DOING PHYSICS WITH MATLAB

THE NEURON MEMBRANE: ION CHANNELS AND GATE VARIABLES

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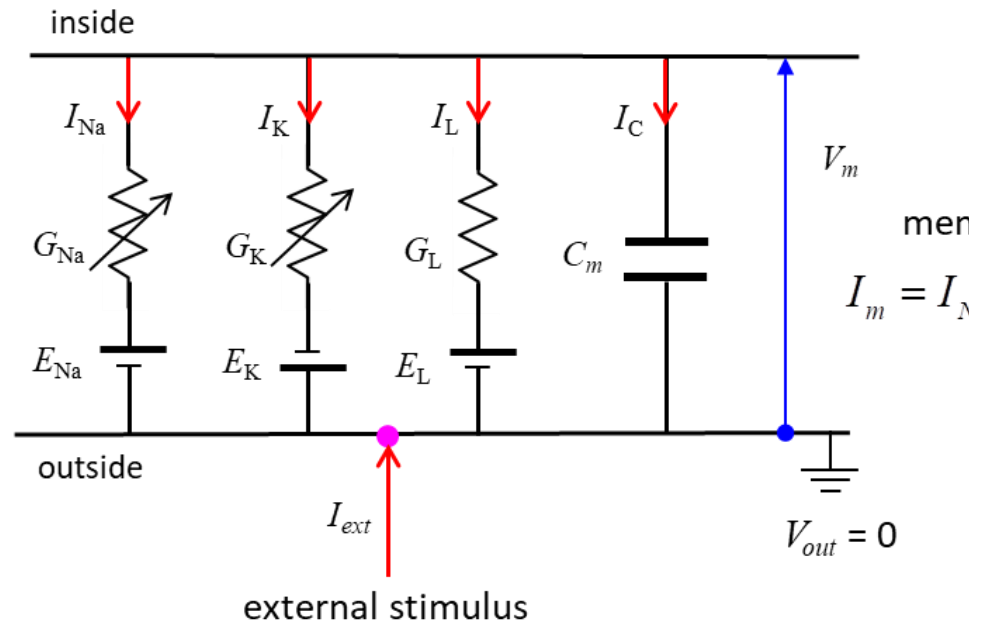

MATLAB

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npHHA.m   bp_neuron_02.m   npIC.m

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.

inside

I_{Na} I_K I_L I_C

V_m

G_{Na} G_K G_L C_m

men

$I_m = I_N$

E_{Na} E_K E_L

outside

I_{ext}

$V_{out} = 0$

external stimulus

Kirchhoff's Current Law:
at a junction

$$\sum I = 0$$

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

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

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 $\rightarrow$ inside ($I <$ 0), I_{Na}, I_K and I_L inside $\rightarrow$ outside ($I > 0$).

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

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

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 except that it contains more types of ion channels. The membrane potential V_m of a neuron is given by

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

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

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

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).

$$(3) \quad \begin{aligned} J_{Na} &= g_{Na} \left(V_m - E_{Na} \right) \\ J_K &= g_K \left(V_m - E_K \right) \\ J_L &= g_L \left(V_m - E_L \right) \end{aligned}$$

inside

membrane

$J_K > 0 \rightarrow dV_m/dt < 0$

$J_{NA} > 0 \rightarrow dV_m/dt < 0$

$J_L > 0 \rightarrow dV_m/dt < 0$

$I_{ext} > 0$

positive charges transferred
from outside to inside,
depolarizing membrane:
V_m increases

