NEURONAL PASSIVE PROPERTIES

Objectives: By the end of this exercise, students will be able to:

- *Explain how, using a mathematical model, resistance and capacitance shape neuronal responses to injected current*
- *Explore the similarities between the model of a neuron and its equivalent circuit representation.*

Précis:

The purpose of this exercise is to give you an opportunity to explore perhaps the simplest model of a neuron: a leaky integrator. Its utility is its lack of active properties; that's correct: the model neuron does not contain voltage-dependent ion channels that are used to generate action potentials; instead, the model mimics the passive behavior of a neuron.

Equivalent Circuit Representation of a Neuron

The neuronal membrane acts as a capacitor: Like all cells in the body, neurons have a phospholipid bilayer. The lipid bilayer consists of ampipathic phospholipids [1]. *Ampipathic* refers to compounds that have both *hydrophilic* (water-loving) **AND** *lipophilic* (fat-loving) properties. The hyrdophilic portion of the phospholipid is the phosphate group; the lipophilic portion is the lipid portion of the molecule. Because of this, ions cannot pass through the lipid bilayer; their charges cannot interact with the non-charged lipid portion of the bilayer. Therefore we can say that the membrane separates ions in the extracellular space from ions in the intracellular space.

It is this separation of charge that confers upon the membrane the physical concept of a *Capacitor*. In the electrical sense, a capacitor is a device that consists of two plates which allow charge to move that are separated by an insulating material. In this case, the phosphate groups on the extra/intra cellular face of the neuron's membrane are the plates, and the lipid portion, in which ions cannot pass, acts as the insulating material. This leads to the other definition of a capacitor: as a device that stores charge. As charges build up on either side of the capacitor, they interact with each other, producing a voltage difference (difference in charge) between the plates. This difference in charge can be quantified by the *Capacitor Equation:*

$$Q = C \cdot V \tag{1}$$

Where Q is the amount of charge stored, C is the Capacitance (a constant, and V is the Voltage. This equation says that as the amount of Capacitance changes, the amount of charge stored changes, and thus the potential difference between the plates of the capacitor changes. How does this relate to the membrane? As charges (Q) align themselves on either side of the neuronal membrane, a potential (V, i.e., the membrane potential) arises between the inside and outside of the neuron. Because the amount of the cell membrane does not change dramatically, its Capacitance is effectively a constant in the equation above.

Channel proteins in the membrane act as resistors: Because ions cannot cross the membrane, they require passages through the membrane that allow them to move from the extracellular space to the intracellular space, or vice-versa. These passages are typically proteins, embedded in the cell membrane, called ion channels. For each ion that a neuron is permeable to, there will be an ion channel of some type that will facilitate the movement of that ion. These channels are of different classes, depending on the mechanism that "gates" their ability to allow ions to pass. For example, the class of channels that will be the focus of this exercise are called ”leak channels” because they are always open and therefore always allow ions to move (or ”leak”) through them.

Because ions have different properties (e.g, atomic radius), the ion channel proteins that allow them to move across the membrane must also be specific for the ionic species that they allow to move through them. This, then, confers upon them the physical concept of a *Resistor* [2]: they resist the movement of ions through them. In the electrical sense, a resistor is a device that impedes electrons from moving down a wire. In the same way, for an ion channel embedded in the membrane of a neuron, the specificity of that channel for a particular ion means that it can impede the movement of ions across the membrane.

Because ion channels can selectively allow ions to move through them, this allows them to produce changes in charge between the intracellular and extracellular space of the neuron. This movement of charge can also contribute to a voltage difference between the inside/outside of the neuron. This difference can be quantified by *Ohm's Law:*

$$V = I \cdot R \tag{2}$$

Where V is the voltage, I is the current, and R is the resistance (for the channels we discuss in this exercise, this is a constant). This equation says that as the amount of Resistance changes, the current flowing through the resistor changes, and thus the voltage changes. How does this relate to the membrane? Channels inserted into the membrane impart a resistance to current flow (i.e., ion movement) between the inside and outside of the neuron. This movement of ions generates a current flow (I) that produces a change in Voltage between the inside and outside of the neuron.

