

1 Single neuron computation and the separation of processing 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 an overview of how sensitive and robust nervous systems are. We consider 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 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

Bags 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 box, 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/cm³* or, in chemistry, in units of moles per liter or *Molar(M)*.

To get a feel for the scale of *moles/liter*, let's 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 $10^8 \text{ ions}/\mu\text{m}^3$ in a cell.

Suppose we set the box up so that, initially, $[Na^+]_{in} = [Cl^-]_{in}$ and $[Na^+]_{out} = [Cl^-]_{out}$. This insures that individual compartments are electrically neutral. Further, we impose $[Na^+]_{out} > [Na^+]_{in}$, 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.

Suppose 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 field 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, μ , caused by the concentration difference, i.e.,

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

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

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

We see immediately that V is on the order of $\frac{k_B T}{e} \approx 25mV$. 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

Because there is a pore, there is a conductance G across the cell. This leads to a fluctuation in the potential, known as the Johnson noise, of size

$$\delta V = \sqrt{\frac{4k_B T \Delta f}{G}} = \sqrt{\frac{k_B T}{C}} = \sqrt{\left(\frac{k_B T}{e}\right) \left(\frac{L}{\epsilon_m}\right) \frac{e}{4\pi a^2}} = \frac{1}{2a} \sqrt{\left(\frac{k_B T}{e}\right) \left(\frac{e}{c_m}\right) \frac{1}{\pi}} \quad (1.3)$$

where we used

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

Further, $C = \epsilon_m$ (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

$$c_m \equiv \frac{\epsilon_m}{L} \approx 1.0 \times 10^{-14} \frac{F}{\mu m^2}. \quad (1.5)$$

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 that for cells the noise level is much less than the thermal voltage $k_B T/e$, where**

$$\frac{k_B T}{e} \approx 25mV \quad (1.6)$$

Only at the smallest structure, the synaptic vesicle with radius $a \approx 10^{-2}\mu m = 10nm$, will the noise level approach the thermal voltage, so that for $a \approx 10^{-2}\mu m$ we have $\delta V \approx 10mV$. Actually, the case of vesicles is interesting, in that we can turn the argument around and 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

$$\Delta V = \frac{k_B T}{e} \ln \frac{[H^+]_{out}}{[H^+]_{in}} = \frac{k_B T}{e} (pH_{in} - pH_{out}). \quad (1.7)$$

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

$$\delta V = \frac{\partial \Delta V}{\partial [H^+]_{in}} \delta [H^+]_{in} = \frac{k_B T}{e} \frac{\delta [H^+]_{in}}{[H^+]_{in}} \quad (1.8)$$

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

$$\frac{\delta [H^+]_{in}}{[H^+]_{in}} = \sqrt{\frac{4e^2}{k_B T C}} = \sqrt{\left(\frac{e}{k_B T}\right) \frac{1}{c_m} \frac{e}{\pi a^2}} \quad (1.9)$$

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

$$a_{crit} = \sqrt{\frac{1}{\pi} \left(\frac{e}{k_B T} \right) \frac{e}{c_m}} \approx 30nm \quad (1.10)$$

This is on the small side of the observed radius of vesicles, or synaptosomes, which is not too bad as an estimate of the smallest "cell".

A slightly different way to look at the noise issue is to recall that $Q = \Delta N e = C \Delta V$, where N is the number of ions responsible for the net charge imbalance across the membrane. If we substitute this expression for C into the formula for Johnson noise, the "Signal-to-Noise" ratio for the cell is

$$\frac{\text{"Signal"}}{\text{"Noise"}} \equiv \frac{\Delta V}{\delta(\Delta V)} = \frac{1}{2} \sqrt{\Delta N \frac{\Delta V}{k_B T / e}} \quad (1.11)$$

The dependence on the square root of ΔN is intuitive. Note that the above expressions need to be modified if the conductance is not set by a static pore, but a pore that fluctuates open and closed. In the latter case, the fluctuations cut off at some high temporal frequency. But the major story holds.

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

$$V_{SS} = \frac{k_B T}{e} \ln \frac{P_{K^+} [K^+]_{out} + P_{Na^+} [Na^+]_{out} + P_{Cl^-} [Cl^-]_{in}}{P_{K^+} [K^+]_{in} + P_{Na^+} [Na^+]_{in} + P_{Cl^-} [Cl^-]_{out}} \approx -50mV \quad (1.12)$$

This relation is derived by considering the diffusion equation for the total flux of ions through the cell membrane and is found in standard textbooks as the Nernst-Planck equation. 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

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

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.

