Introduction to Neurons

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Summary. All living animals obtain information from their environment through sensory receptors, and this information is transformed to their brain where it is processed into perceptions and commands. All these tasks are performed by a system of nerve cells, or neurons. Neurons have four morphologically defined regions: the cell body, dendrites, axon, and presynaptic terminals. A bipolar *neuron* receives signals from the dendritic system; these signals are integrated at a specific location in the cell body and then sent out by means of the axon to the presynaptic terminals. There are neurons which have more than one set of dendritic systems, or more than one axon, thus enabling them to perform simultaneously multiple tasks; they are called *multipolar neurons*.

This chapter is not meant to be a text book introduction to the general theory of neuroscience; it is rather a brief introduction to neurons tailored to the subsequent chapters, which deal with various mathematical models of neuronal activities. We shall describe the structure of a generic bipolar neuron and introduce standard mathematical models of signal transduction performed by neurons. Since neurons are cells, we shall begin with a brief introduction to cells.

1 The Structure of Cells

Cells are the basic units of life. A cell consists of a concentrated aqueous solution of chemicals and is capable of replicating itself by growing and dividing. The simplest form of life is a single cell, such as a yeast, an amoeba, or a bacterium. Cells that have a nucleus are called *eukaryotes*, and cells that do not have a nucleus are called *prokaryotes*. Bacteria are prokaryotes, while yeasts and amoebas are eukaryotes. Animals are multi-cellular creatures with eukaryotic cells. A typical size of a cell is 5–20μm (1μm = 1 micrometer = 10^{-6} meter) in diameter, but an oocyte may be as large as 1mm in diameter. The human body is estimated to have 1014 cells. Cells may be very diverse as they perform different tasks within the body. However, all eukaryotic cells have the same basic structure composed of a nucleus, a variety of organelles

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and molecules, and a *plasma membrane*, as indicated in Figure 1 (an exception are the red blood cells, which have no nucleus).

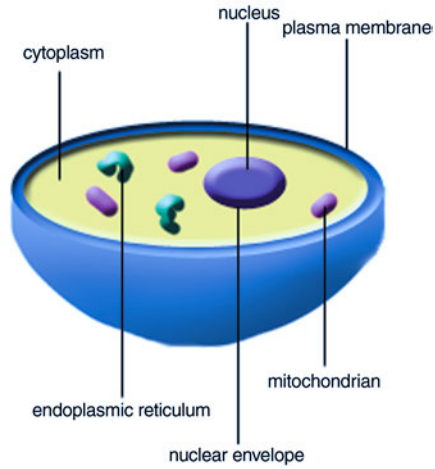


Fig. 1. A cell with nucleus and some organelles.

The DNA, the genetic code of the cell, consists of two strands of polymer chains having a double helix configuration, with repeated nucleotide units A, C, G, and T. Each A on one strand is bonded to T on the other strand by a hydrogen bond, and similarly each C is hydrogen bonded to T. The DNA is packed in chromosomes in the nucleus. In humans, the number of chromosomes in a cell is 46, except in the sperm and egg cells where their number is 23. The total number of DNA base pairs in human cells is 3 billions. The nucleus is enclosed by the nuclear envelope, formed by two concentric membranes. The nuclear envelope is perforated by *nuclear pores*, which allow some molecules to cross from one side to another.

The cell's plasma membrane consists of a lipid bilayer with proteins embedded in them, as shown in Figure 2. The *cytoplasm* is the portion of the cell which lies outside the nucleus and inside the cell's membrane.

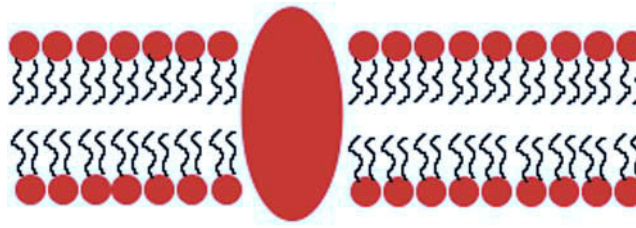


Fig. 2. A section of the cell's membrane.

An *organelle* is a discrete structure in the cytoplasm specialized to carry out a particular function. A *mitochondrion* is a membrane-delineated organelle that uses oxygen to produce energy, which the cell requires to perform its various tasks. An *endoplasmic reticulum* (ER) is another membrane-bounded organelle where lipids are secreted and membrane-bound proteins are made. The cytoplasm contains a number of mitochondria and ER organelles, as well as other organelles, such as *lysosomes* in which intra-cellular digestion occurs. Other structures made up of proteins can be found in the cell, such as a variety of filaments, some of which serve to strengthen the cell mechanically. The cell also contains amino acid molecules, the building blocks of proteins, and many other molecules.

The *cytoskeleton* is an intricate network of protein filaments that extends throughout the cytoplasm of the cell. It includes families of *intermediate filaments*, *microtubules*, and *actin filaments*. Intermediate filaments are rope-like fibers with a diameter of 10nm and strong tensile strength (1nm=1 nanometer=10^{-9} meter). Microtubules are long, rigid, hollow cylinders of outer diameter 25nm. Actin filaments, with diameter 7nm, are organized into a variety of linear bundles; they are essential for all cell movement such as crawling, engulfing of large particles, or dividing. Microtubules are used as a "railroad tract" in transport of vesicles across the cytoplasm by means of motor proteins (see next paragraph). The motor protein has one end attached to the vescicle and the other end, which consists of two "heads", attached to the microtubule. Given input of energy, the protein's heads change configuration (conformation), thereby executing one step with each unit of energy.

Proteins are polymers of amino acids units joined together head-to-tail in a long chain, typically of several hundred amino acids. The linkage is by a covalent bond, and is called a *peptide bond*. A chain of amino acids is known as a *polypeptide*. Each protein assumes a 3-dimensional configuration, which is called a *conformation*. There are altogether 20 different amino acids from which all proteins are made. Proteins perform specific tasks by changing their conformation.

