Single Neuron Computation

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Introduction

Whereas the brain function at the level of neural circuit remains largely a mystery, a great deal is known about the biophysical mechanisms responsible for generating electrical activity at single neuron level. This knowledge provides the building blocks for constructing neural circuit models. In the following few weeks, we will discuss the basic electrical properties of neurons and the mathematical models by which the rich neuronal dynamics can be described and explained quantitatively. We will present simple but useful model neurons, such as the integrate-and-fire model, as well as the more substantially detailed Hodgkin-Huxley model based on the presence of many voltage-dependent conductances. Finally, we will discuss, despite the tremendous success in constructing detailed conductances-based models (albert with many adjustable parameters) to explain the experimental data, we lack a clear understanding how a single neuron can fine-tune itself to generate the stereotypical activity pattern.

Electrical Properties of Neurons

The cytoplasm of a neuron is packed with a variety of ions ($\sim 10^8$), molecules ($\sim 10^7$) , proteins ($\sim 10^5$), etc. Numerous ion-conducting channels are embedded in the membrane of a cell. Many, but not all, channels are highly selective, allowing only a single type of ion to pass through them. The permeability of ions across the membrane together with the difference of the concentration of these ions largely determine the membrane potential of a neuron. By convention, the potential outside a cell is set to 0. Because the cell membrane is more permeable to positive ions such as K^+ and because there is higher concentration of K^+ inside the neuron, K^+ tend to diffuse to the outside (up to a point, as we will explain later) and the excess internal negative charge causes the potential inside the cell membrane to be negative.

Membrane potential, capacitance and resistance

What determines the typical scale of neuronal membrane potential? The membrane potential should be small enough to allow neurons to take advantage of the thermal energy to transport ions across the membrane, but should also be large enough so that the thermal fluctuation does not destroy the electrical signaling in a neuron. These conditions imply that when an ion traverses across the membrane, the energy it gains or loses due to the potential difference may be on the same order of the thermal energy. The thermal energy of single ion is given by $k_B T$, where k_B is the Boltzman constant. Let's denote q as the charge of a single proton, we have

$$qV \sim k_B T \tag{1}$$

. Plugging into the real numbers, $k_B = 8.6 \times 10^{-5}$ eV/K, $T = 300$ K, we found that $V \sim 26$ mV. This sets the overall scale of the membrane potential. Experimentally, the membrane potential of a neuron varies between +50 mV to -80 mV, which is +2 to -3 times the estimated voltage.

Neurons with less complex morphologies have more uniform membrane potentials. These neurons are called electronically compact. When we could ignore the spatial variation of membrane potentials (or they do not seem to play a very important role), the electrical properties of a neuron is largely determined by its membrane capacitance and resistance (or conductance). The membrane capacitance C_m is proportional to the total surface area of a neuron, and the proportionality constant is called the specific membrane capacitance c_m is roughly the same for all neurons, $c_m \approx 10$ nF/mm^2. Surface area of neuron ranges between 0.01-0.1 mm^2, so the membrane capacitance for a whole neuron is typically 0.1-1 nF.

The membrane capacitance determines how much current is required to be injected to a neuron in order to make the membrane potential to change at a given rate. The membrane resistance R_m determines how much the voltage will shift from its current value (ΔV) when a small current is injected into a neuron ($\Delta V = I_m R_m$). The resistance is inversely proportional to the membrane surface area, and the specific membrane resistance r_m is around 1MΩ mm^2. For total surface area ranges between 0.01-0.1 mm^2, the total membrane resistance is about 10-100 MΩ.

The product of membrane capacitance and membrane resistance is called the membrane time constant, $\tau_m = R_m C_m = r_m c_m$, which is independent of the total membrane area of the neuron. It sets the basic time scale for changing the membrane potential, and it typically falls within 10-100 ms.

Reversal potential,Resting state and Equilibrium

Electric forces and diffusion are responsible for driving ions across the cell membrane. When a neuron is at its resting state, the current flow due to electric force should cancel the current flow caused by diffusion. What is the membrane potential at the resting state? Can we calculate it specifically? Without losing generality, Let us consider one case for an positive ion (i.e., K^+) with a negative membrane potential. The ion stays inside the cell and the potential outside the cell is higher than that inside. A positive ion inside the cell can cross the membrane only if it has sufficiently large thermal energy to overcome the electrical barrier. In other words, it must have a thermal energy at least $-zeV$ (where $ze > 0$ is the electric charge of the ion, and $V < 0$ is the membrane potential of the neuron. The probability that an ion has thermal energy E follows the Boltzmann distribution $\frac{1}{Z}\exp(-E/k_BT)$, and the probability that the ion can go cross the barrier is simply $\exp(zeV/k_BT)$: this is determined by integrating the Boltzmann distribution for energies $E \geq -zeV$. A concentration of ions inside the cell, n_{in}, that will be able to move across the membrane would be proportional to $n_{in}\exp(zeV/k_BT)$, and this should balance the ions flowing inside the cell, which will be proportional to n_{out}. Putting these things together, we obtain