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 potential from $V = V_{K^+}$ to $V = \frac{G_{K^+}V_{K^+} + G_{Na^+}(V_\infty)}{G_{K^+} + G_{Na^+}(V_\infty)}$ 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 Dendritic Integration and Communication

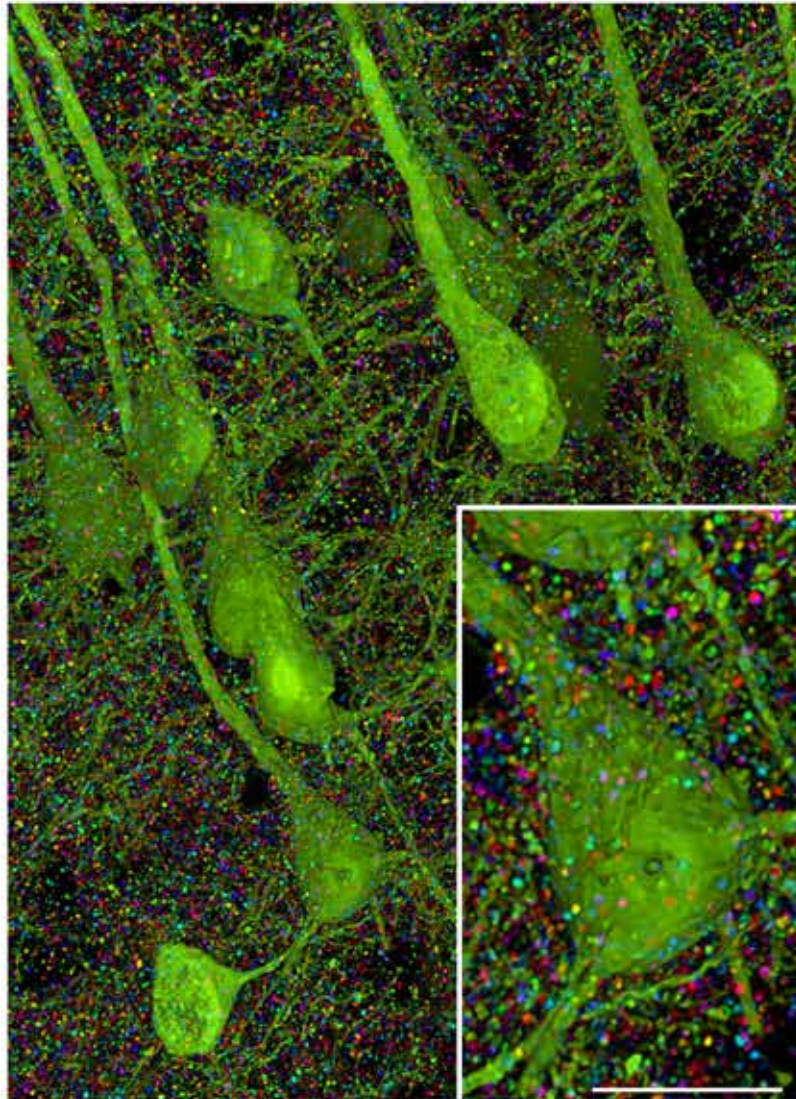
Our final point concerns how a neuron performs logic, which is to say how it separates the integration of synaptic inputs from the decision making that leads to the production of an action potential. We require a band of voltages over which the cell can integrate, that is summate, synaptic inputs. The 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 $k_B T / e \sim 25$ mV. Either way, we see that the scale for integration is always of order $k_B T / e$ 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 $k_B T / 4e$. 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 $\Delta V > k_B T / 4e \approx 6$ 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 Ca^{2+} current. This current peaks at intracellular potentials of about + 5 mV, less than V_{Na^+} of course. Thus there is headroom of order of $2k_B T / e \sim 50$ 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.



