Engineering in Medicine and Biology (BIOM1010)
Tutorial: Modelling Action Potentials

Background

The quantitative description of membrane potential was first provided by Nobel prize winners Hodgkin and Huxley for the giant axon of the squid (Hodgkin and Huxley, 1952). Since ionic mechanisms underlying various excitable cell types are similar, the Hodgkin-Huxley model and its extensions have and remain widely utilised in cardiac, muscle, brain and retinal neuron modelling studies.

Excitable neuronal membranes are composed of micromolecular complexes of proteins and phospholipids (Rouser et al., 1968). This structure (Figure 1) can be described by a capacitor (phospholipids) in parallel with several conductive elements (ionic channels assembled by proteins) with the relationship between transmembrane potential and ionic currents described by the standard space-clamped ordinary differential equation (ODE):

$$dV_m/dt = -(i_{Na} + i_K + i_L)/C_m$$

where i_{Na} and i_K denote the sodium and potassium currents, i_L is a background or leakage current. C_m the membrane capacitance ($\mu F/cm^2$) and t time (s).

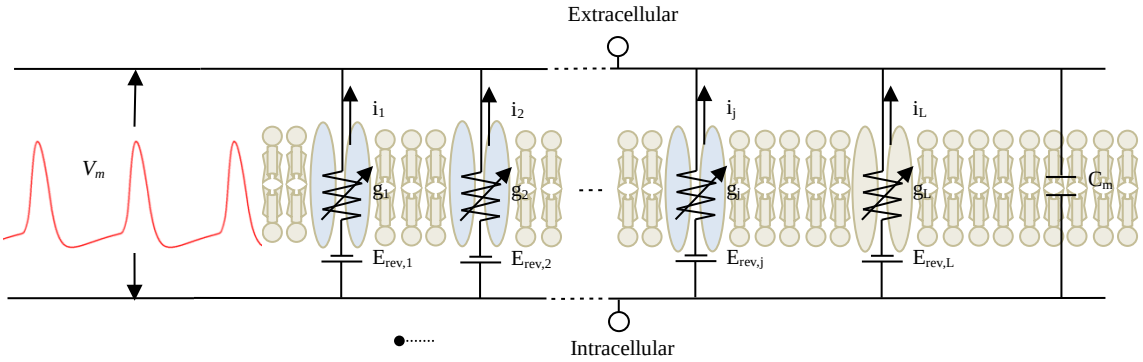

Figure. 1. A general equivalent circuit of excitable cell membrane. The capacitor branch simulates the lipid bilayer, and *j+1* conduction branches represent *j* time-dependent ionic channels and one time-independent background current formed by membrane-spanning proteins. Each conduction branch includes an electromotive force to model the corresponding equilibrium potential. Total membrane current consists of various ionic currents (in our case, only two ionic currents i_K and i_{Na}) and one leakage current i_L.

Task 1: ALL or NONE property of the action potential

When the depolarisation reaches a critical value (the so called threshold), a neuron will fire an action potential. An action potential, unlike a graded potential, is an all-or-none event: it may or may not occur, but when it does occur, it will always be of the same size (i.e. not proportional to the size of the stimulus). To begin:

1. Download the zip file "BIOM1010_ExcitableCell_Model" from the course Moodle page.
2. Unzip the four MATLAB files.
3. Open file named "Neuron_Action_Potential_ALL_or_NONE.m"

The value of the injected current can be varied from 1 to 12 pA/cm^2 in line 13:

```
Stim_Amp_all =[1 2 3 4 6 8 12] ;  % stimulus amplitude (pA/cm^2)
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Using MATLAB, run the file and plot the cell membrane potential in response to the range of injected currents specified in the above line, for 0.002 < t <= 0.004 s. With the injection of a sufficient current pulse, you may exceed the threshold for generation of action potentials. Based on your results, find out:

1. What is the approximate threshold value (mV) and the minimal stimulation amplitude (pA/cm2) which can trigger an action potential.
2. What are the peaks of all generated action potentials (mV) under different current injections.

Task 2: Mechanisms of action potential generation

The membrane of excitable cells contains voltage-gated ion-channels. These channels let through only one particular type of ion, typically Na^+ or K^+, with a high selectivity. Their opening and closing depends on the membrane voltage. In Task 2, you will find out the contribution of Na^+ and K^+ channels in action potential generation. To do this open the file named "Neuron_Action_Potential_Mechanisms".

Using MATLAB, run the file and plot the generated action potential, as well as the maximum number of opening Na^+ and K^+ channels per unit area (μm^2) during an action potential. Based on your results, answer the questions below.

1. Which of the following is a TRUE statement?
    A. The greatest sodium current occurs during the upstroke of the action potential
    B. The greatest potassium conductance occurs during the repolarisation phase of the action potential
    C. The greatest sodium conductance occurs near the peak overshoot potential of the action potential
    D. All of the above are correct

2. Which ion is important for the depolarisation (rising part) and which is important for the repolarisation (falling part) of the action potential? And in what direction do these ions move (i.e. an inward current or an outward current relative to the cell)?
3. How do the Na^+ and K^+ currents compare in their rates of activation?
4. Which current, Na^+ or the K^+, activates at more hyperpolarized levels.
5. Why does the action potential go below the resting potential (hyperpolarisation) after repolarisation?
6. In the "Mechanisms_Function" file increase the sodium conductance (gNA) by a factor of 5 and see what happens to the action potential. This is how a pacemaker in the heart is formed to create a regular depolarisation.

References

FINK, M. & NOBLE, D. 2009. Markov models for ion channels: versatility versus identifiability and speed. Philos T R Soc A, 367, 2161-2179.

HODGKIN, A. L. & HUXLEY, A. F. 1952. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol., 117, 500-44.

ROUSER, G., NELSON, G. J., FLEISCHER, S. & SIMON, C. 1968. Lipid composition of animal cell membranes, organelles, and organs. Biological Membranes. NY, US: Academic Press.