Derivation of the Model:

The model neuron is based on the following equivalent circuit, with an electrode used to pass current into the neuron:

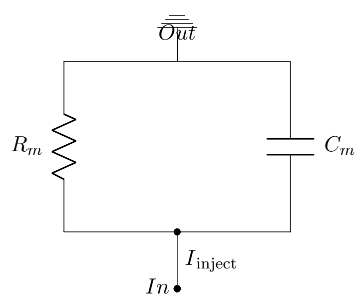

Figure 1: Equivalent circuit model for a passive cell

where C_m represents the membrane capacitance in Farads (F; we will use SI units), and R_m is the membrane resistance in Ohms (Ω). We will then inject a current I_{inject}, at the point “In” on the circuit (“Out” represents the path to ground). I_{inject} has SI units of *Amperes* (A). Current injected into this cell flows across the two arms of the circuit. According to Kirchoff's Law, the current(I_{inject}) injected into the cell (at the point “In”) ***must*** be equal to the current flowing along the two branches of the circuit (i.e., the current flowing through the resistor and across the capacitor) of the cell. We define this for the model by the following equation:

$$I_{\text{inject}} = C\frac{dV}{dt} + \frac{V}{R} \tag{3}$$

We solve this equation for $C\frac{dV}{dt}$ and get (verify this for yourself):

$$C\frac{dV}{dt} = I_{\text{inject}} - \frac{V}{R} \tag{4}$$

This is the *"Current Balance Equation"* for the passive neuron model. It says that the rate of change in voltage is equal to the current flowing through the ion channels (R) plus the current injected. How do these relationships arise?

The term on the left arises from the Capacitor Equation above. Taking the derivative of both sides of the Capacitor Equation (NOTE: C is a constant, and therefore doesn't change) yields:

$$\frac{dQ}{dt} = C\frac{dV}{dt} \tag{5}$$

$\frac{dQ}{dt}$ is, by definition, a current (i.e., the rate of change in charge, Q). Therefore, the first term represents the capacitor current. Reminder: current does not flow *through* a capacitor; rather, the deposition of charge on one side of the capacitor repels like charges away from the other side of the capacitor. In the context of a neuron, this represents depositing charge on the intracellular face of the membrane; this charge repels like charges away from the extracellular face of the membrane.

For the last term on the right: we start with Ohm's Law from above. Solving for I yields:

$$I = \frac{V}{R} \tag{6}$$

Therefore, this term represents the current flowing *through* the resistor. Unlike a capacitor, electrons do flow through a resistor. In the context of a neuron, this represents the flow of ions through ion channels of different types (e.g., leak channels, gated channels, etc.).

Taken together, in terms of the equivalent circuit developed above, the current balance equation says that, in response to a constant current injection, the membrane potential will change until it reaches a particular voltage. We will call this voltage the *Steady-State Voltage* (V_∞). The goal of today's exercise is to explore how the membrane Capacitance (C_m) and resistance (R_m) contribute to:

1. the V_∞ the cell reaches in response to the injected current
2. the time course of the voltage change

In this exercise, we will look at the impact of R and C on V_∞ and how, using this simple model, we can actually determine V at any time t.

Exercises

Running the Model in Matlab

Open Matlab on your computer. Double-click on the file called `passive.m`. This code executes the model. Take a moment to familiarize yourself with the different components of the code. NOTE: You should NOT change anything below line 19 (it says NOTHING TO CHANGE BELOW THIS LINE).

In the following, text you type at the keyboard is typeset `like this`; answers given by Matlab are typeset `like this`; comments in Matlab code are typeset `like this`.

