**Physics 178/278 - David Kleinfeld - Winter 2020 - Week 1**

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# 1 Single neuron computation and the separation of integration and signaling

This overview serves to connect simple notions of statistical physics with neuronal signal integration, decision making, and communication.

## 1.1 Ions and Voltages

A good place to start is with a fundamental issue, the scale of the potentials across cell membranes relative to the thermal noise floor. We further discuss how these potentials are used to form pulses, or action potentials, that allow one cell to communicate with another. We shall see that the Boltzman energy at room temperature, i.e., the thermal energy, serves to define a band of voltages that can be used to integrate and process nervous activity, and that the same energy acts as a barrier to isolate integration of inputs from output and communication.

## 1.2 The Nernst Potential

Containers comprised of lipid walls provide a means to separate high concentrations from low concentrations of ions. Why is this useful? If we recall a little bit of thermodynamics, we realize that a difference in ion concentration leads to a potential, and thus work can be done. Thus, one could conceivably build a device that is capable of communicating to all agents along the surface of a bag, or some topological equivalent, that a disturbance has occurred at a point. Let's run through this.

Consider a world that consists of two compartments, labeled "in" and "out". The compartments are separated by a thin wall. To make this situation somewhat real, we will fill both compartments with water and consider the diffusion of ions in the water. We take these ions to be $Na^+$ and $Cl^-$, the ions that result from dissolving ordinary table salt. On the inside of the container, the concentration of ions is denoted $[Na^+]_{in}$ and $[Cl^-]_{in}$ and on the outside they are denoted $[Na^+]_{out}$ and $[Cl^-]_{out}$, where concentration is in units of $molecules/cm^3$ or, in chemistry, in units of moles per liter or $Molar(M)$.

To get a feel for the scale of $moles/liter$, lets put it into terms relevant for the size of a cell, i.e., ions per cubic micrometer. In a biological cell, the ion concentration is about 0.15 M, so we have about $10^8 ions/\mu m^3$ in a cell.

We set the container up so that, initially, $[Na^+]_{in} = [Cl^-]_{in}$ and $[Na^+]_{out} = [Cl^-]_{out}$. This ensures that individual compartments are electrically neutral. Further, we impose $[Na^+]_{out} > [Na^+]_{out}$, so that the ion concentrations are initially greater on the outside than the inside. Since there is a wall between the two sides, there is clearly no interaction between the two compartments.

We now remove the wall in entirety. What happens? The $Na^+$ ions will flow down their concentration difference, so that ultimately $[Na^+]$ is the same on both sides of the membrane. Similarly, the $Cl^-$ ions will flow down their gradient. Thus after some time the concentration of ions is the same on both sides, so that no energy is extracted from the concentration difference. A side remark is that there is a transient potential difference if the mobility of $Na^+$ and $Cl^-$ are different.

What is the trick necessary to get the concentration difference across the two sides of the wall to turn into a sustained electrical potential? The idea is to make a hole that allows only one kind of ion to pass. This is called an ion selective pore. To be concrete, we open up a hole that allows $[Na^+]$ ions, but not $[Cl^-]$ ions, to pass. This is a $Na^+$ selective pore, or $Na^+$ selective channel. Recall that $[Na^+]$ is higher outside than inside.

The process works as follows:

- Initially, the $[Na^+]$ moves down its concentration gradient, driven by diffusion.
- As $Na^+$ ions move across the wall, the solutions in the two compartments are no longer electrically neutral. Positive charge (from the $Na^+$) leaves the outside and builds up on the inside. This leads to an electric field across the wall.
- The electric fields points from the inside to the outside. This field is the direction that opposes motion of additional $Na^+$ ions.
- In time, the electric field caused by the initial movement of ions points from the inside to the outside. This field is the direction that opposes motion of additional $Na^+$ ions and will prevent any more $Na^+$ ions from moving. As this point the system is in equilibrium.

