DOING PHYSICS WITH PYTHON

THE NEURON MEMBRANE AS A CAPACITOR

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mns005.py calculations of rate constants and gating variables (figures 1 to 8)

mns005vc.py voltage clamp and membrane currents (figure 9)

INTRODUCTION

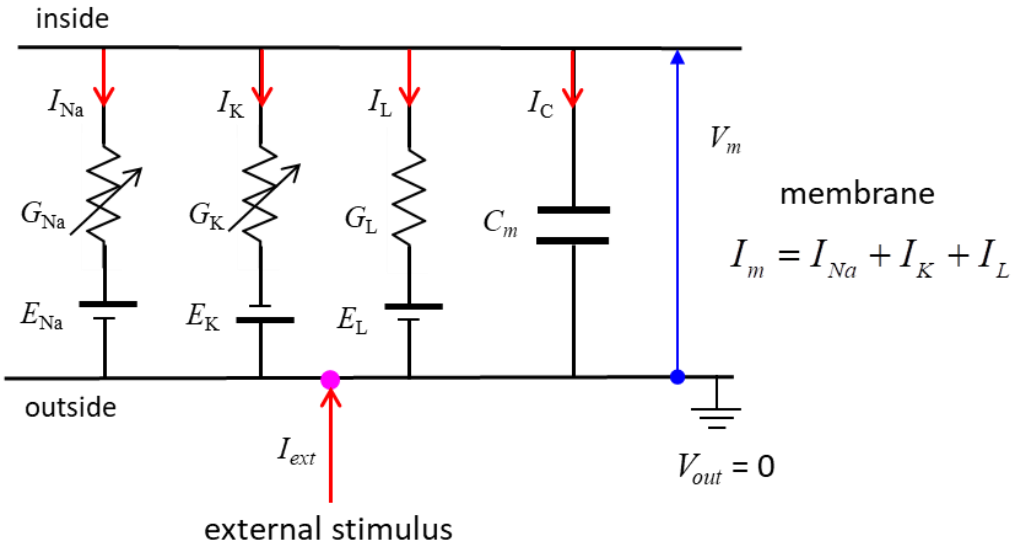
The equations of Hodgkin and Huxley provide a good description of the electrophysiological properties of the giant axon of the squid. These equations capture the essence of spike generation by sodium and potassium ion channels. The basic mechanism of generating action potentials is a short in influx of sodium ions that is followed by an efflux of potassium ions. Cortical neurons in vertebrates, however, exhibit a much richer repertoire of electrophysiological properties

than the squid axon studied by Hodgkin and Huxley. These properties are mostly due to a larger variety of different ion channels.

In biophysically based neural modelling, the electrical properties of a neuron are represented in terms of an electrical equivalent circuit. Capacitors are used to model the charge storage capacity of the membranes (a semipermeable cell membrane separates the interior of the cell from the extracellular liquid and acts as a capacitor). Resistors are used to model the various types of ion channels embedded in the membrane, and batteries are used to represent the electrochemical potentials established by differing intracellular and extracellular ion concentrations. Figure 1 shows the equivalent circuit used by Hodgkin and Huxley in modelling a segment of squid giant axon. The current across the membrane has two major components, one associated with the membrane capacitance and one associated with the flow of ions through resistive membrane channels. They found three different types of ion currents: Na^+, K^+, and a leak current that consists mainly of Cl^- ions. The flow of ions through a cell membrane of a neuron is controlled by special voltage dependent ion channels: Na^+ ion channel, K^+ ion channel and a leak ion channel for all other ions. The neuron can be stimulated by an external current I_{ext} injected into the interior of the neuron.

Electrical potential (voltage) ΔV, current I, area A, current density J, resistance R and conductance G, g are related by the equations

$$R = \frac{1}{G} \qquad I = \frac{\Delta V}{R} = G\,\Delta V \qquad J = \frac{I}{A} \qquad g = \frac{G}{A} \qquad J = g\,\Delta V$$



Kirchhoff's Current Law:
at a junction
$\sum I = 0$

$$I_{Na} + I_K + I_L + I_C - I_{ext} = 0 \qquad I_C = C_M\, dV_m / dt$$

$$dV_m / dt = \left(I_{ext} - I_{Na} - I_K - I_L\right) / C_m$$

Fig.1. Hodgkin – Huxley model: Electrical equivalent circuit for a short segment of squid giant axon. Capacitor (capacitance C_m of the cell membrane); Variable resistors (voltage-dependent Na^+ and K^+ conductances G_{Na}, G_K); fixed resistor (voltage-independent leakage conductance G_L); Batteries (reversal potentials Na^+, K^+ , leakage: E_{Na}, E_K, E_L); Membrane potential $V = V_m = V_{in}$ - V_{out}; External stimulus I_{ext}; Current directions (arrows: I_{ext} outside → inside ($I < 0$), I_{Na}, I_K and I_L inside → outside ($I > 0$).

