Chapter 2

The Neuron at Rest

§ 1. The Neuron Membrane

The outermost boundary surface of the neuron cell is called the plasma membrane. Figure 2.1 illustrates the basic organization of the membrane and the molecular structures that are key to biological signal processing. This qualitative model is called the ***fluid mosaic model*** by cellular biologists. The membrane separates the interior of the cell, called the ***cytoplasm***, from the surrounding ***extracellular region*** of tissue fluid. The cytoplasm contains an aqueous gel, 10 to 20% of which is made up of solids with the rest consisting of water containing a variety of ionized chemicals. For the neuron at rest, this electrolyte is in osmotic equilibrium with the surrounding electrolytic fluid of the extracellular region.

The electrolytic content of the cell differs greatly from that of the external fluid region. The major ionic constituents of the external tissue fluid are sodium (Na^+) and chloride (Cl^-) with lesser amounts of potassium (K^+) and calcium (Ca^{2+}). The major ionic constituents of the cytoplasm are K^+ with lesser amounts of Na^+, Cl^-, and some other chemicals. At rest the cytoplasm contains very little free Ca^{2+} although some of the gelatinous cell structures *store* Ca^{2+}.

Most of the membrane is composed of the ***phospholipid bilayer***. A phospholipid is an amphipathic molecule (meaning that part of it is repelled by water and part is attracted to water) similar to fat. The bilayer forms such that the hydrophobic part of the molecules is placed inside the membrane and the hydrophilic part faces the cytoplasm (in the inner layer) or the extracellular region (in the outer layer). The membrane also contains numerous proteins, a number of which span the membrane wall from cytoplasm to the extracellular region. These proteins constitute the

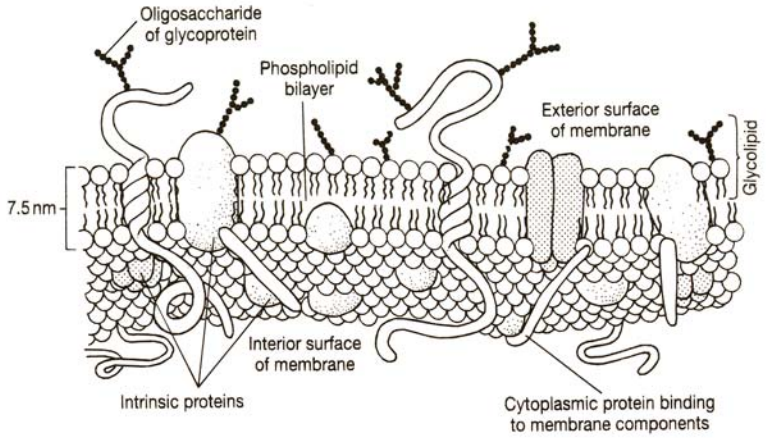

Figure 2.1: Basic structure of the cell membrane

basic signaling instruments of the neuron.

The ease with which a molecule or ion can pass through the membrane from one side to the other is called the membrane's ***permeability*** to that molecule or ion. The permeability of the cell's membrane is determined by two major factors: the permeability of the lipid bilayer and the permeability of the membrane-spanning proteins. The bilayer is impermeable to water and to the major ions Na^+, K^+, Ca^{2+}, and Cl^-. It thus acts as an electrical insulator to current flow by these ions. On the other hand, it is highly permeable to small gas molecules such as nitrous oxide (NO) and carbon monoxide (CO), as well as to arachidonic acids and their metabolites.[1]

Among the membrane-spanning proteins there are many that are capable of forming ***pores*** to act as valves to allow or block current flow of particular types of ions. In the ***open state*** they are permeable to the passage of their specific ions, while in the ***closed state*** they are impermeable to these same ions. We will call these proteins the ***ionotropic channel proteins*** or "channels" for short. Channels that are normally open when the cell is at rest we will call ***normally open channels***. Those that are normally closed when the cell is at rest will be called ***normally closed channels***. For some of these proteins the open or closed state of the channel is determined by the electric potential difference (voltage) across the cell membrane. We will call these the ***voltage-gated channels*** (VGCs). For other proteins, the open or closed state depends on the binding of a neurotransmitter molecule (called a ***ligand***) at a receptor site on the extracellular side of the membrane. We will call these the ***ligand-gated channels*** (LGCs).

