Section 1

Computational Modeling of the Neuron's Electrical Activity

[*Note: Some of the material in this chapter does not apply directly in computational models of neurons, but the knowledge is useful for informing the decisions about what needs to be modelled and the way in which it is modelled.*]

1.1 Neuron Anatomy

The neuron is the basic cell in our body and the building block of the nervous system in vertebrates and most invertebrates from the level of the cnidarians (e.g., corals, jellyfish) upward. A typical neuron (Figure 1.1) consists of

1) **a soma**, its cell body containing a nucleus in which the DNA is located;
2) **the dendrites**, two or more long fibres that carry electric impulses to the cell body; and
3) **an axon**, typically a single fiber that carries the electric impulse away from the cell body.

***Tip**: You can think of a neuron as an electric signal converter: It converts signals that receives as input into a single output.*

Bundles of fibres from neurons are held together by connective tissue and form nerves. If the fibres are axons, they appear white under a microscope or in a CT scan, and therefore we call them white matter. If the fibres consist of dendrites they are called grey matter, for the same reason as before. Some nerves in large vertebrates are several feet long.

A sensory neuron transmits impulses from a receptor, such as those in our palms, tongue or eyes, to a more central location in the nervous system, such as the spinal cord or brain. On the other hand, a motor neuron transmits impulses from a central area of the nervous system to an effector, such as a muscle.

***Question:** How many bits of information can a single neuron send to other neurons, at any given time?* Each neuron may be connected to up to 10,000 other neurons, passing signals to each other via as many as 1,000 trillion synaptic connections, equivalent by some estimates to a computer with a 1-trillion bit per second processor.

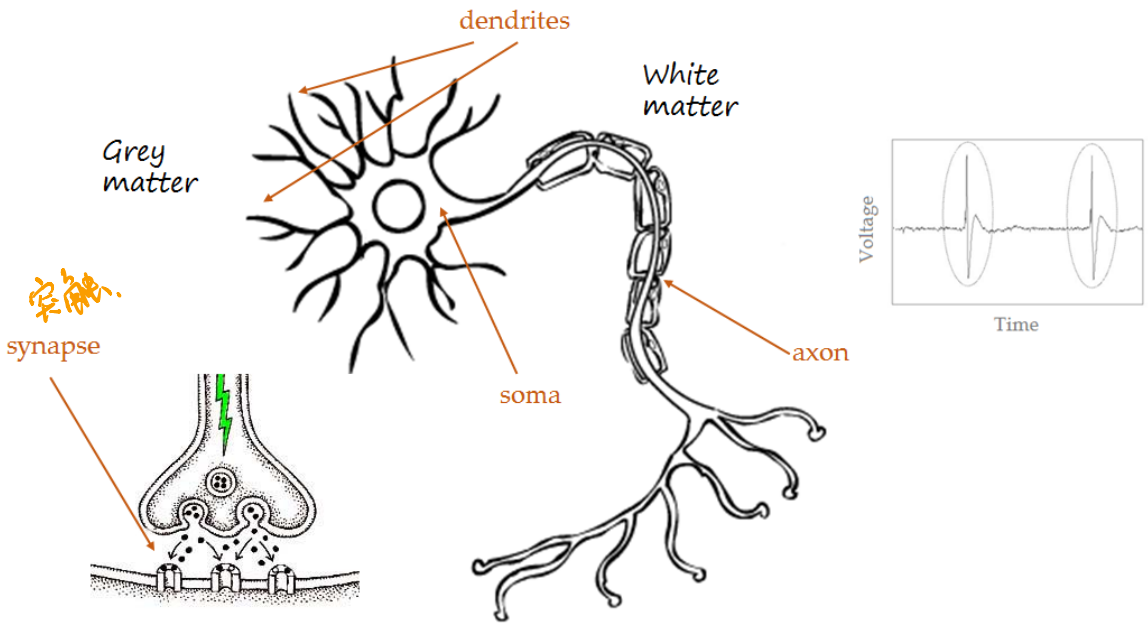

Figure 1.1 A sketch of a typical neuron. Inset: A typical action potential, which is a widespread feature of electric signaling in the nervous system. Action potentials propagate along the membrane, eventually reaching the axonal terminal (synapse).

1.2 Elements of Neuron Electrophysiology

The great majority of the computational models of brain activity lies at the level of the electrical properties of the neurons. That is why we will examine briefly the electrical properties of the neurons and how these can be modeled.

