Neuron Doctrine

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Neuron, Axon, Dendrite

The nervous system comprised of two major categories of cells: neurons (nerve cells) and glia. A typical neuron has two kinds of neuronal processes. A long, thin process called axon often extends far beyond the cell body (soma). The total length of an axonal arbor per neuron is $\sim 4cm$. In contrast, the thick, bushy processes called dendrites are usually close to the soma . The total length of a dendritic arbor is $\sim 4mm$. The dendrites of many vertebrate neurons are decorated with small protrusions called dendritic spines, which likewise function in cell-to-cell information transfer. In mammalian brains, many axons will travel for long distances across different brain areas.

"cell theory" versus "reticular theory". The debate between Santiago Ramón y Cajal and Camillo Golgi.....

Information flow, Synapse, Convergence and Divergence

After systematically observing many types of neurons in different parts of the nervous system, Santiago Ramón y Cajal proposed a theory of dynamic polarization: the transmission of a neuronal signal takes place from dendrites and cell bodies to the axon. Every neuron has (1) a receptive component, the cell body and dendrites; (2)a projective component the axon.

The communication element between two neurons is called **synapse**. The observation of the fine structure of a synapse was made possible through the development of electron microscopy, a technique that allows the visualization of structures with nanometer (nm) resolution. This also sets the final proof that the processes of neurons do not fuse with each other. There are two kinds of synapses in the brain. Chemical synapses between cells is mediated by the release of chemicals called neurotransmitters. Electron micrographs reveal that a 20-100 nm gap, called the synaptic cleft, separates the axon from dendrite. The synaptic partners are not symmetrical: the presynaptic terminal of the neuron contains small synaptic vesicles filled with neurotransmitters, which, upon

stimulation, fuse into the membrane and release the neurotransmitters into the synaptic cleft. The postsynaptic target cell develops a postsynaptic density region that is enriched with receptors on their cell membrane that receive the neurotransmitters.

Neurons can also communicate with each other by electrical synapse between neurons. Here, each partner neuron contributes protein subunits to form gap junction channels that directly link the cytoplasm of two adjacent neurons.

Convergence is defined as the total number of inputs a neuron receives. *Divergence* is defined as the total number of outputs a neuron projects. In mammalian brains, convergence and divergence of a neuron is really high $\sim 10^3 - 10^4$.

Why do we have axons and dendrites?

Wiring Optimization Principles

"After the many shapes assumed by neurons, we are now in a position to ask whether this diversity ... has been left to chance and is insignificant, or whether it is tightly regulated and provides an advantage to the organism. ... we realized that all of the various conformations of the neuron and its various components are simply morphological adaptations governed by laws of conservation for time, space, and material." *Ramon y Cajal*

Given the high convergence and divergence of a neuron, it is a highly challenging task how the nervous system might wire itself to save time, space and material. Below, we will perform a few thought experiments and to argue that the existence of dendrites and axons, as well as the presence of dendritic spines could be a consequence of wiring up a large highly connected neuronal network in an allotted volume. We will also show that the actual lengths of axons and dendrites are close to the minimum length for a given interconnectivity.

Consider that we are wiring up a neuronal network with N neurons . This network may be a cortical column, which is thought as a basic functional unit for brain computation. Within a cortical column, all neurons can potentially make a synapse with each other. We ask: what could be the design that might minimize the total wiring volume?

Design I: Point-to-Point Axons

In the first and the simplest design, a synaptic connection between any pair of neurons requires a dedicated axon, which I call a point-to-point axon. To estimate the total volume of the wiring, we could use a scaling argument. The typical length of an axon that is dedicated to make one connection should be proportional to the linear dimension of the wiring volume R. Let's denote d as

the diameter of the axon, we have

$$R^3 \sim Nld^2.$$

Substituting $l \sim NR$ in the above equation, we obtain

$$R \sim Nd. \tag{1}$$

A cortical column of a mouse brain contains $N = 10^5$ neurons, and the typical diameter of an axon is $d = 0.3\mu m$. Substituting these numbers, we found that $R \sim 3$ cm, which is much larger than the actual ~ 1 mm size of a cortical column.

