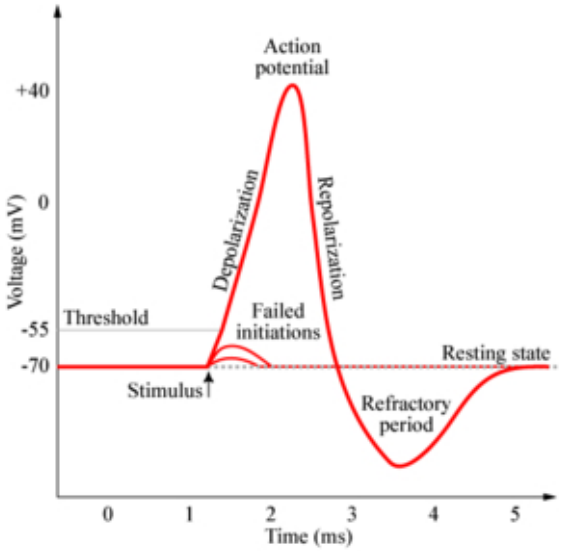
Department of Mathematical Sciences

B12412: Computational Neuroscience and Neuroinformatics

The Hodgkin-Huxley model

Action potentials were characterised by Hodgkin & Huxley in squid. They are a rapid regenerative change in membrane potential that is initially triggered by depolarization. The depolarization opens voltage-gated sodium channels and triggers a transient sodium current. Then as the membrane potential becomes positive, slower voltage-gated potassium channels open to repolarize the membrane to the resting potential. There is a refractory period of insensitivity to depolarization before another action potential can be generated. The action potential threshold is -50 to -55 mV (approached from more negative values) in many cells.



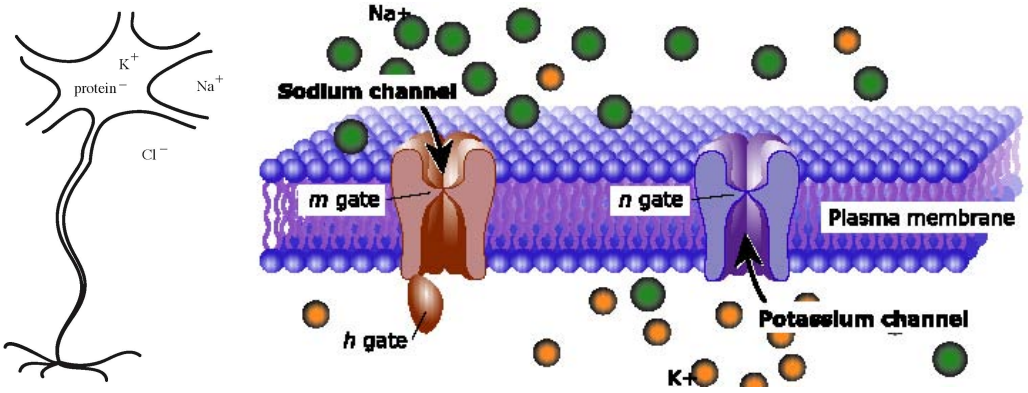
A schematic view of an idealized action potential illustrates its various phases as the action potential passes a point on a cell membrane.

Conductance-based models are the simplest possible biophysical representation of an excitable cell, such as a neuron, in which its protein molecule ion channels are represented by conductances and its lipid bilayer by a capacitor.

The core elements of any biologically realistic model of a neuron are the membrane channel models.

Excitable membrane dynamics

The neuron membrane acts as a boundary separating the intracellular fluid from the extracellular fluid. It is selectively permeable allowing, for example, the passage of water but not large macromolecules. Ions (such as Na^+, K^+ and Cl^-) can pass through the cell membrane, driven by diffusion and electrical forces, and this movement of ions underlies the generation and propagation of signals along neurons. Differences in the ionic concentrations of the intra/extracellular fluids create a potential difference across the cell. If the intra/extracellular potentials are denoted by V_{out} and V_{in} respectively, then the membrane potential is the potential difference across the membrane $V = V_{\text{in}} - V_{\text{out}}$.



Left: Neurons are charged due to an unequal distribution of ions across the cell membrane. The membrane of a neuron is said to be *excitable* and will support an action potential (right) in response to a sufficiently large input. Right: Ionic gates are embedded in the cell membrane and control the passage of ions.

