Mathematical Neuroscience, Edinburgh (Mar 17 - Mar 19, 2008)

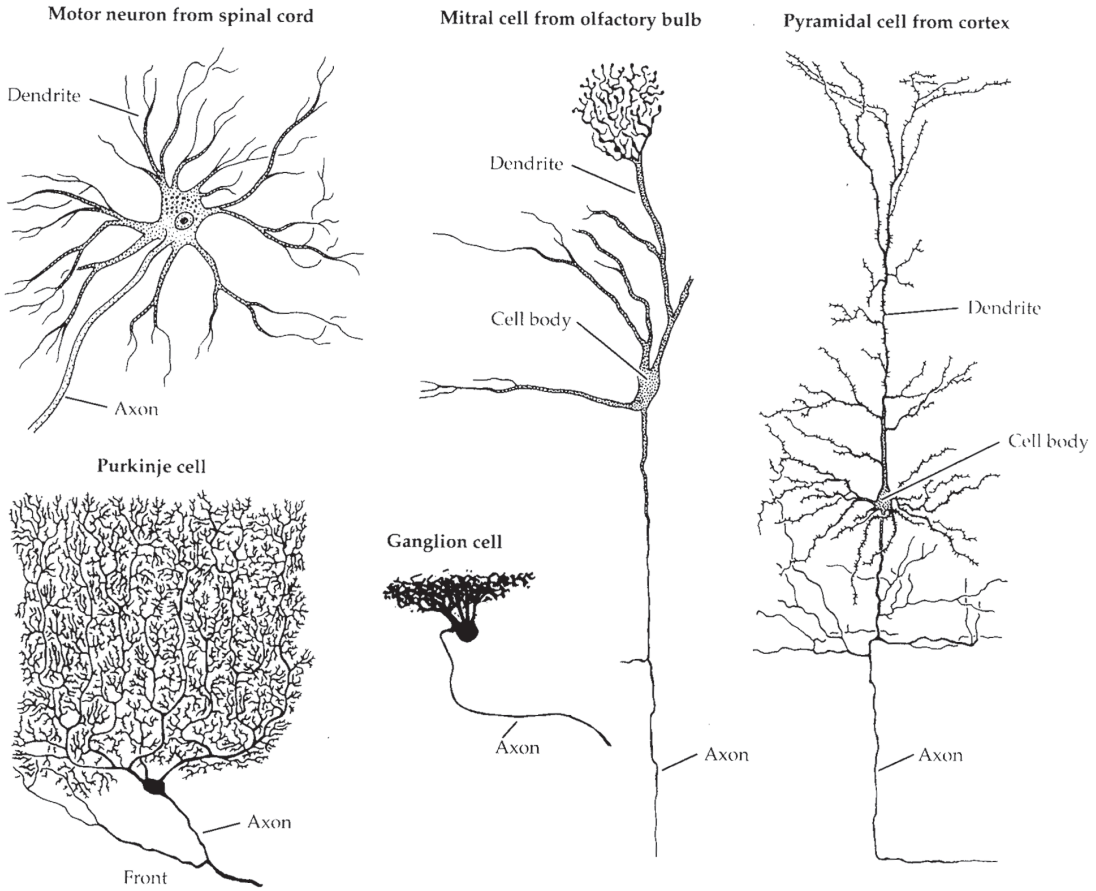
Training Workshop (Mar 16, 2008)

Single neuron models

Lecture summary: Two types of complexity are usually associated with modelling single neurons: the intrinsic properties of the cell membrane that make neuronal dynamics so rich, and the elaborate morphology that allows neurons to receive and integrate thousands of synaptic inputs from other cells. Models that describe the membrane potential of a neuron by a single variable and ignore its spatial variation are called single-compartment models. In this sub-class of models the rich and complex dynamics of real neurons can be reproduced quite accurately by models that include aspects of ionic conductances, known as conductance-based models. To study the effects of dendritic or axonal morphologies on neuronal function, models based on the linear cable theory and multi-compartmental models have to be considered instead. In this lecture, I will review the spatially extended models of neurons by introducing the cable equation and the Rall model of an equivalent cylinder that can be studied analytically. Multi-compartmental conductance-based models that incorporate the complexity of real membrane dynamics but lack mathematical tractability will also be discussed.

The neuron: biological background

The fundamental processing unit of the central nervous system is the neuron. The total number of neurons in the human brain is around 10^{12}. In 1mm^3 of cortical tissue there are about 10^5 neurons.