Many of these membrane-spanning proteins can also have their open or closed state determined by the binding of a phosphate ion on the cytoplasmic side of the membrane. This is one of the end-effect mechanisms by which metabotropic signaling functions. We will call this action a ***phosphate-gated channel*** (PGC). In other cases the binding (or release) of a phosphate on the cytoplasmic side does not directly open or close a channel pore. Instead, it may cause a mechanical change in the shape or orientation of the protein to expose (or to hide) a ligand binding site on the extracellular side. We will call this case a ***phosphate-enabled channel*** (PEC) or a ***phosphate-disabled channel*** (PDC).[2]

Another class of membrane-spanning proteins act as ***active transporters*** of ions across the membrane wall. These proteins are powered by the cell's internal metabolic processes and are called ***pumps***. The combination of ion channel proteins and the action of these pumps is

[1] Arachidonic acid is one of the major "messenger" chemicals involved in metabotropic signaling.

[2] The binding of a phosphate is a process called **phosphorylation**. Removal of the phosphate is called **dephosphorylation**. When the action enables more proteins on the postsynaptic side of a synapse, the synapse is said to be "sensitized." When the action disables more proteins, the synapse is said to be "desensitized." Phosphorylation and dephosphorylation are mechanisms by which the effectiveness of a synapse can be *modulated* from the cytoplasmic side of the neuron.

responsible for determining the resting potential (voltage across the membrane) of the cell. The most important of these pumps insofar as biological signal processing is concerned is called the ***sodium-potassium pump***.

§ 2. The Membrane Potential

§ 2.1 Diffusion and the Nernst Potential

A collection of particles in a medium in which they are free to move will tend to move until their distribution is uniform. This phenomenon is called ***diffusion*** and it is governed by the laws of thermodynamics. If the particles are ions with valence z, each carries an electric charge of ze where $e = 1.60219 \cdot 10^{-19}$ coulombs. Let $[X]$ denote the concentration of ions in moles per liter (M). Statistical mechanics tells us the ion concentration and the electric potential Φ (in volts) in the region are related through the Boltzmann distribution,

$$[X] \propto \exp[-ze\Phi/kT] \ .$$

where $k = 1.38066 \cdot 10^{-23}$ joules/kelvin is the Boltzmann constant and T is the absolute temperature in kelvin.

The membrane presents a barrier to diffusion and thus the concentration of an ion inside the cell may be different from the concentration in the extracellular region. Let $[X]_i$ and Φ_i denote the concentration and electric potential, respectively, inside the cell. Let $[X]_o$ and Φ_o denote these quantities in the extracellular region. We then have

$$\frac{[X]_o}{[X]_i} = \exp\left[\frac{ze(\Phi_i - \Phi_o)}{kT}\right].$$

The voltage $V_X = \Phi_i - \Phi_o$ is the potential difference between the cytoplasm and the extracellular region due to the concentration difference of ion X. It is essentially a battery voltage caused by the difference in ion concentrations. Solving for V_X, we obtain

$$V_X = \frac{kT}{ze} \ln\left(\frac{[X]_o}{[X]_i}\right). \qquad (2.1)$$

This is called the ***Nernst potential*** for the ion.[3]

When several different kinds of ions are present, as they are in the neuron, a Nernst potential can be individually calculated for each type of ion according to (2.1). The ***membrane potential***,

[3] Biologists and chemists may be used to seeing k/e written as R/F where R is the molar gas constant and F is Faraday's constant. Numerically, $k/e = R/F = 86.173 \cdot 10^{-6}$ volts/kelvin.