The various tasks the cell needs to perform are executed by proteins. Proteins are continuously created and degraded in the cell. The synthesis of proteins is an intricate process. The DNA contains the genetic code of the cell. Each group of three letters (or three base pairs) may be viewed as one "word". Some collections of words on the DNA represent *genes*. The cell expresses some of these genes into proteins. This translation process is carried out by several types of RNAs: *messenger* RNA (mRNA), *transfer* RNA (tRNA), and *ribosomal* RNA (rRNA). Ribosome is a large complex molecule made of more than 50 different ribosomal proteins, and it is there where proteins are synthesized. When a new protein needs to be made, a signal is sent to the DNA (by a *promoter* protein) to begin transcribing a segment of a strand containing an appropriate gene; this copy of the DNA strand is the mRNA. The mRNA molecule travels from the nucleus to a ribosome, where each "word" of three letters, for example (A, C, T), called a *codon*, is going to be translated into

one amino acid. The translation is accomplished by tRNA, which is a relatively compact molecule. The tRNA has a shape that is particularly suited to conform to the codon at one end and is attached to an amino acid corresponding to the particular codon at its other end. Step-by-step, or one-by-one, the tRNAs line up along the ribosome, one codon at a time, and at each step a new amino acid is brought in to the ribosome where it connects to the preceding amino acid, thus joining the growing chain of amino acids until the entire protein is synthesized.

The human genome has approximately 30,000 genes. The number of different proteins is even larger; however cells do not generally express all their genes.

The cell's membrane is typically 6–8nm thick and as we said before, it is made of a double layer of lipids with proteins embedded throughout. The lipid bilayer is hydrophobic and selectively permeable. Small nonpolar molecules such as O_2 and CO_2 readily dissolve in the lipid bilayer and rapidly diffuse across it. Small uncharged polar molecules such as water and ethanol also diffuse rapidly across the bilayer. However, larger molecules or any ions or charged molecules cannot diffuse across the lipid bilayer. These can only be selectively transported across the membrane by proteins, which are embedded in the membrane. There are two classes of such proteins: *carrier proteins* and *channel proteins*. Carrier proteins bind to a solute on one side of the membrane and then deliver it to the other side by means of a change in their conformation. Carrier proteins enable the passage of nutrients and amino acids into the cell, and the release of waste products, into the extracellular environment. Channel proteins form tiny hydrophilic pores in the membrane through which the solute can pass by diffusion. Most of the channel proteins let through only inorganic ions, and these are called *ion channels*.

Both the intracellular and extracellular environments include ionized aqueous solution of dissolved salts, primarily $NaCl$ and KCl, which in their disassociated state are Na^+, K^+, and Cl^- ions. The concentration of these ions, as well as other ions such as $Ca2^+$, inside the cell differs from their concentration outside the cell. The concentration of Na^+ and $Ca2^+$ inside the cell is smaller than their concentration outside the cell, while K^+ has a larger concentration inside the cell than outside it. Molecules move from high concentration to low concentration ("downhill" movement). A pathway that is open to this movement is called a *passive* channel or a *leak* channel; it does not require expenditure of energy. An *active transport* channel is one that transports a solute from low concentration to high concentration ("uphill" movement); such a channel requires expenditure of energy.

An example of an active transport is the sodium-potassium pump, pumping $3Na^+$ out and $2K^+$ in. The corresponding chemical reaction is described by the equation

$$ATP + 3Na_i^+ + 2K_e^+ \rightarrow ADP + P_i + 3Na_e^+ + 2K_i^+$$

In this process, energy is expended by the conversion of one molecule ATP to one ADP and a phosphate atom P.

Another example of active transport is the calcium pump. The concentration of free $Ca2^+$ in the cell is 0.1μM, while the concentration of $Ca2^+$ outside the cell is 1mM, that is, higher by a factor of 10^4 (μM=micromole=10^{-6} mole, mM=milimole=10^{-3} mole, mole=number of grams equal to the molecular weight of a molecule). To help maintain these levels of concentration the cell uses active calcium pumps.

An important formula in electrophysiology and in neuroscience is the *Nernst equation*. Suppose two reservoirs of the same ions S with, say, a positive charge Z per ion, are separated by a membrane. Suppose each reservoir is constantly kept electrically neutral by the presence of other ions T. Finally, suppose that the membrane is permeable to S but not to T. We shall denote by $[S_i]$ the concentration of S on the left side or the inner side, of the membrane, and by $[S_o]$ the concentration of S on the right side, or the outer side, of the membrane. If the concentration $[S_i]$ is initially larger than the concentration $[S_o]$, then ions S will flow from inside the membrane to the outside, building up a positive charge that will increasingly resist further movement of positive ions from the inside to the outside of the membrane. When equilibrium is reached, $[S_o]$ will be, of course, larger than $[S_i]$ and (even though each side of the membrane is electrically neutral) there will be voltage difference V_s across the membrane. V_s is given by the Nernst equation

$$V_s = \frac{RT}{ZF} \ell n \frac{[S_o]}{[S_i]}$$

when R is the universal gas constant, F is the Faraday constant, and T is the absolute temperature. For $Z = 1$, temperature=37°C,

$$V_s = 62 \log_{10} \frac{[S_o]}{[S_i]} .$$

By convention, the membrane potential is defined as the difference: The outward-pointing electric field from inside the membrane minus the inward-pointing electric field from outside the membrane.

The ions species separated by the cell membrane, are primarily K^+, Na^+, Cl^-, and $Ca2^+$. To each of them corresponds a different Nernst potential. The electric potential at which the net electrical current is zero is called the *resting membrane potential*. An approximate formula for computing the resting membrane potential is known as the Goldman-Hodgkin-Katz (GHK) equation.

