Neural Computation
Practical 2: The Hodgkin-Huxley model

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1 Aims

- To investigate properties of the action potential as produced under current clamp conditions

- To use the voltage clamp and ion-selective blocking to investigate ionic currents

- To show how the Hodgkin-Huxley model accounts for these properties.

2 Constructing the model in Neuron

We will first construct construct a NEURON simulation based on the Hodgkin-Huxley model of the action potential in a small, isopotential section of the squid giant axon.
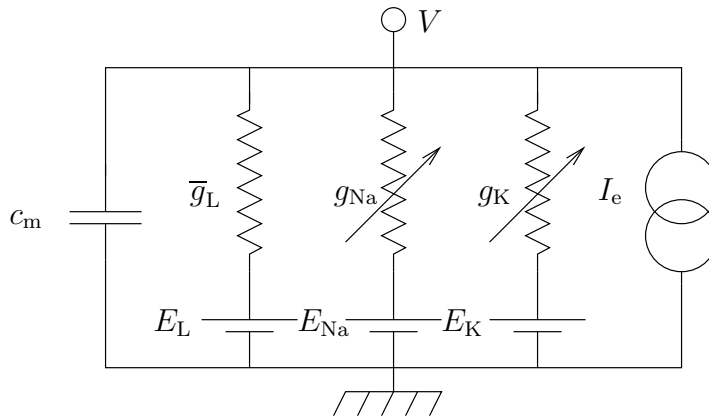

Figure 1: The equivalent electrical circuit

Figure 1 shows the equivalent electrical circuit for the Hodgkin-Huxley model.

- Explain what the different electrical symbols mean.

To create this circuit in NEURON, type in:

```
create soma
access soma
soma insert hh
```

The only line that is different from the first practical is one containing `insert hh`. This inserts Hodgkin-Huxley type channels into the membrane. Use `psection()` to view the parameters. They are the same as those originally used by Hodgkin and Huxley.

Bring up a **RunControl** window and a **Voltage graph** as described in practical 1.
Run the simulation for 100 ms. There are no input currents to the neuron at this point.

- Right- click on the graph and select **View→View=Plot** to see the trace in detail. Describe the behaviour of the membrane potential

- Define the resting membrane potential. What is its value in this case?

3 Current clamp

Now insert an electrode into the neuron by selecting **Tools→Point Processes→Managers→Electrode** from the main menu.

3.1 Fundamental behaviour

In the **I/V Clamp Electrode** window, select the **IClamp** button. Change the `delay` to 20 ms, the `duration` to 1 ms and the amplitude to 2 nA. Finally change the `tstop` in the **RunControl** window to 50 ms. Set the **Keep lines** option on the **Voltage graph**. Now run the simulation 8 times, increasing the `amplitude` by 2 nA each time.

- Describe what you see.

3.2 The threshold

Depending on the dynamics of the various channels, there may be a *voltage threshold* (a critical membrane potential at which an action potential is always produced) or a *current threshold* (a critical level of current injection which always leads to an action potential being produced). For the Hodgkin-Huxley model injected with short pulses of current, the voltage threshold is the relevant type of threshold.

- What is the lowest amplitude current pulse that elicits an action potential? Find this by changing the value of `amplitude`, choosing values with at most 3 significant figures. Rerun the simulation with each new value.

- Increase the stimulus duration to 10 ms. What do you expect for the threshold current? Check your ideas.

- Estimate the threshold voltage. (Note for the experts. Strictly, speaking the threshold voltage in the HH model is not well defined, see Koch for details).

For the next part, the current should be enough to elicit an action potential. However, to make it clear what happens, it shouldn't be too big; 15 nA is a suitable value to set the current to. Duration should be 1ms.

3.3 Refractory periods

We will now investigate the refractory periods of action potential generation using two separate current pulses.
To do this we will need a second electrode. Insert one as earlier on in this section. Set the `duration` of both current clamps to 1 ms. Leave the delay of the first IClamp at 20 ms and set its amplitude such that it produces a single action potential. Now set the `amplitude` of the second IClamp to the minimum current required to elicit action potential you found in section 3.2. Neurons have two refractory periods. Within the absolute refractory period, no second spike can be elicited no matter how strong a current is injected. Within the relative refractory period, a second spike can be elicited but it takes more current that the first spike.

- Estimate the relative refractory period to the nearest millisecond.