V_m, is determined by contributions from all the Nernst potentials and is dependent on the permeability of the membrane for each different type of ion. The membrane potential is given by an equation known as the Goldman-Hodgkin-Katz voltage equation. However, because membrane permeability can be related to the ***electric conductance*** of the membrane for each particular type of ion, we will find it more useful in this book to find V_m using an electric circuit model.

§ 2.2 The Membrane Circuit Model: Qualitative Analysis

Figure 2.2 depicts a schema for representing the electrical action of the cell as a circuit model. Models of this general form are called ***lumped element*** models by electrical engineers and ***single compartment*** models by physiologists. By common convention, the electric potential in the extracellular region is taken as the reference ***ground potential*** and the cytoplasmic electric potential is measured relative to this ground. Thus, the membrane potential V_m represents the total electric potential difference across the wall of the membrane.

The storage of free ions within the cytoplasm is represented by a circuit element called a ***capacitor***. This element is the one depicted at the far right of the circuit diagram. The capacitance C relates the total charge Q (in coulombs) of the stored ions to the membrane voltage according to

$$Q = CV_m . \tag{2.2}$$

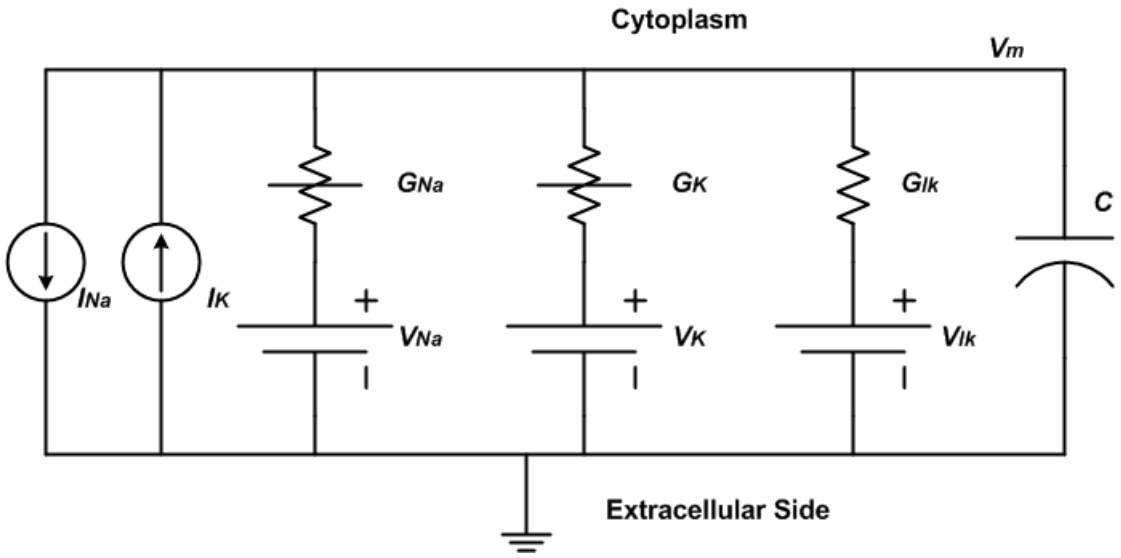

Figure 2.2: Circuit model of membrane potential in the excitable cell. Battery voltages represent the Nernst potentials for the various ions. The insulating membrane wall is represented by the capacitor *C*. Channel conductances are represented by the conductor elements G_{Na}, G_K, and G_{lk}. Current sources I_{Na} and I_K represent the action of the sodium-potassium pumps. Because voltage measurements are always measurements of potential difference, the reference potential is taken to be the extracellular side.

The unit of capacitance is called the farad (F); one farad is equal to one coulomb per volt. The value of C depends only on the thickness of the membrane, its surface area, and its composition of phospholipids and proteins. A typical capacitance value per unit area of cell surface is about 10^{-6} farads per square centimeter = 1 μF/cm^2.