Exercise 1: Effect of Capacitance on the Steady-State Voltage

In this first exercise, we will explore what effect changing the capacitance of the cell has on the voltage that is reached for a given amplitude of current injection. How could you change a cells capacitance. If the membrane itself acts as a capacitor, discuss the relationship between changes in capacitance and the surface area of the cell. Enter your answer below:

____

For this initial set of simulations, you will only be changing the capacitance. This is done by changing line 7 in the Matlab code (should say Cm=1e-9, which means Cm=10^{-9}). For this first run, leave this value at 1e-9. Please be sure to note the following parameters for input resistance (R_{m}) and current injection (Iinject). Can you put these values into "physiological units" (for example, 1e-3V is equal to millivolts):

`Cm=1e-9` ________________

`Rm=10e6` ________________

`Iinject=-1e-9` ________________

Now to the simulation. Make sure line 7 in the code (`Cm`) is reset to `1e-9`. Check that the following lines in the code are set to these values:

```
%% Define Stimulus Parameters
10 Iinject=-1e-9;   % current amplitude (A)
11 tend=1;   % length of simulation (s)
12 tstimstart=0.1;    % time to start current injection (s)
13 tstimend=0.6;    % time to end current injection (s)

%% Define Plot Axis
15 ylo=-inf;  % Sets the y-axis lower limit; sometimes set @ -0.075;
16 yhi=inf;  % Sets the y-axis upper limit; sometimes set @ -0.050;

%% Fit the Data
18 fitter=0; % if you want to fit the data enter 1, otherwise leave at 0
```

(NOTE: The text in green is called a "comment." A % sign tells Matlab to ignore the following text)
Hit the "Run" button located in the top ribbon of the program window. It should produce the following plot:

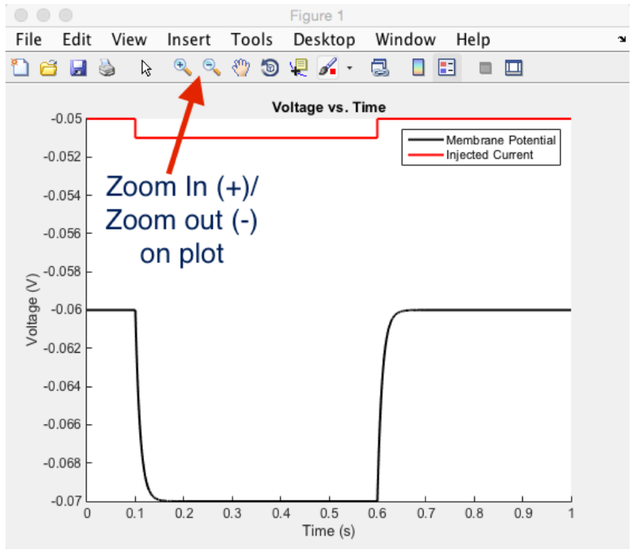

Figure 2: Matlab figure window showing V_m of the passive cell (Black trace) in response to injected current, I_{inject} (red trace)

Take a moment to familiarize yourself with what you are looking at. The red line represents the current injected (the current has been scaled so that it fits on the plot). The black line represents the voltage deflection. Note that, at the beginning of the trace, the *resting membrane potential* is "-60mV (or -0.06 V in SI units)". This is set in line 6 of the Matlab script (`El=-60e-3`).

Has the voltage reached a steady-state (i.e., no longer changing)?

What is the value of the voltage at the moment the current trace turns off? Matlab will tell you what the minimum voltage is in the "Command Window" just below the code (`The voltage at the end of the current injection was`).

To explore the figure, you can select the magnifying glass to zoom in on the plot. Hold and drag the magnifying glass across the voltage trace as it reaches steady state. To restore the original view, simply double click anywhere in the white figure area.

