Lecture 10
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10 Voltage scales of Neuronal Dynamics

We previously learned that neurons use two voltage levels, and at least one voltage dependent conductance, to shift between the two levels. The fundamental scale is the thermal scale, or

$$\frac{k_B T}{e} \approx 25\ mV. \tag{10.1}$$

We now consider this viewpoint in terms of synaptic transmission and noise immunity. We also consider the smallest scale, that of thermal noise, and the consequences of noise.

10.1 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 (Figure 1). The range of this band must clearly be larger than the scale of thermal noise, which we will discuss later but is less than 0.1 mV, and also large compared to the activation of the Na^+-based action potential.

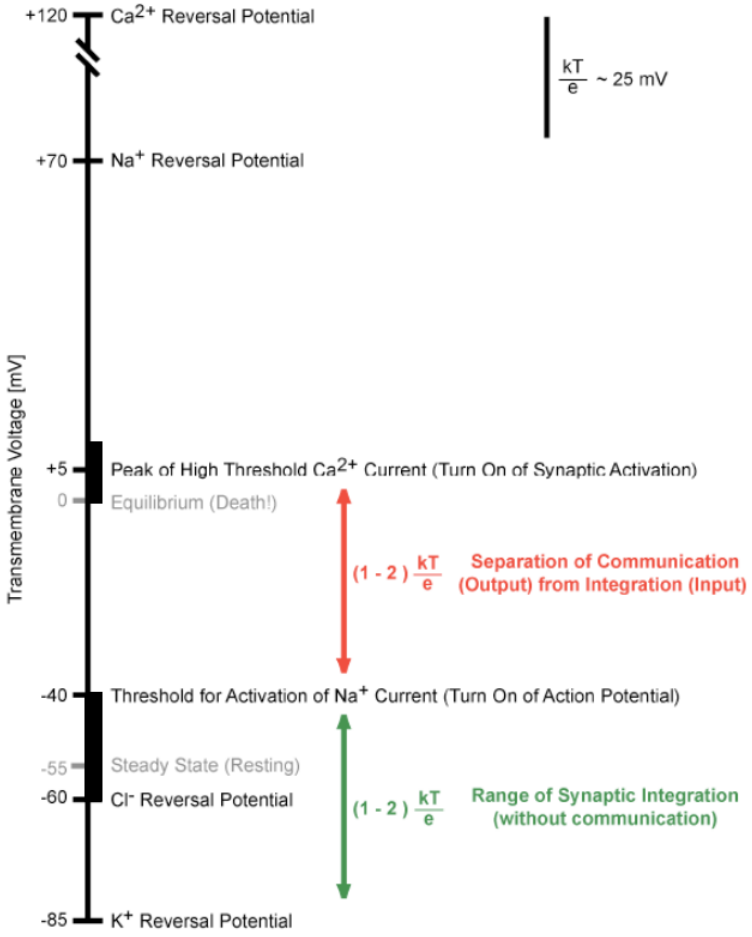
The threshold for spiking, i.e., the transition from the region of synaptic integration to the action potential, is not sharp. Activation of the Na^+ channels occurs over the range of the transition of $P_{act}^{open}(V,\infty)$, where we recall

$$P_{act}^{open}(V,\infty) = \frac{1}{1+e^{-\frac{z'e(V-V_{bias})}{k_B T}}}. \tag{10.2}$$

Empirically, three gates must concurrently open, as implied by the m^α term in the Hodgkin Huxley equation for $dV(t)/dt$, with $\alpha = 3$. On the other hand, the Na^+ only needs to exceed the restoration current. A conservative estimate is one-half voltage range from the slope of the opening curve, i.e.,

$$\text{Range} \equiv \frac{1}{2}\left[\frac{d\left(P_{act}^{open}(V,\infty)\right)^\alpha}{dV}|_{V=V_{bias}}\right]^{-1} \tag{10.3}$$

Figure 1: The voltage scales for a neuron. Most of the time the cell is in the ranges defined by the thick black bands for integrating or communicating.



$$
\begin{aligned}
&= \frac{1}{2}\left[\frac{z'\alpha e}{k_B T}\left(P_{act}^{open}(V,\infty)\right)^{\alpha-1}\left(1-P_{act}^{open}(V,\infty)\right)|_{V=V_{bias}}\right]^{-1} \\
&= \frac{1}{2}\left[\frac{z'\alpha}{2^{\alpha}}\frac{e}{k_B T}\right]^{-1} \\
&= \frac{2^{\alpha-1}}{z'\alpha}\frac{k_B T}{e} \\
&\approx 7\ mV.
\end{aligned}
$$