$$n_{out} = n_{in}\exp(zeE/k_BT). \tag{2}$$

Solving this equation, we have

$$E = \frac{k_BT}{ze}\ln(\frac{n_{out}}{n_{in}}). \tag{3}$$

Equation 3 is the Nernst equation. The potential we derived is also called the reversal potential: the current flow for a particular type of ion switches its direction when crossing the reversal potential. The reversal potential for a K^+, denoted as E_K typically falls in the range between -70 and -90 mV; the reversal potential for Na^+, E_{Na}, is 50 mV or even higher; and E_{Ca}, for Ca^{2+} channels, is even higher, around 150 mV. Cl^- reversal potential are typically around -60 to -65 mV.

The Nernst equation only take into account one type of ion. However, some channels are not quite selective, and we need to combine the current flow from multiple ions, and the result is the Goldman-Hodgkin-Katz formula for reversal potential. I will write down the equation here, and it is your homework to provide the derivation of this formula.

$$E_m = \frac{k_BT}{e}\ln\left(\frac{\sum_{i=1}^{N} P_{M_i^+}[M_i^+]_{out} + \sum_{i=1}^{N} P_{A_j^-}[A_j^-]_{in}}{\sum_{i=1}^{N} P_{M_i^+}[M_i^+]_{in} + \sum_{i=1}^{N} P_{A_j^-}[A_j^-]_{out}}\right). \tag{4}$$

Sodium Anomaly, Ion Pumping and Membrane Current

Now let's go back and revisit the Nernst equation. In the literature, Equation 3 is also called the equilibrium potential: a steady-state membrane potential when the net current flow for a given type of ion is zero. The measured membrane potential of a neuron at the resting state is $\Delta V = -60\ mV$; the equilibrium potential for a K^+, typically falls in the range between -70 and -90 mV; Cl^- equilibrium potential are typically around -60 to -65 mV. Both are fairly close to the resting potential of a neuron. However, there are exceptions.

The equilibrium potential of sodium (+50 mV) is much more positive than the *actual resting potential of a neuron.*

All animal cells have a **sodium anomaly** of this type.

One possible explanation for such sodium anomaly might be that sodium and other ions such as calcium simply cannot permeate the membrane on the time scale of our experiment. This is partially true. In the resting state,

$$g_{\mathrm{K}^+} \approx 25 g_{\mathrm{Na}^+} \approx 2 g_{\mathrm{Cl}^-}$$

. However, the permeability of sodium is not exactly zero. On a longer timescale, the equilibrium would eventually be reached. How could we resolve this paradox?

The term "equilibrium potential" is actually quite misleading. A living cell is not at an equilibrium. Equilibrium is not life; it is death! Cells are constantly burning energy, and to combat to drive towards equilibrium. In fact, a specific molecular machine embedded in the cell membranes is constantly hydrolyzing ATP, then uses some of the resulting energy to pump sodium ions out of the cell. The active outward pumping current is compensating inward leakage sodium current so that the net current at the resting state is zero. At the same time the pump imports potassium, partially offsetting the loss of electric charge from the exported sodium. As a consequence, this working machine keeps $[\mathrm{K}^+]_{in} \gg [\mathrm{K}^+]_{out}$, and $[\mathrm{Na}^+]_{in} \ll [\mathrm{Na}^+]_{out}$.

When a neuron is not at the resting state, the total current flowing across the membrane through all of its ion channels is called the membrane current of the neuron. By convention, the membrane current is defined as positive when positive ions leave the neuron and negative when positive ions enter the neuron. Let us label different types of channels that may have selective permeability of specific types of ions with ndex i. As we discussed before, when the membrane potential of a neuron equals to the reversal potential E_i, $V = E_i$, the net current that traverses that channel becomes zero. For many channels, the current increases or decreases linearly with small difference of $V - E_i$. When we add the contribution from different type of ion channels, we have

$$I_m = \sum_i g_i (V - E_i), \tag{5}$$

where g is the ion channel conductances. In Equation 5, we must distinguish two types of conductances. Many ion channels embedded in the membrane are voltage-gated, and therefore the conductances g_i is also voltage-dependent. Some other conductances may be well approximated as voltage independent, such as the current from ion pump, as well as other leaky ion currents. These time-independent conductances could be lumped together by a single term $\bar{g}_L$, and the leaky membrane current I_L is given by:

$$I_L = \bar{g}_L (V - E_L), \tag{6}$$

where E_L is the resting potential of the neuron. Putting everything together, we may write down

$$C_m \frac{dV}{dt} = -\sum_i g_i(V - E_i) - \bar{g}_L(V - E_L) + I_e. \tag{7}$$