The neurons, as well as all the other cells in our body are bathed in a fluid, called **extracellular fluid**. The extracellular fluid provides a stable environment for cellular operation. It comprises of water, as well as inorganic ions: the main cations are Sodium (Na^+ = 136–145 mEq/L) Potassium (K^+ = 3.5–5.5 mEq/L) and Calcium (Ca^{2+} = 2.2–2.6 mEq/L); the main anions are Chloride (Cl^- = 99–109 mEq/L) Hydrogen Carbonate (HCO_3^- 22–26 mM).

Tip**: Observe closely the numbers of ion concentration: What is the primary cation? How does its concentration compare to the primary anion?* ***What is the consequence of that comparison?

In addition to the extracellular fluid, there is a fluid inside the cells, called **intracellular fluid**. Most of the intracellular fluid is water as well, but there are also ions floating around, just like in the extracellular fluid. The ion concentrations, though, are quite

different from those in extracellular fluid (the intracellular fluid is also different from the extracellular fluid in many other aspects, such as the amount of proteins and nucleic acids but let's stick to the basics for now).

This difference in the ion concentrations between the space inside the cells (neurons) and the space outside the cells creates an electrical potential difference across the cell membrane, called the **membrane potential**. The resting membrane potential, V_m, is typically around -65mV; this means that the potential inside the cell is more negative (more anions and less cations) than the outside.

Ions can penetrate the membrane of the cell (neuron) but they can only do this through specialized openings that are called **ion channels**. In other words, ion channels are pores in the membrane which allow certain ions to flow in or out of the membrane (Figure 1.2). In general, we could assume that there is a specific ion channel that allows the entrance (or exit) for a single ion (please note that channels allow multiple ions to pass through them and they are typically labeled by the ion which they are most permeable but let's keep it simple). To allow the ions to pass through it, the channel needs to be in an **open state**. A channel might be, at any given time to either an open or a closed state, in which ions cannot permeate through the channel. These channels, either in open or closed state, are called **active channels**, in contrast to the **passive channels** that do not change their permeability.

***Important**: Everything that you will hear about electric potential in the brain and neural (electric) activity is due to this movement of ions through ion channels in the cell membrane.*

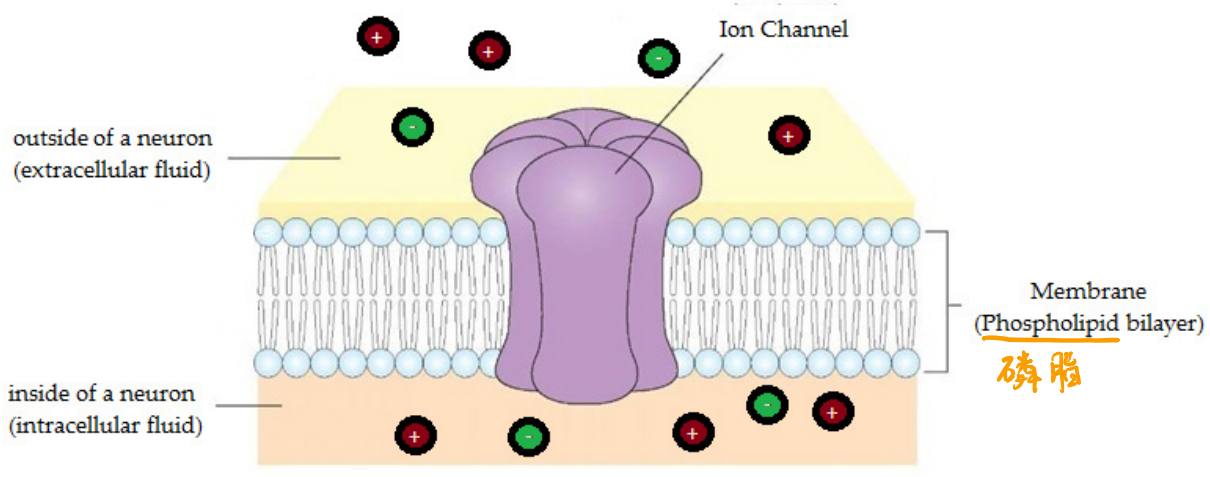

Figure 1.2 Schematic representation of the neuronal membrane

1.2.1 Ions' crossing a Neuronal Membrane is described by Fick's first law of Diffusion

Fick's law of diffusion was derived by Adolf Fick in 1855. It postulates that (1) the flux, J, goes from a region of high concentration to regions of low concentration, and (2) larger concentration gradients result to larger fluxes. In a single dimension, the law is:

$$J = -D\frac{\partial \varphi}{\partial x}$$

where D is the diffusion coefficient, φ is the concentration and x is the single dimension (position).