- In the absence of a signal, there is a resting potential of ~ -65mV.
- During an action potential, the membrane potential increase rapidly to ~ 20mV, returns slowly to ~ -75mV and then slowly relaxes to the resting potential.
- The rapid membrane depolarisation corresponds to an influx of Na^+ across the membrane. The return to -75mV corresponds to the transfer of K^+ out of the cell. The final recovery stage back to the resting potential is associated with the passage of Cl^- out of the cell.

For an animation of channel gating during an action potential see
`http://www.blackwellpublishing.com/matthews/channel.html`

The mathematical model

The conceptual idea behind current electrophysiological models is that cell membranes behave like electrical circuits. The basic circuit elements are 1) the phospholipid bilayer, which is analogous to a capacitor in that it accumulates ionic charge as the electrical potential across the membrane changes; 2) the ionic permeabilities of the membrane, which are analogous to resistors in an electronic circuit; and 3) the electrochemical driving forces, which are analogous to batteries driving the ionic currents. These ionic currents are arranged in a parallel circuit. Thus the electrical behavior of cells is based upon the transfer and storage of ions such as K^+ and Na^+.

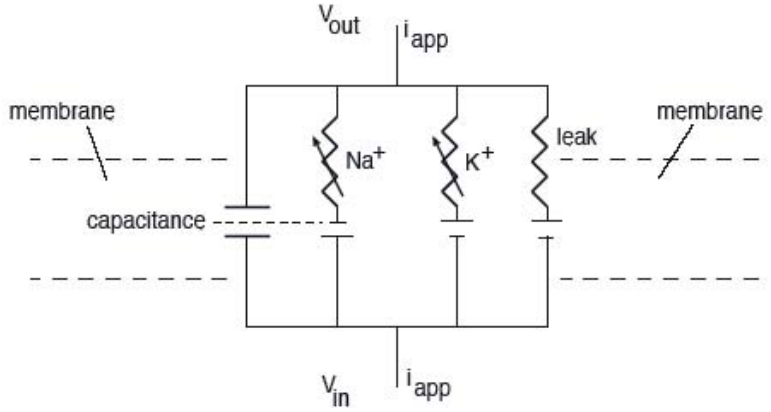
Batteries and the Nernst potential

Ion specific pores create voltage differences. Balancing the electrical and osmotic forces gives the Nernst potential for each ionic species:

$$\Delta V \propto \log \frac{[\mathrm{ion}]_{\mathrm{out}}}{[\mathrm{ion}]_{\mathrm{in}}}.$$

This is the emf (or battery) that drives each ionic species in the electrical circuit shown above. Note that the resting potential is a weighted sum of individual ionic Nernst potentials.

The resting membrane potential is the point at which there is no net current across the membrane. The Goldman-Hodgkin-Katz (GHK) equation gives this value – see Appendix A.



The equivalent electrical circuit for the Hodgkin-Huxley model of squid giant axon. The capacitance is due to the phospholipid bilayer separating the ions on the inside and the outside of the cell. The three ionic currents, one for Na^+, one for K^+, and one for a non-specific leak, are indicated by resistances. The conductances of the Na^+ and K^+ currents are voltage dependent, as indicated by the variable resistances. The driving force for the ions is indicated by the symbol for the electromotive force, which is given in the model by the difference between the membrane potential, $V = V_{in} - V_{out}$ and the reversal potential.

A dynamical electrical circuit

The standard dynamical system for describing a neuron as a spatially isopotential cell with constant membrane potential V is based upon conservation of electric charge, so that

$$C\frac{dV}{dt} = I_{ion} + I_{app}.$$

where C is the cell capacitance, I_{app} the applied current and I_{ion} represents the sum of individual ionic currents:

$$I_{ion} = -g_K(V - V_K) - g_{Na}(V - V_{Na}) - g_L(V - V_L).$$

In the Hodgkin-Huxley model the membrane current arises mainly through the conduction of sodium and potassium ions through voltage dependent channels in the membrane. The contribution from other ionic currents is assumed to obey Ohm's law (and is called the leak current). The g_K, g_{Na} and g_L are conductances (conductance=1/resistance).

Voltage gated channels

Channels are known to have gates that regulate the permeability of the pore to ions (so that $g_K = g_K(V)$ and $g_{Na} = g_{Na}(V)$). These gates can be controlled by membrane potential (and are known as voltage gated channels). Gates are often modelled with a simple two state (open/closed) process, each described by a first order nonlinear ordinary differential equation. Gates can either be activating or inactivating.

