

Electrical Signalling in Excitable Cells

November 22, 2010

The cell membrane is designed to separate the inside of the cell from the outside world. It is primarily composed of a phospholipid bilayer, which is polar on the edges and non-polar in the middle. The membrane is semi-permeable to certain substances, i.e., some ions move through it quickly and others either do not get through or go through slowly. The semi-permeability of the membrane to particular ions allows the cell to maintain a difference in charge between the inside and outside of the cell. The difference in charge (or electrical potential) across the membrane can vary. In order for it to change, ions must move from the inside of the cell to the outside, or vice-versa. A spike in the electrical potential is called an action potential. These action potentials are important to the functioning of neurons and cardiac cells. Much of the workshop will study the behavior of action potentials in cardiac cells.

Since some charged particles (i.e., ions) have difficulty passing through the membrane, there are particular proteins that form channels that allow specific ions to move into and out of the cell. These channels are responsible for the permeability of the membrane. Changes in the channels can change the permeability of the membrane.

There are two types of channels in the membrane. Some are open all the time and allow diffusion of the specific ions. These are called passive channels, and they are the ones that are discussed first. These proteins allow ions to diffuse from areas of high concentration to areas of lower concentration. (The other channels open and close based on the electrical potential of the membrane. These are called voltage-gated channels, and they will be discussed later.)

The channels help to maintain a difference in ion concentration between the inside and the outside of the cell. The inside of the cell has a negative charge relative to the outside, creating a potential difference across the membrane. This membrane potential is maintained by an enzyme, $Na^+/K^+ - ATPase$, also called the sodium/potassium pump. It works in the cell membrane to move three sodium ions outside of the cell and two potassium ions into the cell. This process, unlike

the diffusion through the ion channels, works against the concentration gradient and requires the cell to expend energy derived from ATP.

The major channels used in cardiac cells transport sodium (Na^+), potassium (K^+), and chloride (Cl^-) ions. The cell creates an electrical gradient across the cell membrane by transporting potassium ions into the cell and sodium ions out of the cell and then using the selective channels to maintain equilibria for these three ions.

In excitable cells, such as neurons and cardiac cells, these electrical differences are vital to creating the action potentials, which carry electrical pulses.

1 Ion Equilibrium

To understand the way the electrical gradient is maintained, imagine a cell that only has channels that allow potassium ions to move into and out of the cell. In a standard animal cell, there is a higher concentration of potassium inside the cell than outside the cell. This sets up an outwardly directed ion gradient where potassium ions will tend to diffuse out of the cell by using the protein channels. This gradient creates a chemical force that tends to push the potassium ions out of the cell.

But when the potassium ions leave the cell, negative ions remain inside and build a net negative charge inside the cell. This negative charge attracts the positively charged potassium ions, creating an electrical force that pulls them back towards the inside of the cell. At some point, the chemical outwardly directed force balances the electrical inwardly directed force. Although ions are still moving back and forth (this is an active equilibrium), at this equilibrium point there is no net movement across the membrane.

The Nernst equation describes when the forces reach equilibrium:

$$V_K = \frac{RT}{zF} \ln \frac{[K^+]_{out}}{[K^+]_{in}}$$

Where the variables are:

- R - the gas constant, $8.31J/Kmol$.
- T - the temperature in *Kelvin*. This can be found by adding the temperature in Celsius to $273.15K$.
- z - the valence of the ion. It is $+1$ for potassium and sodium. It is -1 for chloride.
- F - Faraday's constant, $96,500coulombs/mol$.
- $[K^+]_{out}$ - the concentration of potassium ions outside of the cell
- $[K^+]_{in}$ - the concentration of potassium ions inside of the cell.

A standard value of V_K in a typical neuron is $-70mV$. So if the potential difference over the cell membrane is less negative, the potassium ions are moved out of the cell by the chemical force until it reaches this equilibrium point. If, however, the potential difference is more negative, the potassium ions will be moved into the cell by the electrical force to reach equilibrium. Notice that as the difference between inside and outside concentrations get smaller (i.e., the ratio $\frac{[K^+]_{out}}{[K^+]_{in}}$ approaches one), the potential difference gets closer to zero. This makes sense because the chemical gradient also gets smaller.

It may appear that the ratio of the outside and inside potassium concentrations will change as this diffusion occurs across the cell membrane. But the changes in concentration are so small, they cannot be measured; therefore we assume that the concentrations do not change.

Although this example has used the potassium equilibrium, remember that the sodium and chloride ions also have their own equilibrium potential differences. Unlike potassium, there is a higher concentration of sodium outside of the cell than inside, so its equilibrium potential is positive (about $52.4mV$). Chloride, like sodium, has a higher concentration outside of the cell, but it is a negative ion, so its equilibrium potential is negative (about $-57.2mV$).