Now, change line 7 to `2e-9`, and re-run the code. What is the steady-state voltage deflection? Repeat for C_{m} values (do not change the e-9 part of line 8) of 3, 4, 5, 10, and 20. Record your steady-state voltage deflections (i.e., deviation from resting membrane potential) in Table 1 (You've just run the simulation for C_{m}=1):

C_{m} ($\cdot 10^{-9}$F)	V_∞	$\Delta V : V_{\text{rest}} - V_\infty$
1		
2		
3		
4		
5		
10		
20		

Did you reach a steady-state voltage for each value of C_{m}?

Is there a change in the steady-state voltage? Would you expect there to be? Why or why not?

What do you notice about the time course (i.e., the time required to reach 63% (or 1-e^{-1}) of the steady-state voltage) of the voltage-change as you increase C_m?

Exercise 2: Effect of Input Resistance on Steady-State Voltage Deflection

Now, we will only be changing the resistance. Make sure line 7 in the code (C_m) is reset to `1e-9`. Change the following lines in the code (note the semicolon):

```
11 tend=1;
12 tstimstart=0.1;
13 tstimend=0.6;
15 ylo=-0.250;
```

For this set of simulations, you will be changing "`Rm`" on line 8. Run the code for each of the following values of R_m: 10, 20, 30, 40, 50, 100, 200. Record the steady-state value (if reached) for each value of R_m in Table 2.

R_m ($\cdot 10^6$ Ω)	V_∞	$\Delta V : V_\mathrm{rest} - V_\infty$
10		
20		
30		
40		
50		
100		
200		

Did you reach a steady-state voltage for each value of R_m?

Is there a change in the steady-state voltage? Why or why not?

What do you notice about the time course (i.e., the time required to reach 63% of the steady-state voltage) of the voltage-change as you increase R_m?

Exercise 3: Effect of Capacitance on Membrane Time Constant

Until this point, we have focused primarily on the steady-state voltage reached in response to the current injection. Here we want to look at the time course of the change in voltage. All circuits such as that shown in Figure 1 can be characterized by a parameter called the time constant (τ.) It is defined by the following equation:

$$\tau = R_\mathrm{m} \cdot C_\mathrm{m} \tag{7}$$

This equation determines the time it will take for the voltage to reach $\approx 63\%$ of its steady-state value in response to a current injection. τ is one of the fundamental measurements you can make of a neuron, because it will give you a sense of how long it takes for a neuron to reach *threshol*, or the membrane potential at which a neuron will generate an action potential.

What are the units of the time constant? The SI unit for Ohms is: $\Omega = \frac{Volt}{Ampere}$ and for Farads is: $F = \frac{Coulomb}{Volt}$. In the space below, see if you can determine the units (hint: $Ampere$ is $\frac{Coulomb}{s}$.) Please check with an instructor before continuing.

To quantify the effect of R_m and C_m on the time constant we will compute the time constant ourselves, then run a simulated "experiment" to verify the theoretical description of this circuit.

We will use Matlab to perform the simulations, then fit the data to determine the actual time constant of our cell. To do this, you will need to make the following changes to the code (number indicates the line # in the code to change):

```
11 tend=0.5;
12 tstimstart=0;
13 tstimend=0.5;
15 ylo=-inf;
16 yhi=inf;
18 fitter=1;
```

Don't forget the semicolons.
In the table below, enter your values for the time constant, based on the following C_m values (leave R_m at 10e6; don't forget the units!)

C_m ($\cdot 10^{-9}$F)	Calculated τ	Fitted value of τ
1		
2		
3		
4		
5		
10		
20		

Run the code for each value of C_m. Did your theoretical results match with the fitted results?
Now repeat the exercise for different values of R_m (change C_m back to 1e-9).

R_m ($\cdot 10^{6}$ Ω)	Calculated τ	Fitted value of τ
10		
20		
30		
40		
50		
100		
200		

Run the code for each value of R_m. Did your theoretical results match with the fitted results?

Conclusions

What can you conclude about the effect of membrane capacitance on V_∞? The time course of voltage changes?