Electrical activity in neurons is sustained and propagated by ion currents through neuron membranes as shown in figure 1. Most of these transmembrane currents involve four ionic species: sodium Na^+, potassium K^+, calcium Ca^{2+} and chloride Cl^-. The concentrations of these ions are different on the inside and outside of a cell. This creates the electrochemical gradients which are the major driving forces of neural activity. The **extracellular** medium has high concentration of Na^+ and Cl^- and a relatively high concentration of Ca^{2+}. The **intracellular** medium has high concentration of K^+ and negatively charged large molecules A^-. The cell membrane has large protein molecules forming **ion channels** through which ions (but not A^-) can flow according to their electrochemical gradients.

- The concentration asymmetry is maintained through **Passive redistribution**: The impermeable anions A^- attract more K^+ into the cell and repel more Cl^- out of the cell.
- **Active transport**: Ions are pumped in and out of the cell by ionic pumps. For example, the Na^+/K^+ pump, which pumps out three Na^+ ions for every two K^+ ions pumped.

In the Hodgkin – Huxley model only the movement of the sodium, potassium ions are considered, all other ions are considered as part of the leak current.

ION CHANNELS

In this section we give an overview of some of the ion channels encountered in different neurons. The basic equation of detailed neuron models is more or less the same as that of the Hodgkin-Huxley model.

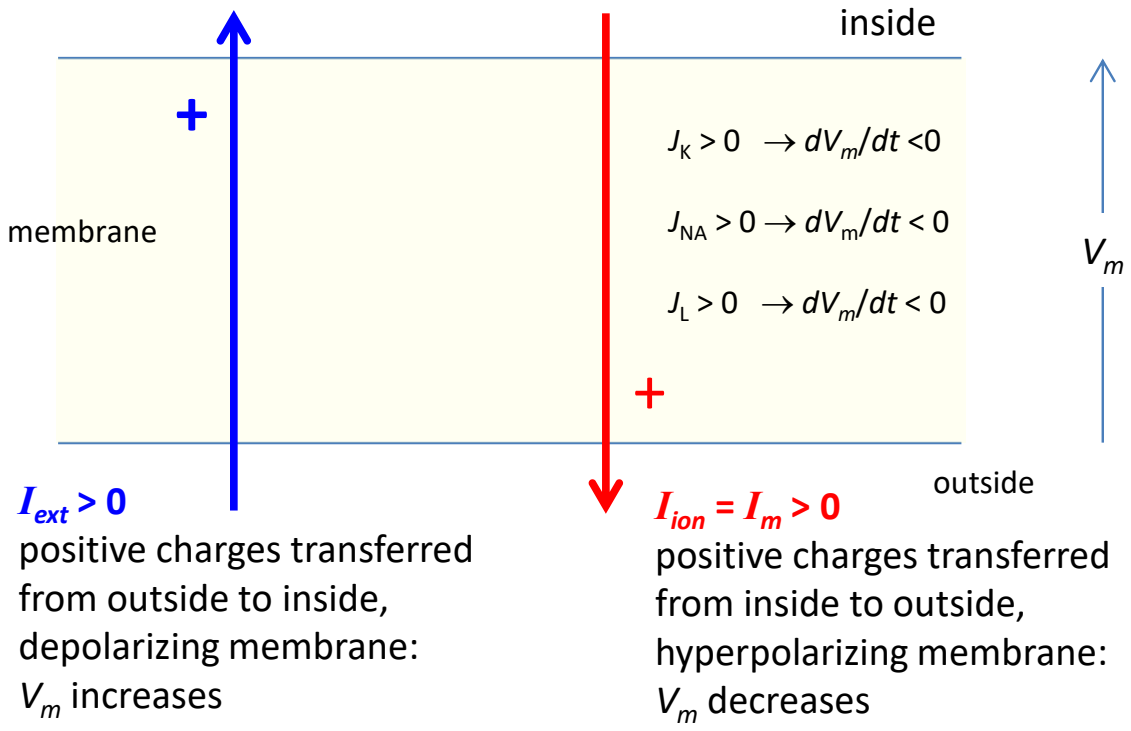


Fig. 2. Sign convention for currents. A positive external current I_{ext} (outside to inside) will tend to depolarize the cell (i.e., make V_m more positive) while a positive ionic current I_{ion} will tend to hyperpolarize the cell (i.e., make V_m more negative).

In a simple model, the Na^+ and K^+ ions are considered to flow through ion channels where a series of gates determine the conductance of the ion channel. The macroscopic conductances of the Hodgkin & Huxley model arise from the combined effects of a large number of

microscopic ion channels embedded in the membrane. Each individual ion channel can be thought of as containing one or more physical gates that regulate the flow of ions through the channel. The variation in conductance g values is determined by the set of **gate variables** k and h and the number of gates p and q

An **activation gate** k $\rightarrow$ conductance increases with depolarization

An **inactivation gate** h $\rightarrow$ conductance decreases with depolarization

The membrane potential V_m of a neuron is given by

$$(1) \qquad c_m \frac{dV_m(t)}{dt} = J_{ext}(t) - \sum_c J_c(t)$$

where c_m is the membrane capacity per unit area, J_{ext} is the synaptic input current density, and J_c is the current density through ion channel c. As in the Hodgkin-Huxley model, sodium and potassium currents are described by equations of the form

$$(2) \qquad J_c = \bar{g}\, k^p\, h^q \left(V_m - E_c\right)$$

where $\bar{g}$ is the maximum conductance of ion channel c, E_c is the reversal potential for ion c, and k and h are activation and inactivation

variables, respectively. The exponents p and q are integer parameters representing the number of gates for ion channel c (figure 3).

