Physics 178/278 - David Kleinfeld - Winter 2021 - Lecture 8

Revised 1 Feb 2021 17:57

8 The Biophysics of Action Potentials in "Point" Neurons 1

We now step back and visit the nature of spike generation by neurons. This is a prelude to a discussion of "realistic" models of neurons, noise in neuronal output and integrations, and a discussion of spike-by-spike synchronization between cells.

Figure 1: Spikes are the currency of neuronal computation and communication. From Bellavance, Takatoh, Lu, Demers, Kleinfeld, Wang and Deschnes, 2017.

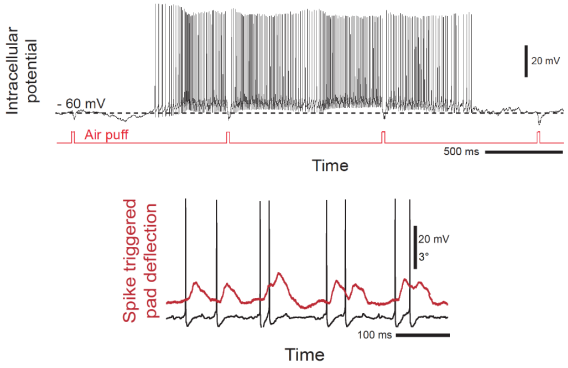
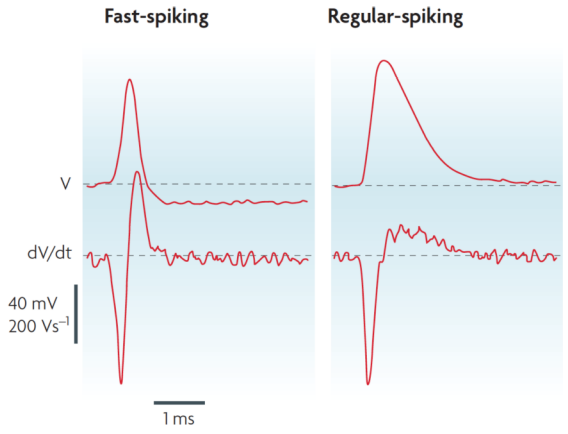


Figure 2: The Na^+ current leads to a similar rise across different classes of neurons. From McCormick, Connors, Lighthall and Prince, 2009.



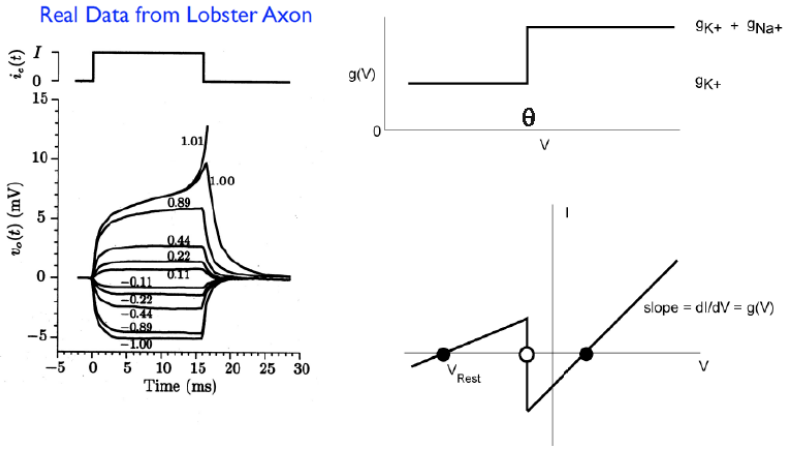
8.1 Fundamentals of the Action Potential

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. The conductance for Na^+ provides the leading edge of the action potential and we now focus on this.

A nice way to think of voltage dependence, 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 $G_{Na^+}(V_\infty)$.

Figure 3: The onset phase of an action potential. The data (left) shows the onset occurs just above a threshold current of $I = 1.00$ while the cartoon shows how a change in the total conductance at threshold voltage, θ, leads to a bistable behavior and switching of the stable point from rest to top of the action potential.



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

Figure 4: The slower recovery phase of an action potential. The Na^+-current begins to turn-off and a K^+ current turns on and the membrane potential returns to rest.