The batteries in the figure represent the electrochemical Nernst potentials for each type of ion. The numerical value of the battery voltage is obtained from (2.1). If the cytoplasmic ion concentration of an ion with positive valence is greater than that of the extracellular concentration (as it is for potassium, K^+), the Nernst potential (e.g., V_K) will be negative. Likewise, if an ion with a negative valence (e.g. chloride) has a great extracellular concentration than cytoplasmic concentration, its Nernst potential (e.g. V_{Cl}, not depicted in Figure 2.2) will be negative because the valence is negative (e.g. $z = -1$ for Cl^-). Battery V_{lk} is a so-called "leakage potential" that is used to model unidentified ionic constituents of the system. Although frequently associated with chloride ions, in fact V_{lk} and its associated conductance G_{lk} are used to account for unknowns encountered in physiological studies.[4] In many experimental cases the membrane potential at rest is either equal to or very nearly equal to the leakage battery voltage. When equality is found it is often possible to related V_{lk} to a particular ion (usually chloride). However, when equality is not obtained it is generally not possible to tie V_{lk} (and G_{lk}) to a *specific* cause, and in this case the current flowing in the leakage leg of the circuit will be a mixture of different ion types. The leakage elements in the model are then merely a phenomenological "correction factor" in the quantitative model.

The effect of non-zero permeability on the flow of ion currents is represented through the various conductors depicted in the figure. Ion current flow through a conductor is directly proportional to the voltage difference across the conductor. This is called ***Ohm's law*** and is expressed in equation form by

$$I_X = G_X\left(V_X - V_m\right) \tag{2.3}$$

when the direction of current flow is from the battery to the cytoplasmic side of the membrane. Parameter G_X is called the ***conductance*** for ion X. Its unit of measure is called the siemens (S), which is 1 ampere/volt = 1 coulomb^2 per joule-second.[5] The horizontal lines added to the

[4] Biologists usually reverse the direction of the batteries for ions where the Nernst potential is negative. The battery voltage is then given by the absolute value of (2.1). This is mathematically identical to the model presented here. However, the model of Figure 2.2 is preferable for writing computer programs to carry out a numerical analysis of the circuit dynamics because it permits identical expressions (differing only in the variables in the equations) to be used in writing the software.

[5] The siemens is named after Sir William Siemens, a German-born British engineer. In older literature, before Sir William was honored by having a physical unit named after him, the unit of conductance was

conductor symbols in Figure 2.2 denote that their conductance values are voltage-dependent. This is because G_{Na} and G_K in this figure represent voltage-gated sodium and potassium ion channels. The leakage conductance is generally not membrane-voltage-dependent, and so this symbol has no horizontal line added to it in the figure.

Current sources I_{Na} and I_K represent the pumping actions of the transporter proteins that maintain the resting cell in its electrochemical equilibrium. The primary importance of including them in the model is to prevent the model from making a very misleading statement about the physiology of the cell. To appreciate this, it is first important to recall that the physics of circuit theory requires that all currents flow in a closed circuit, which means that current exiting one terminal of a battery must return to the other terminal of the battery. For example, Na^+ current must originate from and return to the Na^+ battery.

Now since the three battery voltages are generally different, there is no possible value of V_m that can simultaneously produce zero potential difference across all three conductors. In typical cases V_m is very close to or equal to the leakage term V_{lk}. If for convenience we assume equality, then no current flows through G_{lk}. If the cell is at rest, the membrane voltage is constant, which means the total stored charge Q is also constant and no current flows through the capacitor. (Current is the time rate of change of the quantity of charge; no change means no current). Ohms law tells us that the Na^+ current flowing from the Na^+ battery into the cytoplasm is given by the expression $I_{Na} = G_{Na} (V_{Na} - V_m)$. A similar expression is obtained for the potassium current I_K flowing from the potassium battery to the cytoplasm.[6] If we omitted the current sources from our model, the sodium current would have no pathway to return to the sodium battery *except through the potassium conductance*. But because G_K physically represents potassium conductance channels, *this would be tantamount to saying the sodium is magically transmuted into potassium* in the return pathway. This, of course, is utterly absurd. A similar absurd consequence is obtained for the potassium current. By including the pumping actions represented by the current sources in the model, we remove the taint of alchemy from our model. At rest the numerical value of the sodium pump current must equal the numerical value for I_{Na} obtained from Ohm's law (and similarly for the potassium current source).