$I_{ion} = I_m > 0$

outside

positive charges transfer
from inside to outside,
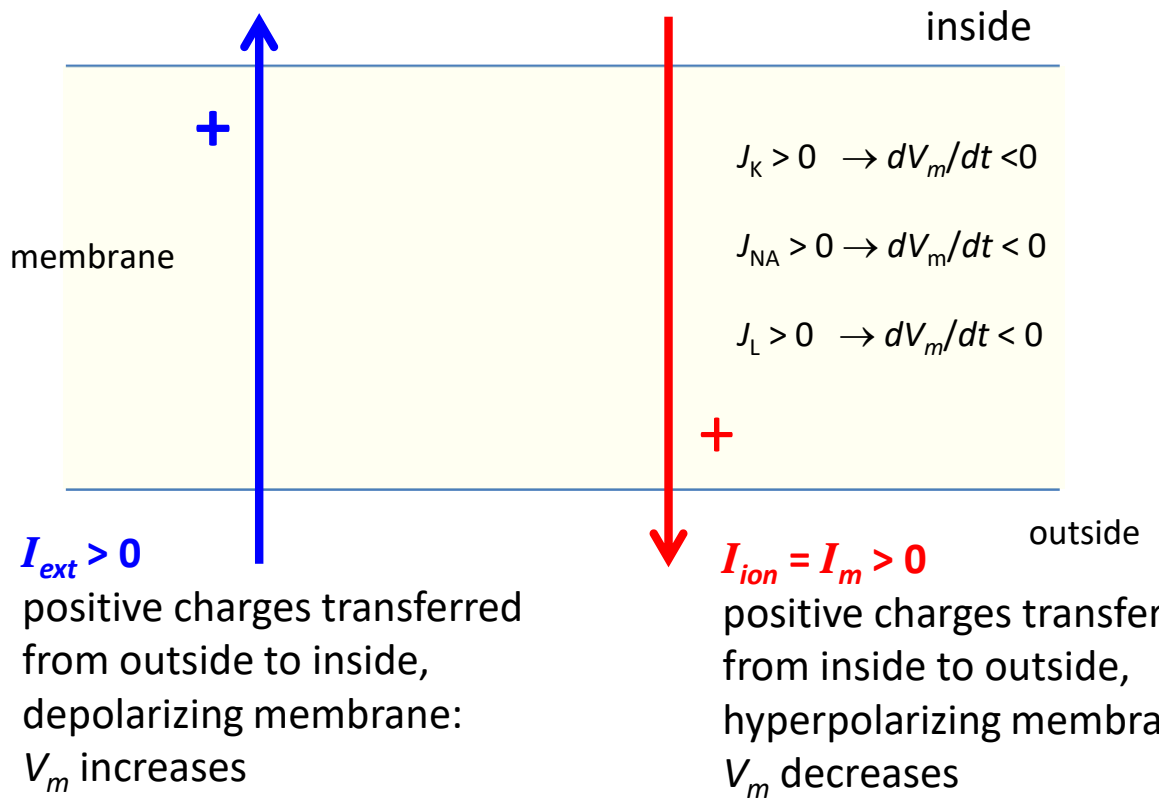hyperpolarizing membra
V_m decreases

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 $V = V_m$ 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

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containing one or more physical gates that regulate the flow of ions through the channel. The variation in 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 Na$^+$ channel is controlled by 3 activation gates and 1 inactivation gate

$$k \rightarrow m \quad p = 3 \quad q = 1 \quad g_{Na} = \overline{g}_{Na\_max} \, m^3 h$$