The result is that the concentration difference in $Na^+$ ions across the wall has been used to form a difference in electrical potential across the cell. The relation between concentration differences and electrical potential is given by the Nernst equation, which equates the electrical potential, eV, with the chemical potential, $\mu$, caused by the concentration difference, i.e.,

$$\mu = \left(\frac{\partial F}{\partial N}\right)_{T,V} = -k_B T \frac{\partial ln Z}{\partial N} = -k_B T \frac{\partial ln \frac{\xi^N}{N!}}{\partial N} = k_B T \, lnN \; + \; \text{constant} \qquad (1.1)$$

for $N >> 1$ so that we can approximate $N!$ by Sterling's formula. Thus

$$V = \frac{k_B T}{e} ln \frac{[Na^+]_{out}}{[Na^+]_{in}} \qquad (1.2)$$

We see immediately that $V$ is on the order of $\frac{k_B T}{e} \approx 25$ mV. Before we worry about details, let's think about how big this is on the scale of the electrical noise expected for this process.

## 1.3 Thermal Fluctuations in Voltage

The pore in the membrane gives rise to a conductance $G$ across the cell. This leads to a fluctuation in the potential, known as the Johnson noise, of size

$$\delta V = \sqrt{\frac{4k_B T \Delta f}{G}} = \sqrt{\frac{k_B T}{C}} \tag{1.3}$$

where we used

$$\Delta f = \int_0^\infty df \, \frac{1}{1 + (2\pi f (C/G))^2} = \frac{G}{4C}. \tag{1.4}$$

Another way to derive the equation fo the noise is us the equipartition theorem to equate the fluctuating energy in the membrane to the thermal energy, i.e.,

$$\frac{1}{2} C \delta V^2 = \frac{1}{2} k_B T \tag{1.5}$$

The capacitance is given by $C = \epsilon_m$ (area/thickness), so that for a thin dielectric sphere of thickness $L$ and radius $a$, $C = \epsilon_m \frac{4\pi a^2}{L}$. For most all cells, the ratio $\frac{\epsilon_m}{L}$ is

$$c_m \equiv \frac{\epsilon_m}{L} \approx 1.0 x 10^{-14} \frac{F}{\mu m^2}. \tag{1.6}$$

Thus

$$\delta V = \sqrt{\left(\frac{k_B T}{e}\right)\left(\frac{L}{\epsilon_m}\right)\frac{e}{4\pi a^2}} = \frac{1}{2a}\sqrt{\left(\frac{k_B T}{e}\right)\left(\frac{e}{c_m}\right)\frac{1}{\pi}}. \tag{1.7}$$

For a neuron of radius $a = 20\mu m$, the noise level is found to be $\delta V \approx 20\mu V$. **The important result is that the membrane noise level for cells is much less than the thermal voltage** $k_B T/e$, where

$$\frac{k_B T}{e} \approx 25 mV \tag{1.8}$$

Only at the smallest structure, the synaptic vesicle, or synaptosome, with outer radius $a \approx 30$ to 50 nm, is the noise level likely to approach the thermal voltage. Let's thus look at the fluctuation in the number of ions across the cell. In synaptic vesicles, the membrane potential $\Delta V$ is set by a hydrogen ion, or $pH$ gradient. Then

$$\Delta V = \frac{k_B T}{e} ln \frac{[H^+]_{out}}{[H^+]_{in}} = \frac{k_B T}{e} \left(pH_{in} - pH_{out}\right). \tag{1.9}$$

Typically, $pH_{in} \approx 5$ and $pH_{out} \approx 7.5$. The variance in the transmembrane voltage in terms of ion concentration is

$$\delta V = \left| \frac{\partial \Delta V}{\partial [H^+]_{in}} \delta [H^+]_{in} \right| = \frac{k_B T}{e} \left| \frac{\delta [H^+]_{in}}{[H^+]_{in}} \right| \tag{1.10}$$

We equate noise level this with the expression for Johnson noise to get

$$\frac{\delta [H^+]_{in}}{[H^+]_{in}} = \sqrt{\frac{e^2}{k_B T C}} = \sqrt{\left(\frac{e}{k_B T}\right)\frac{1}{c_m}\frac{e}{4\pi a^2}} \tag{1.11}$$