There is an object lesson for the model-maker to be had from this simple example. A quantitative model for a system that is intended to speak to physical theory assigns *physical meanings* to the variables and parameters of the model. If one trusts one's model, then one is

known as the "mho" ("ohm" spelled backwards).

[6] If we put in biologically accurate numbers for these quantities, I_K would turn out to be a negative number, meaning that the potassium ions actually flow from the cytoplasm to the extracellular region.

committed to trusting *all the consequences* of that model. If a model consequence is in any way contradicted by experimental evidence – provided the experimental evidence is itself trustworthy – then the model is *untrue*. For the model-maker, the only meaningful definition of truth is *congruence of the model representation with the object the model represents*. Lack of congruence means lack of truth in either one's model or in the "facts" one is thought to possess about the experimental properties of the object or *both*. Contradictions of this sort provide science with questions to be addressed through additional research.

For example, it is often presumed that the current sources in Figure 2.2 represent the action of the sodium-potassium pump alone. Now, the Na^+-K^+ pump has been much studied and it is an accepted finding that this pump pumps 3 Na^+ ions out of the cell for every 2 K^+ ions it pumps into the cell. Therefore if the Na^+-K^+ pump is the sole transporter mechanism (and if $V_m = V_{lk}$) then the magnitudes of the Na^+ and K^+ currents given by Ohm's law can easily be shown to be in a ratio

$$\frac{G_{Na}\left(V_{Na} - V_m\right)}{G_K\left(V_m - V_K\right)} = \frac{3}{2} \ .$$

When measured values are plugged into this expression, the results typically implicate a ratio of sodium to potassium resting conductance on the order of about 1:5 to 1:20 (with some considerable variation in these results in the reported literature). This range is in reasonably fair agreement with conductance ratios determined experimentally by other methods. However, it is not infrequently the case that reported results do not place the resting currents in the 3:2 ratio called for by the model of the Na-K pump. Either the data is inaccurate, or there are other pump mechanisms at work for Na^+ and K^+, or there are some more complicated biophysics being masked by the phenomenological "leakage" component of the model, or all of these possibilities are in play. At this date, a half-century after the pioneering contributions by the Nobel laureates whose work led to the basic model presented here, it seems unlikely that this model is fundamentally flawed. But it seems equally unlikely that everything that *could* be done to improve our understanding of this physiology *has* been done. It might be true that Nobel laureates miss fewer things than the rest of us do, but that does not mean they never miss anything. Young researchers should keep this in mind, too. We can and should respect their achievements and emulate their practice of science, but we need not and should not worship them as gods. Authoritarianism smothers science.

§ 2.3 The Membrane Circuit Model: Quantitative Analysis

The basic law governing the relationship between V_m and the Nernst potentials is Kirchhoff's current law: The sum of the currents leaving any node in a circuit equals zero. In the case of

Figure 2.2, Kirchhoff's law tells us how charge accumulates on the capacitor. For the membrane capacitor,

$$Q = CV_m \quad \Rightarrow \quad \frac{dQ}{dt} = I_C = C\frac{dV_m}{dt}.$$

Using this capacitor law and applying Kirchhoff's law gives us

$$C\frac{dV_m}{dt} + (V_m - V_{Na})G_{Na} + I_{Na} + (V_m - V_K)G_K - I_K + (V_m - V_{lk})G_{lk} = 0.$$