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

$$k \rightarrow n \quad p = 4 \quad q = 0 \quad g_K = \overline{g}_K \, n^4$$

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.
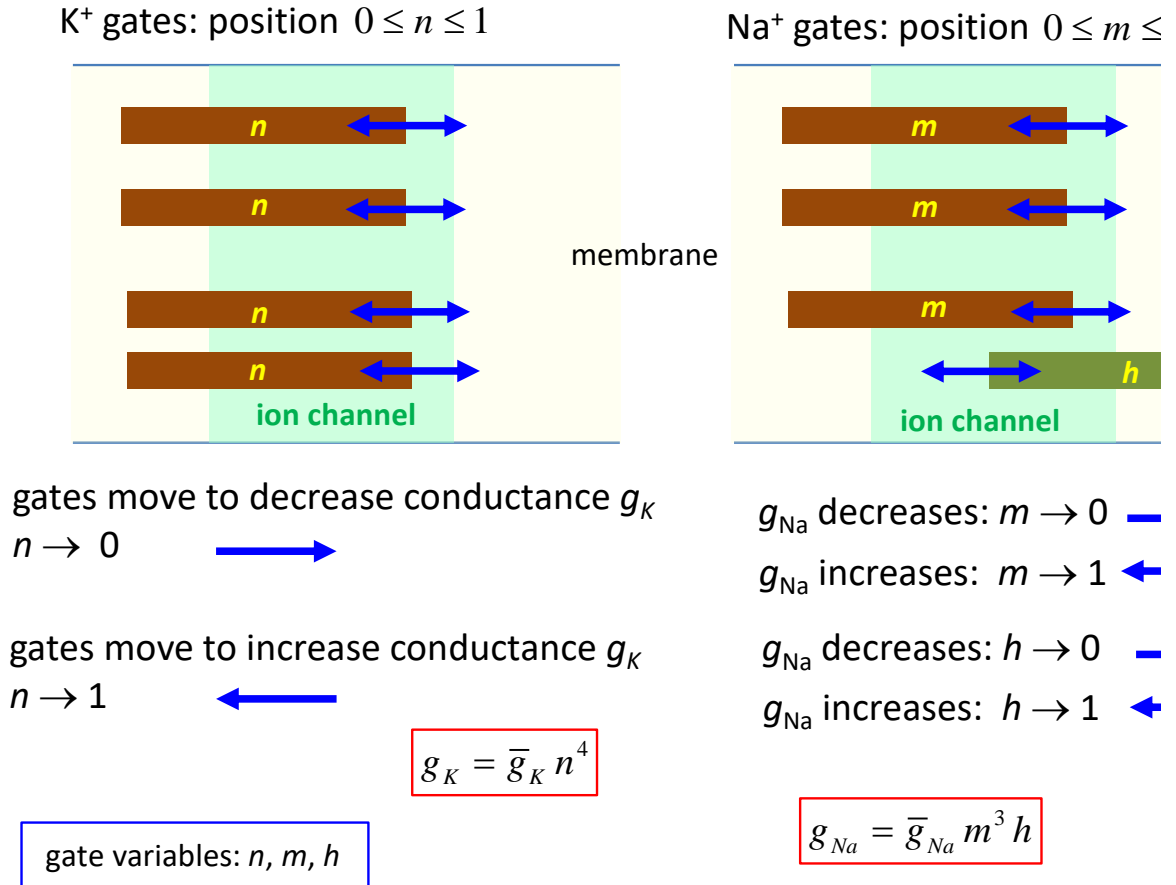
K$^+$ gates: position $0 \le n \le 1$ Na$^+$ gates: position $0 \le m \le$

gates move to decrease conductance g_K
$n \to 0$ ⟶

gates move to increase conductance g_K
$n \to 1$ ⟵

g_{Na} decreases: $m \to 0$ —
g_{Na} increases: $m \to 1$ ⟵

g_{Na} decreases: $h \to 0$ —
g_{Na} increases: $h \to 1$ ⟵

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

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

gate variables: n, m, h

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

The rates of change of the gate variables are described by the equations

(4)

$$\frac{dn}{dt} = \alpha_n \left(1 - n\right) - \beta_n \, n \qquad \frac{dm}{dt} = \alpha_m \left(1 - m\right) - \beta_m \, m \qquad \frac{dh}{dt} = \alpha_h \left(1 - h\right) - \beta_h \, h$$

where the α's and β's are rate constants $\left(x \equiv n \text{ or } m \text{ or } h\right)$

$\alpha \to$ rate of closed gates opening $\beta \to$ rate of

open gates closing

$$\alpha_x (1-x) \quad \text{fraction of gates opening per second}$$

$$\beta_x \qquad \text{fraction of gates closing per second}$$

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

$$\alpha_n = \phi \frac{0.10 \ - \ 0.01 \, dV}{\exp(1 \ - \ 0.1dV) \ - \ 1} \qquad \beta_n \ = \ \phi(0.125)\exp(\text{-}dV \ / \ 80)$$

$$\alpha_m = \phi \frac{2.5 \ - \ 0.1 \, dV}{\exp(2.5 \ - \ 0.1dV) \ - \ 1} \qquad \beta_m \ = \ \phi(4)\exp(\text{-}dV \ / 18)$$

$$\alpha_h = \phi(0.07)\exp(\text{-}dV \ / \ 20) \qquad \beta_h \ = \ \phi \frac{1}{\exp(3.0 \ - \ 0.1 \ dV) \ + \ 1}$$

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. Note: The gain function of the