General synaptic markers

Glutamatergic presynaptic markers

Glutamatergic postsynaptic markers

GABAergic presynaptic markers

GABAergic postsynaptic markers

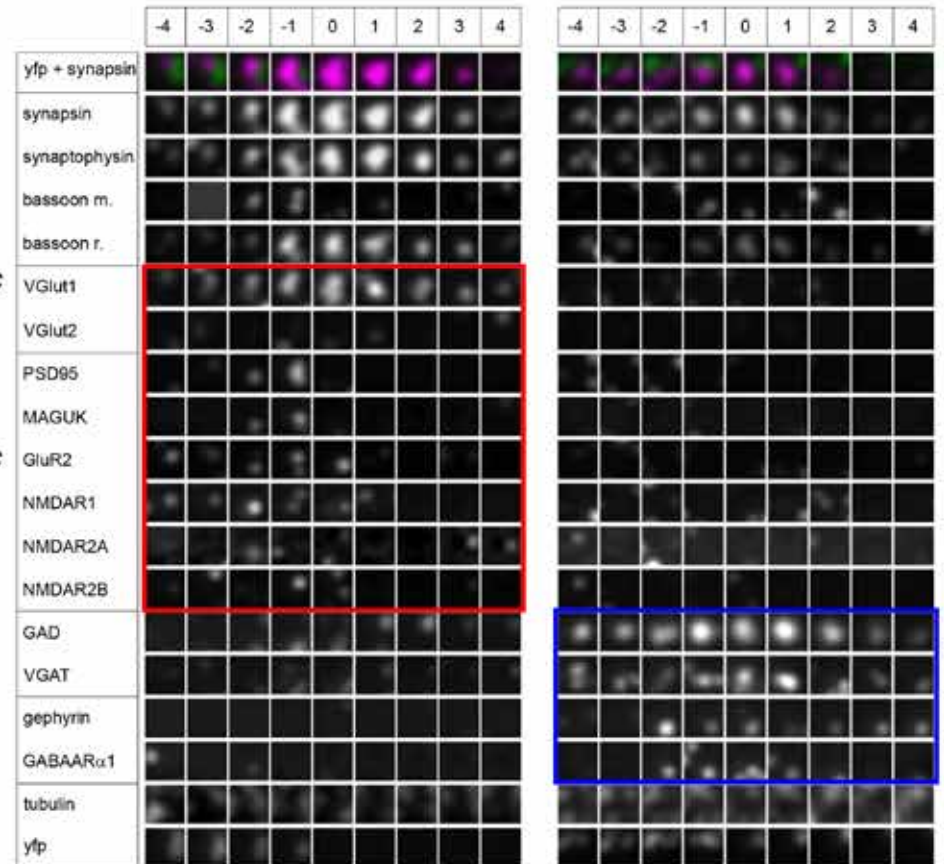
Structural markers

Glutamatergic synapse

GABA synapse

← Serial sections →

← Serial sections →



Micheva KD, Smith SJ (2007) Array tomography: A new tool for imaging the molecular architecture and ultrastructure of neural circuits. *Neuron* 55:25-36.

Micheva KD, Busse B, Weiler NC, O'Rourke N, Smith SJ (2010) Single-synapse analysis of a diverse synapse population: Proteomic imaging methods and markers. *Neuron* 68:639-653.