Re-arranging these terms,

$$C\frac{dV_m}{dt} = -(G_{Na} + G_K + G_{lk})V_m + (G_{Na}V_{Na} - I_{Na}) + (G_K V_K + I_K) + G_{lk}V_{lk}.$$

This is a differential equation governing V_m as a function of time. The battery voltages are governed by the Nernst potential equation (2.1), so we can write the sodium and potassium terms as time functions by expressing the ion concentration in terms of the steady-state concentrations and the time variation in concentrations due to current supplied by the pumps. For the sodium potential, this expression can be written

$$V_{Na} = \frac{kT}{e}\ln\left(\frac{[\mathrm{Na}^+]_o + [\Delta Na^+]}{[\mathrm{Na}^+]_i - [\Delta Na^+]}\right) = \frac{kT}{e}\ln\left(\frac{[\mathrm{Na}^+]_o}{[\mathrm{Na}^+]_i}\right) + \frac{kT}{e}\ln\left(\frac{1 + [\Delta Na^+]/[\mathrm{Na}^+]_o}{1 - [\Delta Na^+]/[\mathrm{Na}^+]_i}\right)$$

where $[\Delta Na^+] > 0$ is the change in Na^+ concentrations as a function of time due to current flow from the sodium pump. The first term in the sum on the right-hand side is the equilibrium potential of the battery, which we will denote as E_{Na}. The second term represents the change in battery voltage, ΔV_{Na}, that would take place from charge pumping. The logarithm identity

$$\frac{A+a}{B-b} = \frac{A}{B}\frac{1+a/A}{1-b/B} \Rightarrow \ln\left(\frac{A+a}{B-b}\right) = \ln\left(\frac{A}{B}\right) + \ln\left(\frac{1+a/A}{1-b/B}\right)$$

has been used to obtain this expression. Because the pump current I_{Na} replenishes the battery, we must conclude that in steady-state equilibrium $G_{Na}\,\Delta V_{Na} - I_{Na} = 0$.

A similar result is obtained for the potassium pump. Using E_K to represent the equilibrium potential for potassium given by the Nernst equation, the differential equation is rewritten as

$$C\frac{dV_m}{dt} = -(G_{Na} + G_K + G_{lk})V_m + G_{Na}E_{Na} + G_K E_K + G_{lk}V_{lk}. \qquad (2.4)$$

We may note that the current source terms vanish from (2.4). This is often used to re-express the

