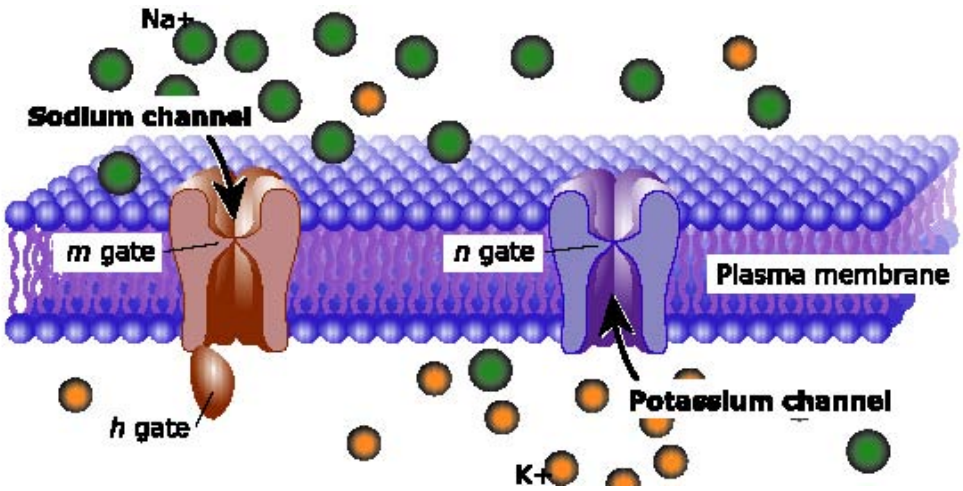
School of Mathematical Sciences

G14TNS Theoretical Neuroscience

Electrophysiology of the neuron

Electrophysiology is the study of ionic currents and electrical activity in cells and tissues. The work of Hodgkin and Huxley in elucidating the mechanism of action potentials in the squid giant axon is one of the major breakthroughs of dynamical modeling in physiology.

The theory of nonlinear dynamical systems can be used to understand and explain neural phenomena at many different levels. In these two lectures we shall focus on the ionic basis of neural excitability and consider the generation of action potentials at the level of the single neuron

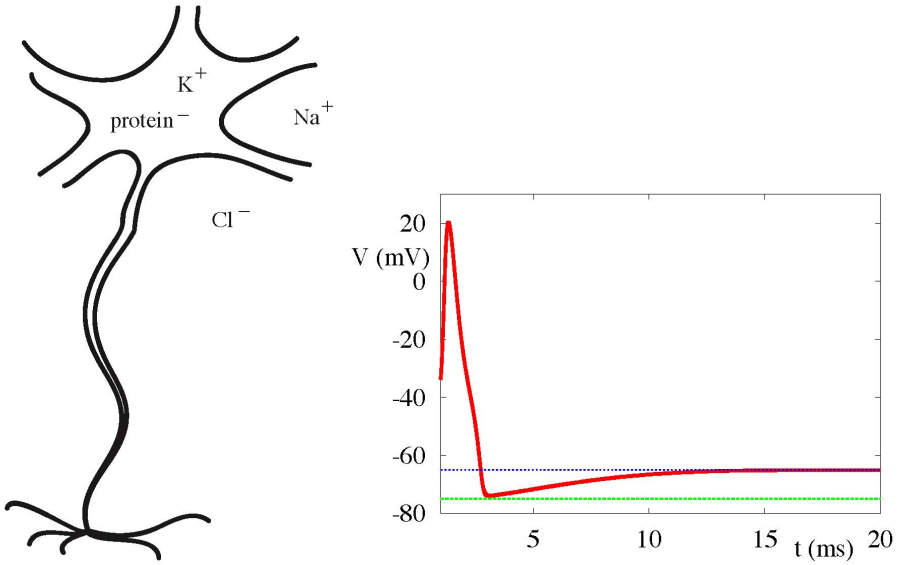


Ionic gates are embedded in the cell membrane and control the passage of ions.