Pia

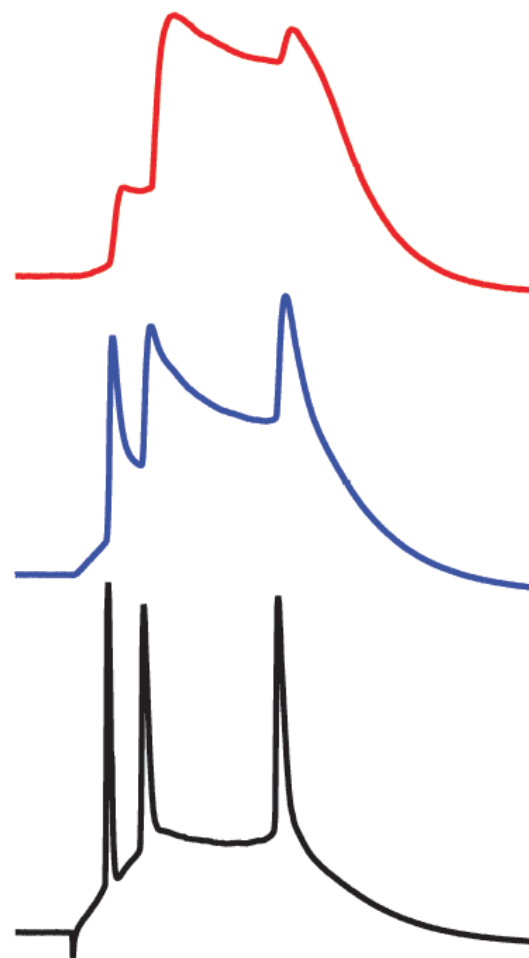
L1

L2/3

L4

L5

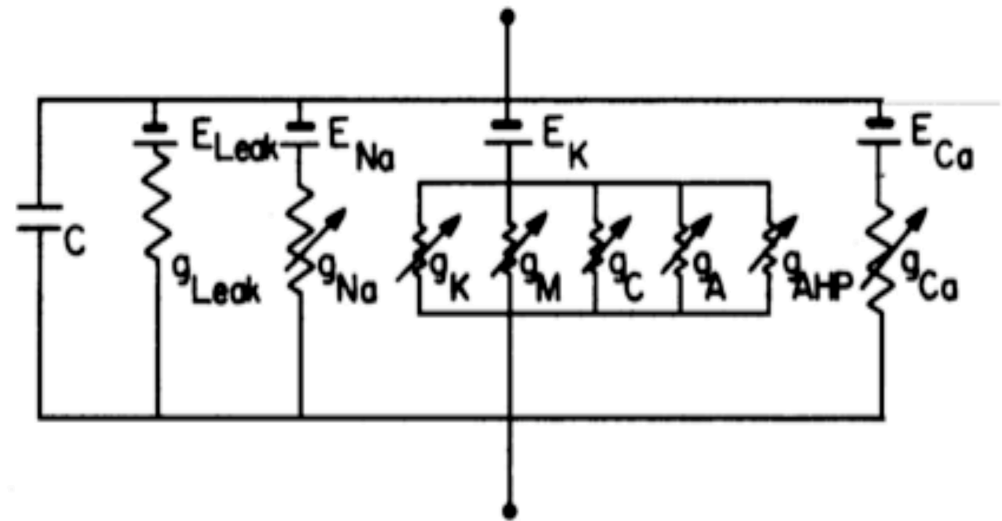
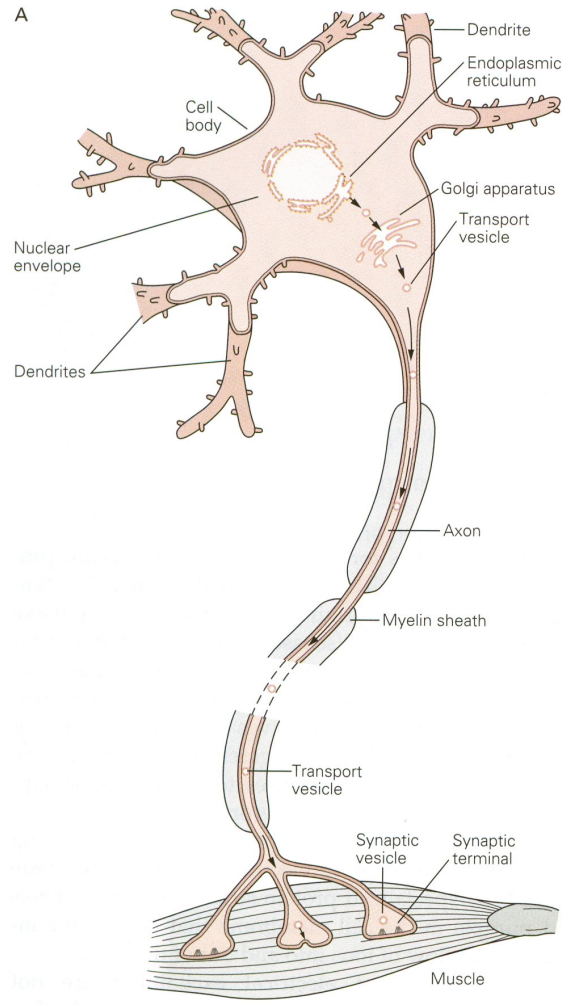
100 μm