For a typical mammalian cell at temperature 37°C,

S	$[S_i]$	$[S_o]$	V_s
K^+	140	5	−89.7 mV
Na^+	5–15	145	+90.7 – (+61.1)mV
Cl^-	4	110	−89mV
Ca^{2+}	1–2	2.5–5	+136 – (+145)mV

where the concentration is in milimolar (mM) and the potential is in milivolt. The negative V_s for $S = K^+$ results in an inward-pointing electric field which drives the positively charged K^+ ions to flow inward. The sodium-potassium pump is used to maintain the membrane potential and, consequently, to regulate the cell volume. Indeed, recall that the plasma membrane is permeable to water. If the total concentration of solutes is low one side of the membrane and high on the other, then water will tend to move across the membrane to make the solute concentration equal; this process is known as *osmosis*. The osmotic pressure, which drives water across the cell, will cause the cell to swell and eventually to burst, unless it is countered by an equivalent force, and this force is provided by the membrane potential. The resting potential for mammalian cells is in the range of -60mV to -70mV.

2 Nerve Cells

There are many types of cells in the human body. These include: (i) a variety of epithelial cells that line up the inner and outer surfaces of the body; (ii) a variety of cells in connective tissues such as fibroblasts (secreting extracellular protein, such as collagen and elastin) and lipid cells; (iii) a variety of muscle cells; (iv) red blood cells and several types of white blood cells; (v) sensory cells, for example, rod cells in the retina and hair cells in the inner ear; and (vi) a variety of nerve cells, or neurons.

The fundamental task of neurons is to receive, conduct, and transmit signals. Neurons carry signals from the sense organs inward to the central nervous system (CNS), which consists of the brain and spinal cord. In the CNS the signals are analyzed and interpreted by a system of neurons, which then produce a response. The response is sent, again by neurons, outward for action to muscle cells and glands.

Neurons come in many shapes and sizes, but they all have some common features as shown schematically in Figure 3.

A typical neuron consists of four parts: *cell body*, or *soma*, containing the nucleus and other organelles (such as ER and mitochondria); branches of *dendrites*, which receive signals from other neurons; an *axon* which conducts signals away from the cell body; and many branches at the far end of the axon, known as *nerve terminals* or *presynaptic terminals*. Nerve cells, body and axon, are surrounded by *glial cells*. These provide support for nerve cells, and they also provide insulation sheaths called *myelin* that cover and protect most of the large axons. The combined number of neurons and glial cells in the human body is estimated at 10^{12}.

The length of an axon varies from less than 1mm to 1 meter, depending on the type of nerve cell, and its diameter varies between 0.1μm and 20μm.

The dendrites receive signals from nerve terminals of other neurons. These signals, tiny electric pulses, arrive at a location in the soma, called the *axon hillock*. The combined electrical stimulus at the hillock, if exceeding a certain

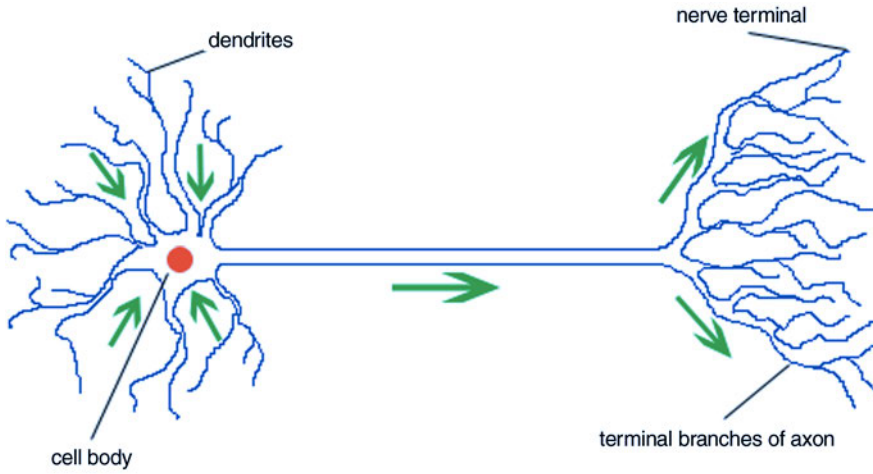


Fig. 3. A neuron. The arrows indicate direction of signal conduction.

threshold, triggers the initiation of a traveling wave of electrical excitation in the plasma membrane known as the *action potential*. If the plasma membrane were an ordinary conductor, then the electrical pulse of the action potential would weaken substantially along the plasma membrane. However, as we shall see, the plasma membrane, with its many sodium and potassium active channels spread over the axon membrane, is a complex medium with conductance and resistance properties that enable the traveling wave of an electrical excitation to maintain its pulse along the plasma membrane of the axon without signal weakening. The traveling wave has a speed of up to 100m/s.

A decrease in the membrane potential (for example, from −65mV to −55mV) is called *depolarization*. An increase in the membrane potential (for example, from −65mV to −75mV) is called *hyperpolarization*. Depolarization occurs when a current is injected into the plasma membrane. As we shall see, depolarization enables the action potential, whereas hyperpolarization tends to block it. Hence, a depolarizing signal is *excitatory* and a hyperpolarizing signal is *inhibitory*.

The action potential is triggered by a sudden depolarization of the plasma membrane, that is, by a shift of the membrane potential to a less negative value. This is caused in many cases by ionic current, which results from stimuli by neurotransmitters released to the dendrites from other neurons. When the depolarization reaches a threshold level (e.g., from −65mV to −55mV) it affects voltage-gated channels in the plasma membrane. First, the sodium channels at the site open: the electrical potential difference across the membrane causes conformation change, as illustrated in Figure 4, which results in the opening of these channels.