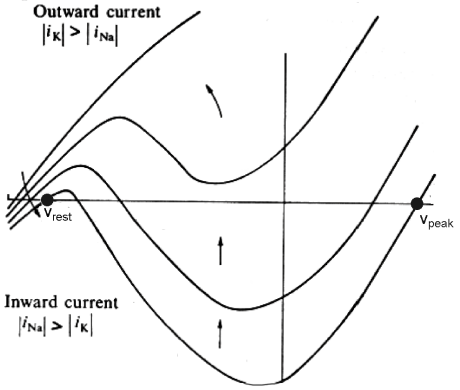
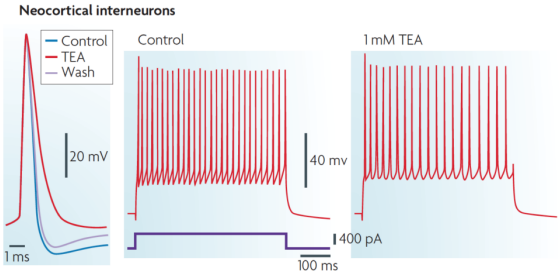


Figure 5: Voltage-gated potassium conductances, which are blocked by TEA, can shape the width of the action potential. From Erisir, Lau, Rudy and Leonard., 1999



and the activation of an additional voltage dependent K^+ current cause the front to decay, so we are left with a pulse.

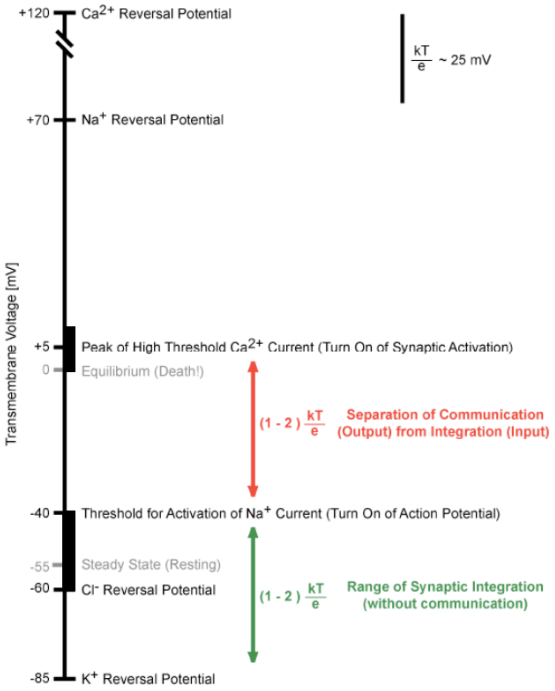
The critical lesson is that neurons use two voltage levels, and at least one voltage dependent conductance, to shift between the two levels.

8.2 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 $\Delta V > k_B T/4e \approx 6$ 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 $k_B T/e \sim 35$ mV. Others may argue that the level is the reversal potential for Cl^-,

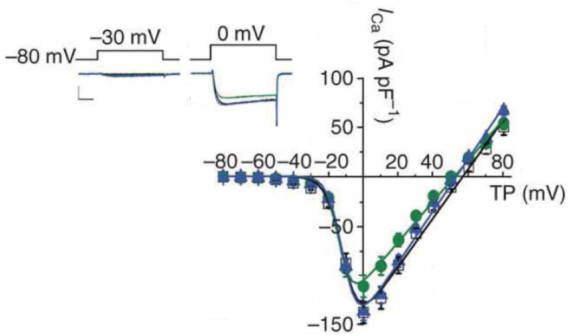
the dominant inhibitory input in mammals. In this case the range is about 1-times $k_BT/e \sim 25$ mV. Either way, we see that the scale for integration is always of order k_BT/e and is always large compared to the noise level across the membrane.

Figure 6: 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.



How how is 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.

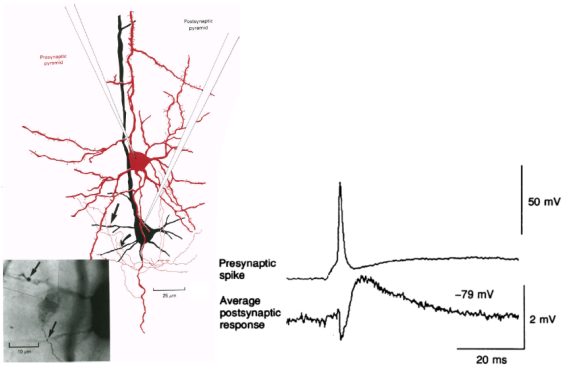
Figure 7: Activation of the voltage-gated calcium current that initiates neurotransmission.



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 mea-

surements, 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 as we will discuss when we consider the balance of excitatory and inhibitory currents in cells.

Figure 8: Synaptic interaction between two infragranular neurons in mouse cortex slice. The post-synaptic potential in this example is unusually large, likely from multiple contacts between the cells.. From Deuchers, Thompson and West, 2001



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 Δ V $> k_BT/4e \approx 6$ mV that governs the activation of the inward Na^+ current.

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 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.

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. 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.

Figure 9: Electronmicrograph of a synapse and scheme of the SNARE/SM protein fusion scheme that regulates Ca^{2+} driven neurotransmission. Scheme from Sudhof, 2013