(3)

$$J_{Na} = g_{Na}(V_m - E_{Na}) \qquad J_K = g_K(V_m - E_K) \qquad J_L = g_L(V_m - E_L)$$

The **Na^+ channel** is controlled by 3 activation gates and 1 inactivation gate

$$k \to m \quad p = 3 \quad q = 1 \quad g_{Na} = \bar{g}_{Na} m^3 h$$

The **K^+ channel** is controlled by 4 n activation gates

$$k \to n \quad p = 4 \quad q = 0 \quad g_K = \bar{g}_K n^4$$

The value of the conductance g depends upon the membrane voltage V_m because the values of n, m and h depend on time, their previous value at an earlier time and the membrane potential. The resting membrane potential is given by the symbols V_{rest} or V_r.

The rates of change of the gate variables are described by equation 4 where α_x and β_x are rate constants $\left(x \equiv n \text{ or } m \text{ or } h\right)$

$$
\begin{aligned}
\frac{dn}{dt} &= \alpha_n (1-n) - \beta_n n \\
\frac{dm}{dt} &= \alpha_m (1-m) - \beta_m m \\
\frac{dh}{dt} &= \alpha_h (1-h) - \beta_h h
\end{aligned}
\qquad (4)
$$

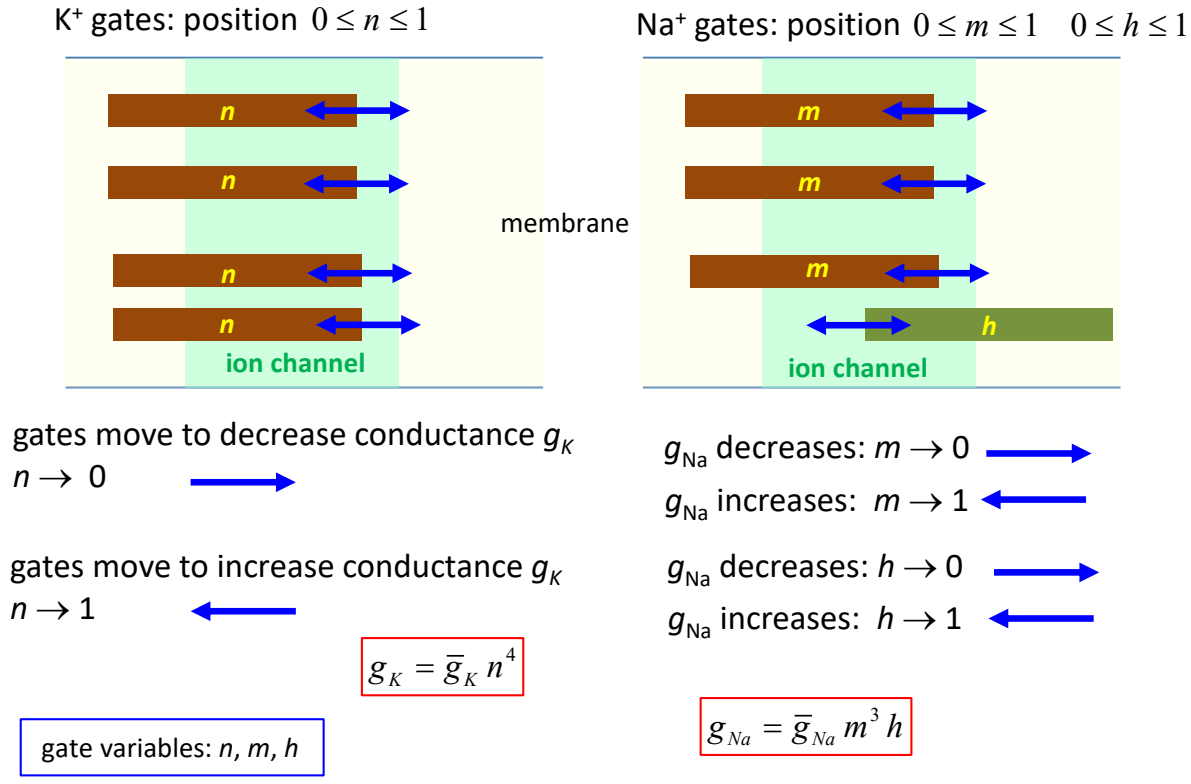


Fig. 3. Ion channels and gate variables for Na^+ and K^+.

