DOING PHYSICS WITH PYTHON

COMPUTATIONAL NEUROSCIENCE

HODGKIN – HUXLEY MODEL

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pyNS003.py

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INTRODUCTION

The core mathematical framework for modern biophysically based neural modelling was developed around 1950 by Alan Hodgkin and Andrew Huxley. They carried out a series of elegant electrophysiological experiments on squid giant neurons which have extraordinarily large diameters (~ 0.5 mm).

Hodgkin and Huxley systematically demonstrated how the macroscopic ionic currents in the squid giant axon could be understood in terms of changes in Na^+ and K^+ conductances in the axon membrane. Based on a series of voltage-clamp experiments, they developed a detailed mathematical model of the voltage-dependent and time-dependent properties of the Na^+ and K^+ conductances. Their model accurately reproduces the key biophysical properties of the action potential. For this outstanding achievement, Hodgkin and Huxley were awarded the 1963 Nobel Prize in Physiology and Medicine.

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 neuron membrane (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 are controlled by special voltage dependent ion channels: Na^+ ion channel, K^+ ion channel and a leak ion channel for all other ions. The neuron is stimulated by an external current I_{ext} injected into the interior of the neuron.

Circuit components (figure 1)

V_m membrane potential [mV] $V_m = V_{\text{in}} - V_{out}$

C_m cell membrane [μF] c_m [μF.cm^{-2}]

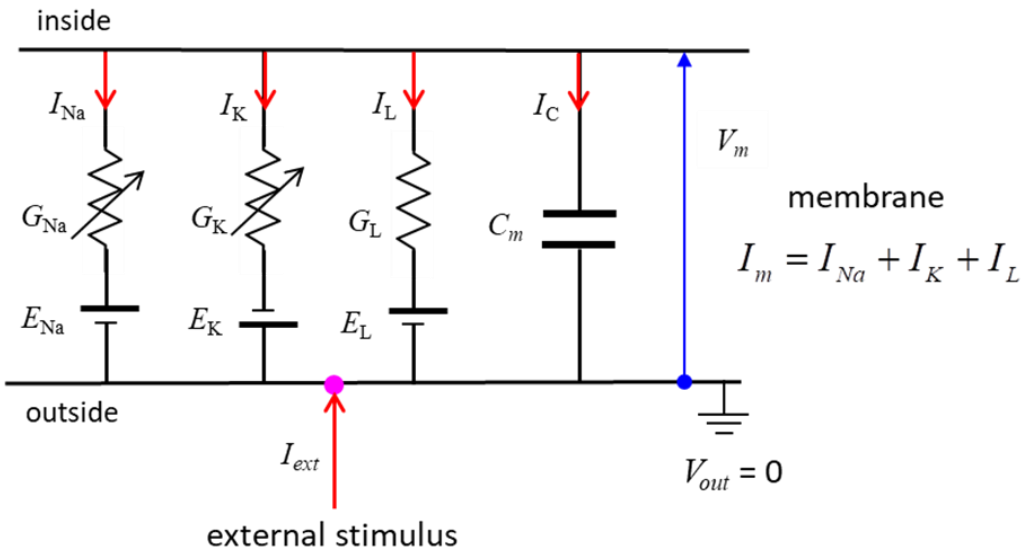
G_{Na}, G_K, G_L voltage-dependent conductances Na^+, K^+ and leak current $G = 1/R$ [mS.cm^{-2}]

E_{Na}, E_K, E_L reversal potentials [mV]

I_{Na}, I_K, I_L ion currents [μA]

$I > 0$ internal $\rightarrow$ external

$I < 0$ internal $\leftarrow$ external



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. Electrical equivalent circuit for a short segment of squid giant axon.

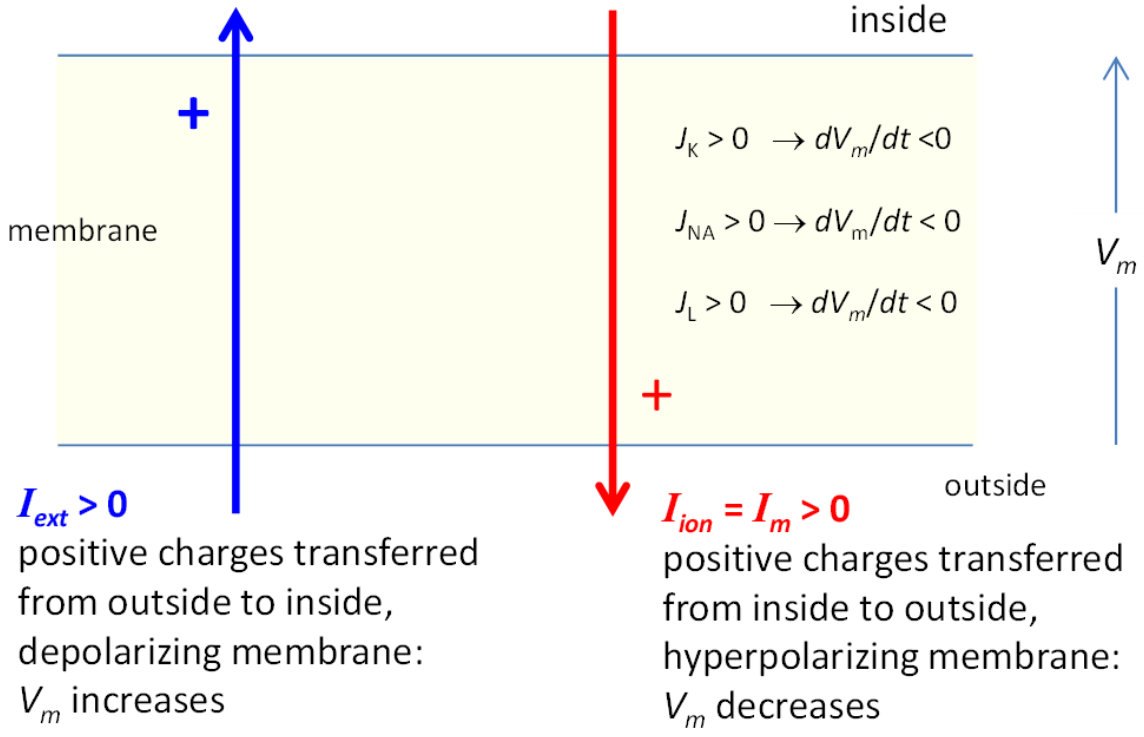


Fig. 2. Sign convention for membrane currents.

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 can flow according to their electrochemical gradients but not the A^- ions.

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.

A mathematical analysis of the equivalent RC circuit for the neuron as shown in figure 1 is outlined by the following equations.

Membrane potential difference measured w.r.t. $V_{out} = 0$

$$V_m = V_{\text{in}} - V_{out}$$

Capacitive current: rate of change of charge Q at the membrane surface

$$I_C = dQ_m / dt$$

Charge stored on surface of membrane

$$Q_m = V_m C_m$$

Differentiating Q w.r.t. t at a fixed position x_0

$$I_C = C_m \, dV_m / dt$$

Membrane current due to movement of ions

$$I_m = I_{Na} + I_K + I_L$$

Kirchhoff's current law (conservation of charge)

$$I_{ext} = I_C + I_m = I_C + I_{Na} + I_K + I_L$$

The fundamental differential equation relating the change in membrane potential to the currents through the membrane for a small segment of the membrane

$$C_m \, dV_m / dt = I_{ext} - I_m = I_{ext} - I_{Na} - I_K + -I_L$$

It is better to use the current density J rather than current I.

$$c_m \, dV_m / dt = J_{ext} - J_m = J_{ext} - J_{Na} - J_K + -J_L$$

where $J = I / A \quad c_m = C_m / A$

Electrical potential ΔV, current I, resistance R and conductance G and current densities are related by the equations

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

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

$$g_L = g_{L\_\max}$$

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 and 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.

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

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

The variation in the conductance values is determined by the set of **gate variables** n, m and h and were determined from experimental data.

The Na^+ channel is controlled by 3m activation gates and 1h inactivation gate $g_{Na} = g_{Na\_\max} m^3 h$.

The K^+ channel is controlled by 4n activation gates $g_K = g_{K\_\max} n^4$.