***Tip**: If you still have trouble getting the insight of Fick's law, try to answer the following questions: Why do we use a plastic stirrer after adding some sugar on our coffee? Does stirring our coffee result to sips of varying sweetness? Why not? Remember: Diffusion arises from the random movement of particles (e.g., ions) a phenomenon known as Brownian motion. This was actually shown by Einstein (1905).*

Under the reasonable assumption that channels are barely wider than the diffusing ions, we can safely regard them as having a single dimension. Let us define the concentration of an ion, X, as [X]. When [X] is different across the sides of the membrane, Fick's law can describe the movement of the ions through a single channel:

$$J_X = -D_X\frac{\partial [X]}{\partial x}$$

where the variables are defined as previously, with the subscript X denoting that the variables refer to the ion X.

As ions are electrically charged (otherwise, we would not call them ions, right?), the difference

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Tip: *By convention, the membrane potential is measured as the potential inside the cell minus the potential outside the cell. The convention for current flowing through the membrane is that it is defined to be positive when there is a flow of positive charge out of the cell, and to be negative when there is a net flow of positive charge into the cell.*

1.3 The Hodgkin – Huxley model of a neural firing

The Hodgkin-Huxley equation is the first and perhaps the greatest success in neurobiological modeling. It consists of a set of differential equations that describe neuronal "firing" and have established a new framework for thinking about the electrical activity of neurons. Since its introduction in 1952, it has been used consistently in the great majority of the models of nerve excitation. Despite the age of the HH model, we will devote some time to it as the methodological approach is still fresh. This work earned Alan Lloyd Hodgkin and Andrew Huxley the 1963 Nobel Prize in Physiology or Medicine. We will see how they used their physical intuition and curve fitting to derive a very useful model of how a neuron outputs an electric impulse, also called a neural spike.

1.3.1 Action Potential

The action potential is the main form of communication within the brain, as well as between the central nervous system and other parts of the body (e.g., muscles). It is a sharp transient rise –a "spike"– in the electrical potential on the membrane of an axon (see Figure 1.1, inset and Figure 1.3). Generally, a neuron stays at a state of rest, unless it receives an excitatory input by an external stimulus (other neurons). If the stimulus exceeds a specific threshold, the neuron's membrane potential quickly rises and then falls back, relaxing to its resting value.

Between the 1930s and the early 1950s, Hodgkin and Huxley demonstrated 3 key facts:

1. An action potential arises from the membrane's changing its conductance (or else, permeability) to particular ions, primarily sodium (Na+) and potassium (K+).

2. Changes in membrane conductance are themselves dependent on the membrane's potential, so that the process involves an element of (positive) feedback.

3. The sodium (Na+) and potassium (K+) currents can be manipulated separately, suggesting that the corresponding conductances are independent.

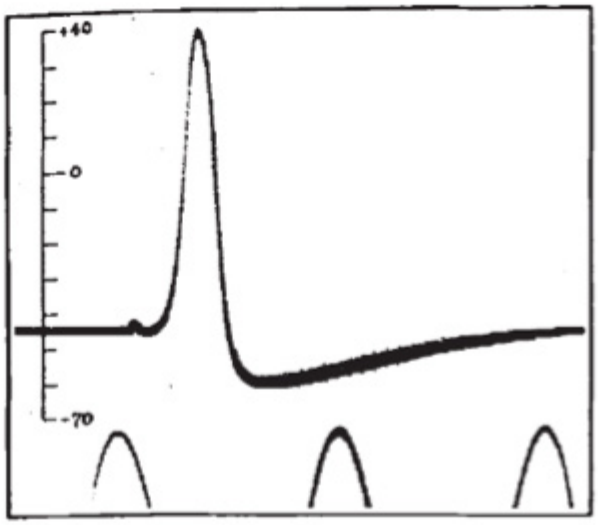


Fig. 2.

ACTION POTENTIAL RECORDED BETWEEN INSIDE AND OUTSIDE OF AXON. TIME MARKER, 500 CYCLES/SEC. THE VERTICAL SCALE INDICATES THE POTENTIAL OF THE INTERNAL ELECTRODE IN MILLIVOLTS, THE SEA WATER OUTSIDE BEING TAKEN AT ZERO POTENTIAL.