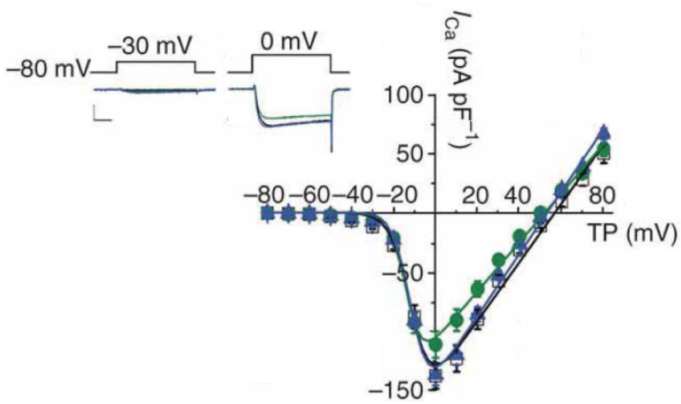
where we used the nominal value z' $\approx$ 4.5. Since all that we need to have is for the Na^+ current exceed all leakage currents, this is an overestimate.

The range of synaptic integration corresponds to the difference between the K^+ reversal potential, i.e., the lowest voltage for inhibitory inputs, and the activation of the Na^+-based action potential, a range of about 1-1/2-times $k_B T/e \sim 35$ mV (Figure 1). Thus is about five-times the range of the active the Na-current Others

may argue that the lowest voltage for the range of synaptic integration is the reversal potential for Cl^-, the dominant inhibitory input in mammals. In this case the range of integration 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 (Figure 1).

How high are the action potentials? We want to isolate the region of integration from that of communication. The above arguments implies that the gap above threshold should be one- to two-times k_BT/e, which is what is found. Further, we need to action potential to turn off synaptic release, This depends on activation an "N"-type CA^{2+} current, which had a peak current for a voltage of +5 mV (Figure 2).

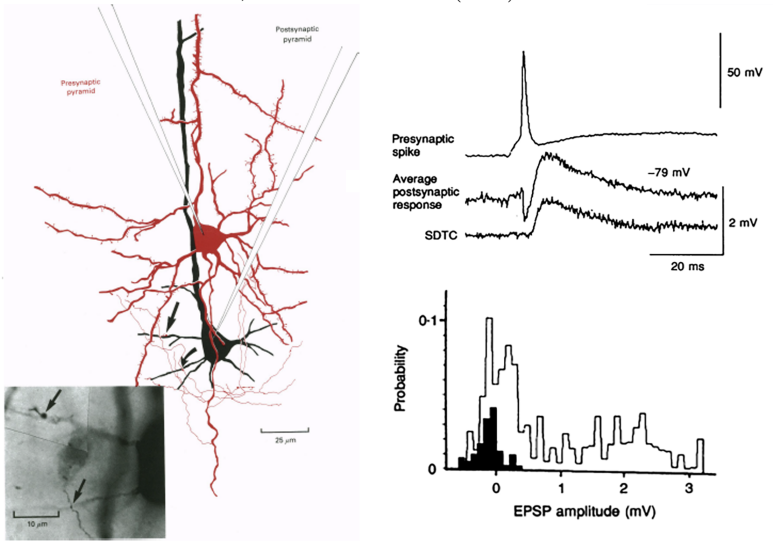
Figure 2: Activation of the voltage-gated calcium current that initiates neurotransmission.



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 (Figure 3). Thus coactivation of a small number of inputs thus can, in principle, drive a neuron to spike (Figure 4). The issue is an open research question that we will soon cover in terms of the balance of excitatory and inhibitory currents in cells. This value is larger than the typical value of postsynaptic inputs.

To recap, the action potential results from an instability in the conductance (negative conductance), such that the direction of the membrane current transiently reverses (growth) in response to a perturbative current. Eventually, the conductance saturates and recovers to a linear response. In both cases, the cell is leaky and

Figure 3: Pair-wise measurements of synaptic potentials among layer 5 and 6 neurons in rat cortex slice. From Deuchars, West and Thomson (1996)



the effective time-constant is transiently very short, so that the width of the action potential is small, less than one millisecond in some cases.