When the sodium channels open, the higher Na^+ concentration on the outside of the axon pressures these ions to move into the axon against the

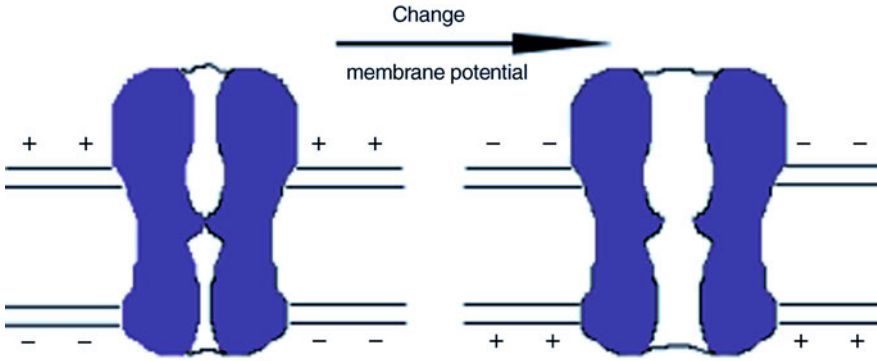


Fig. 4. Change in membrane voltage can open some channels.

depolarized voltage; thus, the sodium ions flow from outside to inside the axon along the electrochemical gradient. They do so at the rate of 10^8 ions per second. This flow of positive ions into the axon further enhances the depolarization, so that the voltage V_m of the plasma membrane continues to increase.

As the voltage continues to increase (but still being negative), the potassium channels at the site begin to open up, enabling K^+ ions to flow out along the electrochemical gradient. However, as long as most of the sodium channels are still open, the voltage nevertheless continues to increase, but soon the sodium channels shut down and, in fact, they remain shut down for a period of time called the *refractory period*.

While the sodium channels are in their refractory period, the potassium channels remain open so that the membrane potential (which arises, typically, to +50mV) begins to decrease, eventually going down to its initial depolarized state where again new sodium channels, at the advanced position of the action potential, begin to open, followed by potassium channels, etc. In this way, step-by-step, the action potential moves along the plasma membrane without undergoing significant weakening. Figure 5 illustrates one step in the propagation of the action potential.

Most ion channels allow only one species of ions to pass through. Sodium channels are the first to open up when depolarization occurs; potassium channels open later, as the plasma potential is increased. The flux of ions through the ion channels is passive; it requires no expenditure of energy. In addition to the flow of sodium and potassium ions through voltage-gated channels, transport of ions across the membrane takes place also outside the voltage-gated channels. Indeed, most membranes at rest are permeable to K^+, and to a (much) lesser degree to Na^+ and Ca^{2+}.

As the action potential arrives at the nerve terminal, it transmits a signal to the next cell, which may be another neuron or a muscle cell. The spacing through which this signal is transmitted is called the *synaptic cleft*. It

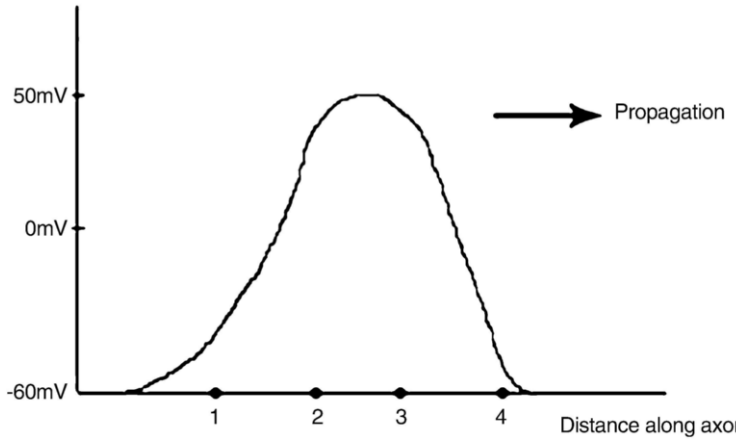


Fig. 5. Propagation of the action potantial. 1: Na+ channels open; 2: K+ channels open; 3: Na+ channels close; 4: k+ channels close.

separates the *presynaptic* cytoplasm of the neuron from the *postsynaptic* cell. There are two types of synaptic transmissions: chemical and electrical. Figure 6 shows a chemical synaptic transmission. This involves several steps: The action potential arriving at the presynaptic axon causes voltage-gated Ca^{2+} channels near the synaptic end to open up. Calcium ions begin to flow into the presynaptic region and cause vesicles containing neurotransmitters to fuse with the cytoplasmic membrane and release their content into the synaptic cleft. The released neurotransmitters diffuse across the synaptic cleft and bind to specific protein receptors on the postsynaptic membrane, triggering them to open (or close) channels, thereby changing the membrane potential to a depolarizing (or a hyperpolarizing) state. Subsequently, the neurotransmitters recycle back into their presynaptic vesicles.

Electrical transmission is when the action potential makes direct electrical contact with the postsynaptic cell. The gap junction in electrical transmission is very narrow; about 3.5nm. Chemical transmission incurs time delay and some variability due to the associated diffusion processes, it requires a threshold of the action potential, and it is unidirectional. By contrast, electrical transmission incurs no time delay, no variability, it requires no threshold, and it is bidirectional between two neurons.