Design II: Axons with *en passant* synapses

Next, we calculate the volume with branching axons, or axons that make *en passant* synapses. In such as design, the axons can make a synapse with every cell body of a neuron it bypasses. Thus the total length of an axon is given by the number of neurons, N, times the typical interneuron distance. Assume uniform distribution of neurons, the typical interneuron distance is given by $R/N^{1/3}$, and thus we have

$$l \sim N^{2/3}R,$$

and the total volume of the neuropil is

$$R^3 \sim Nld^2 \sim N^{5/3}Rd^2.$$

Rewrite this equation, we obtain

$$R \sim N^{5/6}d. \tag{2}$$

Clearly, in the large limit of N, having an *en passant* design is better than point-to-point axon design, as the leading power over N is smaller. Plugging $N = 10^5$ into the Equation 2, we found that $R \sim 4.4mm$. However, this is still much larger than the size of a cortical column.

Design III: Axons and Dendrites

In the axon-only network, each axon has to make its way to every cell body. Rather than integrating the signal at the cell body, a smarter strategy is to introduce another process, which we will call dendrites and to meet the axon halfway. Below we shall calculate the probability that one neuron's axons could meet the other neuron's dendrites.

Axons and dendrites could meet each other if the processes are closer than segment diameter $\sim d$. In other words, if the dendritic and axonal segments could occupy the same voxel with a volume $\sim d^3$, then they can make a synapse

with each other. The probability that axon and dendrites will occupy the same voxel is given by the product of axonal and dendritic volume filling factor $\rho_{a,d}$:

$$P = \rho_a \rho_d,$$

where by symmetry

$$\rho_a = \rho_d = \frac{ld^2}{R^3}.$$

The total number of voxels in the volume is given by $(R/d)^3$, and the total number of contacts between axons and dendrites $n = P(R/d)^3$, and our constraint imposes $n \sim 1$. Putting the above equation together, we have

$$\frac{l^2 d}{R^3} \sim 1. \tag{3}$$

Now by combining the above equation with $R^3 \sim Nld^2$ and excluding l, we found

$$R \sim N^{2/3} d. \tag{4}$$

Comparing equation 4 with the equation 2, the scaling exponent on N is further reduced.

Design IV: Branching Axons and Spiny Dendrites

Design III may be further reduced by the addition of dendritic spines, which expand the reach of the dendrites without increasing their length. Spine has a typical length of 2 μm. However, spine has a very narrow spine neck, and its volume is much smaller than a dendrite with the same length. If we include spines, then Equation 3 becomes

$$\frac{l^2 s}{R^3} \sim 1 \tag{5}$$

Now the size of the neural network become

$$R \sim N^{2/3} \frac{d^{4/3}}{s^{1/3}}. \tag{6}$$

Optimality of the design

Plug Equation 4 back into Equation potential synapse constraint with spine, we found that the length of the process is given by

$$l \sim N \frac{d^2}{s} \tag{7}$$

Indeed, this is the minimum length of the axon/dendrite we could achieve. No other design could reduce the length of the process by order of magnitude.

How does a neuron generate an action potential?

What is the physical basis of information flow within neurons? Studies of muscle contraction in response to electrical stimulation of motor nerves suggested that an elementary nerve impulse underlies different stimulus strength.Edgar Adrian and his group systematically measured nerve impulses from somatosensory neurons that convey information about touch, pain to the spinal cord. They found that individual nerve impulses were of identical size and shape whether strong or weak sensory stimuli were induced. However, increasing the stimulus strength also increased the frequency nerve impulses, but not the inherent properties of each impulse.

The concept of "action potential", and the concept of "firing rate" of a neuron can be introduced.

However, not all neurons fire action potentials. In peripheral sensory regions as well as in some invertebrates (such as *C. elegans* and many neurons in the vertebrate retina),membrane potential of a neuron can change in continuous values as opposed to *all-or-none*, and communication within these neurons use graded potentials.

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, 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.

Membrane potential, capacitance and resistance

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.

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_BT, where k_B is the Boltzman constant. Let's denote q as the charge of a single proton, we have

$$qV \sim k_BT \tag{8}$$

. 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.

