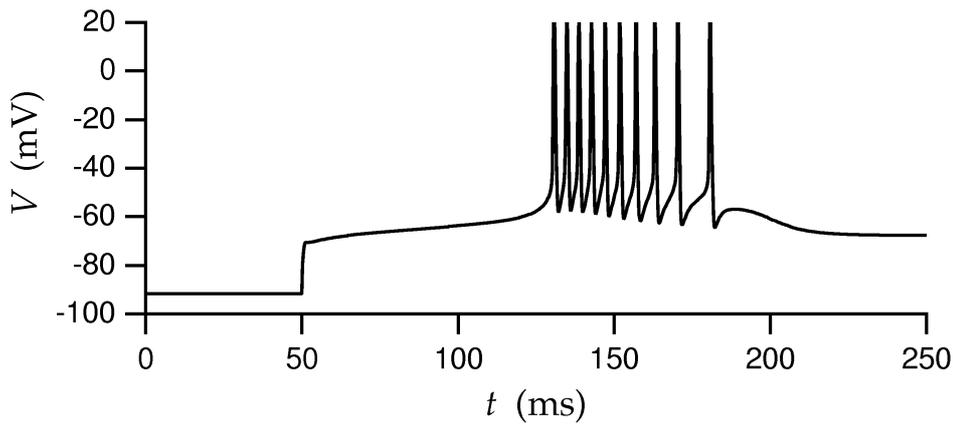
In addition, the transition from no firing for currents less than the threshold value to firing with suprathreshold currents is different when the A-current is eliminated. Without the A-current, the firing rate jumps discontinuously to a nonzero value rather than rising continuously. The HH-Model behaves as in (B).

What is the role of the additional A-current?

Another effect of the A-current is visible when the model neuron was held hyperpolarized by negative current injection for an extended period of time, and then the current was switched to a positive value. While the neuron was hyperpolarized, the A-current deinactivated, that is, the variable b increased toward one. When the electrode current switched sign and the neuron depolarized, the A-current first activated and then inactivated. This delayed the first spike following the change in the electrode current.

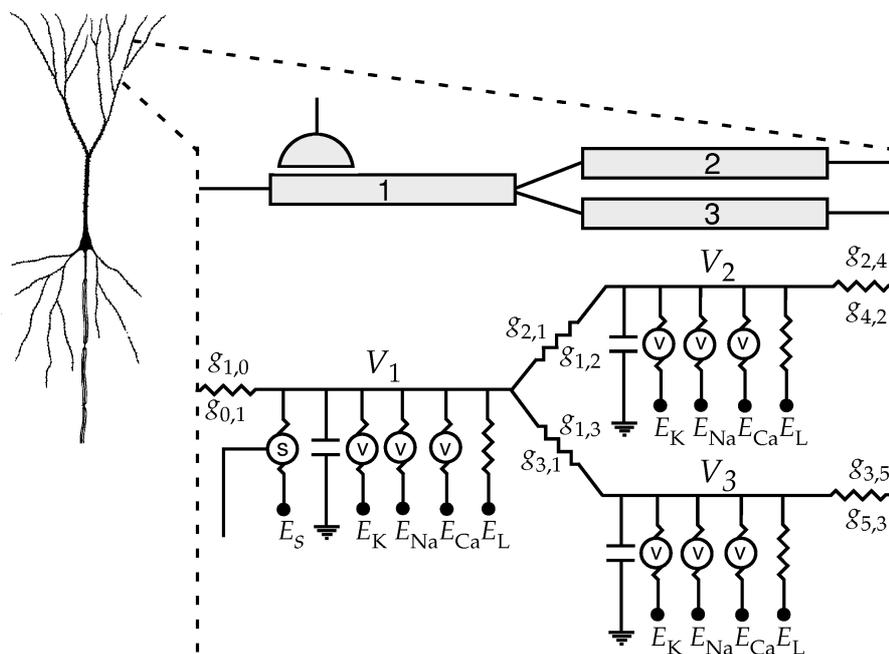


Postinhibitory rebound and bursting



The range of responses exhibited by the Connor-Stevens model neuron can be extended by including a transient Ca^{2+} conductance (refer to $I_{\text{Ca(T)}}$). The model neuron was held hyperpolarized for an extended period by injection of constant negative electrode current. At $t = 50$ ms, the electrode current was set to zero, and a burst of Na spikes was generated due to an underlying Ca^{2+} "spike" (slow transient depolarization). The delay in the firing is caused by the presence of the A-current in the model.