3 Electrical Circuits and the Hodgkin-Huxley Model

The propagation of the action potential along the axon membrane can be modeled as the propagation of voltage in an electrical circuit. Before describing this model, let us review the basic theory of electrical circuits. We begin with

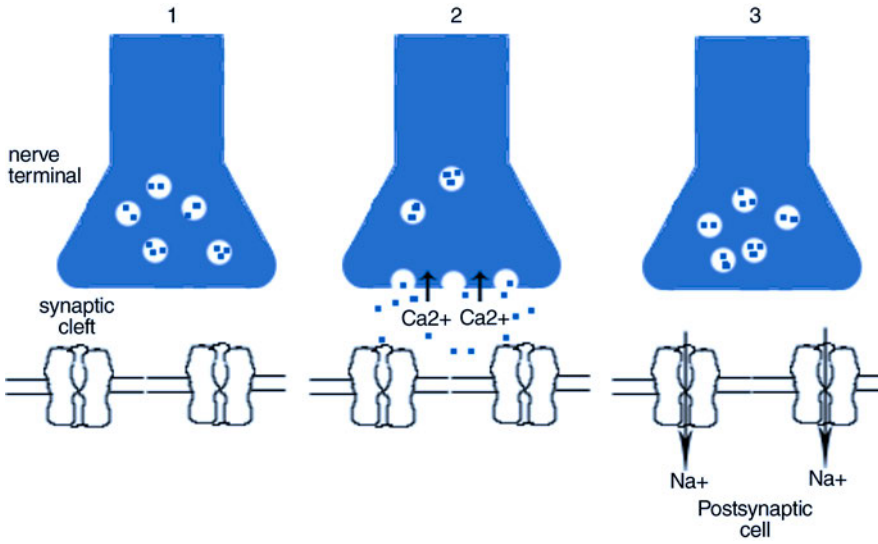


Fig. 6. Synaptic transmission at chemical synapses. 1: Arrival of action potential. 2: Ca^{2+} flows in; vesicles fuse to cytoplasm membrane, and release their contents to the synaptic cleft. 3: Postsynaptic (e.g. Na^{+}) channels open, and Ca^{2+} ions return to vesicles.

the *Coulomb law*, which states that positive charges q_1 and q_2 at distance r from each other experience a repulsive force F given by

$$F = \frac{1}{4\pi\varepsilon_o}\frac{q_1 q_2}{r^2}$$

where ε_0 is the permittivity of space. We need of course to define the unit of charge, C, called *coulomb*. A coulomb, C, is a quantity of charge that repels an identical charge situated 1 meter away with force $F = 9 \times 10^9 N$, where N=newton=10^5 dyne. This definition of C is clearly related to the value of ε_0, which is such that

$$\frac{1}{4\pi\varepsilon_o} = 9 \times 10^9 \frac{Nm^2}{C^2}$$

The charge of an electron is $-e$, where $e = 1.602 \times 10^{-19} C$. Hence the charge of one mole of ions K^+, or of one mole of any species of positive ions with a unit charge e per ion, is $N_A C$ where $N_A = 6.023 \times 10^{23}$ is the *Avogadro number*. The quantity $F = N_A e = 96,495C$ is called the *Faraday constant*.

Electromotive force (EMF or, briefly, E) is measured in volts (V). One volt is the potential difference between two points that requires expenditure of 1 joule of work to move one coulomb of charge between the two points; 1 joule=10^7 erg=work done by a force of one Newton acting along a distance of 1 meter.

Current i is the rate of flow of electrical charge (q):

$$i = \frac{dq}{dt}.$$

Positive current is defined as the current flowing in the direction outward from the positive pole of a battery toward the negative pole; the electrons are then flowing in the opposite direction. In order to explain this definition, consider two copper wires dipped into a solution of copper sulfate and connected to the positive and negative poles of a battery. Then the positive copper ions in the solution are repelled from the positive wire and migrate toward the negative wire, whereas the negative sulfate ions move in the reverse direction. Since the direction of the current is defined as the direction from the positive pole to the negative pole, i.e., from the positive wire to the negative wire, the negative charge (i.e., the extra electrons of the surface atoms) move in the reverse direction.

The unit of current is *ampere*, A: One ampere is the flow of one coulomb C per second.

Ohm's law states that the ratio of voltage V to current I is a constant R, called the *resistance*:

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

R is measured in ohms, $\Omega : \Omega = \frac{1V}{1A}$. Conductors, which satisfy the ohm law are said to be *ohmic*. Actually not all conductors satisfy Ohm's law; most neurons are *nonohmic* since the relation I–V is nonlinear. The quantity $\frac{1}{R}$ is called the *conductivity* of the conductor.

Capacitance is the ability of a unit in an electric circuit, called *capacitor*, to store charge; *capacity* C is defined by

$$C = \frac{q}{V} (C = \text{capacity}) .$$

Where q is the stored charge and V is the potential difference (voltage) across the capacitor.

The unit capacity is *Farad*, F:

$$1F = \frac{1coulomb}{1volt} .$$

A typical capacitor consists of two conducting parallel plates with area S each, separated a distance r by a dielectric material with dielectric constant K_d. The capacity is given by

$$C = \varepsilon_o - K_d - \frac{S}{r} .$$

Later on we shall model a cell membrane as a capacitor with the bilipid layer as the dielectric material between the inner and outer surfaces of the plasma membrane.

It should be emphasized that no current ever flows across a capacitor (although the electric field force goes through it). However, when in an electric circuit the voltage changes in time, the charge on the capacitor also changes in time, so that it appears as if current is flowing. Since $i = \frac{dq}{dt}$ where $q = CV$ is the charge on the conductor, the *apparent* flow across the capacitor is

$$i = C\frac{dV}{dt}$$

(although there is no actual flow across it); we call this quantity the *capacitative current*. This flow merely reflects shifts of charge from one side of the capacitor to another by way of the circuit.

Kirchoff's laws form the basic theory of electrical circuits:

(1) The algebraic sum of all currents flowing toward a junction is zero; here, current is defined as positive if it flows into the junction and negative if it flows away from the junction.
(2) The algebraic sum of all potential sources and voltage drops passing through a closed conduction path (or "loop") is zero.