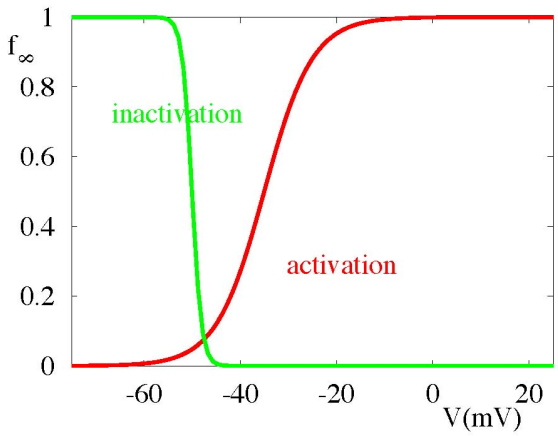
The great insight of Hodgkin and Huxley was to realise that g_K depend upon four activation gates:

$$g_K = \overline{g}_K n^4,$$

whereas g_{Na} depends upon three activation gates and one inactivation gate:

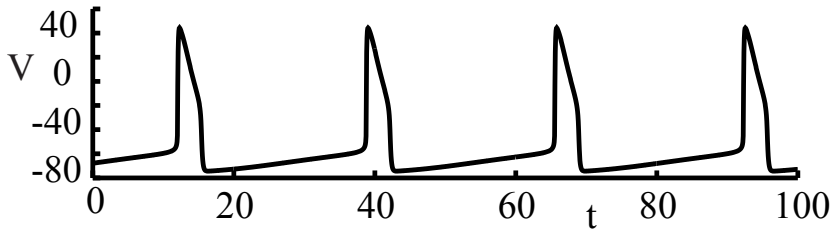
$$g_{Na} = \overline{g}_{Na} m^3 h.$$

The stead-state value of the gate is denoted $f_\infty(V)$ (where f stands for m, n, h).



Activation and inactivation. The sigmoidal function f_∞ is related to the fraction of channels in the open state.

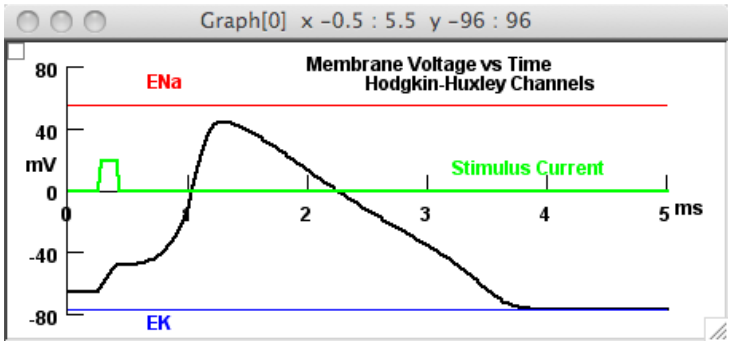
The parameters in conductance-based models (i.e the detailed choice of $f_\infty(V)$ etc.) are determined from empirical fits to voltage-clamp experimental data, assuming that the different currents can be adequately separated using pharmacological manipulations and voltage-clamp protocols. The details (fitted forms) of the Hodgkin-Huxley are listed for completeness in Appendix B.

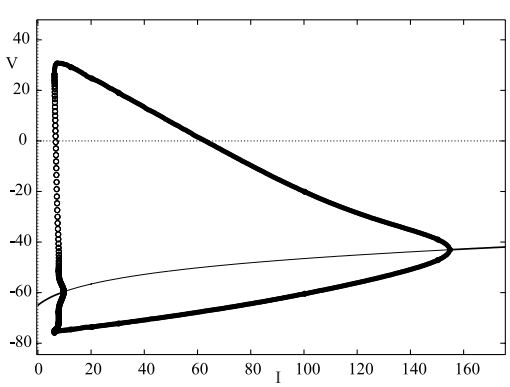


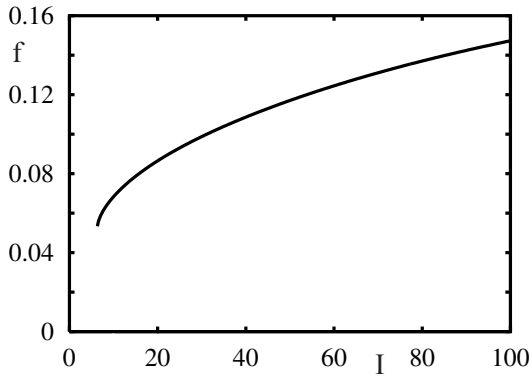
An example of a periodic spike train that can be generated by the Hodgkin-Huxley model under constant current injection.