40 mV

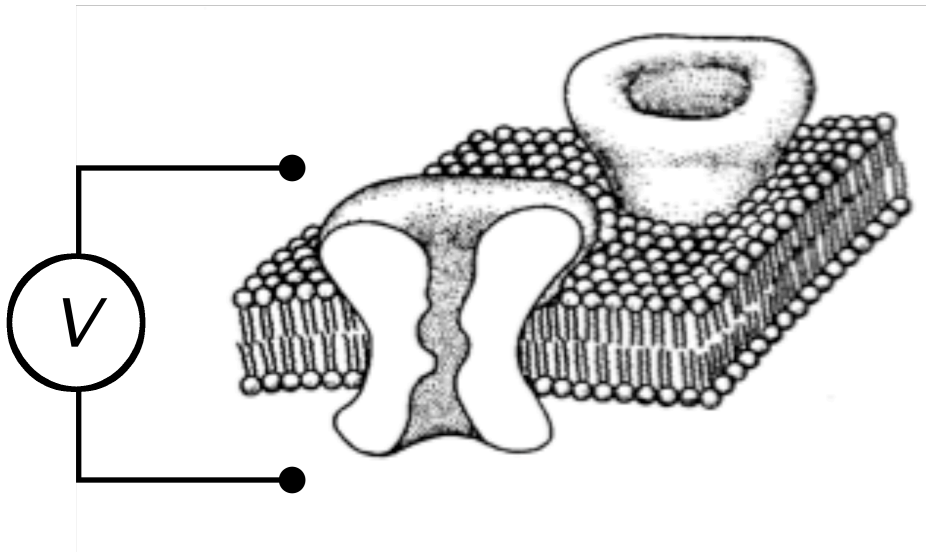
20 ms

Equivalent Circuit Model of a Neuron



Resting Potential: Electrochemical Equilibrium

$$V = \frac{K_B T}{e} \ln \frac{[X]_{out}}{[X]_{in}}$$



$$V = -65 \text{ mV}$$

Common Ionic Concentrations

TABLE 2.1

Extracellular and Intracellular Ion Concentrations

<i>Ion</i>	<i>Concentration (mM)</i>	
	<i>Intracellular</i>	<i>Extracellular</i>
Squid neuron		
Potassium (K ⁺)	400	20
Sodium (Na ⁺)	50	440
Chloride (Cl ⁻)	40–150	560
Calcium (Ca ²⁺)	0.0001	10
Mammalian neuron		
Potassium (K ⁺)	140	5
Sodium (Na ⁺)	5–15	145
Chloride (Cl ⁻)	4–30	110
Calcium (Ca ²⁺)	0.0001	1–2

$$E_K = -75 \text{ mV}$$

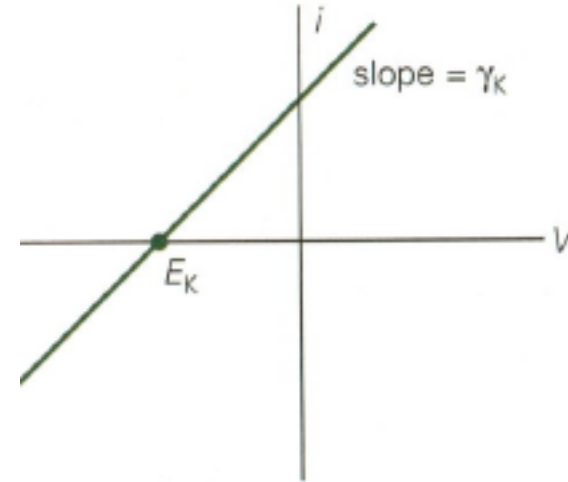
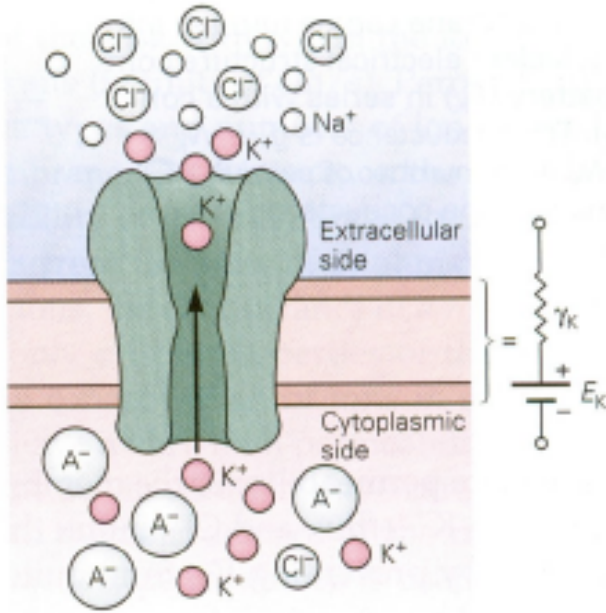
$$E_{Na} = +55 \text{ mV}$$