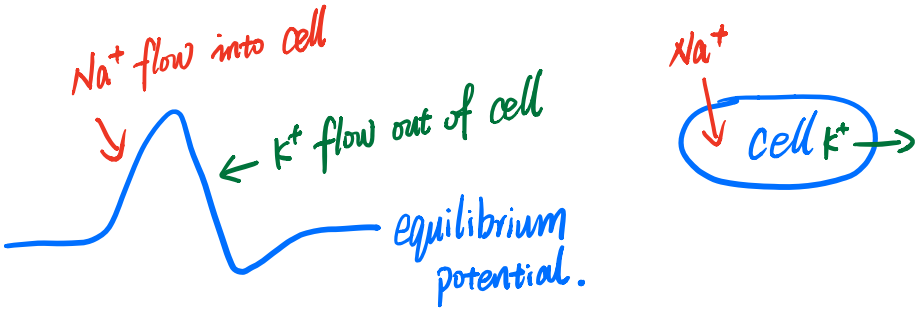
Figure 1.3 The first intracellular recording of an action potential (published in Nature in October of 1939; the paper is barely a page in length and its results went against the current school of thought according to which the action potential was the result of a transient membrane breakdown – therefore the membrane potential was –wrongly- expected to approach zero).

1.3.2 The qualitative explanation of the HH model

As we have discussed before, the resting membrane potential (i.e., when a neuron does not fire or receive inputs), V_m, is non-zero. Each ion species, given its intracellular and extracellular concentration and its intrinsic charge, has a so-called reversal or **equilibrium potential**: a value of such that, if the membrane's potential is equal to it, no net movement of that ion will occur. The difference between an ion's reversal potential and membrane potential generates a driving force, i.e. a tendency of ions to flow in or out of the cell. **In a normal cell at rest, the driving forces are such that sodium will tend to move inwards whereas potassium will tend to flow outwards**. However, at rest the membrane is largely impermeable to ions and so the driving forces do not have an effect on the resting membrane potential.

As we discussed in Section 1.2, there are specific channels within the membrane that conduct either sodium or potassium. When V_m exceeds threshold, these channels kick into

action: **First sodium channels open, raising the membrane's sodium conductance. Sodium flows inwards, in accordance with its driving force, causing V_m to go up**. **Next, potassium channels open, potassium ions flow out, and V_m drops back down**. In this way a spike is generated, with the rising phase caused by sodium influx and the falling phase by potassium efflux.



Section 2

Computational Modeling of the Neuron's Electrical Activity

2.1 Last lectures summary

Up to now, we have learned that

- The neuron is the basic cell that processes or sends information to/from the central nervous system from/to the periphery
- The neuron typically consists of a soma, the dendrites (input gateways) and one axon (output gateway) and communicates by sending spikes (1-bit information)
- The neurons are bathed in the extracellular fluid, which contains ions (cations such as Na^+ and K^+ and anions such as $Cl-$)
- The neuron manipulates the concentration of the ions inside its body, to send/receive information
- The concentrations of the ions between the two sides of the neuron's membrane are different
- This difference in ion concentrations creates the membrane potential, which is about -65 mV (i.e., there are more "negative" ions inside the neuron than outside)
- Ions can penetrate the neuron's membrane through ion channels, which are specialized openings in the membrane that allow certain ions to pass through them
- The movement of ions creates the variation in the membrane potential: a larger concentration difference creates a larger flux of ions (Fick's law of Diffusion) and a larger current travelling in/out of the neuron
- The Hodgkin-Huxley model of neuron (Hodgkin & Huxley, 1952) simulates how a neuron generates an action potential, which is a sharp change in the membrane potential that initiates in the soma and propagates all the way down the neuron's axon, until this potential difference reaches the synapse (the junction between two neurons that communicate)
- Qualitatively, the Hodgkin - Huxley model simulates the opening/closing of three main ion channels (Na^+, K^+, $Cl-$) during the generation of an action potential

***Note**: Before you move forward, please revise the glossary on the next page and make sure that you fully understand all terms listed – to understand means (1) "to know" and (2) "to feel."*

Term	Description
Action Potential	A voltage pulse which is generated in excitable membranes
Capacitance	The ability of an element to hold electrical charge
Conductance	How easily electricity flows through a conductor; It is the reciprocal of resistance
Diffusion	The movement of particles from areas of high concentration to areas of lower concentration
Channels	Proteins found in the cell membrane that selectively allow particular ions to diffuse into and out of the cell
Permeability	The rate of flow of an ion through the cell membrane
Membrane Potential	The difference in voltage across the cell membrane.,
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
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
Voltage-Gated Channels	Membrane proteins that selectively open and close based on the value of the membrane potential

2.1 Modeling the Membrane Potential: The Nerst and the Goldman Equations

Due to their relative concentrations inside and outside the cell (see Figure 2.1), sodium and chloride ions naturally try to move into the neuron and potassium naturally tries to move out of the neuron, based on the diffusion process.

passive channel

How is this gradient maintained? In other words, why there is no depletion of ions that flow into or out of the cell?

passive channel and Resting Potential.