In summary, the basic assumptions in all conductance-based models are: the different ion channels in the cell membrane are independent from each other, activation and inactivation gating variables are voltage-dependent and independent of each other for a given ion channel type,each gating variable follows first-order kinetics, and the model cell compartment is isopotential. A description of some other popular membrane currents is given in Appendix C.

To explore the model run the **NIA2 tutorial - The Na Action Potential**. Write your name in capitals on a blank sheet of paper and record your answers to the questions raised in the tutorial. **These will be collected at the end of the session by the lecturer**.







Left: Bifurcation diagram of the Hodgkin-Huxley model as a function of the external drive I. Black circles show amplitude of stable limit cycle, open circles indicate unstable limit cycle behaviour. Solid line shows stable fixed point, thin line shows unstable fixed point behaviour. Right: Frequency of oscillation as a function of external drive.

Appendix A: The Goldman-Hodgkin-Katz

The Goldman-Hodgkin-Katz (GHK) voltage equation is used in cell membrane physiology to determine the potential across a cell's membrane taking into account all of the ions that are permeant through that membrane.

The GHK equation is a variation on the Nernst equation. The Nernst equation can essentially calculate the membrane potential of a cell when only one ion is permeant, as long as the concentrations of that ion both inside and outside the cell are known. The Nernst equation cannot, however, deal with cells having permeability to more than one ion. The GHK voltage equation is not exact and makes assumptions with regards to the mechanism of diffusion, which influences the final result.

The GHK equation for N positive ionic species and M negative is

$$\mathrm{E_m} = \frac{\mathrm{RT}}{\mathrm{F}} \ln\left(\frac{\sum_{\mathrm{i}}^{\mathrm{N}} \mathrm{P_{M_i^+}}[\mathrm{M_i^+}]_{\mathrm{out}} + \sum_{\mathrm{j}}^{\mathrm{M}} \mathrm{P_{A_j^-}}[\mathrm{A_j^-}]_{\mathrm{in}}}{\sum_{\mathrm{i}}^{\mathrm{N}} \mathrm{P_{M_i^+}}[\mathrm{M_i^+}]_{\mathrm{in}} + \sum_{\mathrm{j}}^{\mathrm{M}} \mathrm{P_{A_j^-}}[\mathrm{A_j^-}]_{\mathrm{out}}}\right)$$

It is similar to the Nernst equation but has a term for each permeant ion.

- $\mathrm{E_m}$ is the membrane potential.
- $\mathrm{P_{ion}}$ is the permeability for that ion.
- $[\mathrm{ion}]_{\mathrm{out}}$ is the extracellular concentration of that ion.
- $[\mathrm{ion}]_{\mathrm{in}}$ is the intracellular concentration of that ion.
- R is the ideal gas constant.
- T is the temperature in Kelvin.
- F is the Faraday constant.

Appendix B: Mathematical details of the Hodgkin-Huxley model

The gating variables satisfy the nonlinear ordinary differential equations

$$\dot{m} = \frac{m_\infty(V) - m}{\tau_m(V)}, \qquad \dot{n} = \frac{n_\infty(V) - n}{\tau_n(V)}, \qquad \dot{h} = \frac{h_\infty(V) - h}{\tau_h(V)}.$$

The six functions $\tau_X(V)$ and $X_\infty(V)$, $X \in \{m, n, h\}$, are obtained from fits with experimental data. It is common practice to write

$$\tau_X(V) = \frac{1}{\alpha_X(V) + \beta_X(V)}, \qquad X_\infty(V) = \alpha_X(V)\tau_X(V)$$

The details of the final Hodgkin-Huxley description of nerve tissue are completed with:

$$\begin{aligned}
\alpha_m(V) &= \frac{0.1(V+40)}{1-\exp[-0.1(V+40)]} & \alpha_h(V) &= 0.07\exp[-0.05(V+65)] \\
\alpha_n(V) &= \frac{0.01(V+55)}{1-\exp[-0.1(V+55)]} & \beta_m(V) &= 4.0\exp[-0.0556(V+65)] \\
\beta_h(V) &= \frac{1}{1+\exp[-0.1(V+35)]} & \beta_n(V) &= 0.125\exp[-0.0125(V+65)]
\end{aligned}$$

$C = 1\mu$F cm^{-2}, $g_L = 0.3$mmho cm^{-2}, $g_K = 36$mmho cm^{-2}, $g_{Na} = 120$mmho cm^{-2}, $V_L = -54.402$mV, $V_K = -77$mV and $V_{Na} = 50$mV. (All potentials are measured in mV, all times in ms and all currents in μA per cm^2).