Supplementary Information

- An animation of diffusion facilitated by a transmembrane channel can be seen here: http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter2/animation__how_facilitated_diffusion_works.html
- This is a good place to view the applet about ion diffusion at <http://thevirtualheart.org/java/rick/diffuse.html>. Look at all four examples. The fourth example shows diffusion of a single ion through a membrane.
- A useful reading at this point is Ermentrout, R. B. (2010), *Mathematical Foundations of Neuroscience: The Hodgkin-Huxley Equations*, pp. 1-3. For a derivation of the Nernst equation, see pp. 3 - 5.
- Use HHSim to try the first set of exercises at <http://www-2.cs.cmu.edu/~dst/HHsim/exercises.html#part1>

2 Membrane Potential

While the previous section looked at the equilibrium potential of a single ion type, there are multiple ion types that can be moved through the cell membrane. For now we focus on the major three ions - potassium, sodium and chloride.

As there are different types of channels for each of the different ions, the permeability of the cell membrane for each ion is different. So there is a permeability for potassium, P_{K^+} , for sodium, P_{Na^+} , and for chloride, P_{Cl^-} . Also there are many more potassium channels and chloride channels than there are sodium channels. Since these passive channels are always open, the permeability is due to the number of channels in the membrane. How do the different types of channels combine to make the resting potential (i.e., the potential when the membrane has not been stimulated) of the cell membrane?

Given the values of these permeabilities and the Nernst equation, the resting potential of the membrane can be determined using the Goldman-Hodgkin-Katz voltage equation, more commonly known as the Goldman equation. Unlike the Nernst equation, this formula has a term for each available ion. (In fact, the Nernst equation can be thought of as a special case of the Goldman equation with only one available ion.)

$$V_r = \frac{RT}{F} \ln \frac{(P_{Na^+}[Na^+]_{Out} + P_{K^+}[K^+]_{Out} + P_{Cl^-}1[Cl^-]_{In})}{(P_{Na^+}[Na^+]_{In} + P_{K^+}[K^+]_{In} + P_{Cl^-}1[Cl^-]_{Out})}$$

(Notice that for the chloride ion, with its negative valence, the concentration inside the cell is over the concentration outside of the cell.)

In most cells, the resting permeability of potassium is greater than that of sodium and chloride. Therefore, the resting potential of the membrane will be close to the equilibrium potential of potassium. These permeabilities will change during excitation as will be shown in the following sections. Some typical values for a squid axon at 20°C are listed here (Ermentrout, p. 7):

Ion	Inside Concentration (mM)	Outside Concentration (mM)	Permeability(Ratio)
K^+	400	10	1
Na^+	50	460	0.03
Cl^-	40	540	0.1

You can use these values to find the resting potential of $-71mV$, which is close to the potassium's equilibrium potential of $-70mV$. If this membrane potential becomes more positive (i.e. closer to zero), the cell has been *depolarized*. If it becomes more negative, it is called *hyperpolarized*. These changes happen in excitable cells due to changes in permeability.

Supplementary Information

- Further reading about the generation of resting membrane potential can be found here: <http://instruct1.cit.cornell.edu/courses/bionb491/labresources/week4,%20Feb%209-11/Wright04.pdf>
- Another useful reading is Gilmore, R. F. *Electrophysiology of the Heart*, pp. 1-4

- A Nernst/Goldman equation simulator can be found here:
<http://www.nernstgoldman.physiology.arizona.edu/>

3 The Action Potential

Excitable cells, like neurons and cardiac cells, generate brief spikes in the membrane potential. The cell quickly becomes depolarized, then hyperpolarized and finally comes back to a resting state. These spikes are called action potentials and are generated by changes in the membrane permeabilities. These changes are controlled by the voltage-gated channels found in the cell membrane. The mechanism for these pulses were found by Hodgkin and Huxley when they studied the squid axon.

Remember that the resting potential (about $-70mV$) is close to the equilibrium potential of potassium because there are so many open passive potassium channels. The membrane can change that membrane potential by opening many sodium channels so that the membrane potential is close to that of sodium (about $+50mV$). To achieve this effect, the membrane has voltage-gated sodium channels.

These channels open when there is a depolarization (increase in membrane potential) near them. Once open, sodium ions can flow into the cell, causing further depolarization which opens more channels and lets in even more sodium ions. This process goes on until the membrane potential is close to the equilibrium potential of sodium. At that point, the sodium channels close and the membrane is no longer permeable to sodium.