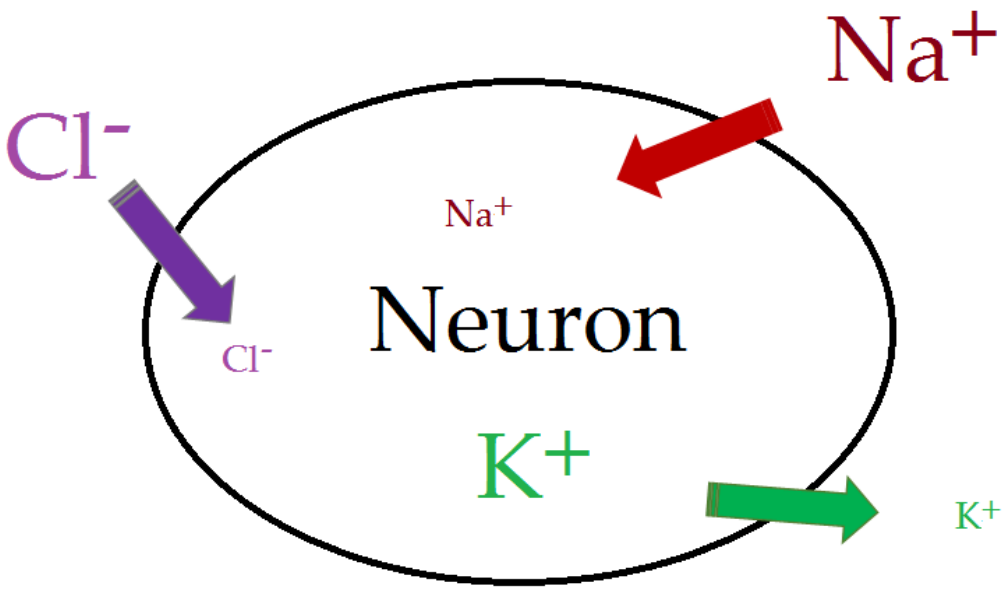


Figure 2.1 The relative concentration of the most important ions inside and outside the neuron; colored arrows depict the concentration gradient for each ion.

Let's assume that a neuron has channels that allow only one type of ions, e.g., potassium ions, to pass through them. Since the concentration of potassium ions is much higher inside the neuron than outside the neuron, there is an outwardly directed ion gradient that makes the potassium ions to diffuse out of the cell. But when the positively charged potassium ions leave the neuron, the internal of that neuron becomes more negatively charged. It is this negative charge that attracts the positively charged potassium ions from the extracellular fluid. In other words, there are two forces applied to the same ions, one is the chemical outwardly directed force (due to concentration gradient) and the other is the electrical inwardly directed force (due to a "charge gradient"). Although this movement of ions never ends, at some point, the membrane reaches an equilibrium potential difference when there is no net movement across the membrane. This potential difference, E, which is specific for each ion, X, is described by another famous equation, called the **Nerst** equation:

$$E_X = \frac{RT}{z_X F} ln \frac{[X]outside}{[X]inside}$$

Where R is the gas constant (8.31J/Kmol); T is the temperature in Kelvin; z is the valence of the ion (+1 for potassium and sodium, −1 for chloride); F is Faraday's constant, (96,500coulombs/mol) and $[X]outside/[X]inside$ is the concentration of ions outside of/inside the cell, respectively.

Question: *What is the physiological meaning of the ln function? It might help to sketch the ln function and think of it as a mapping function.*

Going back to our example with the potassium ions, if the potential difference over the neuron membrane is less negative, then the potassium ions are moved out of the cell by the chemical force until the neural cell reaches the 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 $\frac{[X]outside}{[X]inside}$ approaches one), E_X gets closer to zero. This makes sense because the chemical gradient also gets smaller.

Question: *The Nerst equation models the equilibrium potential to increase with the increase of the temperature, T. Why? What is the direct effect of increasing the temperature of a cell?*

increasing in speed of ion movement.

Up to now, we have looked at the equilibrium potential of the potassium ion, although we know that there are at least two more main ion types that pass through the cell membrane. We can determine the resting potential of the membrane using the Goldman equation, which has a term for each of the main ions. (In fact, the Nernst equation can be thought of as a special case of the Goldman equation with only one available ion.)

$$V = \frac{RT}{F} ln\left(\frac{P_{Na}^{+}[Na^{+}]outside + P_{Na}^{+}[K^{+}]outside + P_{Cl}^{-}[Cl^{-}]inside}{P_{Na}^{+}[Na^{+}]inside + P_{K}^{+}[K^{+}]inside + P_{Cl}^{-}[Cl^{-}]outside}\right)$$

where P refers to the permeability of each ion. The relative permeability ratios for the main ions are $P_K^+/P_{Na}^+/P_{Cl}^- = 1/0.03/0.1$ (these values are for the squid axon at 20°C).