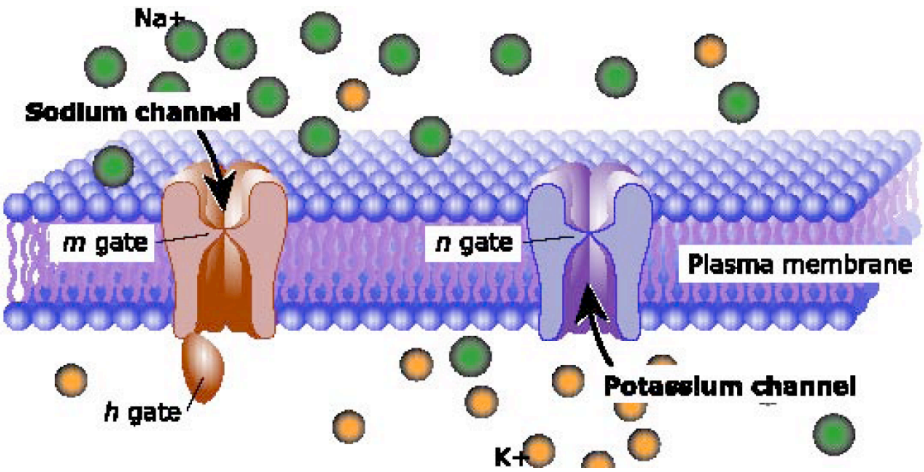
- Three main structures can be identified in a typical neuron: dendritic tree, cell body or soma, and axon. These roughly correspond to the input, processing and output functions respectively. The *dendritic tree* is a branched structure that forms the main input pathway of a neuron. It sums the output signals received from surrounding neurons in the form of an electrical potential, which diffuses along the tree to the soma. If the total potential at the soma exceeds a certain threshold value, the neuron produces a short electrical spike or *action potential*, which is then conducted along the *axon*. The axon itself branches out so that the pulse is transmitted to several thousand target neurons.

- The contacts of the axon to target neurons are either located on the dendritic tree or directly on the soma, and are known as *synapses*. Most synapses are chemical contacts, that is, the arrival of an action potential at the synapse induces the secretion of a neurotransmitter that in turn leads to a change in the potential of the membrane of the target neuron. Depending on the type of synapse, an incoming pulse either causes an increase in electrical potential (excitatory synapse) or a decrease (inhibitory synapse).

- The total input to a neuron is continuous-valued (the resulting electrical potential at the soma), whereas the output is discrete (either it fires a pulse or it does not).

- A single neuron may have thousands, tens of thousands or hundreds of thousands of synapses. However, the brain as a whole is sparsely connected since a neuron will only be connected directly to a tiny fraction of other neurons.

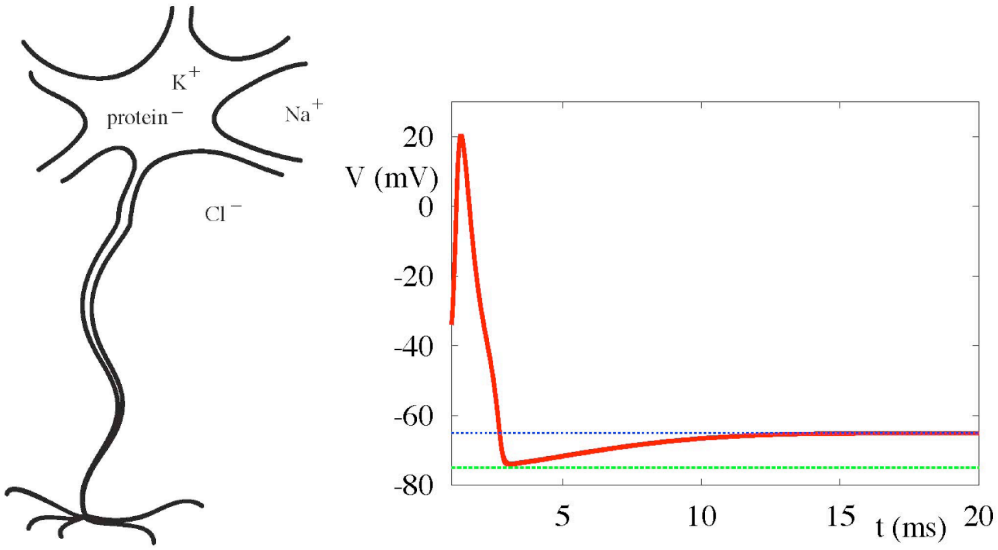
- Inputs received by a neuron produce electrical transmembrane currents that change the membrane potential of the neuron. Voltage-sensitive channels embedded in the neuronal membrane can lead to the generation of an *action potential* (or *spike*). An action potential lasts about 1msec. Synaptic transmission can last from a few to a few hundred msec. Changes in synaptic potential induced by the arrival of an action potential can last from 1msec to many minutes.