We give a simple application of Kirchoff's laws for the circuits described in Figures 7a and 7b. In figure 7a two resistors are in sequence, and Kirchoff's laws and Ohm's law give

$$E - 1R_1 - 1R_2 = 0\,.$$

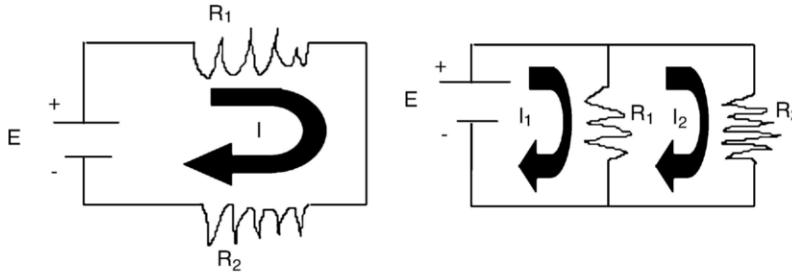


Fig. 7.

If the total resistance in the circuit is R, then also $E = IR$, by Ohm's law. Hence $R = R_1 + R_2$. By contrast, applying Kirchoff's law to the circuit described in Figure 7b, where the two resistances are in parallel, we get

$$I_1 = \frac{V}{R_1}, I_2 = \frac{V}{R_2}, \quad \text{and} \quad R = \frac{V}{I} \quad \text{where} \quad I = I_1 + I_2\,,$$

so that

$$\frac{1}{R} = \frac{1}{R_1} + \frac{1}{R_2}\,.$$

Capacitors introduce time element into the analysis of current flow. Indeed, since they accumulate and store electrical charge, current and voltage changes are no longer simultaneous. We shall illustrate this in an electric circuit, which resembles the cell membrane of an axon, as shown in Figure 8.

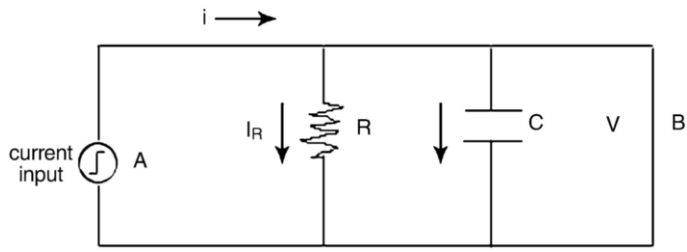


Fig. 8. Current step input.

On the left side A we introduce a current step i, as input, and on the right side B we measure the output voltage V; the capacitor C represents the capacity of the axon membrane and the resistor R represents the total resistivity of the ion channels in the axon. Thus, the upper line with the input $i \rightarrow$ may be viewed as the inner surface of the cell membrane, whereas the lower line represents the outer surface of the membrane.

By Kirchoff's laws and Ohm's law,

$$I_R = \frac{V}{R}, I_C = C\frac{dV}{dt}$$

and

$$iR = (I_R + I_C)R = V + RC\frac{dV}{dt}$$

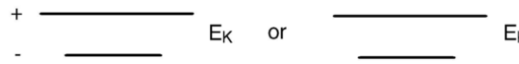
so that

$$V = iR\left(1 - e^{-t/RC}\right).$$

Hence the voltage does not become instantly equal to iR (as it would be by Ohm's law if there was no capacitor in the circuit); V is initially equal to zero, and it increases to iR as $t \rightarrow \infty$.

Figure 9 describes a more refined electric circuit model of the axon membrane. It includes currents through potassium and sodium channels as well as a leak current, which may include Cl^- and other ion flows. For simplicity we have lumped all the channels of one type together as one channel and represented the lipid layer as a single capacitor; a more general model will be given in §4.

Since K^+ has a larger concentration inside the cell that outside the cell, we presume that positive potassium ions will flow outward, and we therefore denote the corresponding electromotive force E_K by



The reverse situation holds for Na^+. The conductivity of the channels K^+, Na^+ and the leak channel L are denoted by g_K, g_{Na}, and g_L, respectively.

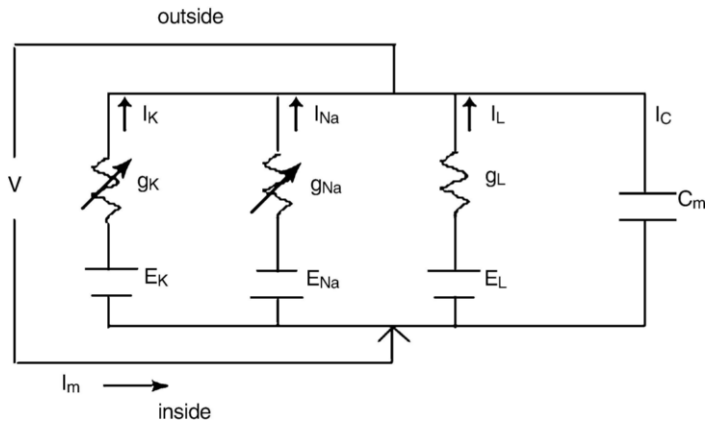


Fig. 9. An electric circuit representing an axon membrane.

By Kirchoff's laws we get

$$I_m = C_m \frac{dV}{dt} + I_K + I_{Na} + I_L$$

where V is the action potential and I_m is the current injected into the axon. We assume that the leak channel is ohmic, so that

$$I_L = g_L(V - E_L), g_L \text{ constant}$$

where E_L is the Nernst equilibrium voltage for this channel. On the other hand the conductivities g_K and g_{Na} are generally functions of V and t, as pointed out in §2, so that

$$I_K = g_K(V,t)(V - E_K), I_{Na} = g_{Na}(V,t)(V - E_{Na})$$

where E_K and E_{Na} are the Nernst equilibrium voltages for K^+ and Na^+. Thus, we can write

$$I_m = C_m \frac{dV}{dt} + g_K(V,t)(V - E_K) + g_{Na}(V,t)(V - E_{Na}) + g_L(V - E_L). \quad (1)$$