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 $V = V_{\text{in}} - V_{\text{out}}$.

- 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`



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.

1 Modelling the single neuron

Qualitative features of the dynamics of excitable/oscillatory processes are shared by broad classes of neuronal models. These features are expressed in models for single cell behavior and they include excitability and threshold behavior, beating and bursting oscillations, bistability and hysteresis, etc.

Our goal here is to illustrate, by exploiting specific models of excitable membrane, some of the concepts and techniques which can be used to understand, predict, and interpret these dynamic phenomena. The mathematical methods to be used include, graphical/geometric representation of the dynamics (phase plane analysis), and analytic formulae for characterizing thresholds and stability conditions. The concepts are from the qualitative theory of nonlinear differential equations and nonlinear oscillations, and from perturbation and bifurcation theory. The topics we will cover include steady states, trajectories, limit cycles, stability and bifurcation of solutions.

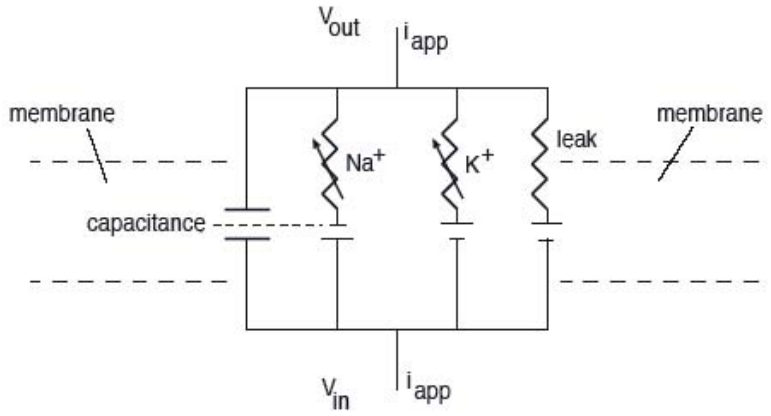
The Hodgkin-Huxley model

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^+.

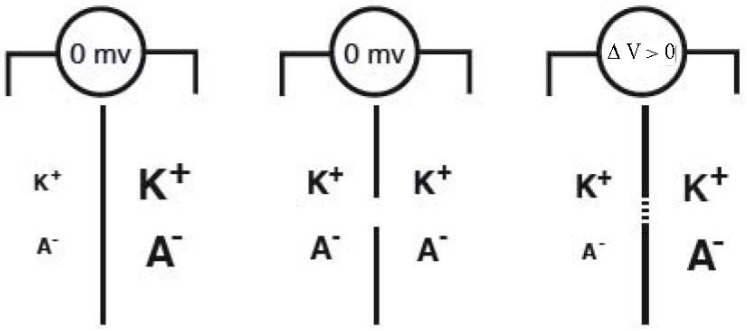
Batteries and the Nernst potential

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

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



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.



Left: concentration and charge are balanced on each side of the membrane, so there is no potential difference across the membrane, $\Delta V = 0$. Middle: Due to a nonselective pore, charge and concentration are balanced everywhere, and so there is no ΔV across the membrane. Right: K^+ selective pore allows K^+ but not A^- to pass through the membrane. K^+ moves to equilibrate concentration until counterbalanced by the accumulating negative charge, because A^- cannot move resulting in $\Delta V \neq 0$. .

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.

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 (1952) 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). We describe these gates with a simple two state (open/closed) Markov process:

$$C \underset{k^-}{\overset{k^+}{\rightleftharpoons}} O.$$

Denoting the fraction of open channels by f_0 means that

$$\frac{df_0}{dt} = -k^- f_0 + k^+(1 - f_0) = \frac{f_\infty - f_0}{\tau},$$

where

$$f_\infty = \frac{k^+}{k^+ + k^-}, \qquad \tau = \frac{1}{k^+ + k^-}.$$

Because ionic channels are composed of proteins with charged amino acid side chains the potential difference across the membrane can influence the rate at which the transitions from the open to closed state occur and the rate constants are expected to have the (Arrhenius) form

$$k^+ = k_0^+ e^{-\alpha V}, \qquad k^- = k_0^- e^{-\beta V},$$

so that

$$f_\infty = \frac{1}{1 + k_0^-/k_0^+ e^{(\alpha-\beta)V}} = \frac{1}{1 + e^{-(V-V_0)/S_0}},$$

where

$$V_0 = \frac{1}{\beta - \alpha}\ln(k_0^-/k_0^+), \qquad S_0 = \frac{1}{\beta - \alpha}.$$