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

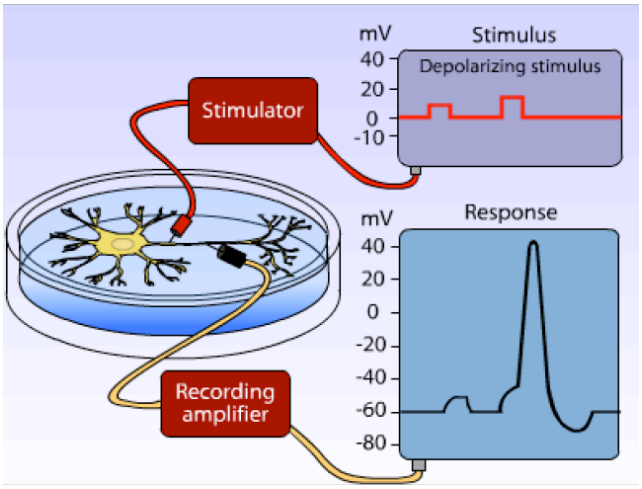
The neuron membrane acts as a boundary separating the intracellular fluid from the extracellular fluid. It is selectively permeable allowing, for example, the passage of water but not large macromolecules. Ions (such as sodium (Na^+), potassium (K^+) and chloride (Cl^-)) can pass through the cell membrane, 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.



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

An example of the experimental setup *in vitro*:

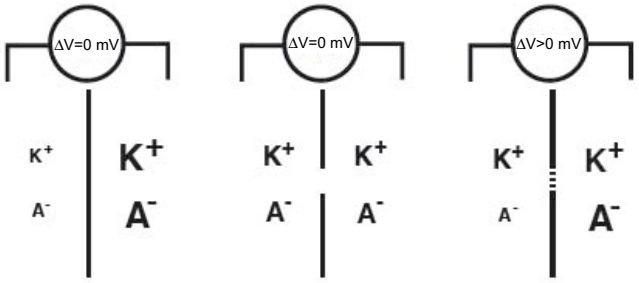


The current injected into the cell (the stimulus) and the corresponding voltage response are shown. If the stimulus is sufficient to push the membrane potential past the firing threshold for the neuron (such as the second stimulus), an action potential is generated.

Single-compartment models

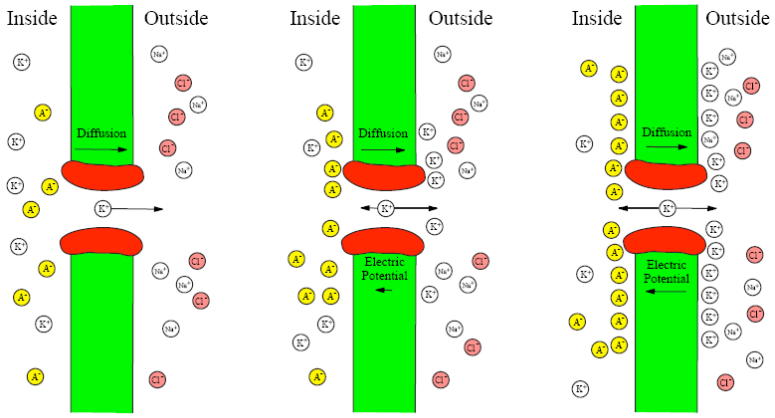
The Nernst potential

The electrical behaviour of cells is based upon the transfer and storage of charge. Biological fluids (such as cytoplasm and extracellular fluid) contain numerous ions. Consider the case where the two ions K^+ and any anion (a negatively charged ion) A^- are present across the membrane:



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 $\Delta V \neq 0$.

Ion specific pores create voltage differences.



Diffusion of K^+ ions down the concentration gradient through the membrane (a) creates an electric potential force directed at the opposite direction (b) until the diffusion and electrical forces counter each other (c) resulting in the Nernst equilibrium potential for K^+.