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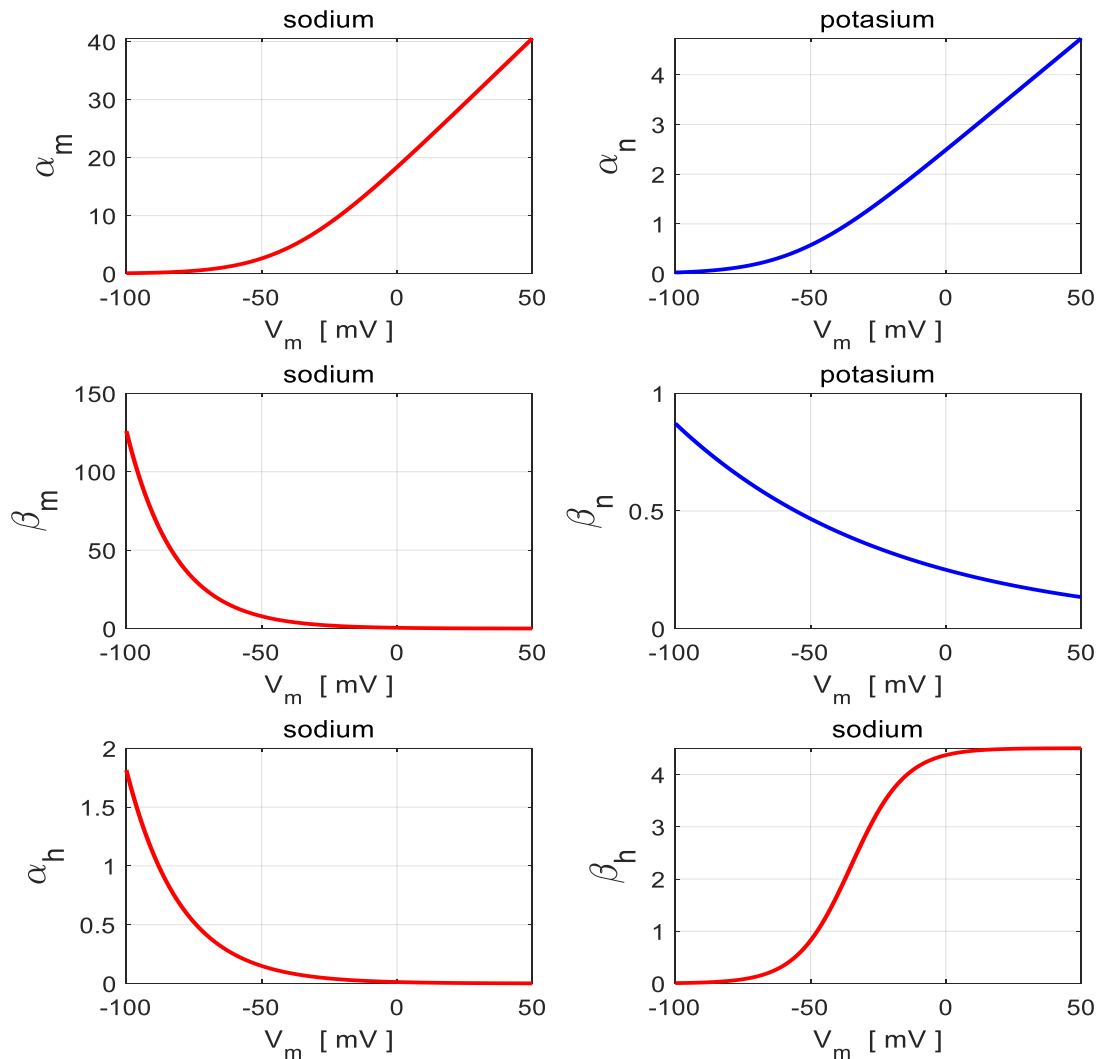Hodgkin-Huxley model is discontinuous at the firing threshold.