$\alpha \to$ rate of closed gates opening

$\alpha_x (1-x)$ fraction of gates opening per second

$\beta \rightarrow$ rate of open gates closing

β_x fraction of gates closing per second

$$\phi = 3^{\left(\frac{T\text{-}6.3}{10}\right)} \qquad dV = V_m - V_{rest}$$

$$\alpha_n = \phi \frac{0.10 \text{ - } 0.01\, dV}{\exp(1 \text{ - } 0.1 dV) \text{ - } 1}$$

$$\alpha_m = \phi \frac{2.5 \text{ - } 0.1\, dV}{\exp(2.5 \text{ - } 0.1 dV) \text{ - } 1}$$

$$\alpha_h = \phi(0.07) \exp(\text{-}dV / 20)$$

$$\beta_n = \phi(0.125) \exp(\text{-}dV / 80)$$

$$\beta_m = \phi(4) \exp(\text{-}dV / 18)$$

$$\beta_h = \phi \frac{1}{\exp(3.0 \text{ - } 0.1\ dV) + 1}$$

The various functions for α and β are empirical functions of V_m that have been adjusted by Hodgkin and Huxley to fit the data of the giant axon of the squid.

In order to getter a better understanding of the three gating variables m (K^+) and n, h (Na^+) given in equation 4, it is convenient to rewrite each of the equations in the form where $x = m$ or n or h

(5A) $$\frac{dx}{dt} = \alpha_x (1 - x) - \beta_x x$$

(5B) $$\frac{dx}{dt} = \frac{1}{\tau_x}(x_\infty - x)$$

(5C) $$x_\infty = \frac{\alpha_x}{\alpha_x + \beta_x} \qquad dx / dt = 0 \quad \text{asymptotic value of } x$$

(5D) $$t_x = \frac{1}{\alpha_x + \beta_x} \qquad \text{time constant}$$

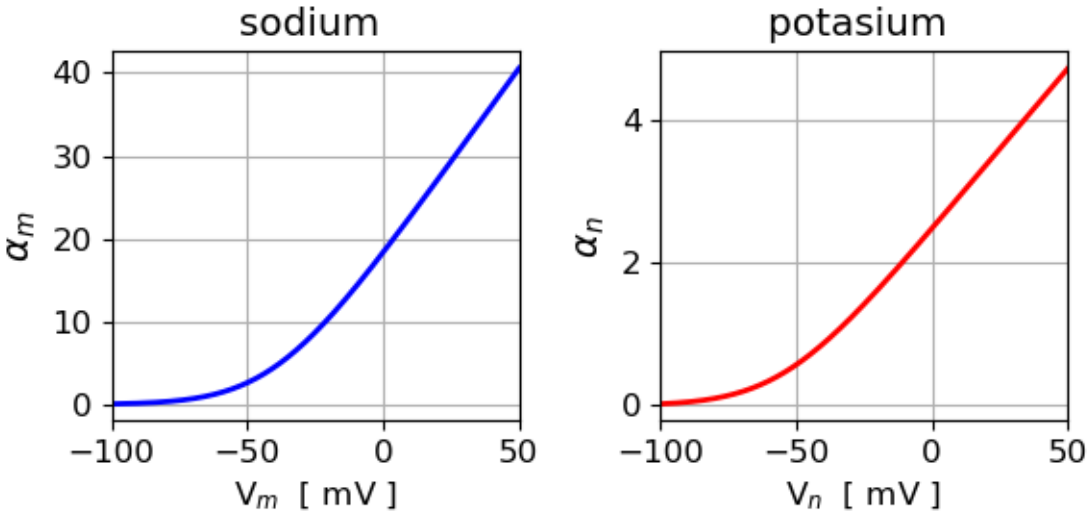


Fig. 4. When the membrane depolarized as the membrane potential increases, the rate of opening the Na^+ channels is much faster than the opening of K^+ channels.