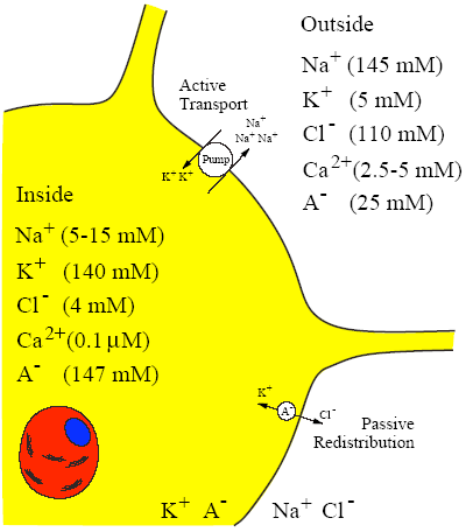
Balancing the electrical and osmotic forces gives the Nernst potential for each ionic species:

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

The Nernst potential represents the equilibrium of the thermodynamic system and the tendency for the system to move toward the equilibrium potential is the basis of the *ionic battery* used in the modelling of electrophysiological phenomena. In electrophysiology, the equilibrium potential is called the *reversal potential*.

The flow of Na^+ and Ca^{2+} ions is not significant, at least at rest, but the flow of K^+ and Cl^- ions is. This, however, does not eliminate the concentration asymmetry for two reasons:

- *Passive redistribution*. The impermeable A^- attract more K^+ into the cell and repel more Cl^- out of the cell (thereby creating concentration gradients).
- *Active transport*. Ions are pumped in and out of the cell via ionic pumps. For example, the Na^+-K^+ pump pumps out three Na^+ ions for every two K^+ ions pumped in (thereby maintaining concentration gradients).



Equilibrium Potentials

$$\begin{aligned}
Na^+ \quad & 62 \log \tfrac{145}{5} = 90 \text{ mV} \\
& 62 \log \tfrac{145}{15} = 61 \text{ mV} \\
K^+ \quad & 62 \log \tfrac{5}{140} = -90 \text{ mV} \\
Cl^- \quad & -62 \log \tfrac{110}{4} = -89 \text{ mV} \\
Ca^{2+} \quad & 31 \log \tfrac{2.5}{10^{-4}} = 136 \text{ mV} \\
& 31 \log \tfrac{5}{10^{-4}} = 146 \text{ mV}
\end{aligned}$$

Ion concentrations in a typical mammalian neuron.

The conductance-based membrane model

Our task in modelling electrophysiological phenomena is to describe how the conductance of the membrane to various ions changes with time and then to keep track of the changes in current and voltage that result.

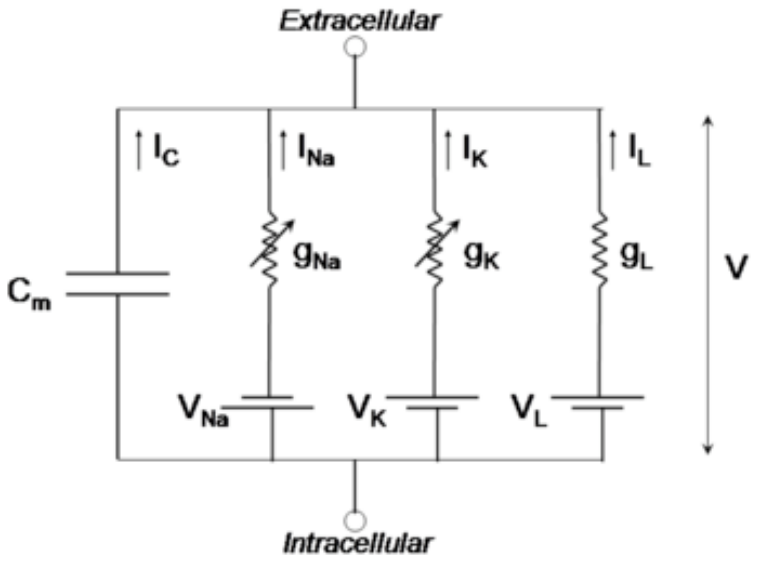
Ohm's law: the current flows down a voltage gradient in proportion to the resistance in the circuit

$$I = \frac{V}{R} = gV$$

g is conductance (=1/resistance)

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 (see the diagram of the electrical circuit). Thus the electrical behavior of cells is based upon the transfer and storage of ions such as K^+ and Na^+.