$$E_{Cl} = -70 \text{ mV}$$

$$E_{Ca} \approx +150 \text{ mV}$$

Out of Equilibrium

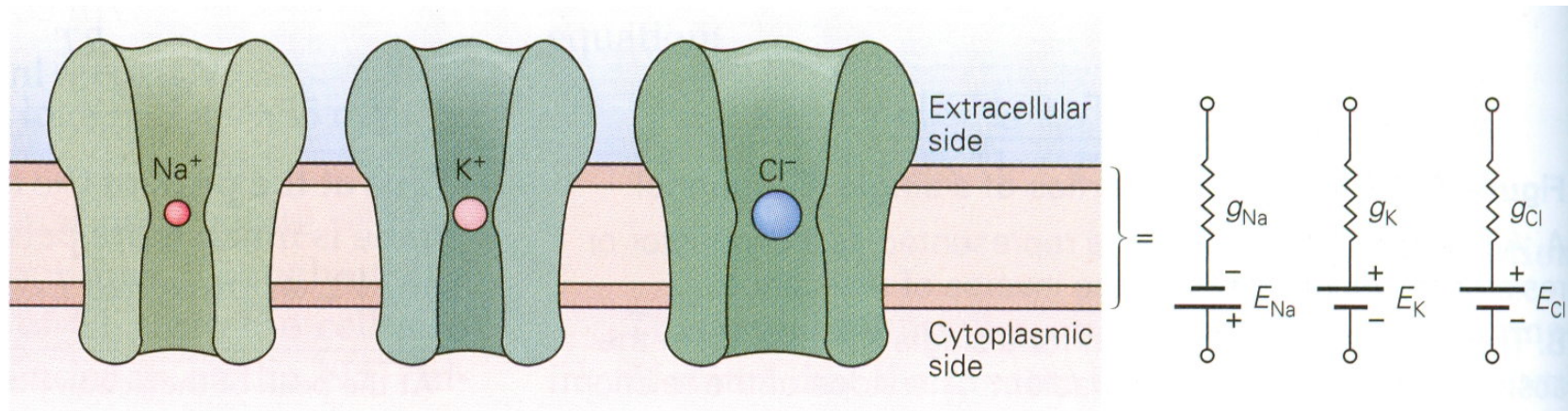
- For $V > V_x$ current flows into cell: $I_x > 0$
- For $V < V_x$ current flows out of cell: $I_x < 0$
- I - V curve (current-voltage):