The value of the conductances g_{Na}, g_K 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 rates of change of the gate variables are described by the equations

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

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

$\alpha \rightarrow$ rate of closed gates opening

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

$\beta \rightarrow$ rate of open gates closing

$\beta_x \rightarrow$ fraction of gates closing per second

$$\phi = 3^{\left(\frac{T\text{-}6.3}{10}\right)}$$

$$dV = V_m - V_{rest}$$

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

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

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

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

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

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

If there is no external stimulus $J_0 = 0$ and $V_m = V_{rest}$ then $J_m = 0$ and V_m does not change with time t as $dV_m / dt = 0$. A stimulus as a result of a current injection into the axon results in the membrane potential either increasing above or decreasing below the resting membrane potential.

The charge per unit area Q deposited into intracellular region by the external stimulus J_{ext} is given by $Q = \int J_{ext}\, dt$. If the stimulus is strong enough, an action potential can be evoked.

A typical action potential is shown in figure 3.

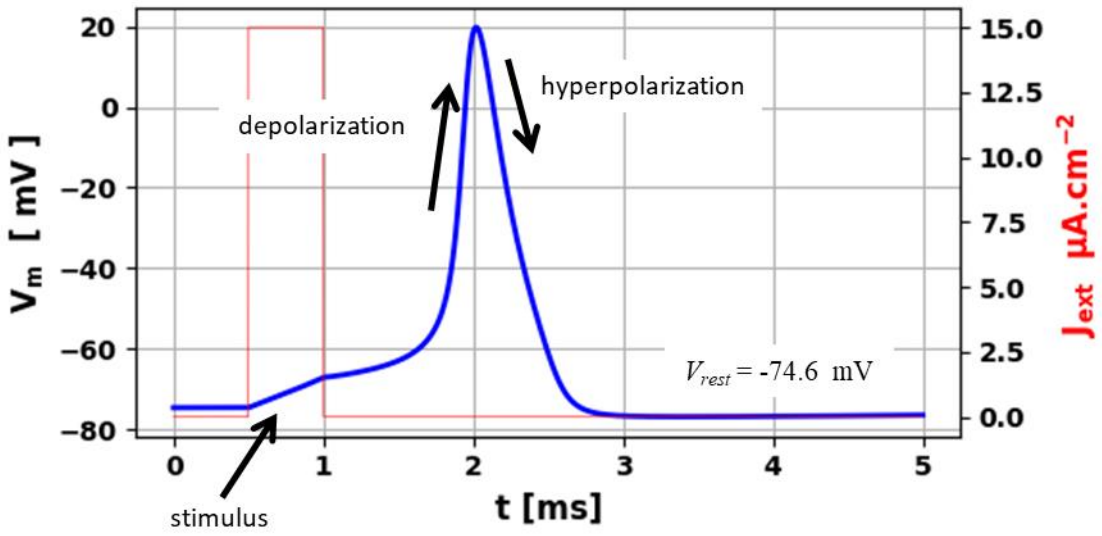


Fig. 3. Typical action potential. Action potential produced by an external current pulse. The time course of the membrane shows the action potential (positive peak) followed by a relative long refractory period where the potential is below the resting potential.

SIMULATIONS

Python is used to solve the Hodgkin-Huxley equations for different external current stimulations as described below for the Python Code **pyNS003.py**. The Code is constructed as a sequence of Cells.

- Set grid and simulation time
- Set the default HH model parameters
- Initialize all the time dependent arrays
- Setup the external current density. A current density is selected with the variable flag.
- Set up the initial values for the time dependent arrays. For the initial conditions, the membrane potential is set at its resting value where the membrane current is zero.

$$V(0) = V_{rest} = x$$
$$J_{ext}(0) = J_{Na}(0) + J_K(0) + J_L(0) = 0$$
$$g_{Na}(0)(x - E_{Na}) + g_K(0)(x - E_K) + g_L(0)(x - E_L) = 0$$

  The unknown value x for membrane potential at t = 0 is found using the Python function solve (from sympy import solve). Note the value x returned has to be converted to a float.
- The ode for the membrane potential is solved using a finite difference method. At each time step the values of the rate constants (α, β), gate variables (n, m, h), conductances (g) and current densities (J) are computed.
- Calculation of the variables J_m, dv/dt, d^2v/dt^2, Q

- Console output
- Graphical output
- Save figures as png files

```
#%%
import numpy as np
from numpy import pi, sin, cos, exp, linspace, zeros, amax, array,
ones
import matplotlib.pyplot as plt
from scipy.integrate import odeint, quad, dblquad, simps
import time
from sympy import solve, symbols

tStart = time.time()

#%%  INPUTS / SIMULATION TIME
N = 9999     # Grid points
tMax = 5.0   # Simulation time [ms]
t = np.linspace(0,tMax,N)
dt = t[2] - t[1]

#%%   FIXED PARAMETERS
T = 20          # temperature [20 deg C]
eps = 1e-16

EN = 50         # reversal voltage Na+ [mV]
EK = -77        # reversal voltage K+  [mV]
EL = -76        # reversal voltage leak [mV]
C  = 1.0        # membrane capacitance/area  [uF.cm^-2]

GK = 36         # K+ max conductance [mS.cm^-2]
GN = 120         # Na+ conductance [mS.cm.-2)]
GL = 0.3        # max leakage conductance [mS.cm-2]
```

```
#%% SETUP TIME DEPENDENT MATRICES
V    = zeros(N)      # membrane potential (mV)
JN   = zeros(N)      # Na+ current density (uA.cm^-2)
JK   = zeros(N)      # K+  current density (uA.cm^-2)
JL   = zeros(N)      # leakage current density (uA.cm^-2)
Jm   = zeros(N)      # membrane current (uA.cm^-2)
Jext = zeros(N)      # External current stumulus  (uA.cm-2)

gN = zeros(N)      # Na+ conductance
gK = zeros(N)      # K+ conductance
gL = GL*ones(N)       # gL conductance

n    = zeros(N)      # K+ gate parameter
m    = zeros(N)      # Na+ gate parameter
h    = zeros(N)      # Na+ gate parameter

#%% EXTERNAL CURRENT STIMULUS
flag = 1

J0 = 15.0          # Amplitude of pulse

if flag == 1:    # Pulse   t1 (on) / t2 (off)
  t1 = 0.5; t2 = 1.0
  N1 = round(t1/dt); N2 = round(t2/dt)
  Jext[N1:N2] = J0

#%% INITIAL VALUES
phi = 3**((T-6.3)/10)    # temperature dependent variable
dV = 0
An0 = phi * (eps + 0.10 - 0.01 * dV) / (eps + exp(1 - 0.1 * dV) - 1)
Am0 = phi * (eps + 2.5 - 0.1  * dV)  / (eps + exp(2.5 - 0.1 * dV) - 1)
Ah0 = phi * 0.07 * exp(-dV / 20)

Bn0 = phi * 0.125 * exp(-dV / 80)
```

```
Bm0 = phi * 4 * exp(-dV/18)
Bh0 = phi * 1 / (exp(3.0 - 0.1 * dV) + 1)

n0 = An0/(An0+Bn0); n[0] = n0
m0 = Am0/(Am0+Bm0); m[0] = m0
h0 = Ah0/(Ah0+Bh0); h[0] = h0

gN0 = GN*m0**3*h0; gN[0] = gN0
gK0 = GK*n0**4   ; gK[0] = gK0
gL0 = gL[0]

x = symbols('x')   # find resting membrane potential
z = solve(gN0*(x-EN)+gK0*(x-EK)+gL0*(x-EL), x)
Vrest = z[0]
Vrest = float(Vrest)
V[0] = Vrest

JN0 = gN0*(Vrest - EN); JN[0] = JN0
JK0 = gK0*(Vrest - EK); JK[0] = JK0
JL0 = gL0*(Vrest - EL); JL[0] = JL0
Jm0 = JN0 + JK0 + JL0 ; Jm[0] = Jm0

#%% SOLVE ODE
for s in range(N-1):

    dv = V[s] - Vrest
    An = phi * (eps + 0.10 - 0.01 * dv) / (eps + exp(1 - 0.1 * dv) - 1)
    Am = phi * (eps + 2.5 - 0.1  * dv)  / (eps + exp(2.5 - 0.1 * dv) - 1)
    Ah = phi * 0.07 * exp(-dv / 20)

    Bn = phi * 0.125 * exp(-dv / 80)
    Bm = phi * 4 * exp(-dv/18)
    Bh = phi * 1 / (exp(3.0 - 0.1 * dv) + 1)

    n[s+1] = n[s] + dt * (An *(1-n[s]) - Bn * n[s])
```

```
    m[s+1] = m[s] + dt * (Am *(1-m[s]) - Bm * m[s])
    h[s+1] = h[s] + dt * (Ah *(1-h[s]) - Bh * h[s])

    gK[s+1] = n[s+1]**4 * GK
    gN[s+1] = m[s+1]**3 * h[s+1] * GN

    JK[s+1] = gK[s+1] * (V[s] - EK)
    JN[s+1] = gN[s+1] * (V[s] - EN)
    JL[s+1] = gL[s+1] * (V[s] - EL)

    V[s+1] = V[s] + (dt/C) * (-JK[s+1] - JN[s+1] - JL[s+1] + Jext[s+1])

Jm = JN + JK + JL
vDot = np.gradient(V,dt)            # dv/dt
vDot2 = np.gradient(vDot,dt)        # d2v/dt2

# Charge delivered by external current Q [ nC.cm-2]
Q = simps(Jext,t)


#%% CONSOLE OUTPUT
print(' ')
print('Charge delivered by Jext  Q = %0.2f nC' %Q )
s = time.time() - tStart; print('Execution time = %2.2f' %s)
```