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



The equivalent circuit representation of a cell membrane.

leak, are indicated by resistances. The conductances of the Na^+ and K^+ currents are voltage dependent, as indicated by the variable resistances. Let V_K and V_{Na} denote the K^+ and Na^+ reversal potentials determined by the Nernst potential. When the membrane potential equals the reversal potential, say V_K, the K^+ current, denoted as I_K ($\mu A/cm^2$), is zero (this is the definition of the Nernst equilibrium potential for K^+). Otherwise, the K^+ current is proportional to the difference of potentials (using Ohm's law):

$$I_K = g_K(V - V_K).$$

Here g_K (mS/cm^2) is the conductance of the K^+ channel and $(V - V_K)$ is the K^+ *driving force* across the membrane. In a cell with many different ions the total current is the sum of the individual ionic currents:

$$I_{ion} = \sum I_i = \sum g_i(V - V_i) = g_K(V - V_K) + g_{Na}(V - V_{Na}) + \dots .$$

Since the membrane acts as a capacitor, the capacitive current across the membrane can be defined as

$$I_{cap} = C\frac{dV}{dt},$$

where C ($\mu F/cm^2$) is the capacitance of the membrane and V is the membrane potential (the potential difference between the inside and outside of the cell). According to Kirchoff's law, the total current I_{app}, flowing across a patch of a cell membrane is the sum of the membrane capacitive current I_{cap} and all the ionic currents

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

This leads to the ODE of the membrane model

$$C\frac{dV}{dt} = -\sum_i g_i(V - V_i) + I_{app}$$

In case of two ionic currents, I_K and I_{Na}, we have

$$C\frac{dV}{dt} = -g_K(V - V_K) - g_{Na}(V - V_{Na}) + I_{app}.$$

The Hodgkin-Huxley model

Channels can be thought to have *gates* that regulate the permeability of the pore to ions. These gates can be controlled by membrane potential, producing *voltage-gated* channels; by chemical ligands, producing *ligand-gated* channels; or by a combination of factors. In a series of experiments in 1952, Alan Hodgkin and Andrew Huxley established experimentally the voltage dependence of ion conductances in the electrically excitable membrane of the squid giant axon.

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 included as the leak current, i.e. the ODE for V includes the following term

$$-g_K(V - V_K) - g_{Na}(V - V_{Na}) - g_L(V - V_L),$$

where g_K, g_{Na} and g_L are conductances of potassium, sodium and leak channels respectively.

Voltage-gated channels

The mathematical description of voltage-dependent activation and inactivation gates is based on the mechanism

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

and can be described by

$$\frac{df_O}{dt} = \frac{f_\infty - f_O}{\tau},$$

where $f_\infty = k^+/(k^+ + k^-)$ and $\tau = 1/(k^+ + k^-)$. However, what distinguishes a voltage-dependent gating mechanism from a passive mechanism is the voltage dependence of the rate constants k^+ and 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 form

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

where k_0^+ and k_0^- are independent of V. Therefore,

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

where

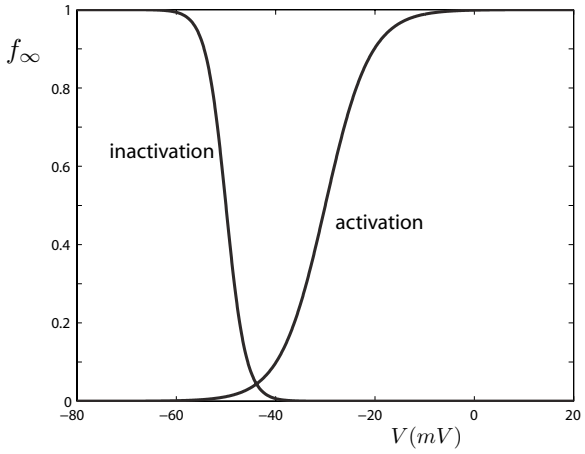
$$V_0 = \frac{1}{\beta - \alpha} \ln(k_0^-/k_0^+), \qquad S_0 = \frac{1}{\beta - \alpha},$$

i.e. the fraction of open channels f_∞ depends on the membrane voltage. Hence from the form of f_∞ we see that gates can either be activating ($S_0 > 0$) or inactivating ($S_0 < 0$).

Since gates can be controlled by membrane potential, the conductances, such as g_K and g_{Na}, depend on V, i.e $g_K = g_K(V)$ and $g_{Na} = g_{Na}(V)$.

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

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



The fraction of open channels $f_\infty(V)$.