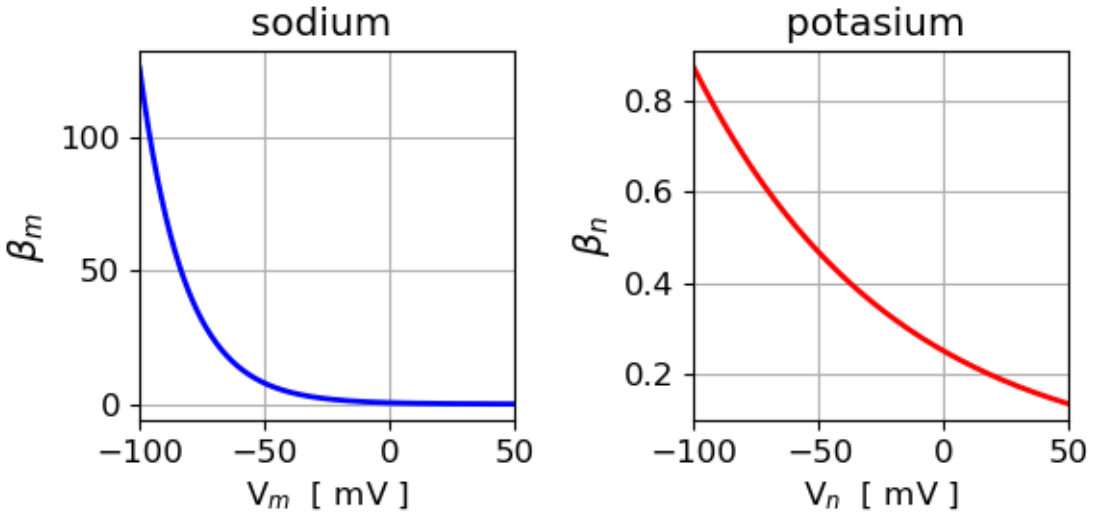


Fig. 5. When the membrane depolarized as the membrane potential increases, the rate of closing the Na^+ channels is much faster than the closing of K^+ channels.

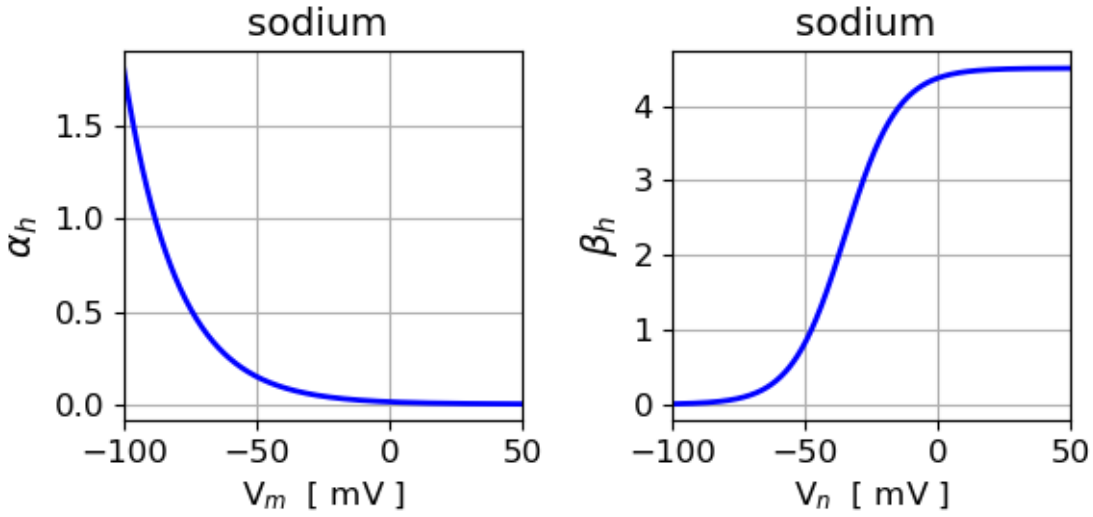


Fig. 6. Inactivation Gate variable *h* for Na^+.