Square pulse stimulus (flag = 1)

```
if flag == 1:    # Pulse   t1 (on) / t2 (off)
  J0 = 20      # Amplitude of pulse
  t1 = 0.5; t2 = 1.0
  N1 = round(t1/dt); N2 = round(t2/dt)
  Jext[N1:N2] = J0
```

A square pulse current stimulus of duration 0.5 ms is used as the external current source (flag = 1).

If insufficient charge Q is not transferred to the neuron by the external current stimulus, then no action potential is generated (figure 4A: $J_0 = 12.2\ \mu A.cm^{-2}$). If no action potential is fired, then only a small rise in the membrane potential occurs and then the membrane potential slowly decays back to the resting potential.

There is a threshold, when the external stimulus exceeds some critical value an action potential is produced. The threshold for the injected current density is about 12.3 $\mu A.cm^{-2}$ (figure 4B).

The action potential rises more rapidly and to a higher peak value when $J_0 = 20\ \mu A.cm^{-2}$ compared with $J_0 = 12.4\ \mu A.cm^{-2}$.

The injected current J_{ext} acts as a **bifurcation** parameter. Slight variation in J_{ext} near the threshold may or may not evoke an action potential.

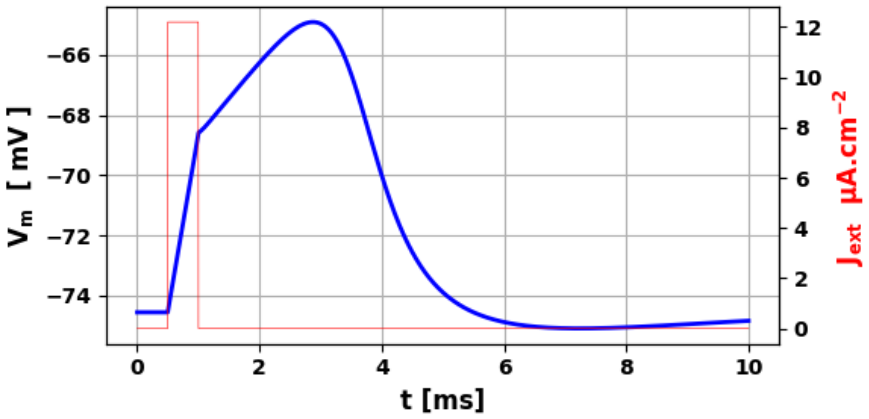


Fig. 4A. J0 = 12.2 uA Q = 6.1 nC Vmax = -64.9 mV

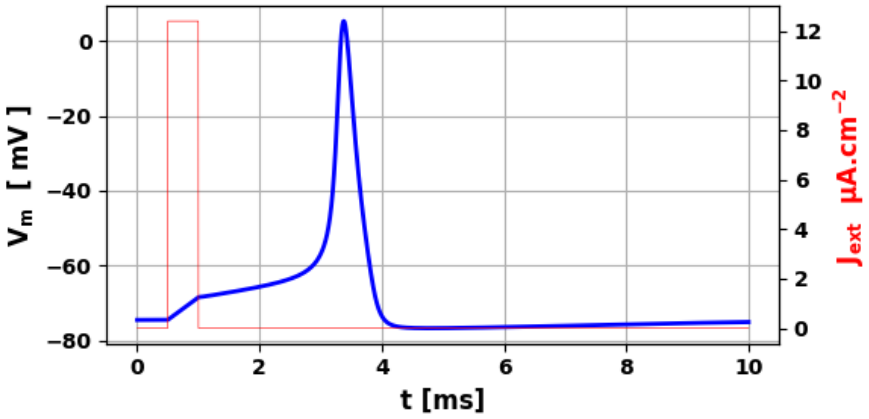


Fig. 4B. J0 = 12.4 uA Q = 6.2 nC Vmax = 5.4 mV

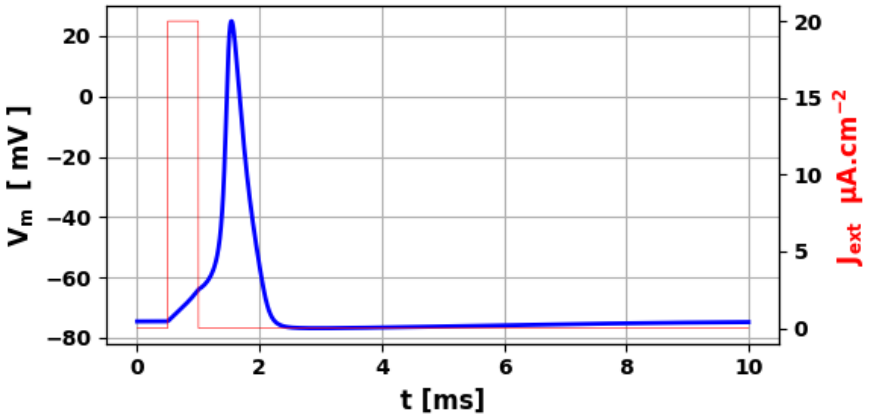


Fig. 4B. J0 = 20.0 uA Q = 10.0 nC Vmax = 25.0 mV

If the external stimulus current is greater than some threshold value, then an action potential is generated (figure 5). Figure 5A shows a short pulse and figure 5B shows a longer pulse of half the width and twice the height of figure 5A pulse. The pulse with the greatest amplitude and shortest duration produces the action potential which rises most rapidly and with the greatest depolarization.