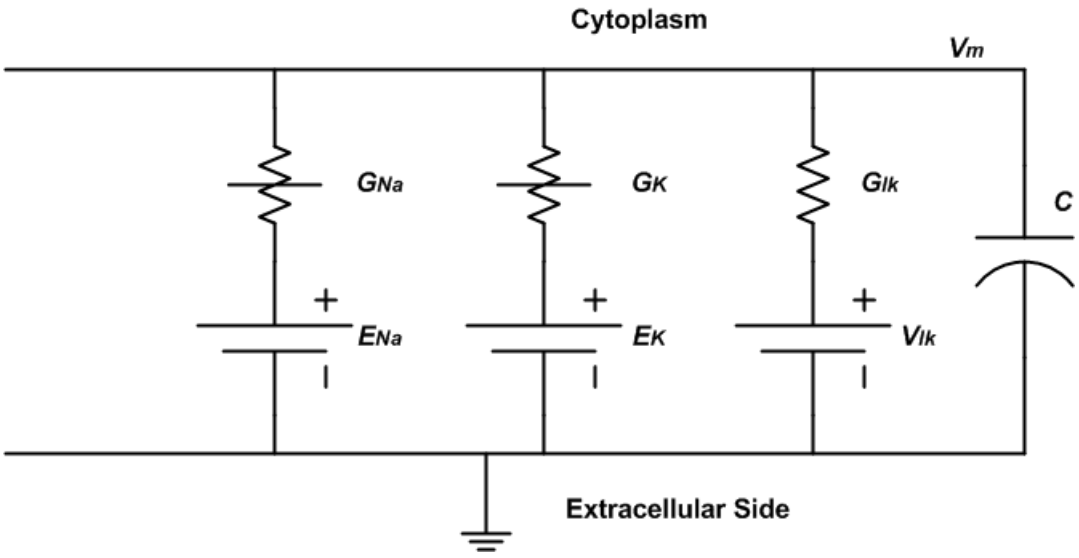

Figure 2.3: Equivalent form of figure 2.2 with current pumps absorbed into the equilibrium constraint of the Nernst potentials. The ion current return paths in this circuit no longer carry any physical significance.

circuit of Figure 2.2 as shown in Figure 2.3. Note that an abstraction is introduced into the circuit diagram by this step, and we can no longer make a physical association for the current return paths in steady state equilibrium. This is an example of how and when the introduction of modeling simplification by abstraction is obtained at the cost of disconnecting the mathematical representation of a system from the underlying physical picture of that system.

In equilibrium V_m does not change as a function of time. Therefore $dV_m/dt = 0$ in (2.4) and we obtain

$$V_m = \frac{G_{Na}E_{Na} + G_K E_K + G_{lk}V_{lk}}{G_{Na} + G_K + G_{lk}} \quad \text{(in steady-state equilibrium).} \qquad (2.5)$$

This equation is the circuit model counterpart to the Goldman-Hodgkin-Katz voltage equation, which expresses the same result in terms of membrane permeability and ion concentrations. Electrical engineers call the V_m in (2.5) the ***Thévenin equivalent voltage source*** of the battery and conductance part of the circuit in Figure 2.3. Likewise, the denominator term on the right-hand side of (2.5) is called the ***Norton equivalent conductance*** of the circuit. If we multiply both sides of (2.5) by the Norton equivalent conductance the result is called the ***Norton equivalent current source***. Thévenin and Norton equivalents are commonly used in circuit analysis to simplify the mathematical analysis.

The ratio

$$\tau = \frac{C}{G_{Na} + G_K + G_{lk}} \overset{\Delta}{=} \frac{C}{G_{Nor}} \qquad (2.6)$$

has units of seconds (when C is in farads and G_{Nor} is in siemens) and is called the ***time constant*** of the circuit. The word "constant" is somewhat misleading in the case of the neuron circuit model because G_{Na} and G_K are voltage-dependent (and therefore not constants), but the terminology derives from linear circuit analysis (where the conductances *are* constants). If a tiny perturbation is introduced into V_m, say by injecting a miniscule amount of charge into the cell, so that the voltage-dependent conductances do not change significantly, then τ can be measured from the initial slope of the natural response of (2.4) as the membrane voltage returns to its resting potential. If one knows C, τ, and the ratios of the conductances, then the numerical value of the individual conductances can be calculated. How to do this is left as exercise 2.3 for the student.

Exercises

2.1. Given the following ion concentrations

$[Na^+]_o = 460$ mM; $[Na^+]_i = 50$ mM
$[K^+]_o = 10$ mM; $[K^+]_i = 400$ mM
$[Cl^-]_o = 540$ mM; $[Cl^-]_i = 80$ mM

find the Nernst potentials for the three ions at $T = 290$ kelvin.

2.2. A basic theorem from the mathematics of differential equations says that for an ordinary first-order differential equation with constant coefficients of the form

$$\frac{dy(t)}{dt} + g\, y(t) = K$$

where g and K are constants, the solution $y(t)$ is given by

$$y(t) = \frac{1}{\mu(t)}\left[\int^t \mu(s) K ds + c\right]$$

where $\mu(t)$ is called the ***integrating factor***,

$$\mu(t) = \exp\left[\int^t g\, dt\right],$$

and c is a constant determined by the initial condition $y(0)$. Use this theorem to solve equation (2.4) for the initial condition $V_m(0) = V_r + v$ where V_r is the steady-state membrane potential (the resting potential) and v is a small perturbation. Assume v is small enough that the conductances do not change over time. Identify the time constant in this solution.