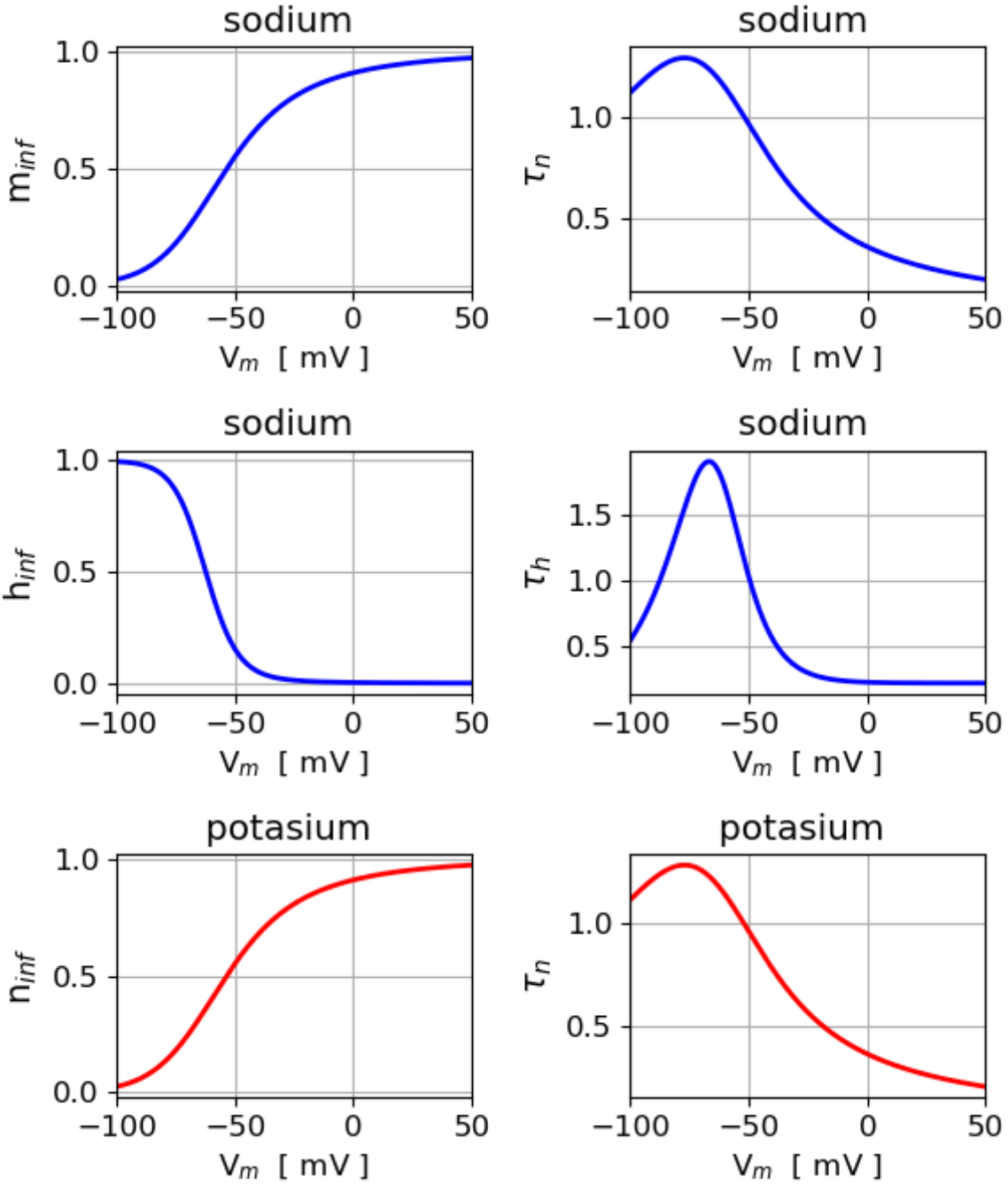


Fig. 7. The steady values of (m_∞, h_∞, n_∞) and their corresponding time constants (τ_m, τ_h, τ_n). The variables m and n are activating gate variables (increase in values as V_m increases). h is an inactivating gate variable (h decrease as V_m increases). The activation of the sodium ion channel (m) for the influx Na^+ is much quicker than the response of the out flux of K^+ ions (n) or the deactivation of the sodium ion channels (h) since $\tau_m << \tau_n \quad \tau_m << \tau_h$.

VOLTAGE-CLAMP SIMULATIONS

In many of the experiments performed by Hodgkin and Huxley, they held the membrane at a fixed voltage by inserting an electrode into the axon of a squid.

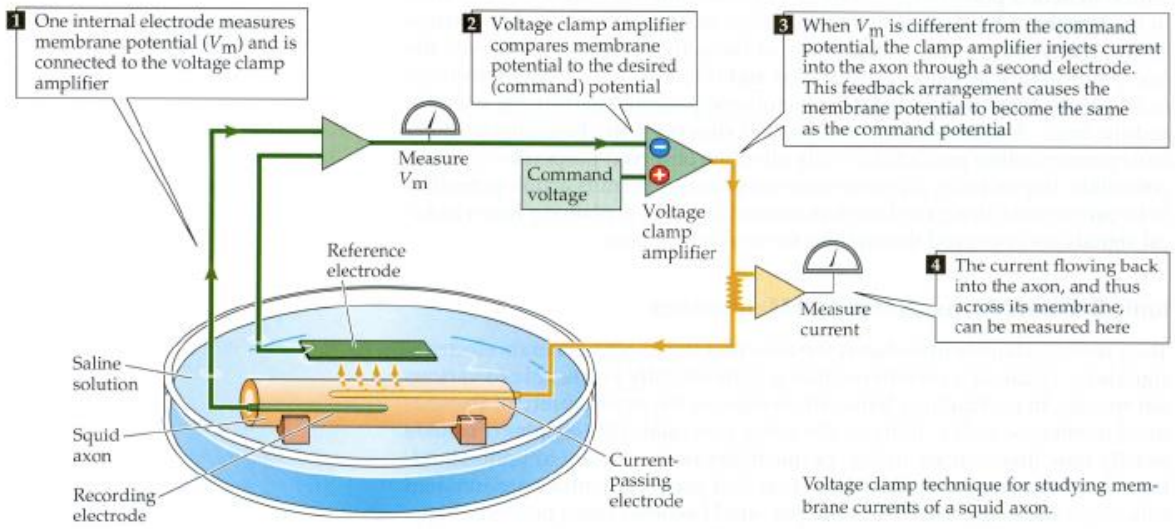


Fig. 8. Voltage-clamp of a squid axon.

The Python code **mns005vc.py** is used to calculate and display the voltage-clamp, the current densities (J_m, J_L, J_K and J_{Na}), the gate variables (n, m, h) and the conductances (g_{Na}, g_K). Th Euler method is used to solve the ODEs given by equation 4.

The gate variables, conductances and current densities are very dependent upon the strength of the voltage clamp and the temperature.