Hodgkin and Huxley made experiments on the giant squid axon, which consisted of clumping the voltage at different levels and measuring the corresponding currents. Making some assumptions on the structure and conformation of potassium and sodium gates, they proposed the following equations:

$$g_K(V,t) = n^4 g_K^*, g_{Na}(V,t) = m^3 h g_{Na}^* \tag{2}$$

where n, m, h are the *gating variables* (g_L is neglected here), and $g_K^* = \max g_K$, $g_{Na}^* = \max g_{Na}$. The variables n, m, h satisfy linear kinetic equations

$$\begin{aligned} \frac{dn}{dt} &= \alpha_n(1-n) - \beta_n n, \\ \frac{dm}{dt} &= \alpha_m(1-m) - \beta_m m, \\ \frac{dh}{dt} &= \alpha_n(1-h) - \beta_h h\,. \end{aligned} \tag{3}$$

By fitting coefficients they obtained the empirical formulas

$$\begin{aligned} \alpha_n(V) &= 0.01\frac{-V+10}{\left[e^{(-V+10)/10}-1\right]}\,, \\ \beta_n(V) &= 0.125e^{-V/80}\,, \\ \alpha_m(V) &= 0.1\frac{-V+25}{\left[e^{(-V+25)/10}-1\right]}\,, \\ \beta_m(V) &= 4e^{-V/18},\ \alpha_h(V) = 0.07e^{-V/20},\ \beta_h(V) = \frac{1}{e^{(-V+30)/10}+1}\,. \end{aligned} \tag{4}$$

The system (1)–(4) is known as the *Hodgkin-Huxley equations*. They form a system of four nonlinear ordinary differential equations in the variables V, n, m, and h. One would like to establish for this system, either by a mathematical proof or by computations, that as a result of a certain input of current I_m there will be solutions of (1)–(4) where the voltage V is, for example, a periodic function, or a traveling wave, as seen experimentally. This is an ongoing active area of research in the mathematical neuroscience.

The Hodgkin-Huxley equations model the giant squid axon. There are also models for other types of axons, some involving a smaller number of gating variables, which make them easier to analyze.

In the next section we shall extend the electric circuit model of the action potential to include distributions of channels across the entire axon membrane. In this case, the action potential will depend also on the distance x measured along the axis of the axon.

4 The Cable Equation

We model an axon as a thin cylinder with radius a. The interior of the cylinder (the cytoplasm) is an ionic medium which conducts electric current; we shall call it a *core conductor*. The exterior of the cylinder is also an ionic medium, and we shall assume for simplicity that it conducts current with no resistance. We introduce the following quantities:

r_i = axial resistance of the core conductor, $\frac{\Omega}{cm}$,
R_i = specific intercellular resistance, $\Omega \cdot cm$,
r_m = membrane resistance, $\Omega \cdot cm$,
R_m = specific membrane resistance, $\Omega \cdot cm^3$,
c_m = membrane capacitance, $\frac{F}{cm}$,
C_m = specific membrane capacitance, $\frac{F}{cm^3}$.
Then

$$R_i = \pi a^2 r_i, R_m = 2\pi a r_m, C_m = \frac{c_m}{2\pi a}; \tag{5}$$

the first equation, for example, follows by observing that r_i may be viewed as the resistance of a collection of resistances R_i in parallel.

Denote by x the distance along the axis of the core conductor, and by V_i the voltage in the core conductor. We assume that the current flows along the x-direction, so that V_i is a function of just (x, t). By Ohm's law

$$\frac{\partial V}{\partial x} = -i_i r_i \, .$$

Where i_i is the intracellular current; for definiteness we take the direction of the current flow to be in the direction of increase of x. Hence

$$\frac{\partial^2 V_i}{\partial x^2} = -r_i \frac{\partial i_i}{\partial x}. \tag{6}$$

If current flows out of (or into) the membrane over a length increment Δx then the current decreases (or increases) over that interval, as illustrated in Figure 10.

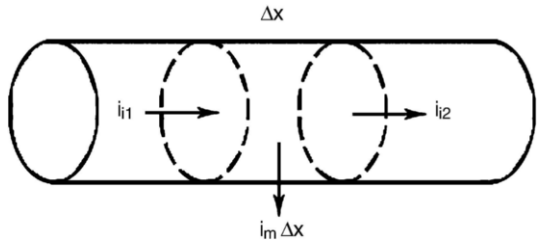


Fig. 10. Decrease in current i_i due to outflow of current i_m.

Denoting by i_m the flow, per unit length, out of (or into) the membrane, we have

$$i_2 - i_1 = -i_m \Delta x \, ,$$

or

$$i_m = -\frac{\partial i_i}{\partial x} \, .$$

Combining this with (6), we find that

$$\frac{1}{r_i}\frac{\partial^2 V_i}{\partial x^2} = i_m \tag{7}$$

The membrane potential is $V = V_i - V_e$ where V_e, the external voltage, is constant since we have assumed that the extracellular media has no resistance.

We now make the assumption that there are many identical circuits distributed all over the surface of the membrane, as illustrated in Figure 11.

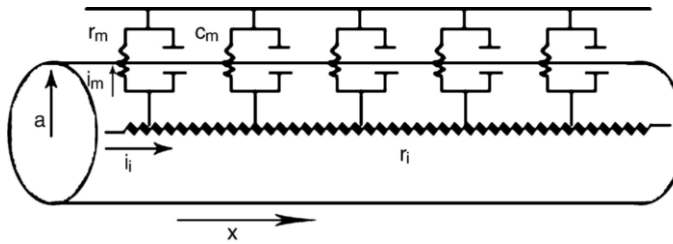


Fig. 11. Current flow along a cylindrical axon with many R-C circuits on the membrane.