- Now change the delay and amplitude of the second pulse to estimate the absolute refractory period. Be careful during this exercise when classifying the response due to the second current pulse as a genuine action potential. Look at the time course and amplitude of the response.

- Which mechanisms are responsible for the refractory periods.

*If you put in lots of current and get something that looks like an action potential, try halving the current injection. Do you get something that is about half as high (relative to the resting potential) as you had with the first current injection? If so, it's **not** an action potential as the active channels aren't adding anything to your current injection. (Technically speaking, the V-I characteristic should be nonlinear.)*

Delete one of the current clamps you created by pressing its **Close** button.

4 Repetitive firing

Longer current pulses than we have been using so far can generate multiple action potentials. Set the following parameter values and rerun the simulation:

```
IClamp Onset Delay :   50
IClamp Duration:  100
IClamp amplitude:   10
Tstop:  200
```

You will see a train of spikes.

- Research the relation between number of spikes and the injected current. (The so called F/I curve)

- Plot the F/I curve. One option is to create a datafile from the UNIX commandline. Enter your results in the datafile in two columns: first column the current, in the second the frequency. Plot the datafile with "gnuplot". Alternatively, use a spreadsheet.

4.1 Blocking conductances

Hodgkin and Huxley had to change the concentration of sodium and potassium in order to see how each affected the action potential. However, in the 1960s, methods for blocking channels pharmacologically were developed. Tetrodotoxin (TTX) is isolated from the Japanese puffer fish *fugu* and blocks Na^+ channels involved in generating action potentials[1]. Tetraethylammonium (TEA) blocks K^+ channels.

The effect of blocking one or other conductance can easily be tested with this simulation. We can change parameters from the command line, as we did in practical 1. However a convenient way to view and change the parameters of the compartment is to select **Tools→Distributed mechanisms→Viewers→Shape name**. This brings up a dialog box with a list of sections in the bottom right corner. Double-click on `soma` (the only item in the list). You should now have a dialog box with a number of parameters in it.

- To block the potassium conductance set `gkbar hh` to zero. Rerun the simulation. Describe what you see. What can you deduce from this?

- Return `gkbar hh` to its original value by clicking on the red ticked box next to it. Now swap to blocking the sodium conductance by setting `gnabar hh` to zero. Describe what you see. What can you deduce from this?

- Take intermediate values of the densities and take higher than normal as well. Does the behaviour follow your intuition ?

- Research how the F/I curve changes with different densities settings.

Restore the orginal settings by clicking on the red ticked boxes before continuing.

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[1]Tetrodotoxin may also be used by Caribbean witch-doctors to create zombies (through brain damage from anoxia)

5 Voltage Clamp

Convert the current clamp to a voltage clamp by clicking on its `VClamp` button. Set the testing level duration to 15 ms and its amplitude to 0 mV. Click on the **VClamp.i graph** button. A current axis should appear.

Now run the simulation for 15 ms. We will try to indentify the different components of the current. First of all, block just the sodium current and run the simulation again.

- Describe what you see. Are the currents inwards or outwards?

- Define the terms *activation* and *inactivation*.

- How do they apply to what you see?

Now unblock the sodium current, block the potassium current and run the simulation again.

- Describe what you see. Are the currents inwards or outwards?

- Which of the terms *activation* and *inactivation* apply to the current you see?

- Block both currents. What is left ?

6 Putting it all together

We now study the individual currents during a spike. Go back to current clamp, and make the neuron spike. Make sure that all currents are unblocked again. Open a **State axis** from the **Graph** menu and plot `soma.m_hh`, `soma.h_hh` and `soma.n_hh` on this axis. Open a **current axis** and plot the conductances `soma.gna_hh`, `soma.gk_hh` and `soma.gl_hh`.

- Which of the state variables m, n and h are activating and which are inactivating?

- Explain how the different graphs are related to each other.

7 Extra: Spikes without K channels

(In case you thought you understood it). It turns out to be possible to generate spike-like events without a K conductance. Block the K conductance. Play with the other conductances (including leak conductance) to show this effect. What is the advantage of the biological solution of having K channels?

8 Extra: Temperature

The temperature has a strong effect on the HH equations. Let's warm the squid to room temperature (`celsius = 20` on the commandline.)
Look at the spike frequency and the shape and amplitude of the spikes at this temperature.
Research the channel densities required at higher temperatures.