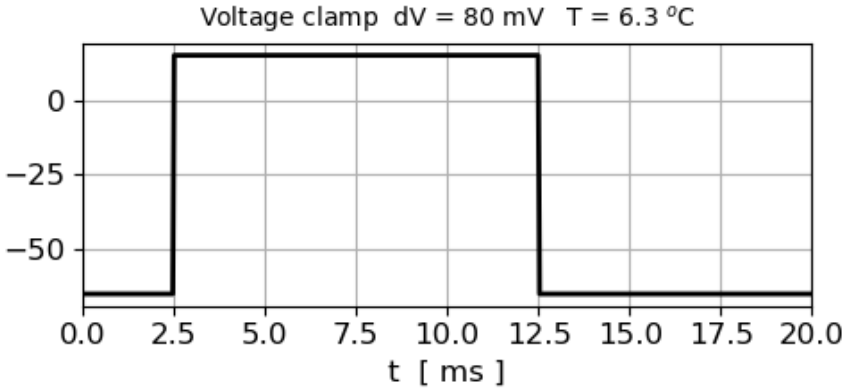


Fig. 9.1. The voltage clamp: duration 10 ms and height 80 mV

*T*emperature T = 6.3 °C

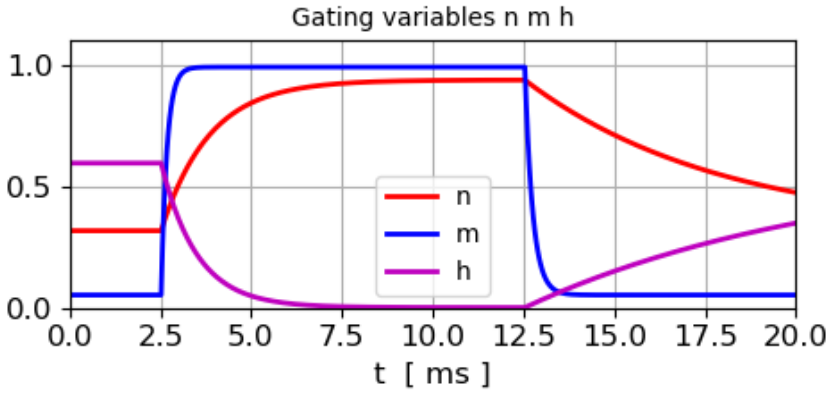


Fig. 9.2. Gate variables *n* (K^+) and *m, h* (Na^+).

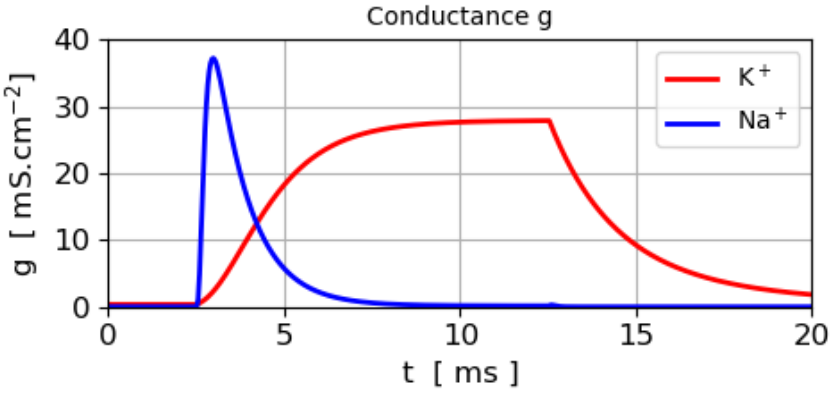


Fig. 9.3. K^+ and Na^+ conductances. The change in the Na^+ conductance increases and decreases much more rapidly then for the K^+ conductance.

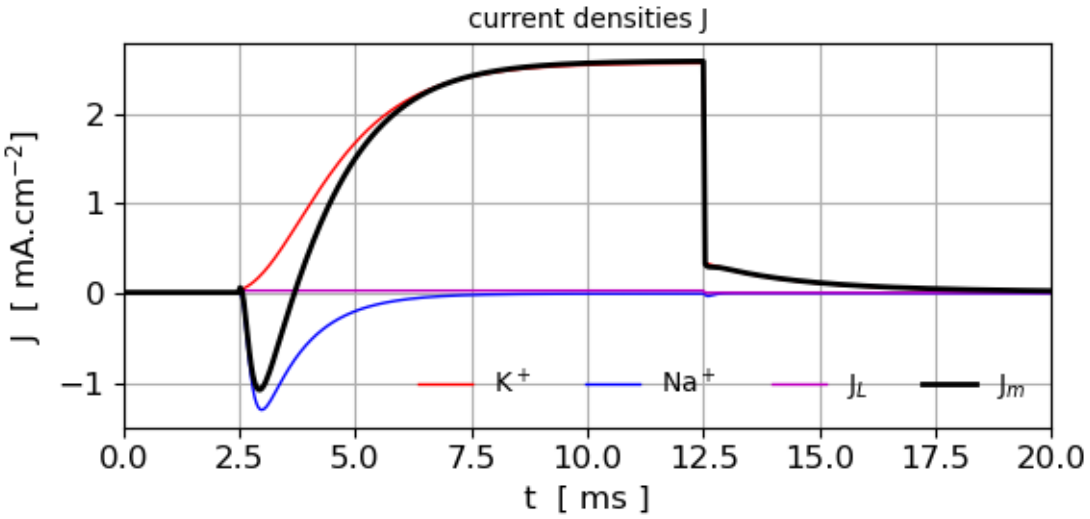


Fig. 9.4. Current densities: K^+, Na^+, leakage and net membrane current.