Important: *The neurons are able to communicate by manipulating their ion permeability.*

channels.

Note: *You can build your intuition on the Nerst/Goldman equations with the Nerst/Goldman equation simulator that is available here: http://www.nernstgoldman.physiology.arizona.edu/ What is happening to the equilibrium voltage when you increase the temperature or when you inverse the ratio? Try different values for the potassium concentrations on the Nerst equation simulator.*

Question: Could we ever be able to build a model with just passive elements? What is a typical curve we expect to get out of a passive element? What is the reason for the presence of the active elements? Are these elements linear or nonlinear?

2.3 The Equivalent Circuit Model: A Passive Neuron

As we have said before, the neuron's membrane is a very good electrical insulator and will not allow the ions to pass through. This gives to the membrane capacitive properties, which essentially can be summarized by the following equation:

$$Q = C \cdot V$$

where V is the voltage difference between the intra- and the extra- cellular areas, Q is the differential distribution of electrical charges across the membrane and C is the **membrane capacitance** (a constant, because it is an intrinsic property of the membrane). Changes in the membrane potential are made through ion channels, which allow for ionic currents to pass through them. However, this passage of ions is not instantaneous and we can model the ion channels as simple **resistors**. In addition, the concentration gradient for each of the ions results to a voltage difference that can be modeled as a **battery** that sets the resting membrane potential for that ion. Modeling a membrane as an electrical circuit is shown in Figure 2.2.

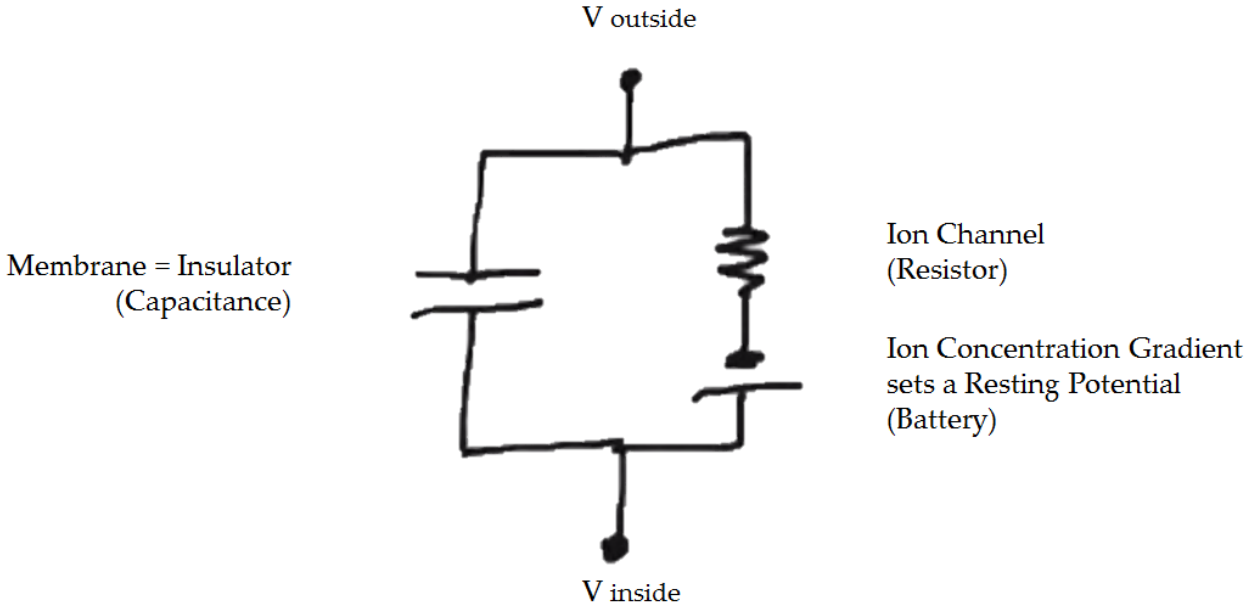


Figure 2.2 Modeling the main properties of a membrane function using equivalent electrical circuit components.

***Aim**: We will now build our insight on how we could use this basic model to study the dynamics of a neuron's function*

Taking all these into account, Hodgkin and Huxley presented in 1952 an equivalent circuit for the axon's membrane (Figure 2.3) that can represent the membrane potential of an excitable neuron.