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

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

Here the variable m for Na^+ (similarly, the variable n for K^+) denotes the probability of an activation gate being in the open state and h denotes the probability of an inactivation gate being in the open state. $\overline{g}_K$ and $\overline{g}_{Na}$ are the *maximal conductances* of the populations of K^+ and Na^+ channels respectively. The factors n^4 and m^3h model the average proportions of channels in the open states for potassium and sodium. The gating variables have to satisfy the following equations

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

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:

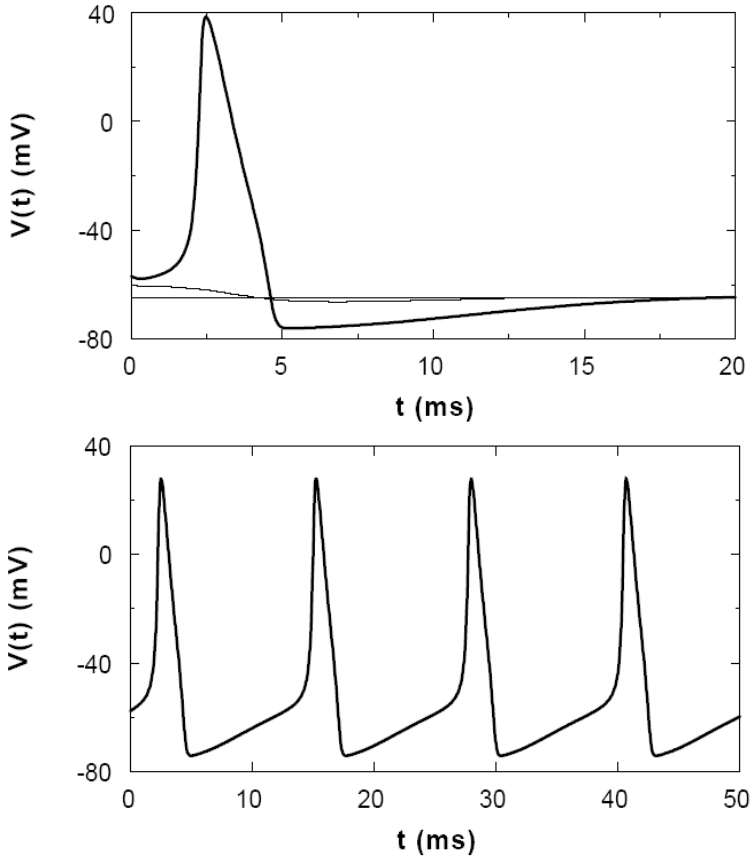
$$\begin{aligned}
\alpha_m(V) &= \frac{0.1(V+40)}{1 - \exp[-0.1(V+40)]} & \alpha_h(V) &= 0.07\exp[-0.05(V+65)] \\
\alpha_n(V) &= \frac{0.01(V+55)}{1 - \exp[-0.1(V+55)]} & \beta_m(V) &= 4.0\exp[-0.0556(V+65)] \\
\beta_h(V) &= \frac{1}{1 + \exp[-0.1(V+35)]} & \beta_n(V) &= 0.125\exp[-0.0125(V+65)]
\end{aligned}$$

The primary equations for the Hodgkin-Huxley model:

$$C\frac{dV}{dt} = -\bar{g}_{Na}m^3h(V - V_{Na}) - \bar{g}_K n^4(V - V_K) - \bar{g}_L(V - V_L) + I_{app},$$

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m}, \qquad \frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}, \qquad \frac{dn}{dt} = \frac{n_\infty - n}{\tau_n}$$

$C = 1\ \mu F/cm^2$, $g_L = 0.3$ mS/ cm^2, $g_K = 36$ mS/cm^2, $g_{Na} = 120$ mS/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 $\mu A/cm^2$).



Left: The solution of the HH equations with $I_{app} = 0$ and three different initial conditions $V(0) = -65$, $V(0) = -60$ and $V(0) = -57$ mV. When the initial value exceeds ≈ -59 mV, an action potential is produced. Right: Continuous spiking occurs under the same conditions with an applied current $I_{app} = 15$.