Fig. 4. Plots of the rate constants
(T = 20 ^{o}C and V_{rest} = -65 mV).   npIC.m

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

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

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

(5C) $x_\infty = \dfrac{\alpha_x}{\alpha_x + \beta_x}$

$dx / dt = 0$ asymptotic value of x

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

For a fixed voltage V_m, the variable x approaches the value
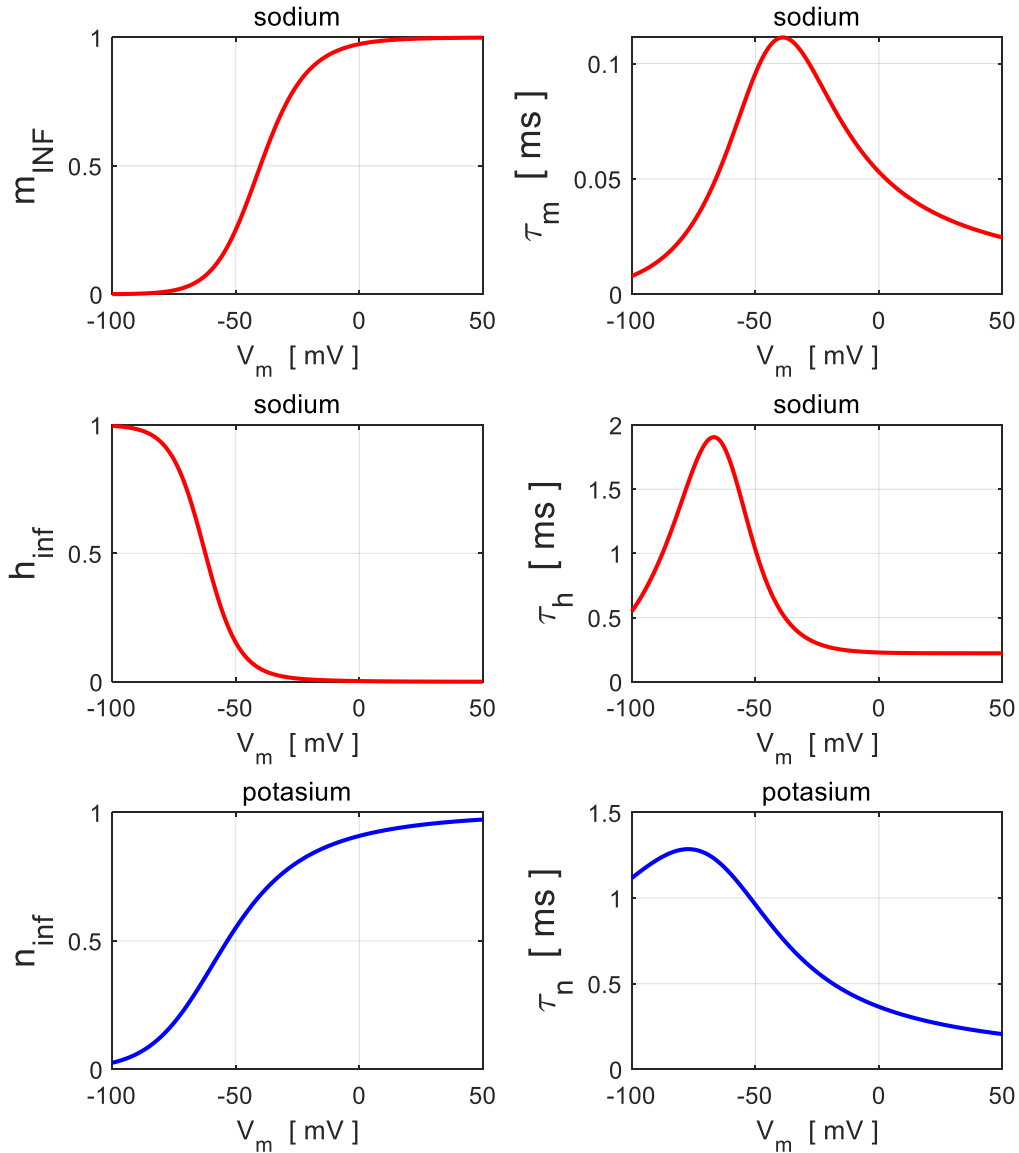
$x_\infty (V_m)$ with a time constant $t_x (V_m)$.

Fig. 5. The steady values of (m_∞, h_∞, n_∞) and their corresponding time constants (τ_m, τ_h, τ_n) as functions of the membrane potential. 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

$\tau_m \ll \tau_n \quad \tau_m \ll \tau_h$.

T = 20 ^{o}C and V_{rest} = -65 mV   npIC.m

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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.