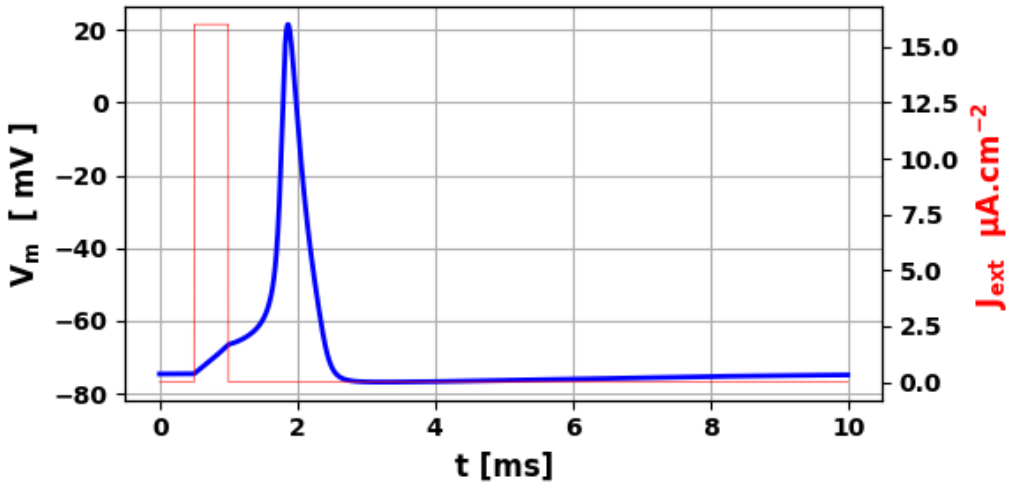


Fig. 5A. J0 = 16.0 uA Q = 8.0 nC T = 0.05 ms Vmax = 21.4 mV

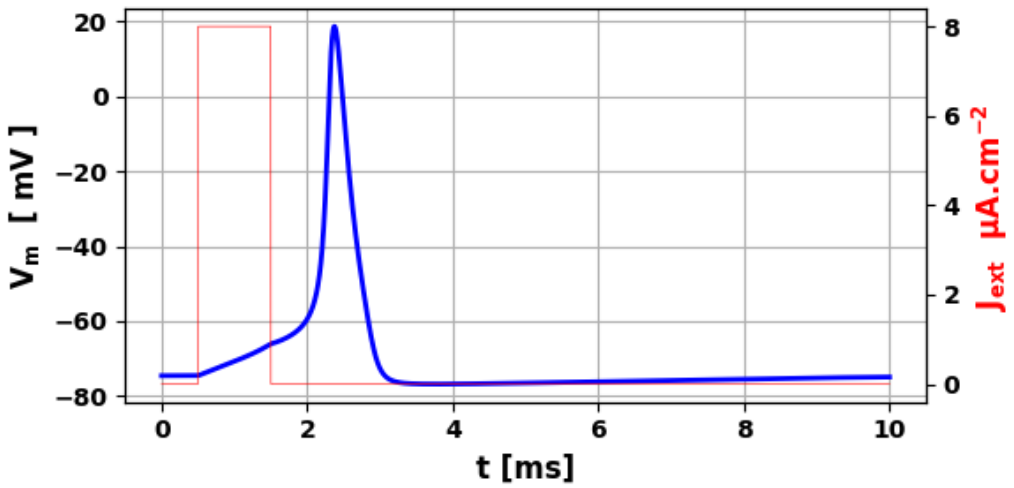


Fig. 5B. J0 = 8.0 uA Q = 8.0 nC T = 1.00 ms Vmax = 18.7 mV

The Action Potential

Figure 6 shows a typical action potential that is fired due to external current pulse.

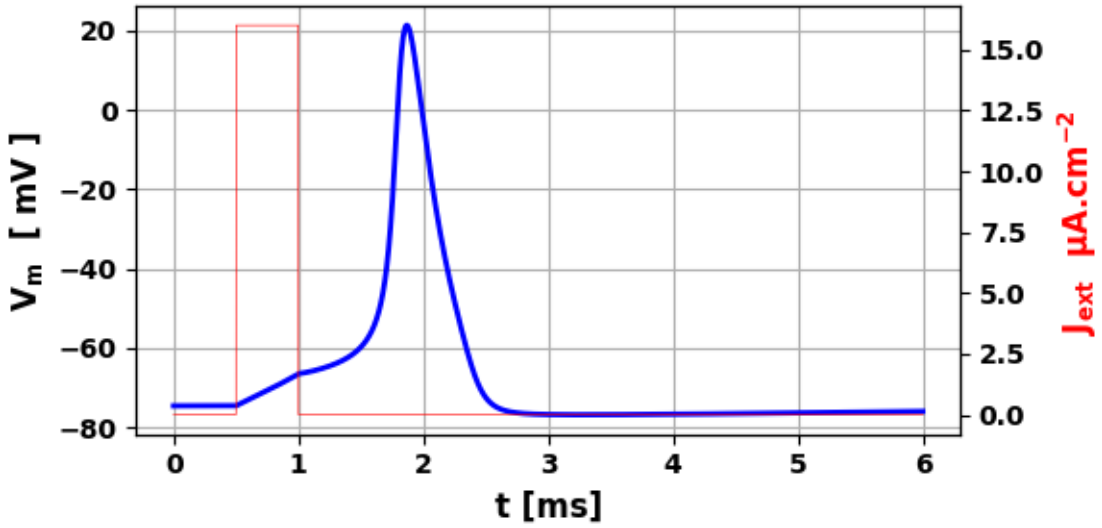


Fig. 6. Action potential produced by an external current pulse of sufficient height and duration. The time course of the membrane shows the action potential (positive peak) followed by a relative long refractory period where the potential is below the resting potential.

The Gate Variables, conductances and ion current densities

Figure 7 shows the time variation of the gate variables ***n***, ***m*** and ***h***. For the sodium ions Na^+, the value of the activation gate ***m*** rises rapidly to a peak and then rapidly decreases back to zero, whereas the inactivation gate, ***h*** falls from its steady-state value to nearly zero and slowly returns to its steady-state value. The activation gate ***n*** for potassium rises quickly and then falls slowly, with the peak width in the order of 2 ms.

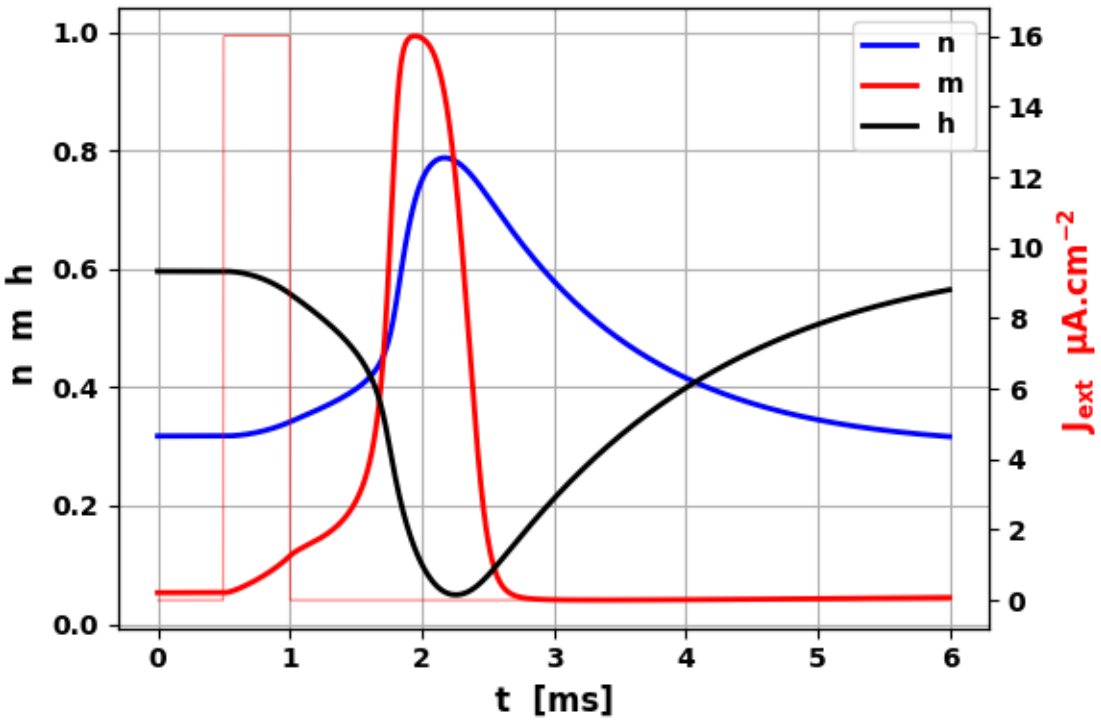


Fig. 7. The gate variables ***n***, ***m*** and ***h***.

The external current stimulus causes a rise in the membrane potential and this results in an increase in the value of ***m*** (activation gate) and the decrease in the value of ***h*** (inactivation gate), therefore an increase in the Na^+ conductance g_{Na}. As a result, positive sodium ions flow into the cell and raise the membrane potential even further. If this positive feedback is large enough, an action potential is initiated. At high values of V_m, the sodium conductance is shut off due to the factor ***h***. The time constant for h is always larger than ***m***. Thus, the variable ***h*** which closes the channels reacts more slowly to the voltage increase than the variable ***m*** which opens the channel. On a

similar slow time scale as shown by the variation in the activation gate ***n*** for K+, the potassium K^+ current sets in. Since it is a current in outward direction, it lowers the potential. The overall effect of the sodium and potassium currents is a short action potential followed by a negative overshoot (figures 6, 7, 8, 9 and 10).