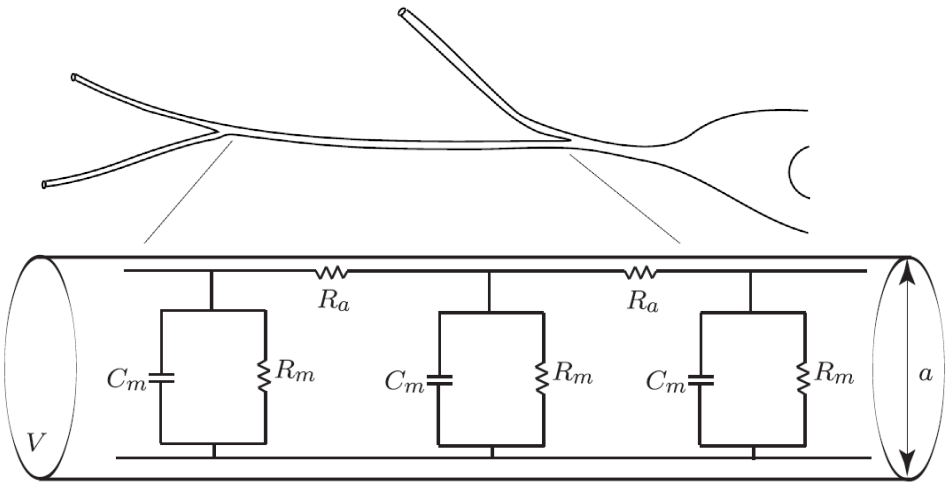
Spatially extended models

Linear cable theory

Cable theory was originally applied to the conduction of potentials in an axon by Hodgkin and Rushton (1946) and was later applied to the dendritic trees of neurons by Wilfrid Rall (1962). The theory itself is much older and was first developed for analyzing underwater telegraph transmission

cables. The general problem addressed by cable theory is how potentials spread in a dendritic tree. A typical neuron has thousands of synaptic inputs spread across its surfaces. Cable theory is concerned with how these inputs propagate to the soma or the axon initial segment, how these inputs interact with one another, and how the placement of an input on a dendritic tree affects its functional importance to the neuron.

Dendritic and axonal cables are typically narrow enough that variations of the potential in the radial or axial directions are negligible compared to longitudinal variations. Therefore, the membrane potential along a neuronal cable is expressed as a function of a single longitudinal spatial coordinate x and time, $V(x,t)$. The dendritic or axonal cable can be visualised as a cylindrical membrane surrounding an intracellular fluid phase of constant cross-sectional area.



The electrical equivalent circuit of the cable model.

The relation between intracellular axial current $I_a(x)$ and the intracellular voltage V_i is given by Ohm's law

$$V_i(x) - V_i(x + \Delta x) = I_a(x) r_a \Delta x.$$

After rearranging and taking the limit $\Delta x \to 0$ we have

$$\lim_{\Delta x \to 0} \frac{V_i(x + \Delta x) - V_i(x)}{\Delta x} = \frac{\partial V_i}{\partial x} = -r_a I_a(x). \tag{1}$$

We assume that the fibre is immersed in a large volume of extracellular fluid. The extracellular resistance may than be neglected and the transmembrane voltage V may be identified with V_i, since the extracellular potential V_e will be constant and is conveniently assumed to be zero.

The axial current may change either as a result of current crossing the cell membrane or as a result of current applied through an internal electrode. Hence at all points apart from those at which current is applied from an electrode, the rate of change in I_a with distance along the cable must be equal and opposite to the density of the membrane current I_m

$$\frac{\partial I_a}{\partial x} = -I_m. \tag{2}$$

We may combine (1) and (2) by differentiating equation (1) to give

$$\frac{\partial^2 V}{\partial x^2} = -r_a \frac{\partial I_a}{\partial x}$$

and, thus,

$$\frac{1}{r_a}\frac{\partial^2 V}{\partial x^2} = I_m. \tag{3}$$

The equation for the membrane current has the form

$$I_m = c_m\frac{\partial V}{\partial t} + \frac{V}{r_m}. \tag{4}$$

Combining (3) and (4) we obtain the basic differential equation of cable theory

$$\boxed{\frac{1}{r_a}\frac{\partial^2 V}{\partial x^2} = c_m\frac{\partial V}{\partial t} + \frac{V}{r_m}}$$

Here c_m and r_m are the capacity and resistance, respectively, of the membrane enclosed by a unit length of cable. The constants r_m, c_m, and r_a are related to R_m, C_m, and R_a by the equations

$$\begin{aligned} r_m &= \frac{R_m}{\pi a}, \\ c_m &= \pi a C_m, \\ r_a &= \frac{4R_a}{\pi a^2}, \end{aligned}$$

where R_m is the specific membrane resistance, C_m is the specific membrane capacity, R_a is the specific cytoplasmic resistivity, and a is the cable diameter. The linear cable theory assumes that r_m, c_m, and r_a are independent of V, x, and t. Introducing the *space constant* $\lambda = \sqrt{r_m/r_a}$ and the membrane *time constant* $\tau = r_m c_m$ the cable equation may also be written as

$$\tau\frac{\partial V}{\partial t} = \lambda^2\frac{\partial^2 V}{\partial x^2} - V.$$

The independent variables can be redefined in terms of the dimensionless quantities,

$$X = x/\lambda \qquad \text{and} \qquad T = t/\tau.$$

The linear cable equation then becomes

$$\boxed{\frac{\partial V}{\partial T} = \frac{\partial^2 V}{\partial X^2} - V}$$