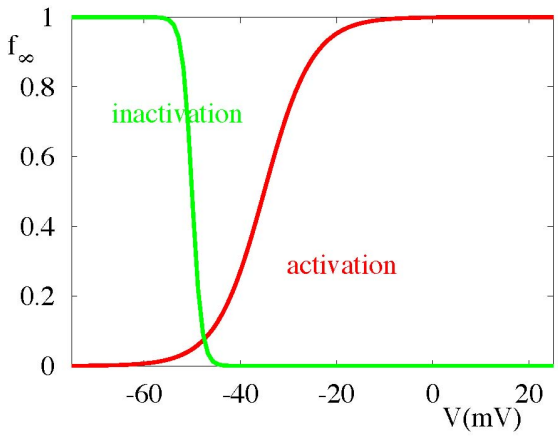
Hence from the sigmoidal form of f_∞ we see that gates ca either be activating ($S_0 > 0$) or inactivating ($S_0 < 0$).

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

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

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

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



Activation and inactivation.

where

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

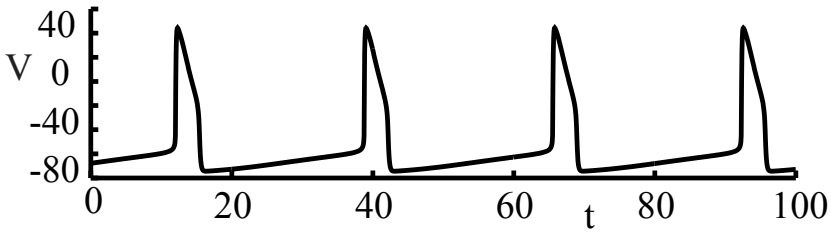
The six functions $\tau_X(V)$ and $X_\infty(V)$, $X \in \{m, n, h\}$, are obtained from fits with experimental data. It is common practice to write

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

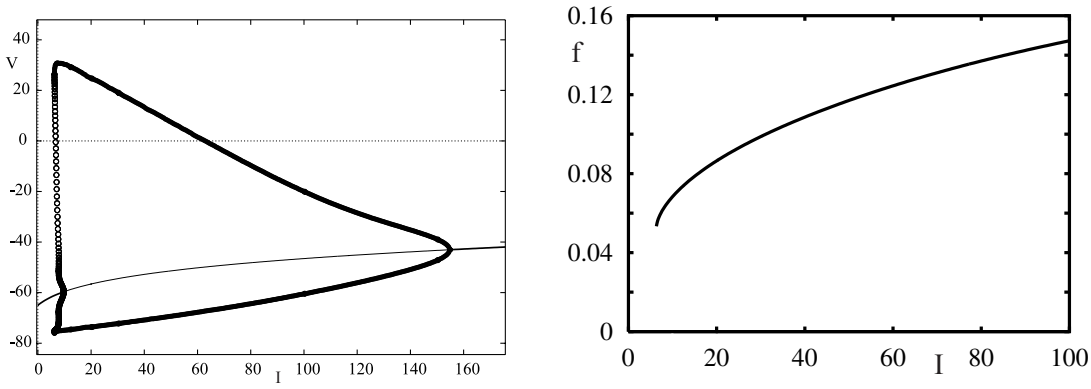
The details of the final Hodgkin-Huxley description of nerve tissue are completed with:

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

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



Periodic spike train that can be generated by the HH model under constant current injection.



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.