The trajectory of the membrane potential is shown in the phase portrait plot (figure 8).

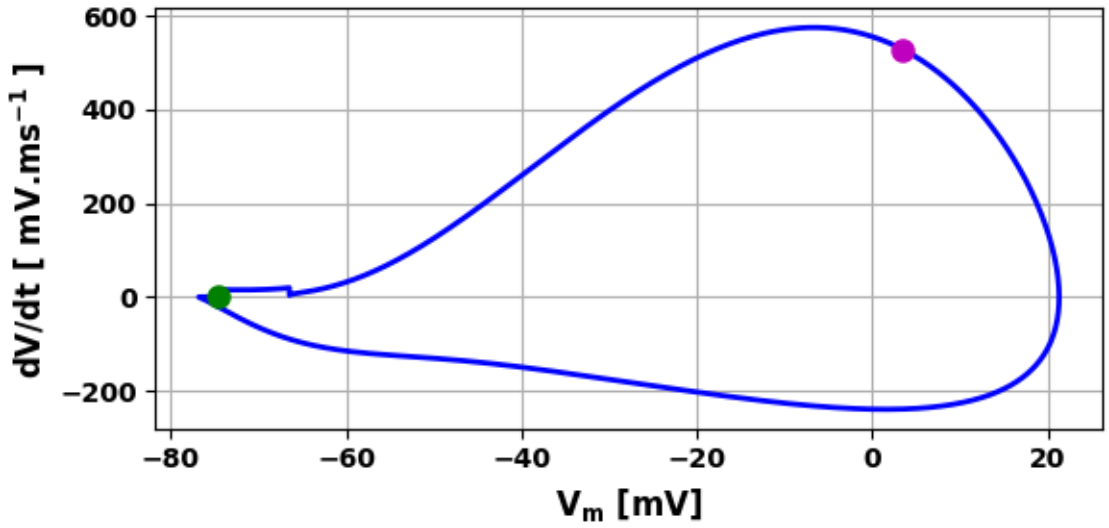


Fig. 8. Phase portrait plot. The membrane potential which equals the rest potential is a stable equilibrium point. The time evolution in the phase portrait plot is clockwise. Green dot start (t = 0) and the red dot a small time increment later.

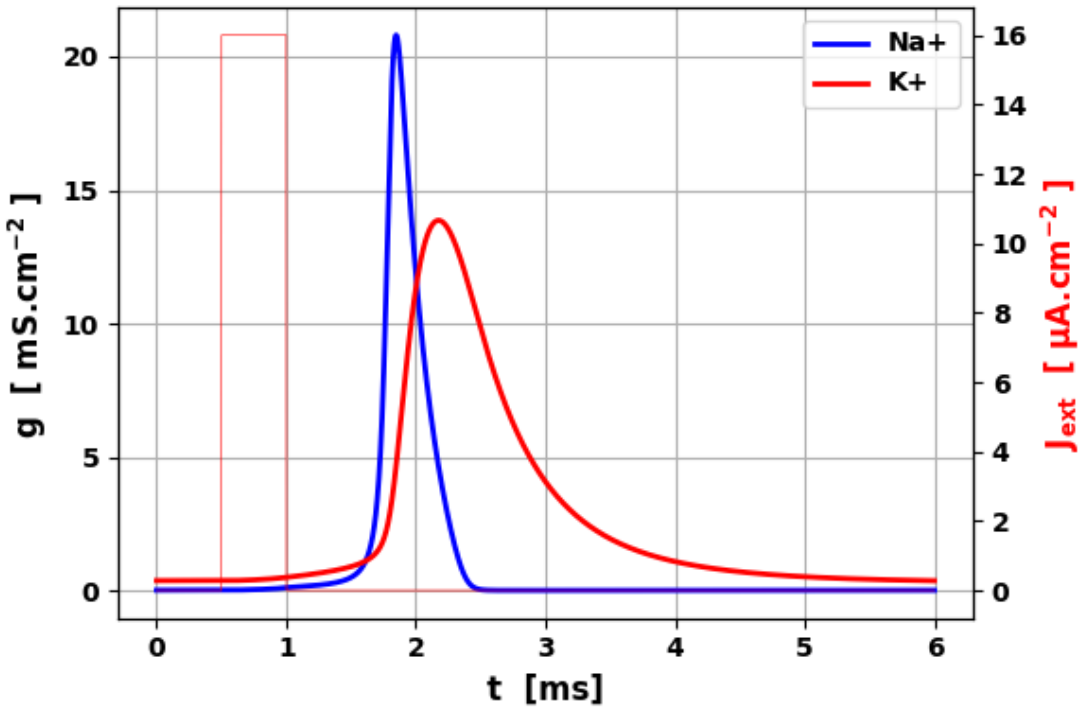


Fig. 9. Sodium and potassium conductances.

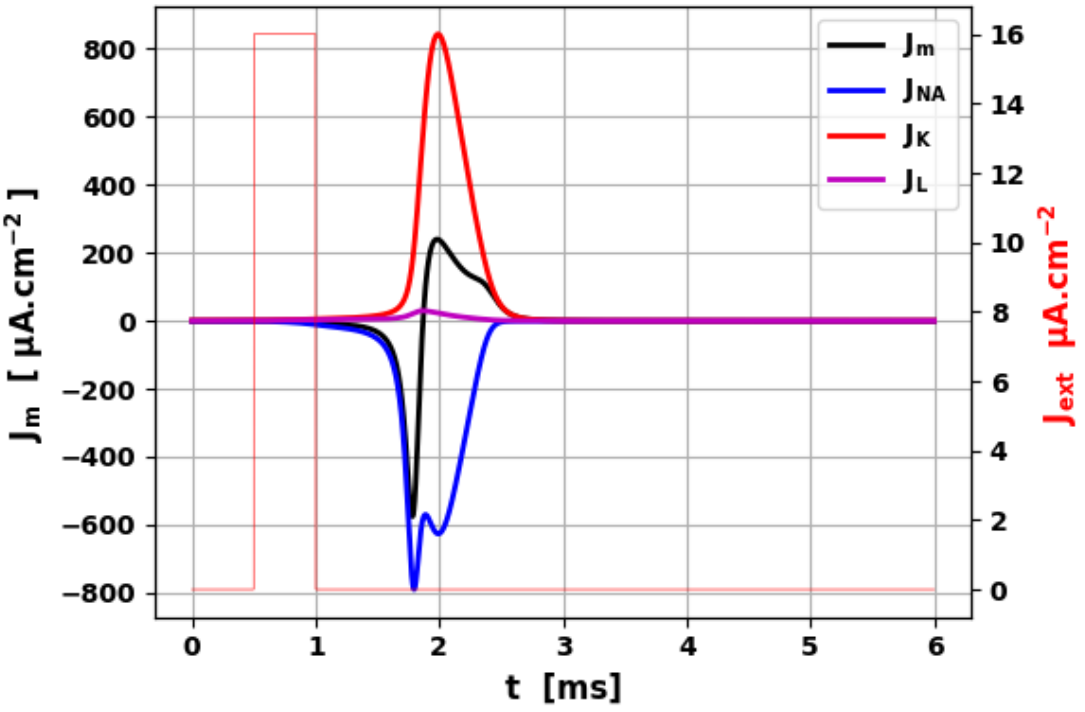


Fig. 10. Ion currents (current into cell is negative and a current out of the cell is negative).