Let $\overline{V}(s)$ be the Laplace transform of $V(T)$. Then assuming $V(X,0) = 0$ the last equation transforms to

$$\frac{d^2\overline{V}}{dX^2} - (s+1)\overline{V} = 0.$$

The general solution to this equation is

$$\overline{V} = \overline{A}\exp\{-X\sqrt{s+1}\} + \overline{B}\exp\{X\sqrt{s+1}\},$$

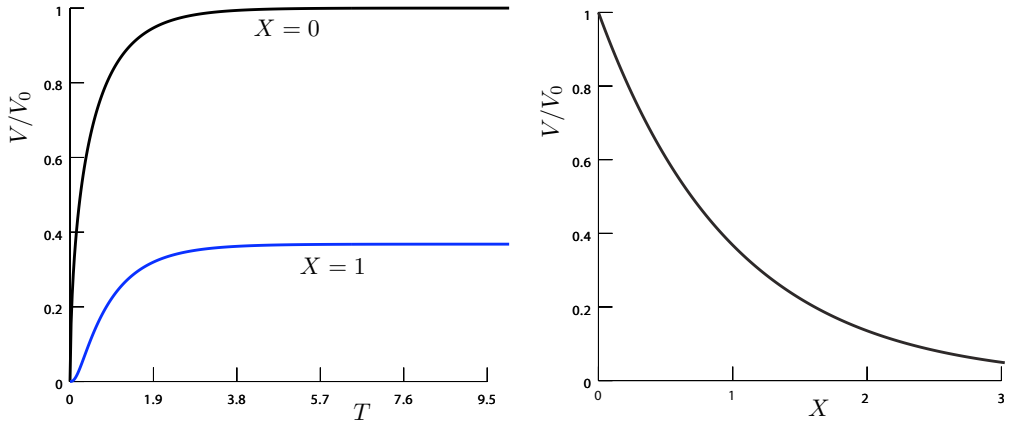
where $\overline{A}$ and $\overline{B}$ are constants or functions of s. In order to obtain particular solutions, $\overline{A}$ and $\overline{B}$ must be determined from the boundary conditions for each case.

Response of infinite cable to a constant current I_0 at $X = 0$

$$V(X,T) = \frac{I_0}{4}\left[\exp(-X)\operatorname{erfc}\left(\frac{X}{2\sqrt{T}} - \sqrt{T}\right) - \exp(X)\operatorname{erfc}\left(\frac{X}{2\sqrt{T}} + \sqrt{T}\right)\right] \tag{5}$$

When $T \to 0$, $\operatorname{erfc}(T) \to 0$, $\operatorname{erfc}(-T) \to 2$ and equation (5) becomes

$$V = \frac{I_0}{2}\exp\left(-\frac{x}{\lambda}\right).$$



The Green's function method

Consider the following cable equation

$$V_t = DV_{xx} - \frac{V}{\tau} + I, \qquad 0 < x < L,\ t > 0, \tag{6}$$

where $D = \lambda^2/\tau$ is the diffusion coefficient and $I(x,t)$ is the input current. To solve (6) we will need *boundary conditions* at the endpoints. We also need to specify the initial value of the depolarisation

$$V(x,0) = v_0(x), \qquad 0 \le x \le L.$$

The Green's function $G(x,y,t)$ for equation (6) with some boundary conditions is the solution of

$$G_t = DG_{xx} - \frac{G}{\tau} + \delta(x-y)\delta(t), \qquad 0 < x < L, 0 < y < L,$$

which satisfies the same boundary conditions and $G = 0$ for $t < 0$. Thus G is the depolarization that results when a unit charge is delivered instantaneously at $t = 0$ at the point y.

Once $G(x,y,t)$ is known the depolarization $V(x,t)$ may be found from the following formula for any suitable current density $I(x,t)$,

$$V(x,t) = \int_0^L G(x,y,t)v_0(y)dy + \int_0^L \int_0^t G(x,y,t-s)I(y,s)dsdy.$$

The proof can be found in [1].

The Green's function on $(-\infty,\infty)$

The Green's function $G_\infty(x,y,t)$ for the cable equation on the interval $(-\infty,\infty)$ with boundary conditions $\lim_{|x|\to\infty} G_\infty(x,y,t) = 0$ takes the form

$$G_\infty(x,y,t) = \frac{\exp(-t/\tau)\exp(-(x-y)^2/(4Dt))}{\sqrt{4\pi Dt}}, \qquad t > 0.$$

References

[1] H.C. Tuckwell. *Introduction to theoretical neurobiology. Volume 1: Linear cable theory and dendritic structure*. Cambridge Studies in Mathematical Biology, vol. 8, 1988.

Y Timofeeva 2008