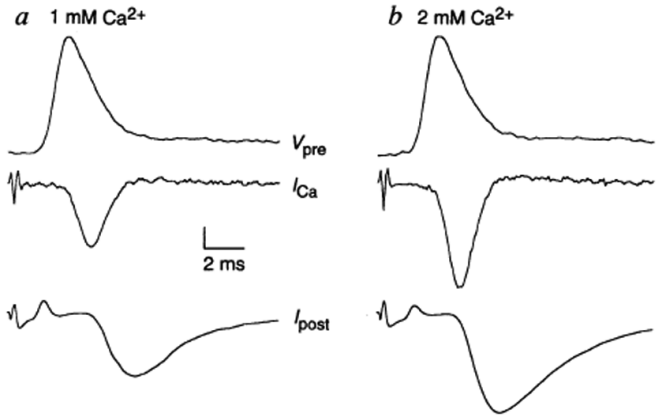
10.2 Synaptic interaction

Synaptic activation, which we will not discuss in detail, depends on a chemical cascade that is initiated by the activation of a high-threshold voltage gated (N-type) Ca^{2+} current (Figure 5). 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.

10.3 Thermal Fluctuations

Now that we know the scale of the voltages, we next consider the size of the intrinsic fluctuations in the membrane voltage. Ion flow across the membrane is defined by a net conductance, G, across the cell. This leads to a fluctuation in the potential (Figure 6), known

Figure 4: Synaptic transmission at two levels of $[Ca^{2+}]_{external}$. Top level is presynaptic potential, the middle is presynaptic $[Ca^{2+}]_{intracellular}$, and the bottom is postsynaptic current (bar = 46 pA). The data is taken at 18C; the time delay is shorter (0.5 ms versus 2 ms) at T = 25C. From Sabatini and Regehr 1996



as the Johnson noise, of size

$$\begin{aligned} \delta V &= \sqrt{\frac{4k_BT\Delta f}{G}} \\ &= \sqrt{\frac{k_BT}{C}} \end{aligned} \tag{10.4}$$

where we used

$$\begin{aligned} \Delta f &= \int_0^\infty df\ \frac{1}{1+(2\pi f(C/G))^2} \\ &= \frac{G}{4C}. \end{aligned} \tag{10.5}$$

This noise has the same spectral power density at all frequencies. This is different that other sources of noise, like $1/f$ noise, that has origins in processes occurring of a variety of energy scales (Figure 7).

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

$$\frac{1}{2}C\delta V^2 = \frac{1}{2}k_BT \tag{10.6}$$

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

$$\delta V = \sqrt{\left(\frac{k_BT}{e}\right)\left(\frac{L}{\epsilon_m}\right)\frac{e}{4\pi a^2}} \tag{10.7}$$

Figure 5: Electron micrograph of a synapse and scheme of the SNARE/SM protein fusion scheme that regulates Ca^{2+} driven neurotransmission. Scheme from Sudhof, 2013

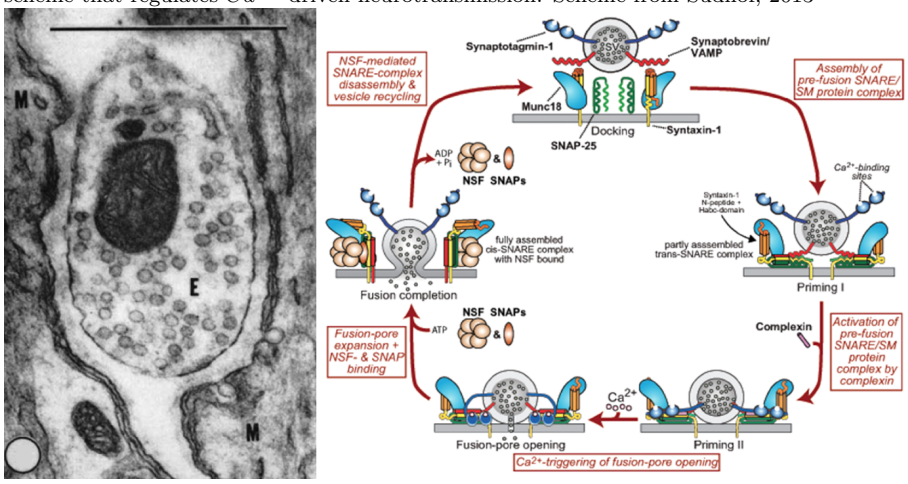
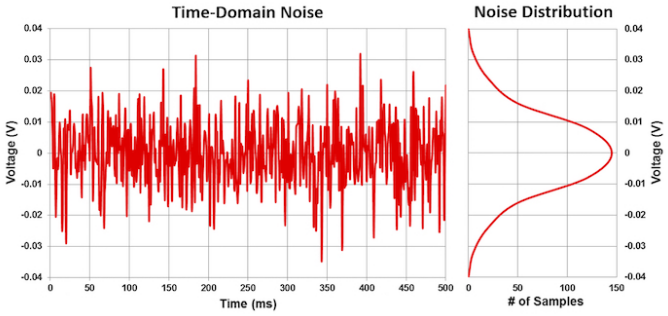