An interesting number is the value of the radius $a$ for which the fluctuations in ion concentration are of order unity, i.e., $\frac{\delta[H^+]_{in}}{[H^+]_{in}} \approx 1$. We call this $a_{crit}$, where

$$a_{crit} = \sqrt{\frac{1}{4\pi}\left(\frac{e}{k_B T}\right)\frac{e}{c_m}} \approx 7nm \tag{1.12}$$

This corresponds to an inner diameter of 15 nm. The walls add about another 10 nm for a total outer diameter of $\approx$ 25 nm, which is a a bit less than the observed outer diameter of vesicles . Not too bad as an estimate of the smallest "cell".

In the larger picture, the cell membrane may have selectively permeable channels to more than one ion. Thus the final potential may represent a steady state rather than an equilibrium value. In fact, nature uses two ions, $K^+$ and $Na^+$, to set two potentials, one low and one high. The presence of a voltage-dependent (nonlinear) conductance, one of the major findings of the century, allows the cell to switch between these two levels.

Let's review the gist of this - the details will be the topic of another lecture. In the simplest, or Hodgkin Huxley cell, there are three major conductances, those due to $K^+$, $Na^+$, and $Cl^-$. The equilibrium potential for each of these ions is

- $V_{K^+} = \frac{k_B T}{e} ln \frac{[K^+]_{out}}{[K^+]_{in}} \approx -75mV$
- $V_{Na^+} = \frac{k_B T}{e} ln \frac{[Na^+]_{out}}{[Na^+]_{in}} \approx +50mV$
- $V_{Cl^-} = \frac{k_B T}{e} ln \frac{[Cl^-]_{out}}{[Cl^-]_{in}} \approx -55mV$

The steady state potential for a system with these three ions and associated membrane permeabilities $P_{Na^+}$,$P_{K^+}$, and $P_{Cl^-}$, is derived by considering the diffusion equation for the total flux of ions through the cell membrane and is found is standard textbooks an the Nerst-Planck equation.

$$V_{SS} = \frac{k_B T}{e} ln \frac{P_{K^+}[K^+]_{out} + P_{Na^+}[Na^+]_{out} + P_{Cl^-}[Cl^-]_{in}}{P_{K^+}[K^+]_{in} + P_{Na^+}[Na^+]_{in} + P_{Cl^-}[Cl^-]_{out}} \approx -50mV \tag{1.13}$$

The important point is that the steady state potential is dominated by the ion that has the maximal conductance. The resting level is dominated by the $K^+$ conductance.

## 1.4 Fundamentals of the Action Potential

The essential ingredient that allows signaling is that the conductance for $Na^+$ is voltage dependent. This is reminiscent of the drain-to-source conductance in a FET, which is a nonlinear function of the voltage to the gate.

A nice way to think of this, which we will discuss in detail, is that the current-voltage relationship has an essential nonlinearity. Thus for small disturbances of the membrane potential, the cell returns to the resting potential. However, for current injections beyond some critical value, the potential will jump to a new

equilibrium point. A simplified model makes use of a voltage dependent change in the conductance for one of two ions. To be concrete, we take a cell with a solely Ohmic potassium current, $G_{K^+}$, and a voltage dependent sodium conductance, $G_{Na^+}(V)$, that has a value of zero below a threshold potential, $V_{th}$, and that is constant above $V_{th}$ with value $G_{Na^+}(V_\infty)$.