The depolarization produced by the clamp causes a transient increase in Na^+ into the cell. The rise in the K^+ current from the cell occurs more slowly and is maintained as long as the membrane is depolarized.

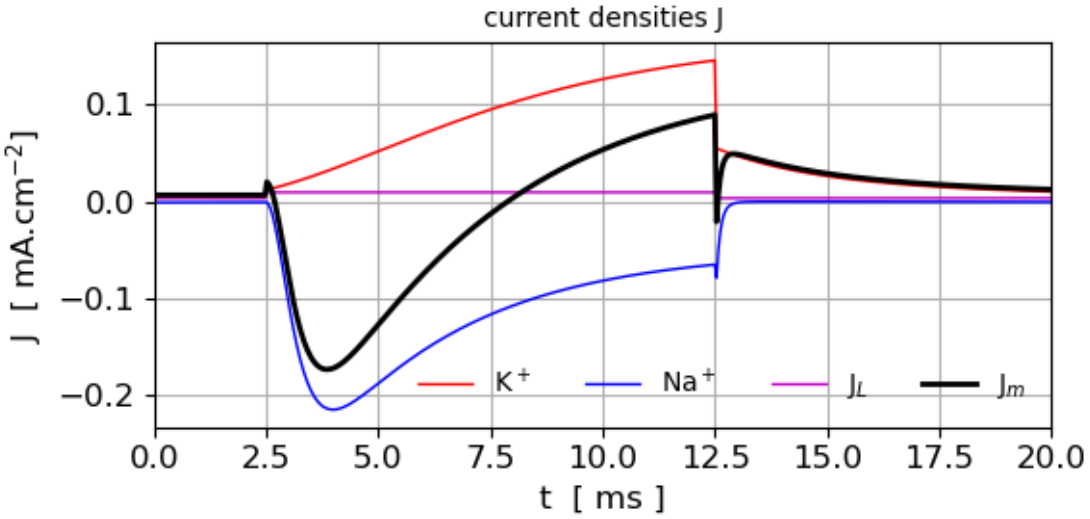


Fig. 9.5. Current densities: $T = 6.3$ ºC and clamp $dV = 20$ mV.

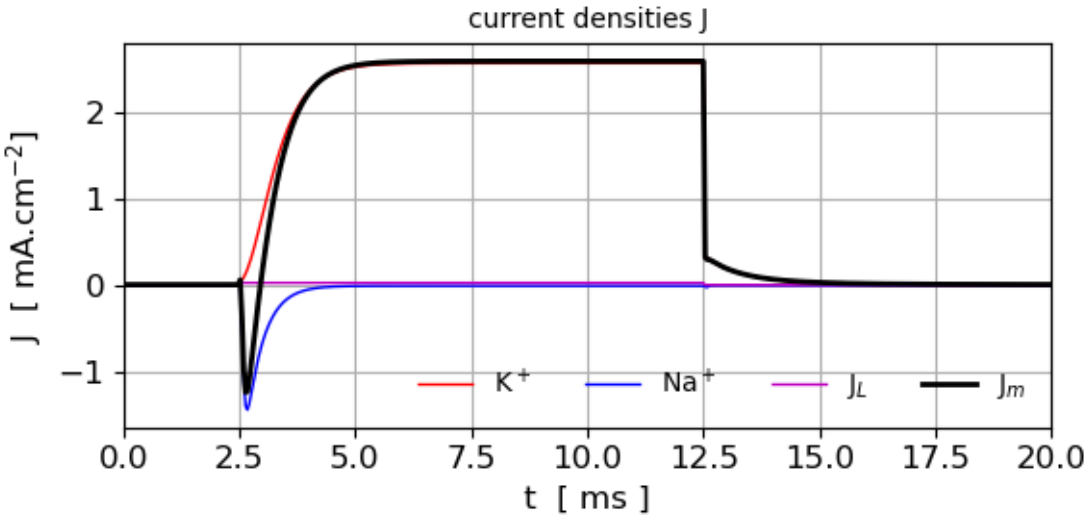


Fig. 9.6. Current densities: $T = 20$ ºC and clamp $dV = 80$ mV.

The rate of rise of the Na^+ and K^+ currents increases with increasing temperature and increasing the size of the voltage clamp. Also, the peak values of Na^+ and K^+ currents are significantly increased as the clamp voltage is increased.