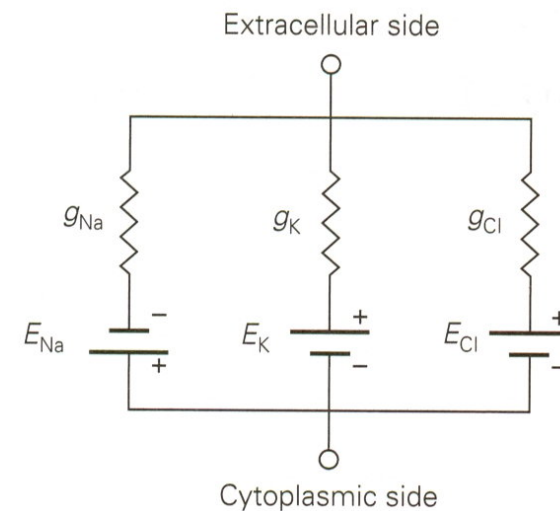
$$I_K = \gamma_K (V - V_K)$$

Multiple Kinds of Ions

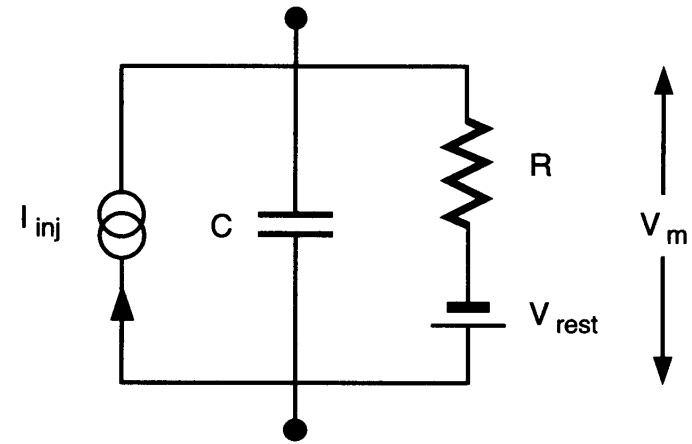
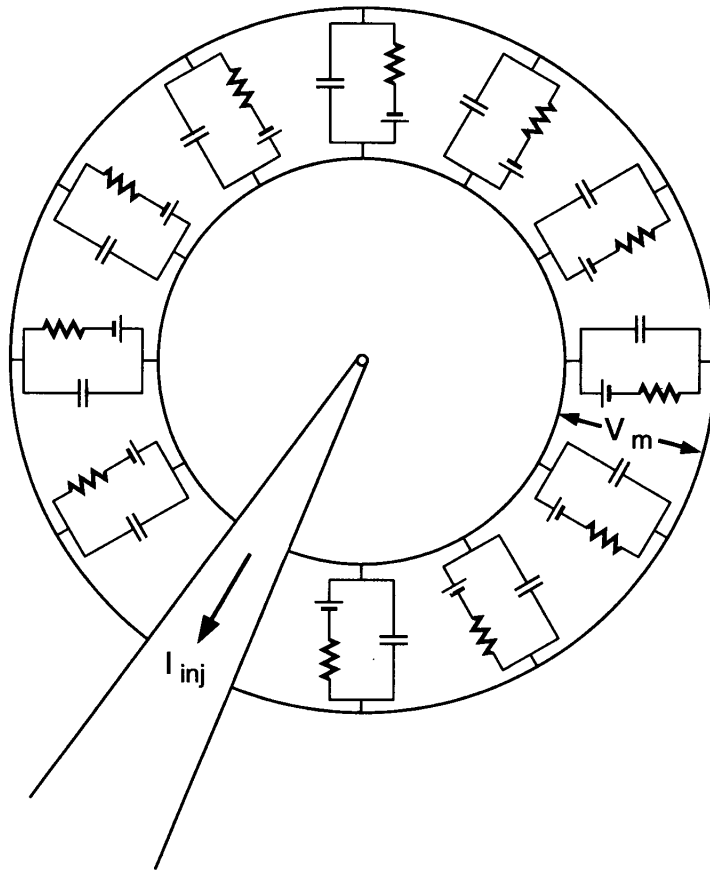
- Several I - V curves in parallel:



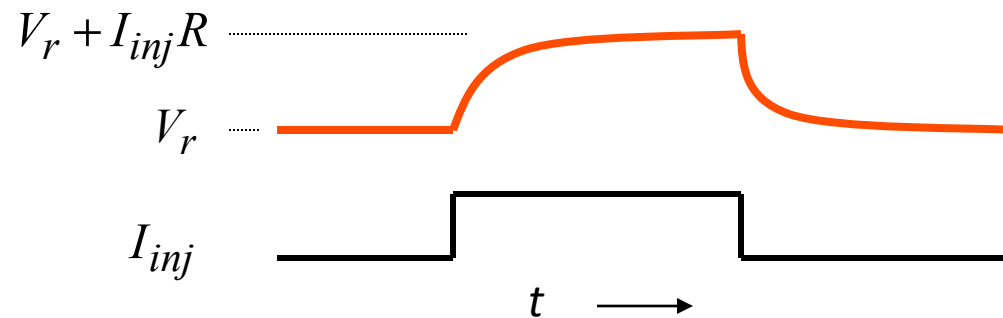
- New equivalent circuit:



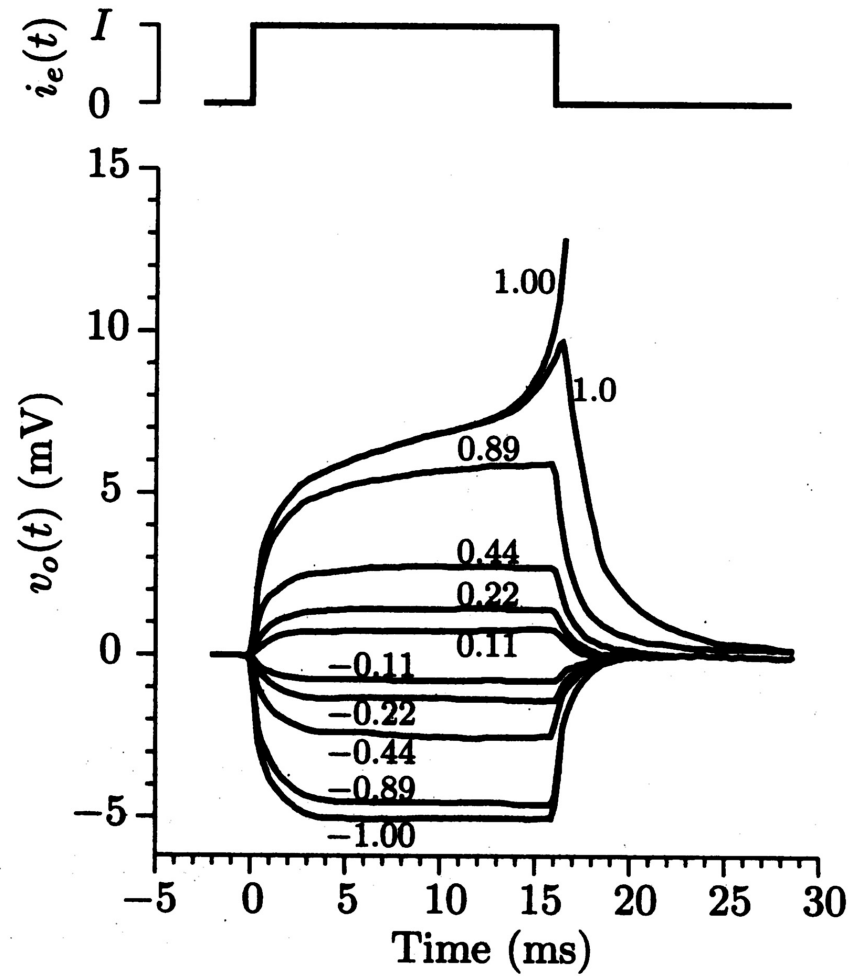
Compact Cell Model (isopotential voltage)