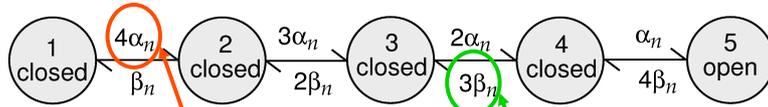
Multi-compartment models



Channels

K⁺ channel:

The Hodgkin and Huxley equations describe voltage-dependent conductances arising from a large number of channels. Each channel alone can be described on basis of state-space models.



State-space model of a single K⁺ channel with 5 states. E.g. State 1: all 4 gates are closed.

Ion through one channel:

$$i = \bar{g}P(V - E)$$

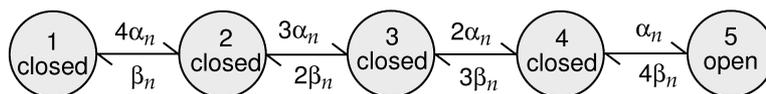
$$P = \{0,1\}$$

Probability to switch from state 1 to state 2.

Probability to switch from state 4 to state 3.

Markov process: transition from one state to the next does not depend on the history

Channels



$$\dot{p}_1 = \beta_n p_2 - 4\alpha_n p_1$$

$$\dot{p}_2 = 4\alpha_n p_1 + 2\beta_n p_3 - (\beta_n + 3\alpha_n) p_2$$

$$\dot{p}_3 = 3\alpha_n p_2 + 3\beta_n p_4 - (2\beta_n + 2\alpha_n) p_3$$

$$\dot{p}_4 = 2\alpha_n p_3 + 4\beta_n p_5 - (3\beta_n + \alpha_n) p_4$$

$$\dot{p}_5 = \alpha_n p_4 - 4\beta_n p_5$$

n : Probability of being in the open state

$1 - n$: Probability of being in the closed state

$$p_1 = (1 - n)^4$$

$$p_2 = \binom{4}{1} n (1 - n)^3$$

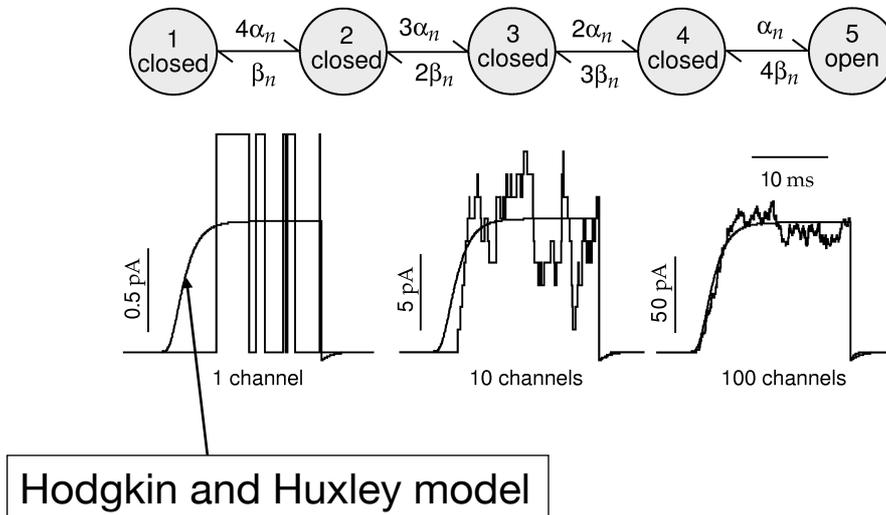
$$p_3 = \binom{4}{2} n^2 (1 - n)^2$$

$$p_4 = \binom{4}{3} n^3 (1 - n)$$

$$p_5 = n^4$$

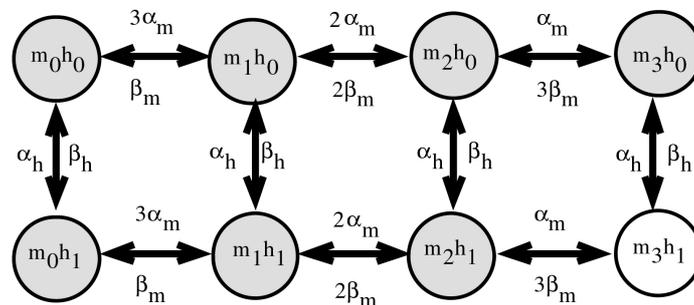
Channels

Comparison between the Hodgkin & Huxley model and the detailed Markovian approach:



Channels

Na⁺ channel:



The approach is equivalent to the K^+ channel.

Channels

Na⁺ channel:

Recent findings suggest that the activation and inactivation do not act independently. Thus, a state dependent and voltage independent inactivation mechanism is suggested.