1 One internal electrode measures
membrane potential (V_m) and is
connected to the voltage clamp
amplifier

2 Voltage clamp amplifier
compares membrane
potential to the desired
(command) potential

3 When V
potentia
into the
This fee
membra
as the co

Measure
V_m

Command
voltage

Voltage
clamp
amplifier

Reference
electrode

Measure
current

Saline
solution

Squid
axon

Recording
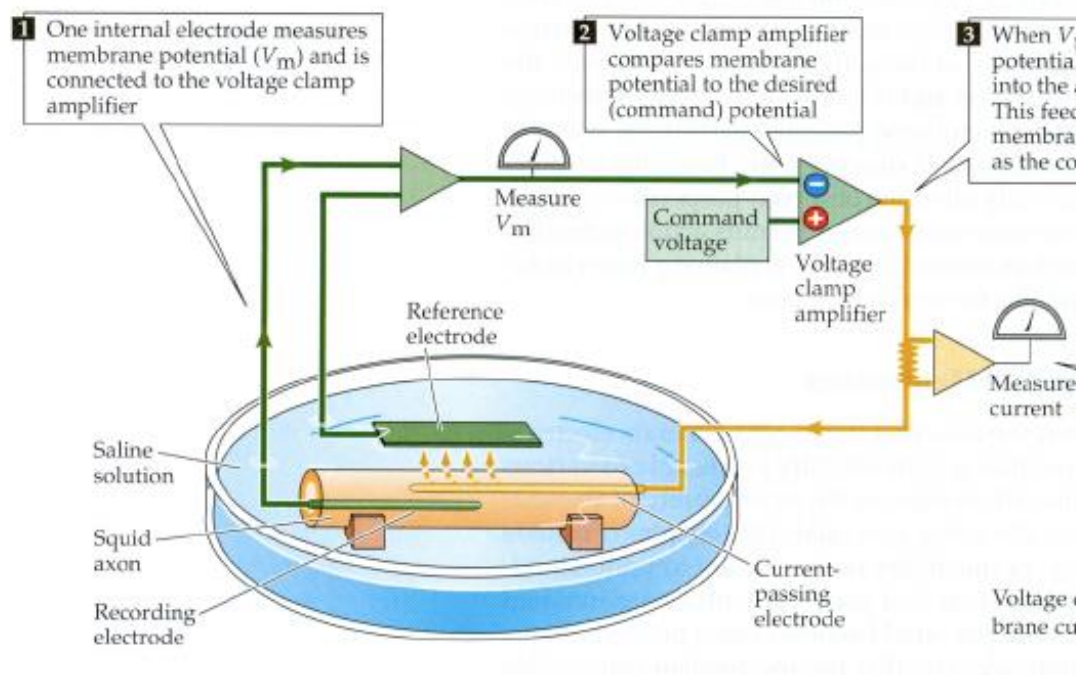electrode

Current-
passing
electrode

Voltage
brane cu

Fig.   6.   Voltage-clamp of a squid axon.

The Matlab m-script **bp_neuron_02.m** can be used to calculate
and display the voltage-clamp, the current densities (J_m, J_L, J_K and
J_{Na}), the gate variables (m, m^3, h and n, n^4) and the conductances
(g_{Na}, g_K). Sample graphical outputs are shown in figure 7 for
voltage clamps of +20 mV and +80 mV.

Outline the m-script bp_neuron_02.m structure

- Default resting potential V_r = -65 mV

- Voltage clamp is given as a long pulse

- Rate constants α and β are calculated using the functions **alpha.m** and **beta.m**