As we discussed in the previous lectures, neurons have long axons and dendrites for receiving inputs and sending outputs to thousands other neurons. The dendritic and axonal intracellular resistance could cause substantial difference in membrane potential in different part of a neuron. 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

$$n_{out} = n_{in}\exp(zeE/k_BT). \tag{9}$$

Solving this equation, we have

$$E = \frac{k_BT}{ze}\ln(\frac{n_{out}}{n_{in}}). \tag{10}$$

Equation 10 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.

$$E_m = \frac{k_BT}{e}\ln\left(\frac{\sum_{i=1}^{N} P_{M_i^+}[M_i^+]_{out} + \sum_{i=1}^{N} P_{A_j^-}[A_j^-]_{in}}{\sum_{i=1}^{N} P_{M_i^+}[M_i^+]_{in} + \sum_{i=1}^{N} P_{A_j^-}[A_j^-]_{out}}\right). \tag{11}$$

Sodium Anomaly, Ion Pumping and Membrane Current

Now let's go back and revisit the Nernst equation. In the literature, Equation 10 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,

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

. However, the permeability of sodium is not exactly zero. On a longer time-scale, 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 $[K^+]_{in} \gg [K^+]_{out}$, and $[Na^+]_{in} \ll [Na^+]_{out}$.

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

$$I_m = \sum_i g_i (V - E_i), \tag{12}$$

where g is the ion channel conductances. In Equation 12, 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:

$$I_L = \bar{g}_L(V - E_L), \tag{13}$$

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

$$C_m \frac{dV}{dt} = -\sum_i g_i(V - E_i) - \bar{g}_L(V - E_L) + I_e. \tag{14}$$

Integrate-and-Fire Models

Neurons possess a large repertoire of voltage-gated ion channels that regulate the membrane conductances, making the neuronal activity higher nonlinear. One prominent feature in the activity pattern of many invertebrate and vertebrate neurons is the existence of action potential, or spike. In mammalian brains, action potential is the basic unit for information transmission. Clearly, the above-mentioned RC circuit cannot be used to describe such nonlinear dynamics. It was in 1952, through a series of elegant experimental and theoretical papers, Hodgkin and Huxley provides a detailed biophysical description of action potential generation and propagation. This work won them the Nobel Prize in 1963.

We will ignore Hodgkin and Huxley, temporarily. On the other hand, neuron models can be simplified and simulations can be accelerated dramatically if the biophysical mechanisms responsible for action potentials are not explicitly included in the model. Integrate-and-fire model (I-F model) is a much simplified, but extremely useful model to describe spike generation. It is widely used in the neuroscience community. In the I-F model, we ignore the voltage dependent term in Equation 14. We only include the linear leaky term together with an *ad-hoc* spiking event. Here the spike is modelled as the point event and it does not have temporal width. The timing of a spike is defined as the time where the membrane potential V reaches the firing threshold value, V_{th}, from below. Whenever a spike occurs the voltage is reset immediately to a lower value, which for simplicity will be taken as $V_{reset} = E_L$. In other words, $V(t^-_{spike}) = V_{th}$, and $V(t^+_{spike}) = V_{reset}$. Now if we define a new variable

$$\tilde{V} = (V - V_{reset})/(V_{th} - V_{reset}),$$

and denote

$$I_c = g_L(V_{th} - V_{reset}),$$

the RC equation together with the resetting event can be rewritten as

$$\begin{aligned} \tau \frac{d\tilde{V}}{dt} &= -\tilde{V} + \frac{I_e}{I_c} \\ \tilde{V}(t^-_{spike}) &= 1 \\ \tilde{V}(t^+_{spike}) &= 0 \end{aligned} \tag{15}$$

To understand the input-output relationship of a neuron, an important quantity that needs to be derived is the dependence of the firing rate, f, on the applied external current I_e. This can be calculated straightforwardly. The time that required to reach the threshold membrane potential is simply given by

$$\frac{I_e}{I_c}(1 - \exp(-t/\tau)) = 1 \tag{16}$$

Rearrange this equation and note that $f = 1/t$, we obtain

$$f = -\frac{1}{\tau \ln(1 - I_c/I_e)}. \tag{17}$$

For large current I_e, using $\ln(1 + x) \approx x$, the f-I relationship reduces to

$$f \approx \frac{I_e}{I_c \tau} \tag{18}$$

The firing rate grows linearly with the input current for large I_e.

Now let us examine some experimental data. Real neuron exhibits spike-rate adaptation: the interspike intervals lengthen over time when a constant current is injected into the cell, before a steady-state value is reached. Nevertheless, if one only uses the first two spikes fired by the neuron in response to the injected current, the results agree quite well with the I-F model. The steady-state firing rate can also be fitted by an I-F model, but using a different set of parameters. Another important factor we have not taken into account in our simplest model is the refractory effect: the probability that a neuron fires significantly reduced for a short period of time after the appearance of a spike. This can also be incorporated into the model.