Appendix C: Some other membrane currents

From Harry Erwin's NeuroWiki: http://scat-he-g4.sunderland.ac.uk/~harryerw/phpwiki/index.php

Purkinje cells show sodium-dependent action potentials in the soma and calcium-based action potentials in the dendritic tree. They have $I_{Na,p}$ channels that create a plateau potential in conjunction with the calcium currents, resulting in a structured burst much longer than the afference.

Thalamic relay neurons produce a burst if the cells starts out negative to -75 mV and a four spike transfer sequence if positive to -65 mV. This reflects low-threshold calcium channels.

Some cells (pacemakers) spike repetitively without input. This seems to involve $I_{Na,p}$ currents.

Inner hair cells have persistent voltage-sensitive calcium currents localized in the presynaptic terminals that trigger vesicle release (probably Glu) as a poisson process. Depolarisation of the cell via potassium channels in the hairs increases the rate of Ca^{2+} flow and so modulates the vesicle release. The more sensitive the hair cell, the higher the rate of spontaneous release.

$I_{Na,t}$ Transient sodium current involved in action potential generation. Rapidly activates and rapidly inactivates. Dominant in axons and cell bodies. Activation threshold in Aplysia is about -25 mV. Activates within a few ms and is steeply voltage dependent with half maximal conductance at about -8 mV. Inactivates with a time constant of $10 - 20$ ms.

Steady-state inactivation is voltage dependent in Helix aspersa with half-inactivation around -30 mV. Exponential recovery with a time constant of about 30 ms. In vertebrates, these channels appear somewhat faster than in squid.

$I_{INa,p}$ Persistent and noninactivating sodium current. Much smaller in amplitude than $I_{Na,t}$. Plays an interesting role in the neuron. Activated by depolarization bringing the membrane potential close to the action potential threshold. Markedly enhances the response to excitation and keep the cell moderately depolarised for extended periods.

I_T Low threshold "Transient" calcium current. Rapidly inactivates. Threshold is more negative than -65 mV. Rhythmic burst firing. Depolarization to -60 mV inactivates this current and eliminates the bursting. Reactivated by repolarization.

I_L High threshold "Long-lasting" calcium current. Slowly inactivates. Threshold about -20 mV. Calcium spikes in dendrites. Involved in synaptic transmission.

I_N "Neither" calcium current. Rapidly inactivates. Threshold about -20 mV. Calcium spikes in dendrites. Involved in synaptic transmission.

I_P "Purkinje" calcium current. Threshold about -50 mV.

I_K Potassium current activated by strong depolarization. "Delayed rectifier." Repolarizes the membrane after an action potential. Part of the HodgkinHuxley model. Common in the CNS and supplemented by other currents in mammals. Activates at membrane potentials positive to -40 mV and strengthens with depolarisation. Slowly inactivates. Inactivation complete at about $+10$ mV. Recovery from inactivation takes seconds. Also passes some other ions at low concentration.

I_C Potassium current activated by calcium concentration increases within the cell (I_L and I_N) and very sensitive to membrane potential depolarization. General category – $I_{K,Ca}$. Plays a role in action potential repolarization and interspike interval. This current (reflecting calcium ion influx from the I_L current) produces enhanced repolarization after each action potential. Inactivates quickly upon repolarization.

I_{AHP} Slow afterhyperpolarization potassium current (very slow). Sensitive to calcium concentration increases within the cell (I_L and I_N) and a number of neurotransmitters, but insensitive to membrane potential. General category – $I_{K,Ca}$. Supports slow adaptation of action potential discharge in the hippocampus and cortex.

I_A Transient, inactivating potassium current. Plays a role in action potential repolarization and in delaying onset of firing. Basically, the action potential is delayed until I_A shuts down. Activates in response to membrane potentials positive to -60 mV, but then inactivates rapidly. Reactivates in response to repolarization. Kinetics resemble the fast voltage-dependent sodium inward current.

I_M Muscarinic potassium current. Activated by depolarization to about -65 mV. Noninactivating. Spike frequency adaptation. Quiets the cell after an initial spike. Blocked by stimulation of muscarinic cholinergic receptor agonists.

I_h Depolarizing mixed cation (Na^+ and K^+) current activated by hyperpolarization. Rhythmic activities. Slow time course. May control the communication of synaptic inputs to the soma of cortical pyramidal cells. Has cAMP receptors that modulate the voltage dependence.

$I_{K,leak}$ Potassium current that maintains the neuronal resting potential.

S Coombes 2010