There are also voltage-gated potassium channels which open when the membrane depolarizes. These open more slowly than the sodium channels. So as the sodium channels reach their peak, the potassium channels are opening and potassium begins to stream out of the cell. This movement of ions causes the membrane to hyperpolarize until it is close to the equilibrium potential of potassium. At this point, the voltage-gated channels are inactive and will not be able to open until the membrane is depolarized again. The passive channels (which, remember, are always open) then allow diffusion to bring the membrane back to resting potential. Also $Na^+/K^+ - ATPase$ will pump sodium out of the cell and potassium back into the cell.

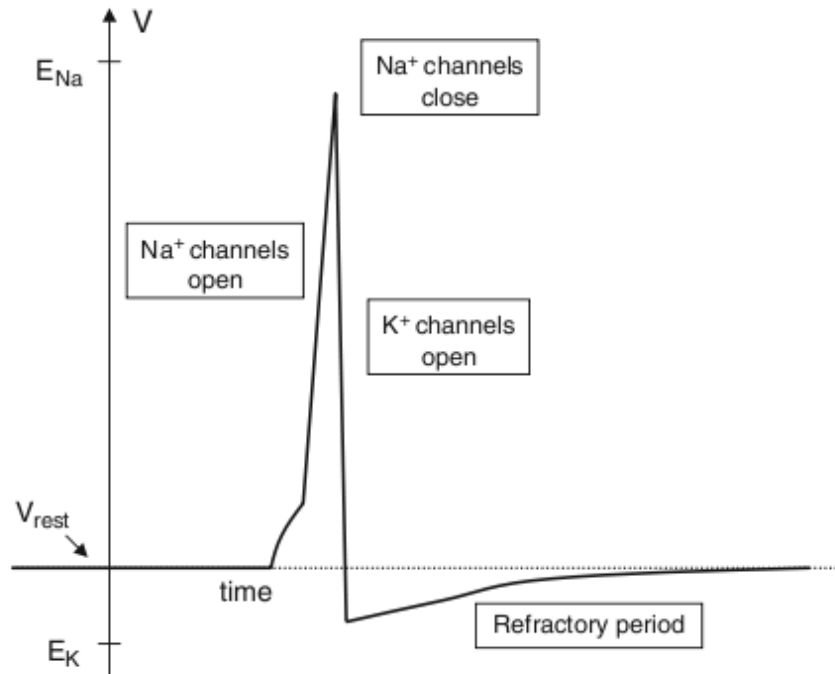


Fig. 1.7 The action potential. During the upstroke, Na^+ channels open and the membrane potential approaches the Na^+ Nernst potential. During the downstroke, Na^+ channels are closed, K^+ channels are open, and the membrane potential approaches the K^+ Nernst potential

(Ermentrout, p. 18)

Supplementary Information

- Additional reading about the basic action potential is in Ermentrout, G. B. and Terman, D. H.(2010) *Mathematical Foundations of Neuroscience: The Hodgkin-Huxley Equations*, section 1.7
- Wikipedia's description of Action Potentials is here: http://en.wikipedia.org/wiki/Action_potential
- A very useful animation can be found here: http://mcb.berkeley.edu/courses/mcb64/action_potential.html
- Another animation is here: <http://bcs.whfreeman.com/thelifewire/content/chp44/4402002.html>

4 Equivalent Circuits

The Goldman equation is useful for looking at the cell membrane when it is at rest. It is not, however, useful for studying how the membrane reacts to changes in

the membrane permeabilities. To look at these responses, there is another way of exploring the electrical properties of the cell membrane. That is to think of it as an electrical circuit. This is known as the equivalent circuit model. In this model, the channels are represented by resistors, the concentration gradients are represented by batteries and the charge stored in the membrane is represented as a capacitor.

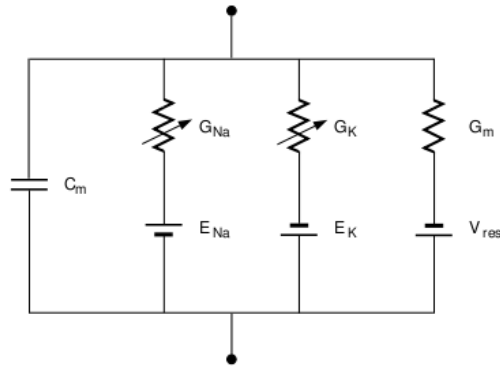


Figure 6.2: ELECTRICAL CIRCUIT FOR A PATCH OF SQUID AXON

Hodgkin and Huxley modeled the membrane of the squid axon using four parallel branches: two passive ones (the membrane capacitance C_m and the leak conductance $G_m = 1/R_m$) and two time- and voltage-dependent ones representing the sodium and the potassium channels.