By Kirchoff's laws (cf. Section 3) the flow i_m satisfies

$$i_m = c_m\frac{\partial V}{\partial t} + \frac{V_i - V_e}{r_m}\,. \tag{8}$$

Combining this with (7) we get

$$\frac{r_m}{r_i}\frac{\partial^2 V}{\partial x^2} = r_m c_m\frac{\partial V}{\partial t} + V\,.$$

Setting

$$\tau_m = r_m c_m = R_m C_m, \lambda = \sqrt{\frac{r_m}{r_i}} = \sqrt{\frac{R_m}{R_i}}\frac{a}{2}\,,$$

we arrive at the *cable equation*

$$\lambda^2\frac{\partial^2 V}{\partial x^2} = \tau_m\frac{\partial V}{\partial t} + V, \tag{9}$$

or, with $X = \frac{x}{\lambda}$, $T = \frac{t}{\tau_m}$,

$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} - V\,. \tag{10}$$

The specific current of the membrane, I_m, is related to the current i_m by $i_m = 2\pi a I_m$. Hence (7) can be written in the form

$$\frac{a}{2R_i}\frac{\partial^2 V}{\partial x^2} = I_m \, . \tag{11}$$

In the above analysis the current im was modeled using the configuration of R-C units as in Figure 11. Let us now specialize to the case of the giant squid axon, as illustrated in Figure 7, with the leak flow neglected. Then, as in §3,

$$I_m = C_m \frac{\partial V}{\partial t} + I_K + I_{Na}$$

so that, by (11),

$$\frac{a}{2R_i}\frac{\partial^2 V}{\partial x^2} = C_m \frac{\partial V}{\partial t} + g_K(V,t)(V - E_k) + g_{Na}(V,t)(V - E_{Na}) \tag{12}$$

where g_K, g_{Na} are as in the Hodgkin-Huxley equations. The *spatial Hodgkin-Huxley system* consists of the equations (2)–(4) and (12).

We return to the cable equation (9) and note that this equation can also model the voltage in any dendritic branch. But since the dendritic tree is quite complex in general (see Figure 3), it is difficult to the compute the total voltage, which sums up all the voltage inputs that go into the axon hillock. There is however one special case where V can be easily computed. This case was identified by Rall, and it assumes a very special relationship between some of the dendritic branches. In order to explain the *Rall Theory*, we begin with a situation in which a current I_0 is injected into an infinite core conductor (with $^-\infty < x < \infty$) at $x = 0$. Then current $I_0/2$ flows to the right and current $I_0/2$ flows to the left, so that the potential V satisifies

$$\frac{\partial V}{\partial x}(+0) - \frac{\partial V}{\partial x}(-0) = -r_i I_0 \, . \tag{13}$$

The stationary solution of the cable equation in the semi-infinite portion $0 < x < \infty$ is then

$$V(x) = r_i \frac{I_0}{2} \lambda e^{-x/\lambda} \, . \tag{14}$$

Note that the factor $e^{x-\lambda}$ accounts for the current leak through the membrane: If there is no leak then $V(x) = V(0)$. The resistance of the cable is then

$$V(0)\frac{I_0}{2} = \frac{(R_m R_i/2)^{1/2}}{\pi a^3} \, .$$

Hence the conductivity of the core conductor is

$$G = K d^{3/2} \quad \text{where} \quad K = \frac{\pi}{2}(R_m R_i)^{-1} \tag{15}$$

where d is the diameter of the cable.

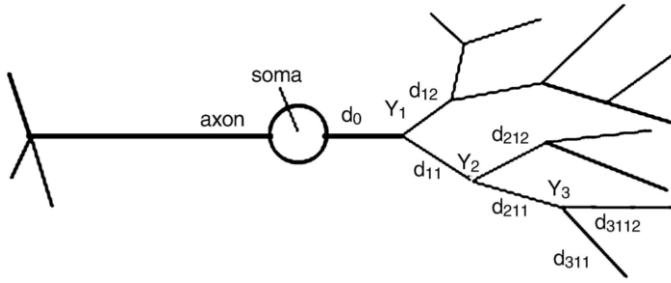


Fig. 12. Schematic diagram of a neuron with a branched dendritic tree.

Suppose the dendritic tree has a form as in Figure 12. We assume that each of end-branch is infinitely long, so that its conductivity is given by (15) where d is its diameter.

The conductances of the end-branches with diameters d_{3111} and d_{3112} are $K(d_{3111})^{3/2}$ and $Kd_{3112}^{3/2}$ respectively. Since the total conductances are just the sum of all the parallel conductances, if the diameter d_{211} is such that

$$d_{211}^{3/2} = d_{3111}^{3/2} + d_{3112}^{3/2} \tag{16}$$

then we may replace the two branches at Y_3, d_{3111} and d_{3112}, by one semi-infinite branch, which extends d_{211} to infinity; it is assumed here that R_m and R_i (hence K) are the same for all branches.

We can now proceed to do that same reduction at the branch point Y_2. If the diameter d_{11} is such that

$$d_{11}^{3/2} = d_{211}^{3/2} + d_{212}^{3/2} \tag{17}$$

then we may replace the two branches at Y_2, d_{211}, and d_{212}, by the branch d_{211} extended to infinity.

Proceeding in this way with the other branch points, we may also replace the part of the tree branching from d_{12} by the branch d_{12} extended to infinity. Finally, if the diameter d_0 is such that

$$d_0^{3/2} = d_{11}^{3/2} + d_{12}^{3/2} \tag{18}$$

then we may replace the two branches at Y_1 by the branch d_0 extended to infinity.

In conclusion, the Rall Theory asserts that if the dendritic branches satisfy the relations (16), (17), ..., (18), then the dendritic tree is equivalent to one semi-infinite core conductor of diameter do. This result holds for general dendritic trees provided

$$d_p^{3/2} = \Sigma d_D^{3/2}$$

when d_P is in any *parent* dendritic branch and d_D varies over its *daughter* dendritic branches.

The above analysis extends to the case where all the end-branches are of the same length L and all other branches are of length smaller than L. In this case, formula (15) is replaced by

$$G = Kd^{3/2} \tanh L \, .$$

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References [1] and [3] give a descriptive theory of neuroscience, and references [2] and [4] focus more on the modeling and the mathematical/computational aspects of neurons.