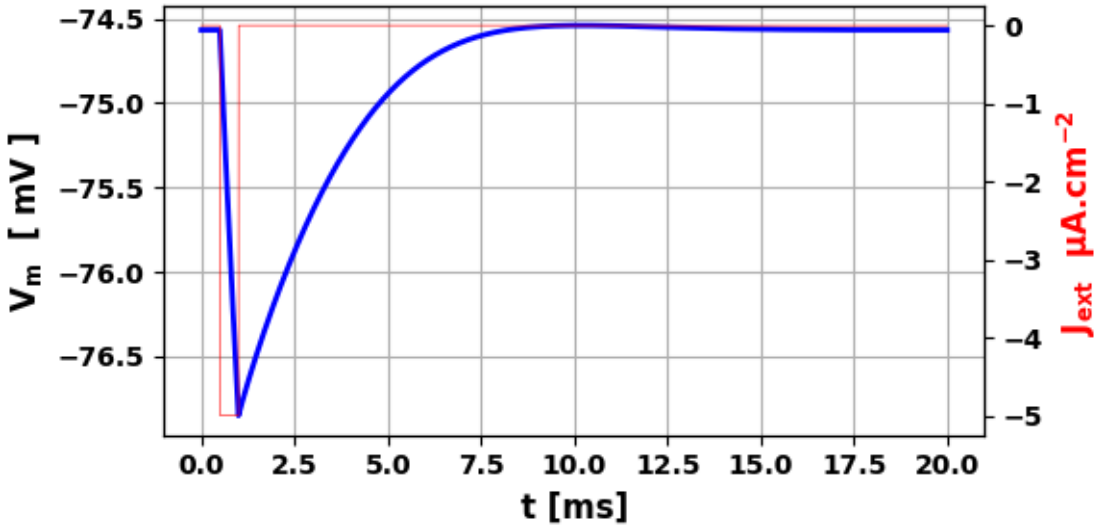


Fig. 11. A small negative pulse (duration 0.50 ms and height -5.0 µ A.cm^{-2}) causes the membrane potential to be more hyperpolarized before slowly returning to the resting value.

DUAL PULSE STIMULI (flag = 2)

```
if flag == 2:    # Dual pulses
  J0 = 20        # Amplitude of pulse
  p = 0.5        # pulse width
  t1 = 0.5; t2 = t1+p; 1.0; t3 = 7.0; t4 = t3+p
  Jext[t>t1] = J0; Jext[t>t2] = 0; Jext[t>t3] = J0; Jext[t>t4] = 0
```

We can compute the membrane potential time evolution when it is excited by two identical pulses. The initial external current pulse is sufficiently strong to excite a spike. Whether a second spike is

generated depends upon the time delay of the second pulse. A second action potential is only produced when sufficient time has passed for the membrane voltage to return to nearly its resting potential.

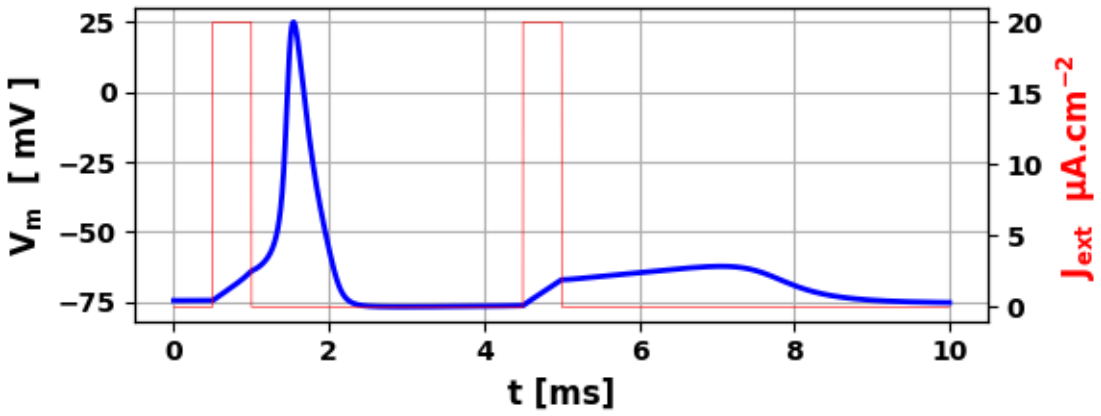


Fig. 12A. Time delay between the two pulses is 3.50 ms (4.5 – 1.0). No action potential is generated.

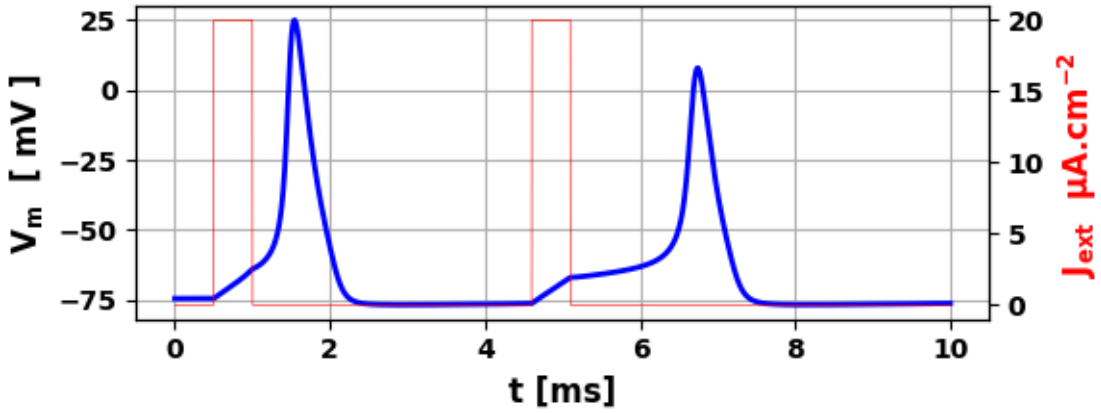


Fig. 12B. Time delay between the two pulses is 3.60 ms (4.6 – 1.0). A second action potential is generated with a lower amplitude.

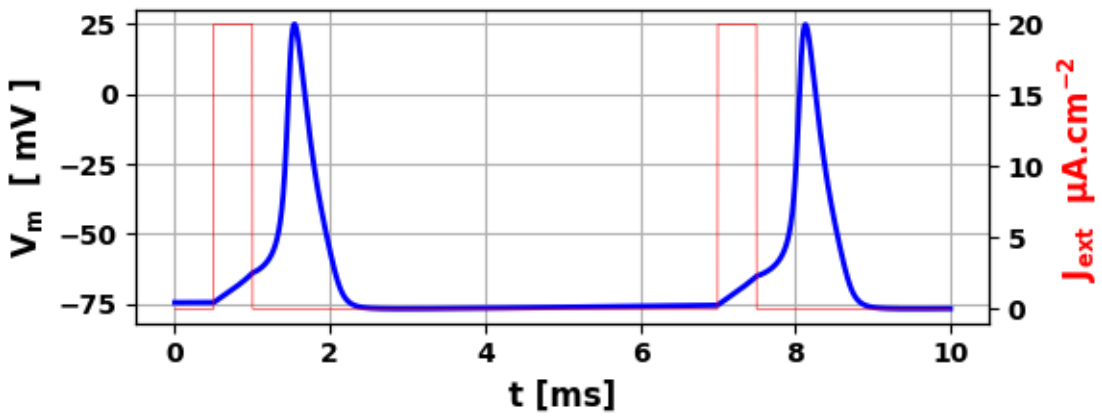


Fig. 12C. Time delay between the two pulses is 6.00 ms (7.0 – 1.0). A second action potential is generated with the same amplitude if the delay between the two pulses is long enough.

Refractoriness is the fundamental property of an excitable medium that does not to respond to a stimulus. For a neuron, the **refractory period** is the time interval during which a neuron is incapable of repeating another action potential. It is the time for the membrane potential to return to a value close to its resting value. From figure 12A, the refractory period is about 3.50 ms. If the second pulse occurs in a time interval less than 3.50 ms, no action potential is produced.

Refractoriness occurs, firstly due to the hyperpolarizing spike after-potential which is lower than the resting membrane potential. Hence, more time is needed to reach the firing threshold. Secondly, since a large portion of the ion channels are open immediately after a spike, and the resistance of the membrane is reduced compared to the situation at rest.