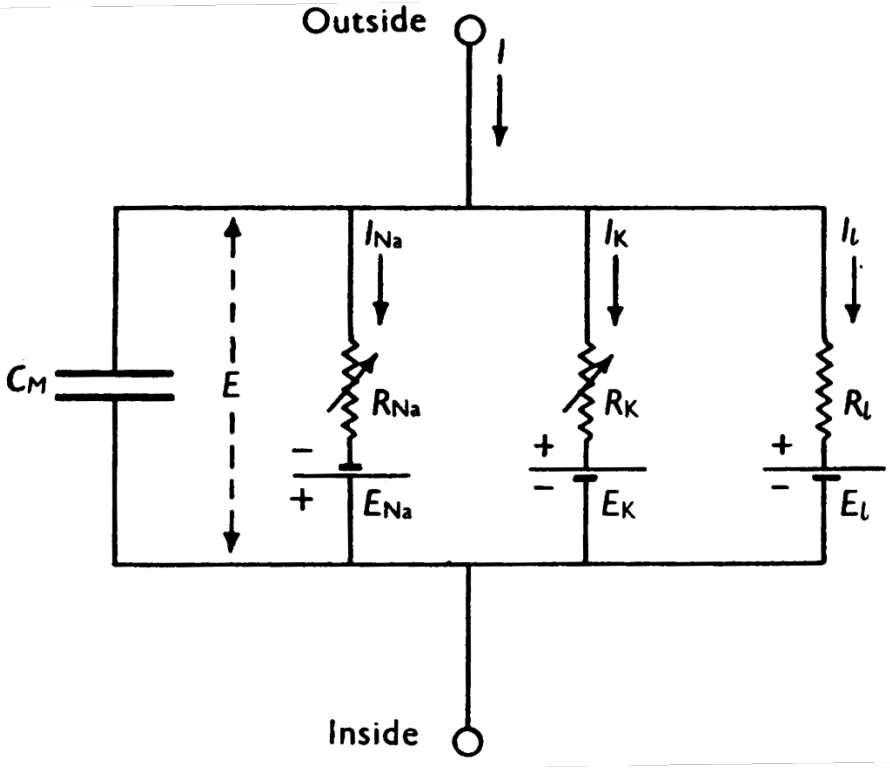


Figure 2.3 Equivalent circuit for a small area of an axon's membrane. (Source: Hodgkin and Huxley, [1952])

Additional Reading

Ermentrout, G. B. (2010) Mathematical Foundations of Neuroscience, Sections 1.1 – 1.7.

Section 3

Computational Modeling of the Neuron's Electrical Activity

3.1 Hodgkin – Huxley Channel Models

Hodgkin and Huxley have introduced **voltage-dependence** into their models of active conductance for ion channels (Figure 5.1). This voltage-dependence is very important and essential to have on this model; a passive membrane by itself, as we have seen in Lecture 3, is only going to approach exponentially some steady state. These voltage-dependent nonlinearities are needed for the system to generate an action potential (spike).

Let's assume that we look only at the sodium ionic current. Hodgkin and Huxley have modeled this ionic current, I, as:

$$I_{Na} = g_{Na}(V - E_{Na})$$

where g_{Na} is the conductance of the sodium channels (the reciprocal of the resistance), and $V - E_{Na}$) is the driving force, the difference between the membrane potential, V, and the equilibrium potential for sodium, E_{Na}, and corresponds to the drop in voltage across the "resistor".

Now, we want to introduce the voltage dependence. E_{Na} is a constant, because it is determined by the balance of the sodium ions between the inside and the outside of the cell membrane; this balance is well maintained by the sodium-potassium ion pumps. Therefore, E_{Na} cannot have any dynamics. The voltage-dependent component of the current I_{Na} comes from g_{Na} by opening more channels and therefore allowing more sodium ions to pass through the membrane. Since an ion channel cannot open or close instantaneously, g_{Na} is a function of both time and voltage.

Hodgkin and Huxley introduced the idea of modeling the ion conductance, say the sodium conductance, with the following equation:

$$g_{Na} = \overline{g_{Na}} m(v,t) h(v,t)$$

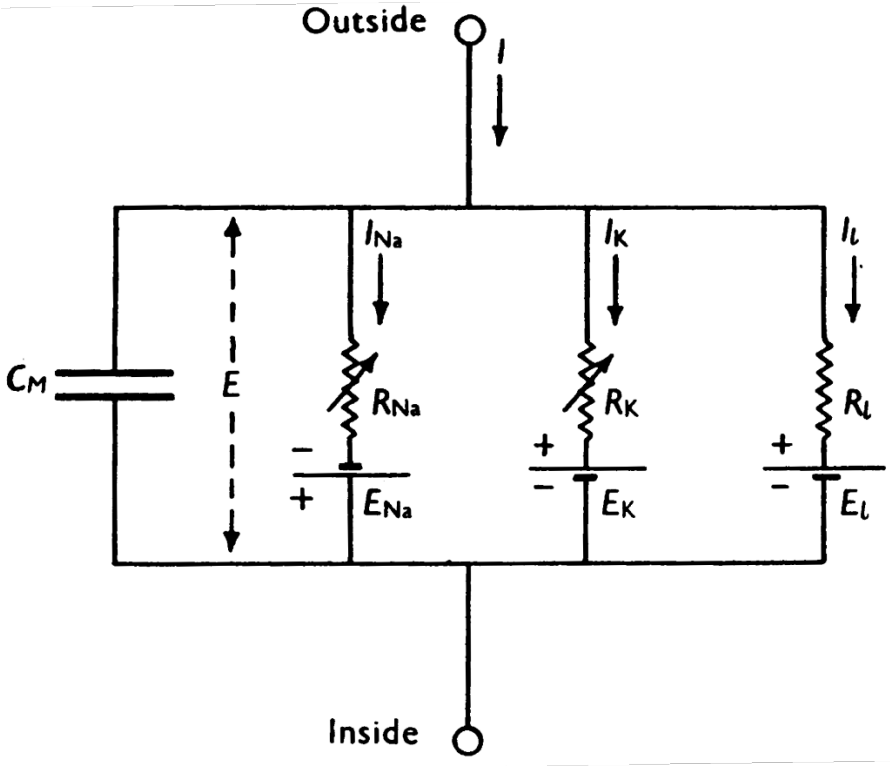


Figure 3.1 Equivalent circuit for a small area of an axon's membrane. (Source: Hodgkin and Huxley, [1952])

where $\overline{g_{Na}}$ is called the maximum conductance and relates to the total number of sodium channels within the cell and is equal to the number of channels times the amount of conductance of a single channel; $m(v,t)$ and $h(v,t)$ are called the **gating variables**, where m is the proportion of ion channels in which the activation gate is open and h is the proportion of ion channels in which the inactivation gate is open. Sodium ion channels are the most complicated (for our case) channels as they have both activation and inactivation gates; the other two channels (potassium and chloride channels) are much simpler as they only have activation channels.

Question: *What was the major assumption that Hodgkin and Huxley made with respect to the independence of the activated and the inactivated ion gates? Please recall, we are multiplying* $m(v,t)$ *and* $h(v,t)$.

The next question is how we can model the gating variables, m and h. Hodgkin and Huxley modeled these variables as state variables that can be in two different states, the activated and inactivated state. We have seen the first-order kinetics of switching between the two states in Lecture 3, reproduced here for your convenience:

$$1 - m \;\frac{\vec{\alpha}}{\vec{\beta}}\; m$$

$$1 - h \;\frac{\vec{\alpha}}{\vec{\beta}}\; h$$

The gating variables are voltage-dependent; we have examined their dynamics:

$$\tau_m \frac{dm}{dt} = m_{ss} - m$$

$$\tau_h \frac{dh}{dt} = h_{ss} - h$$

where $\tau_{m,h} = \frac{1}{a+\beta}$ are the time constants and $m, h_{ss} = \frac{\alpha}{a+\beta}$ are the steady states of that system; α and β are the rates that determine the switching between the active and the inactive state. Please note that the α and β for the two systems are different.

3.2 The Hodgkin – Huxley Squid Axon Model

Now that we have described the most important aspects of the Hodgkin-Huxley model, we can introduce the entire set of the equations for it. Please note that the experimental and simulation work was conducted on the squid axon's action potential:

$$C\frac{du}{dt} = 1 - g_{Na}m^3h(V - V_{Na}) - g_K n^4(V - V_K) - g_L(V - V_L)$$
$$\frac{dm}{dt} = a_m(V)(1 - m) - b_m(V)m$$
$$\frac{dh}{dt} = a_h(V)(1 - m) - b_h(V)h$$
$$\frac{dn}{dt} = a_n(V)(1 - n) - b_n(V)n$$

where the equations for the rate variables

$$a_m(V) = \frac{0.1(V + 40)}{1 - \exp\left(-\frac{V + 40}{10}\right)}$$
$$b_m(V) = 4\exp\left(\frac{-V + 65}{18}\right)$$
$$a_h(V) = 0.07\exp(-\frac{V + 65}{20})$$

$$b_h(V) = 1/(1 + \frac{\exp(-(V+35))}{10})$$
$$a_n(V) = 0.01(V+55)/(1 - \exp\left(-\frac{V+55}{10}\right))$$
$$b_n(V) = 0.125\exp(-\frac{V+65}{80})$$

are empirically found (H-H used experimental data from the giant squid that best fit the model equations).