(Koch, p. 140)

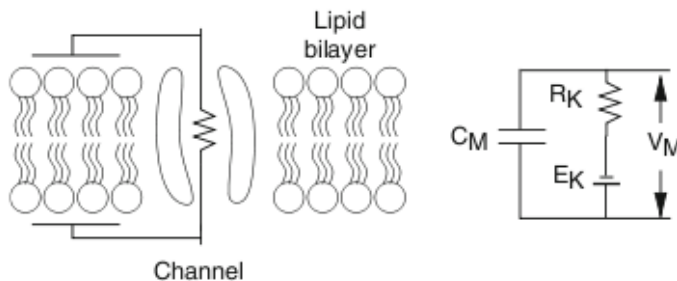


Fig. 1.2 The cell membrane showing the insulating lipid bilayer and a K^+ channel, which allows current to flow. The equivalent electrical circuit is shown on the right

(Ermentrout, p. 9)

In a capacitor, the total stored charge is the potential difference times the capacitance. In this case, the stored charge is the product of the membrane capacitance and the membrane potential:

$$q = C_M V_M$$

Since current is the flow of charge, we can find the current moving across the capacitor by differentiating this equation with respect to time, giving the formula:

$$\frac{dq}{dt} = C_M \frac{dV}{dt} = I_{Cap}$$

There are also currents moving across the membrane due to the movement of the different ions. For example, there is a current due to the movement of potassium ions. From Ohm's law, we know that current is the product of voltage and conductance, g (which is the reciprocal of resistance). Since E_{K^+} (the Nernst potential of potassium) is the potential from the "potassium battery," the force driving the current due to potassium ions is the difference between the membrane potential and that battery potential.

$$I_K = g_K(V_M - E_K)$$

There is a similar current due to the movement of sodium ions. As noted before, according to Hodgkin and Huxley's model, action potentials are driven primarily by the movement of sodium and potassium ions. There is, however, movement of other ions and the small current generated by these other ions is called the leakage current.

So the total membrane current can be represented by the total of these currents:

$$I_M = C_M \frac{dV}{dt} + I_K + I_{Na} + I_{Leak} = C_M \frac{dV}{dt} + g_K(V_M - E_K) + g_{Na}(V_M - E_{Na}) + g_L(V_M - E_L)$$

Supplementary Information

- Additional reading about this model can be found in Ermentrout, G. B. (2010) *Mathematical Foundations of Neuroscience*, Sections 1.4-1.5.
- Another source is the first section of Peterson, J. (2002) *The Basic Hodgkin-Huxley Model* found at <http://www.ces.clemson.edu/~petersj/BioEng/SimpleGates/SimpleGates002.html>

Table of Units

<i>Quantity</i>	<i>Unit</i>	<i>SI Derived Unit</i>
Capacitance (C)	Farad (F)	Coulombs/Volt (C/V)
Concentration	Molarity (M)	moles/Liter (mol/L)
Electrical Charge (q)	Coulomb (C)	second-Ampere ($s \cdot A$)
Electrical Conductance (g)	Siemens (S)	Amperes/Volts (A/V)
Electrical Current (I)	Ampere (A)	(Base Unit)
Potential Difference (E or V)	Volt (V)	Joule/sec·Ampere ($J/s \cdot A$)

Glossary

Action Potential	A voltage pulse which is generated in excitable membranes., 1
Capacitance	The ability of a body to hold electrical charge.of the capacitor., 7
Capacitor	An electronic component that can store and release electric charge., 6
Channels	Proteins found in the cell membrane that selectively allow particular ions to diffuse into and out of the cell., 1
Conductance	How easily electricity flows through a conductor. It is the reciprocal of resistance., 8
Diffusion	The movement of particles from areas of high concentration to areas of lower concentration, 1
Equilibrium Potential	The potential difference at which the force on an ion due to a concentration gradient is balanced by the electrical force on the ion due to a charge gradient., 3
Equivalent Circuit Model	A way of modeling the cell membrane as an electrical circuit., 6
Membrane Potential	The difference in voltage across the cell membrane., 1
Passive Channels	Membrane proteins that always allow specific ions to pass through the membrane. These channels are always open and ion movement through them is due to diffusion., 1
Permeability	The rate of flow of an ion through the cell membrane., 1
Resting Potential	The potential difference maintained by the cell membrane when the cell is at rest. It is caused by the difference in ion concentrations on the outside and inside of the cell., 3

Voltage-Gated Channels Membrane proteins that selectively open and close based on the value of the membrane potential., 1