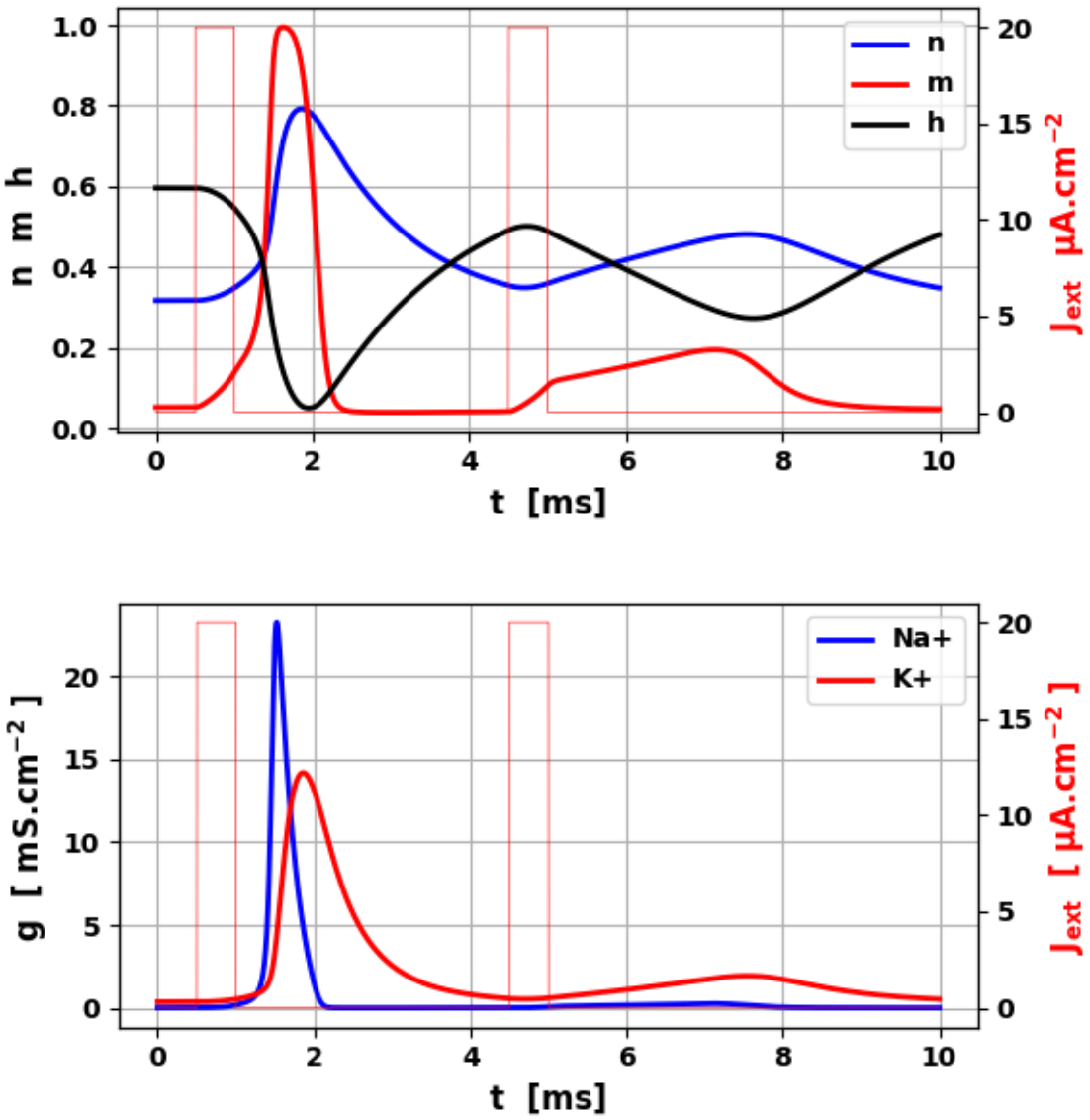


Fig. 13. The gates are more closed than open when the second pulse arrives which results in the small values of the Na^+ and K^+ conductances. Therefore, the membrane is not depolarized and no action potential fires.

Multiple current pulses: pulse train (flagJ = 3)

```
if flag == 3:    # Square wave: pulse train
  J0 = 100     # Amplitude of pulse
  p = 2        # period [ms]
  Jext = J0*sin(2*pi*t/p)
  Jext[Jext>0] = J0; Jext[Jext<0] = 0
```

You can study the response of the membrane potential to a series of square pulses of uniform amplitude.

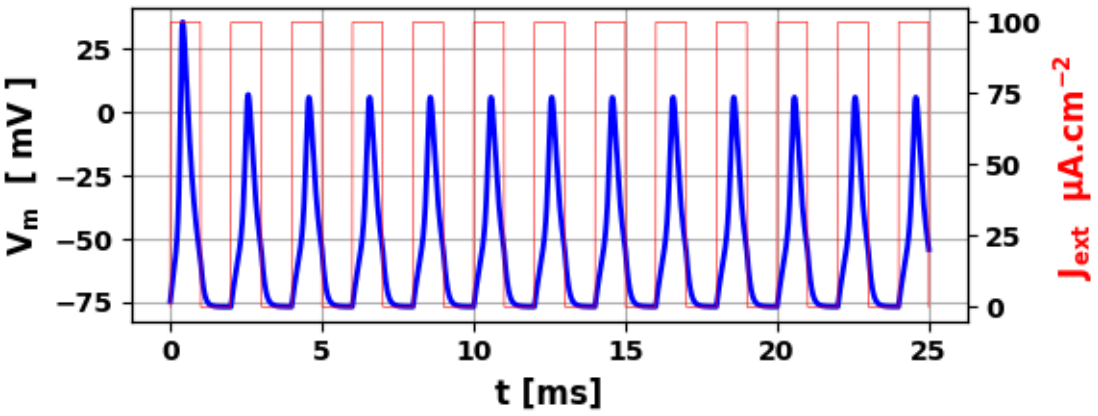


Fig. 14A. A regular pulse train stimulus excited the neuron. The pulse amplitude is 100 μA.cm^{-2} and the period of the stimulus is 2.0 ms and frequency 0.50 Hz. If the frequency is not too high and the amplitude of the pulses is great enough, then a periodic sequence of action potentials is generated.

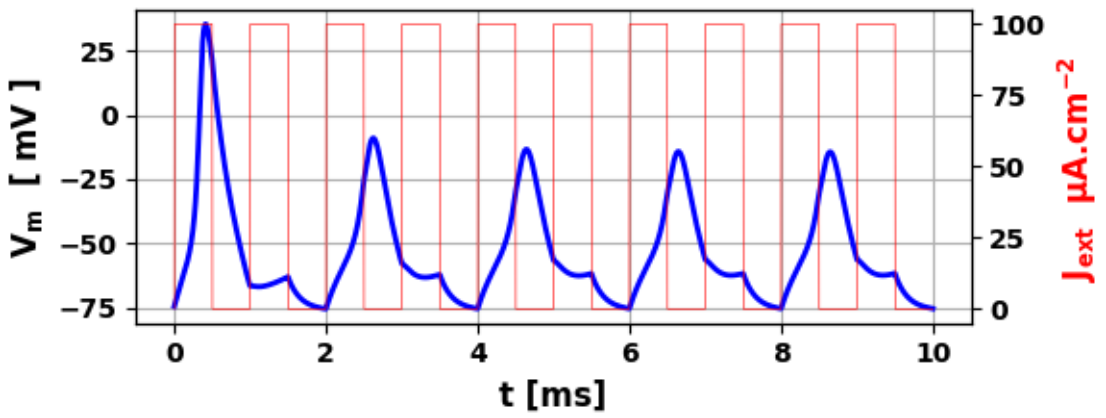


Fig. 14B. A regular pulse train stimulus excited the neuron. The pulse amplitude is 100 μA.cm^{-2} and the period of the stimulus is 0.2 ms and frequency 5.0 Hz. At the higher frequency, not all pulses give rise to an action potential.