What can you conclude about the effect of membrane resistance on V_∞? The time course of voltage changes?

Appendix: Solution to the Current Balance Equation

Here we want to develop an intuition for what the *"Current Balance Equation"* tells us by deriving a general solution for this equation. As you will see, we can use this intuition to understand how conductance-based models work.
We begin with equation 4 above:

$$C\frac{dV}{dt} = I_{\text{inject}} - \frac{V}{R} \tag{8}$$

Multiply both sides by R to get:

$$RC\frac{dV}{dt} = RI_{\text{inject}} - V \tag{9}$$

$R \cdot C$, as you recall, is the definition of τ the time constant:

$$\tau\frac{dV}{dt} = RI_{\text{inject}} - V \tag{10}$$

Note that, in this form, all of the relevant terms on the right-hand side of the equation are in Volts (in the derivation section above, the terms were in Amps). This equation says that the rate of change of V is equal to V itself. We would like to know V at any given time, not $\frac{dV}{dt}$. In practice, this can be very difficult. In this case, however, we can generate a solution. What we can do is imagine the situation wherein V is not changing. In this specific case, $\frac{dV}{dt}$ becomes 0:

$$0 = RI_{\text{inject}} - V \tag{11}$$

We call this instance (when V is not changing), the *Steady-State Voltage*. We can now solve for V:

$$V = RI_{\text{inject}} \tag{12}$$

This equation says that V will be equal to $R \cdot I_{\text{inject}}$. This is key! It says that, at steady state, V will be equal to Ohms Law! We designate this V as V_∞ :

$$V_\infty = RI_{\text{inject}} \tag{13}$$

We can now plug this new term into 10 above:

$$\tau\frac{dV}{dt} = V_\infty - V \tag{14}$$

It is this general equation that lies at the heart of most, if not all, conductance based models. Dividing by τ yields:

$$\frac{dV}{dt} = \frac{V_\infty - V}{\tau} \tag{15}$$

What this equation says is that V will approach its *Steady-State* value at a rate proportional to the time constant, τ. Taken together, if you can determine V_∞ (*WAY EASIER SAID THAN DONE*) and τ, you can use this equation to determine V[1] at all times.

Equations of this form have the general solution

$$V(t) = V_\infty - (V_\infty - V_0)e^{\frac{-t}{\tau}} \tag{17}$$

How to parse this equation? I find it useful to take the limits of time (aka "boundary conditions;" that is, when t=0 and when $t = \infty$.)

- $t = 0$. In this case, the term $e^{\frac{-t}{\tau}}$ becomes $e^{\frac{0}{\tau}}$, which is e^0, which is one. Equation 17 becomes:

  $$V(t) = V_\infty - (V_\infty - V_0), \tag{18}$$

  which is V_0, or the membrane potential from which you start.

- $t = \infty$. In this case, the term $e^{\frac{-t}{\tau}}$ becomes $e^{\frac{-\infty}{\tau}}$, which is $e^{-\infty}$ (because the ∞ term $\gg \tau$) , which is zero. Equation 17 becomes:

  $$V(t) = V_\infty - (V_\infty - V_0) \cdot 0, \tag{19}$$

  which is V_∞, or the steady-state voltage reached after an infinite amount of time.

In the Hodgkin-Huxley model, V_∞ is joined by variables for the in/activation gates that govern the dynamics of ion channels that are present in the membrane.

References

[1] Alberts, B, Johnson, A, Lewis, J, Raff, M, Roberts, K, Walter, P *Molecular Biology of the Cell.* Garland Science, 2008

[2] Kandel, ER, Schwartz, JH, Siegelbaum, SA, and Hudspeth, AJ. *Principles of Neural Science.* McGraw-Hill Professional, 2013.

[1] For most conductance-based models, you typically see equations like these in the following format for a given variable (in/activation gates, e.g.)

$$\frac{dX}{dt} = \frac{X_\infty - X}{\tau_X}. \tag{16}$$