2.3. Given $C = 0.1$ μF, $\tau = 7.69$ ms, and conductance ratios G_{Na}:$G_K = 1$:20, G_{Na}:$G_{lk} = 1$:5, find the numerical values for the three conductances in Figure 2.3. If $E_{Na} = 55$ mV, $E_K = -75$ mV, and $V_{lk} = -69$ mV, what is the equilibrium value for V_m ?

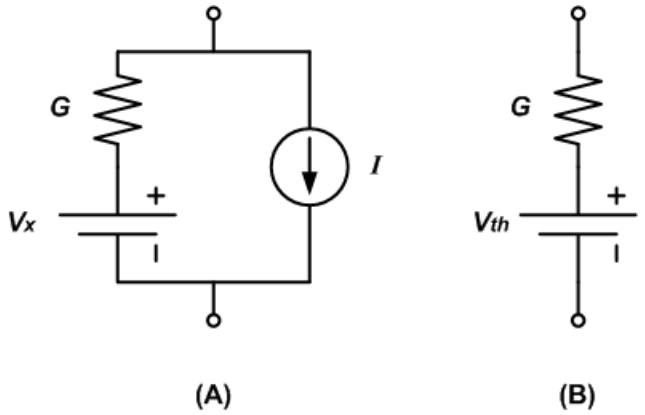

Figure P2.5

2.4. A single membrane-spanning protein forming a channel pore has a characteristic channel conductance g and can be modeled as a conductance in series with a battery V_X representing the electrochemical potential for the ion X conducted by the channel pore. Prove that a region of the membrane with surface area A and channel pore density N/A can be modeled by a single conductance $G_X = N \cdot g$ in series with a single battery V_X.

2.5. Figure P2.5 shows two circuits. Prove the terminal characteristics (that is, the voltage and current characteristics at the circuit terminals) are identical if and only if $V_{th} = V_x - I/G$. (Hint: attach an arbitrary conductance G_L to the terminals of each circuit and use Kirchhoff's current law to show the voltage across G_L and the current through G_L are identical for both circuits).

2.6. The text showed how current source I_{Na} can be eliminated from Figure 2.2 to obtain Figure 2.3. Show how current source I_K can similarly be eliminated for the equivalent circuit model.

2.7. You have just read two research papers published in two different journals. Both report on experimental findings for the same type of neuron. The principal finding of the first paper is a circuit model like that of Figure 2.2. The author reports a membrane resting potential of – 69 mV ± 1 mV, V_{Na} = + 55 mV, G_{Na} = 0.5 μS, V_K = – 75 mV, G_K = 10 μS, V_{lk} = – 69 mV, and G_{lk} = 2.5 μS. The author ascribes the leakage terms to "the chloride channel." He describes the two current sources as "the $Na^+ - K^+$ pump" but does not provide numerical values for either current source. The second paper describes results for the same type of neuron obtained under identical physiological test conditions. Its principal finding is that the sodium-potassium pump currents are 96 nA for Na^+ and 64 nA for K^+. These two findings are not consistent with each other. Why? Show that the findings can be made consistent if the leakage term in Figure 2.2 is appropriately modified. (Hint: Use your results from exercise 2.5). (Note: This is a challenging exercise).

2.8 Your office mate works in the laboratory next door to yours. He has read the second paper described in exercise 2.7 and strongly disagrees with its finding. He tells you that he has conducted the same experiment under the same conditions and finds the sodium-potassium pump currents to be 75 nA and 50 nA, respectively, for sodium and potassium. Can the circuit model reported in exercise 2.7 be made consistent with his findings too? Explain your answer.

2.9. Does the fact that the circuit model of exercise 2.7 can be made consistent with the findings of the second paper in exercise 2.7 prove that these findings are correct? Explain your answer.