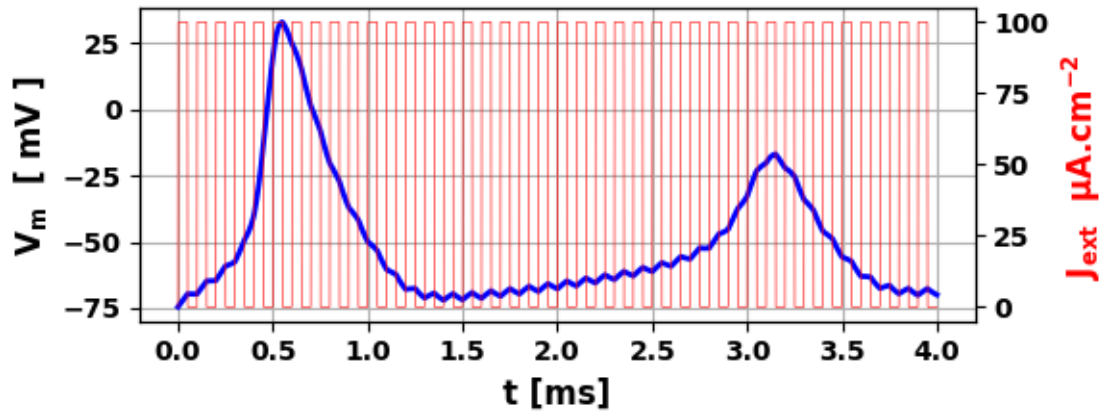


Fig. 14C. If the pulse rate is too rapid, then not all action potentials are generated and a regular firing pattern is not established. Pulse train period is 0.1 ms and frequency 10 Hz.

Step current input flag = 4

```
if flag == 4:
    J0 = 30
    t1 = 5
    Jext[t>t1] = J0
```

We can model the response of the membrane potential to a step input. Figure 14 shows the membrane potential for a series of step functions with increasing amplitude.

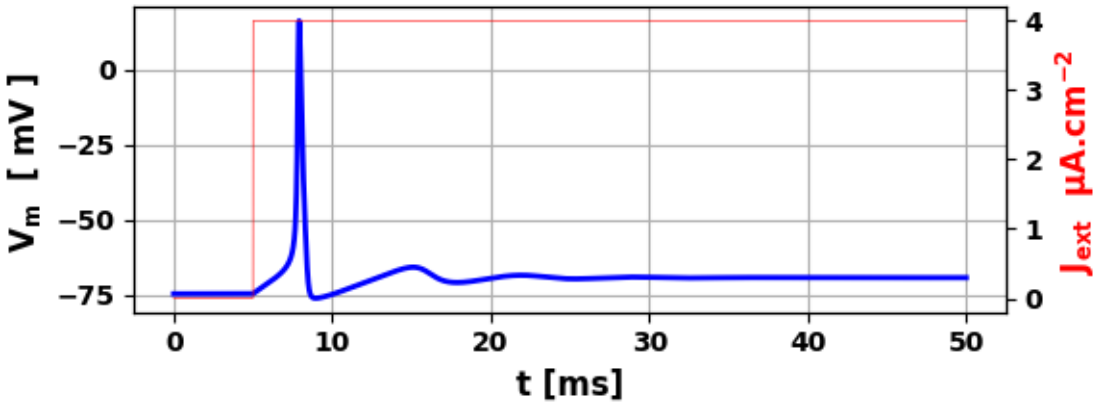


Fig. 15A. Jext = 4.0 μA.cm^{-2}

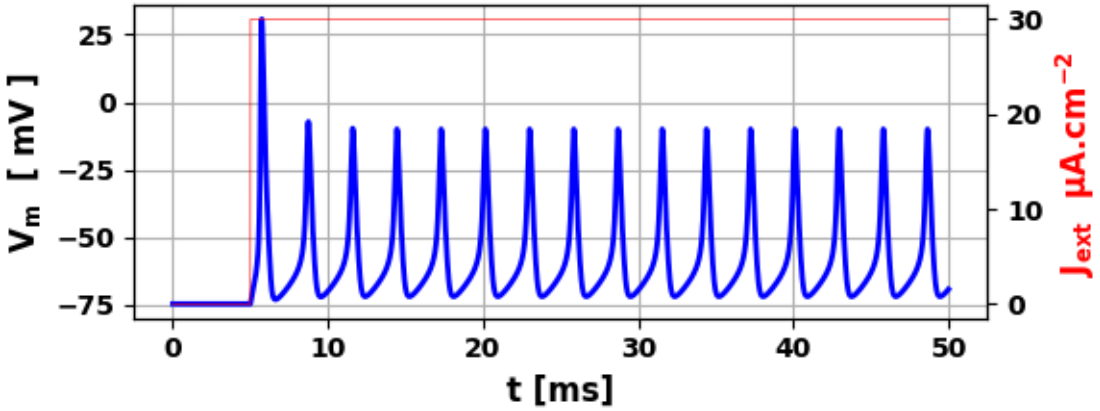


Fig. 15A. Jext = 30.0 μA.cm^{-2}

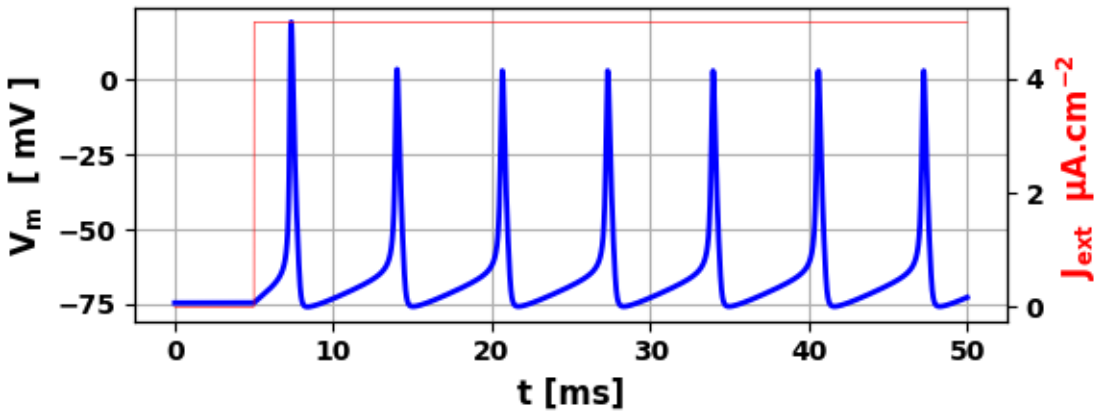


Fig. 15C. Jext = 5.0 μA.cm^{-2}

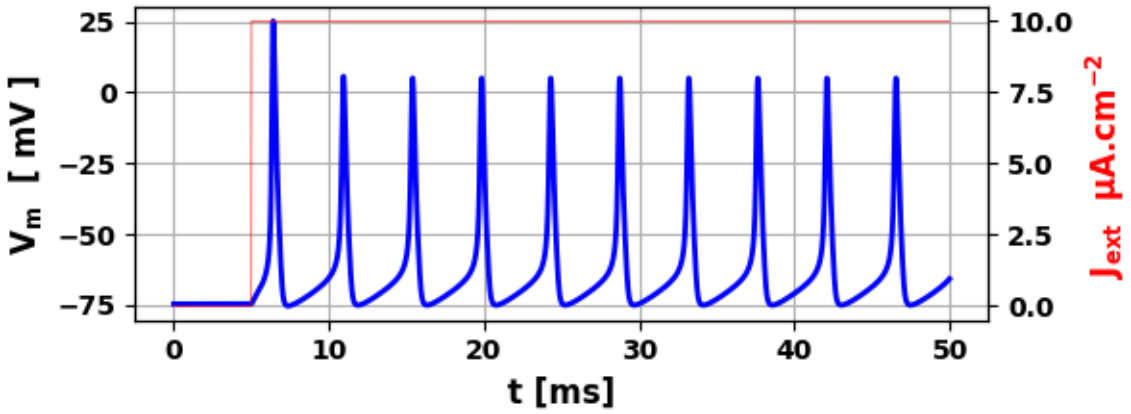


Fig. 15D. Jext = 10.0 μA.cm^{-2}

A constant current injection is used to stimulate the neuron. The stimuli are switched on at time t = 5.0 ms. If the size of the step is less than 5 μA.cm^{-2} then an action potential is not produced. A current density stimulus of 5 μA.cm^{-2} produces a set of regular spikes. As the size of the step is increased, the frequency of the repetitive firing increases but the degree of depolarization decreases. If the step size is too great however, a series of spikes is not produced.

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.