- As the time variable is incremented, the gates variables (n, m, h) then the conductances (g_{Na} and g_K) then the current densities (J_{NA}, J_{Na} and J_M) are calculated for each time step. The gate variables are calculated from equation (12) by using **the finite difference method** to approximate the first derivative:

```
nt(c+1) = nt(c) + dt * (An(c) *(1-nt(c)) - Bn(c) *
nt(c));
mt(c+1) = mt(c) + dt * (Am(c) *(1-mt(c)) - Bm(c) *
mt(c));
ht(c+1) = ht(c) + dt * (Ah(c) *(1-ht(c)) - Bh(c) *
ht(c));
```
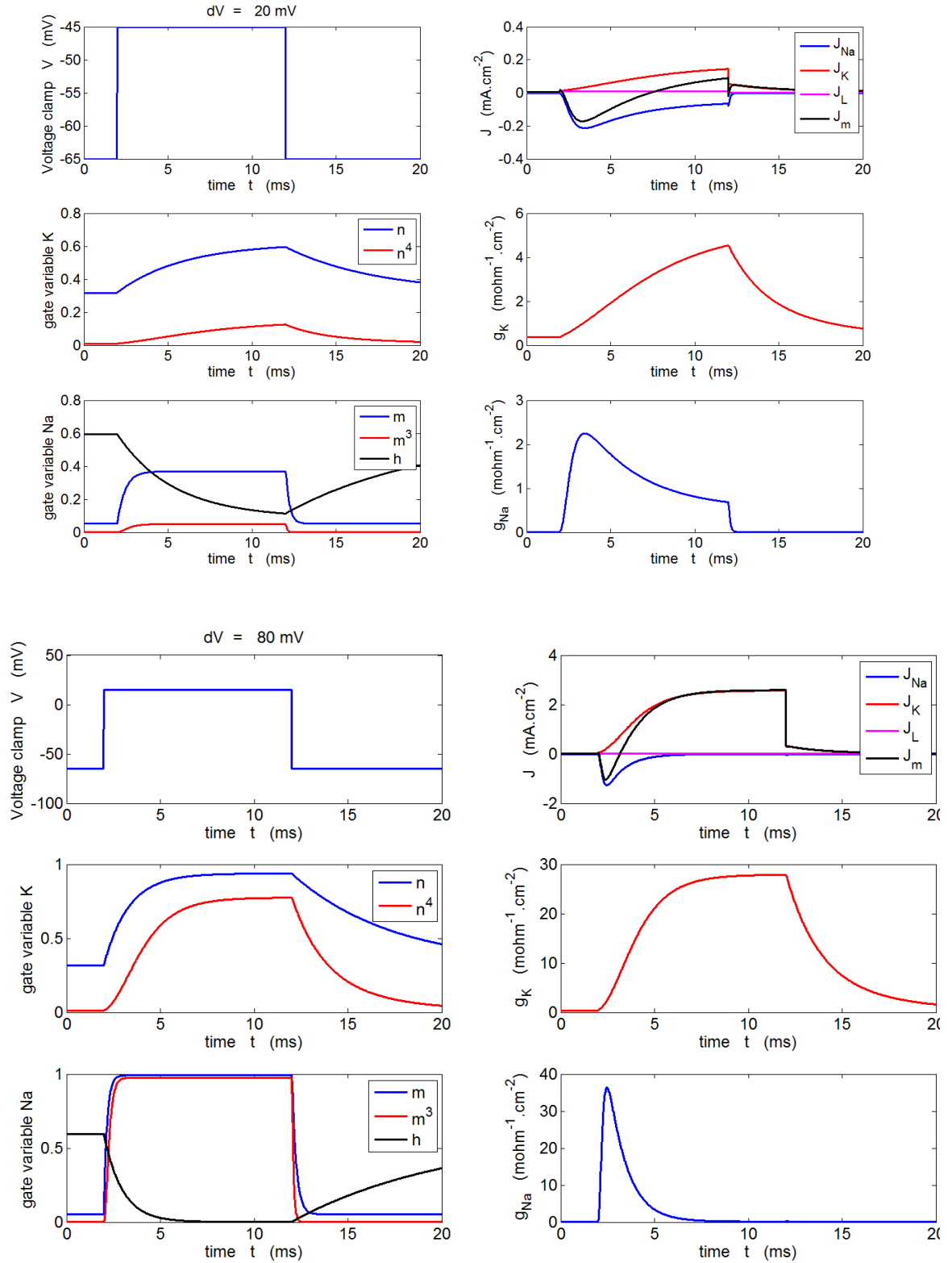
Fig. 7. Variation in the gate variables, conductances and current densities for a voltage-clamp applied to the axon. The depolarization produced by the clamp causes

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. The rate of rise of the Na+ and K+ currents increases with increasing size of the voltage clamp and the peak values of Na^+ and K^+ currents are significantly increased as the clamp voltage is increased, the peak values are over 100 times the magnitudes in the resting membrane.

bp_neuron_02.m