Thus we have a current-voltage relation given by

$$I(V) = \begin{cases} G_{K^+}V - G_{K^+}V_{K^+} & \text{if } V < V_{th} \\ \left(G_{K^+}G_{Na^+}(V_\infty)\right)V - \left(G_{K^+}V_{K^+} + G_{Na^+}(V_\infty)V_{Na^+}\right) & \text{if } V > V_{th} \end{cases}$$

where, in this approximation, $V_{Na^+}$ and $V_{K^+}$ are the $Na^+$ and $K^+$ Nernst potential for sodium and potassium, respectfully. This relation is discontinuous at $V_{th}$ and Ohmic below and above this potential. There are two equilibrium values for $V$ below or above $V > V_{th}$. These are found by setting $I(V) = 0$, so

$$V_{equil} = \begin{cases} V_{K^+} & \text{if } V < V_{th} \\ \frac{G_{K^+}V_{K^+} + G_{Na^+}(V_\infty)}{G_{K^+} + G_{Na^+}(V_\infty)} & \text{if } V > V_{th} \end{cases}$$

We consider a pulse of current that causes the cell to change from the lower to the upper curve. This represents the front of the action potential. The shift in equilibrium potential from $V_{K^+}$ to $\frac{G_{K^+}V_{K^+} + G_{Na^+}(V_\infty)}{G_{K^+} + G_{Na^+}(V_\infty)}$ occurs in roughly $10^{-4}s$. On the longer time scale of $10^{-3}s$, relaxation processes associated with the $Na^+$ current and the activation of an additional voltage dependent $K^+$ current cause the front to decay, so we are left with a pulse.

**The critical lesson is that neurons use two voltage levels, and at least one voltage dependent conductance, to shift between the two levels.**

We now know how neurons signal, and that the signaling, at least in principle, operates well above the physical limits to membrane noise. We put off the issue of variability in the transmission of spikes between cells - suffice it to say that at some synapses, e.g., those formed as calyces, the failure rate is very low indeed.

## 1.5 Separation of Subthreshold Dendritic Integration and Communication

Our final point concerns how a neuron performs logic, which is to say how it separates the integration of synaptic inputs from the decision making that leads to the production of an action potential. We require a band of voltages over which the cell can integrate, that is summate, synaptic inputs. The range of this band must clearly be larger than the scale of thermal noise and also large compared to the activation of the $Na^+$-based action potential. Given the experimental fact that the $Na^+$ channel turns on through the action of 4 charges, the range of synaptic integration is expected to exceed $\Delta V > k_BT/4e \approx 6$ mV. This range corresponds to the difference between the $K^+$ reversal potential (the lowest voltage for inhibitory inputs) and the activation of the $Na^+$-based action potential, a range of about 1-1/2-times $k_BT/e \sim 35$ mV. Others may argue that the level is the reversal potential for $Cl^-$,

the dominant inhibitory input in mammals. In this case the range is about 1-times $k_BT/e \sim 25$ mV. Either way, we see that the scale for integration is always of order $k_BT/e$ and is always large compared to the noise level across the membrane.

How large are the post-synaptic potentials that impinge on the cell? This distribution has been measured by a number of investigators in pair-electrode measurements, where current is injected into the presynaptic cell to induce an action potential and measured in the post-synaptic. cell. The typical values are around 0.5 mV or less, or a very small fraction of $k_BT/4e$. But a small percentage, maybe 5 %, come in at a few millivolts. Thus coactivation of a small number of inputs can, in principle, drive a neuron to spike. The issue is an open research question; see handout on Mrsic-Flogel data.

The above argument suggest that the cell has headroom for integration without firing an action potential for insignificant changes in input. We now consider how a cell can isolate the synapse from integration. The idea is that the action potential must be large enough activate a process whose turn-on occurs far from the range of synaptic activation. This implies that the activation of synaptic transition, which occurs over a range voltage, must be separated from the range of voltage $\Delta$ V $> k_BT/4e \approx 6$ mV that governs the activation of the inward $Na^+$ current.

Synaptic activation depends on a chemical cascade that is initiated by the activation of a high-threshold voltage gated (N-type) $Ca^{2+}$ current. This current peaks at intracellular potentials of about + 5 mV, significantly less than $V_{Na^+}$ . Thus there is headroom of order of $2k_BT/e \sim 50$ mV that separates the turn-on of the action potential from the turn-on of synaptic transmission, so that dendritic integration *per se* cannot lead to synaptic release, or communication, until the threshold for spiking is crossed. Further, the shape of the action potential will impact the total flux through the high-threshold voltage gated $Ca^{2+}$ current to influence synaptic release.