Figure 6: Johnson noise and Gaussian amplitude distribution



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$$= \frac{1}{2a}\sqrt{\left(\frac{k_B T}{e}\right)\left(\frac{e}{c_m}\right)\frac{1}{\pi}}.$$

For most all cells, the ratio $\frac{\epsilon_m}{L}$ is

$$\begin{aligned} c_m &\equiv \frac{\epsilon_m}{L} \\ &\approx 0.9x10^{-14}\frac{F}{\mu m^2} \end{aligned} \tag{10.8}$$

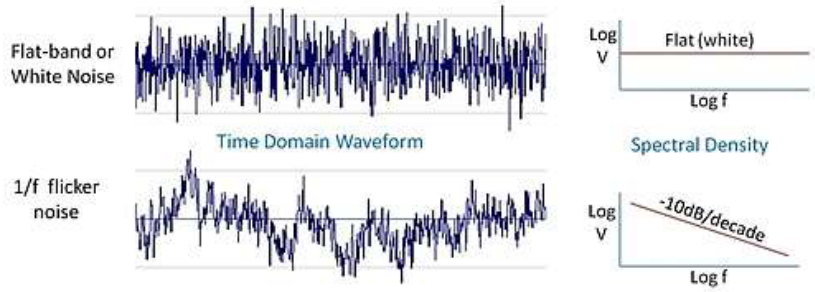
and

$$\frac{e}{c_m} = 1.8 \times 10^{-2}\frac{mV}{\mu m^2} \tag{10.9}$$

so that

$$\delta V \approx \frac{190\mu V}{a\ (\text{in } \mu m)}. \tag{10.10}$$

Figure 7: Johnson noise and 1/f noise



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For a cell of radius $a = 10\mu m$,

$$\delta V \approx 20\mu V. \tag{10.11}$$

The important result is that the membrane noise level for cells is much less, by three orders of magnitude, than the thermal voltage k_BT/e.

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 ΔV is set by a hydrogen ion, or pH gradient. Then

$$\begin{aligned} \Delta V &= \frac{k_BT}{e} ln \frac{[H^+]_{out}}{[H^+]_{in}} \\ &= \frac{k_BT}{e} \left(pH_{in} - pH_{out} \right). \end{aligned} \tag{10.12}$$

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

$$\begin{aligned} \delta V &= \left| \frac{\partial \Delta V}{\partial [H^+]_{in}} \delta [H^+]_{in} \right| \\ &= \frac{k_BT}{e} \left| \frac{\delta [H^+]_{in}}{[H^+]_{in}} \right| \end{aligned} \tag{10.13}$$

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

$$\begin{aligned} \frac{\delta [H^+]_{in}}{[H^+]_{in}} &= \frac{e}{k_BT} \sqrt{\frac{k_BT}{C}} \\ &= \sqrt{\left(\frac{e}{k_BT} \right) \frac{1}{c_m} \frac{e}{4\pi a^2}}. \end{aligned} \tag{10.14}$$

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

$$a_{crit} = \sqrt{\frac{1}{4\pi}\left(\frac{e}{k_B T}\right)\frac{e}{c_m}} \tag{10.15}$$

$$\approx 7nm \tag{10.16}$$

This corresponds to an inner diameter of 15 nm. The walls add about another 10 nm for a total outer diameter of ≈ 25 nm, which is a bit less than the observed outer diameter of vesicles (Figure 8). Not too bad as a limiting estimate of the smallest "cell".

Figure 8: Synapse loaded with vesicles