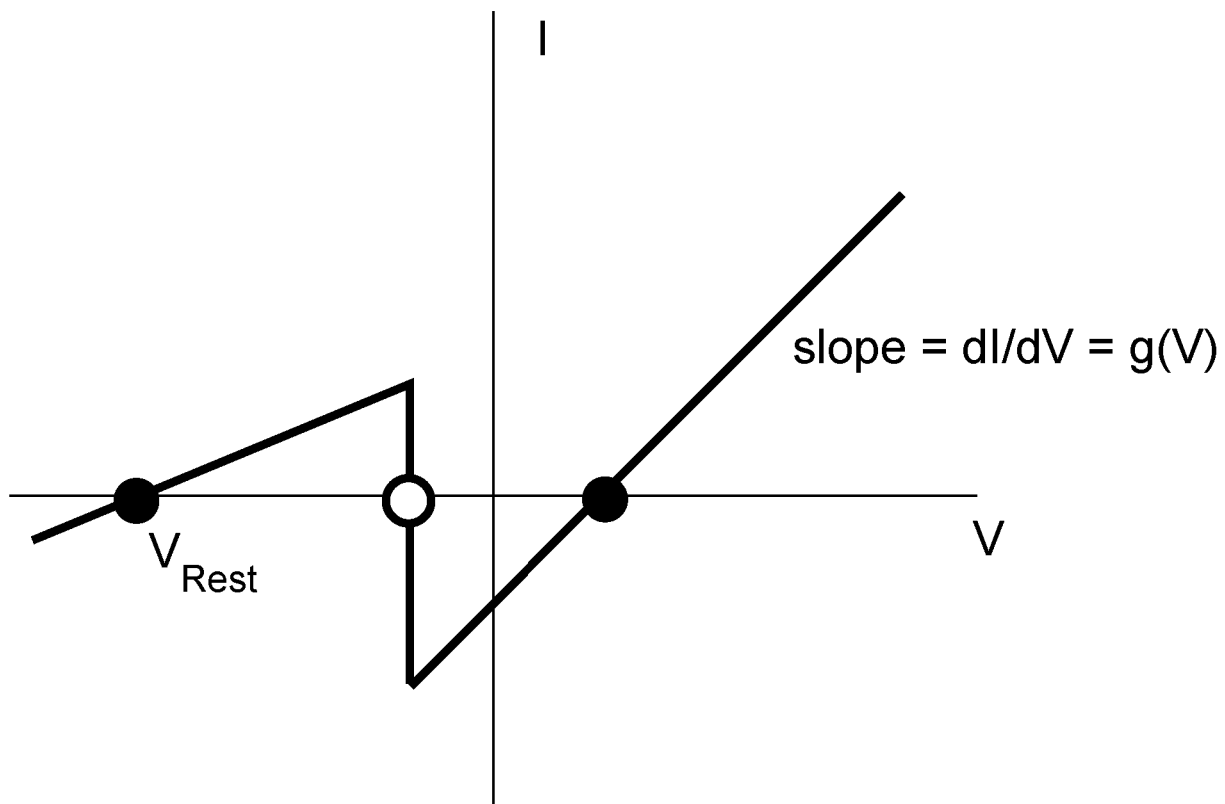
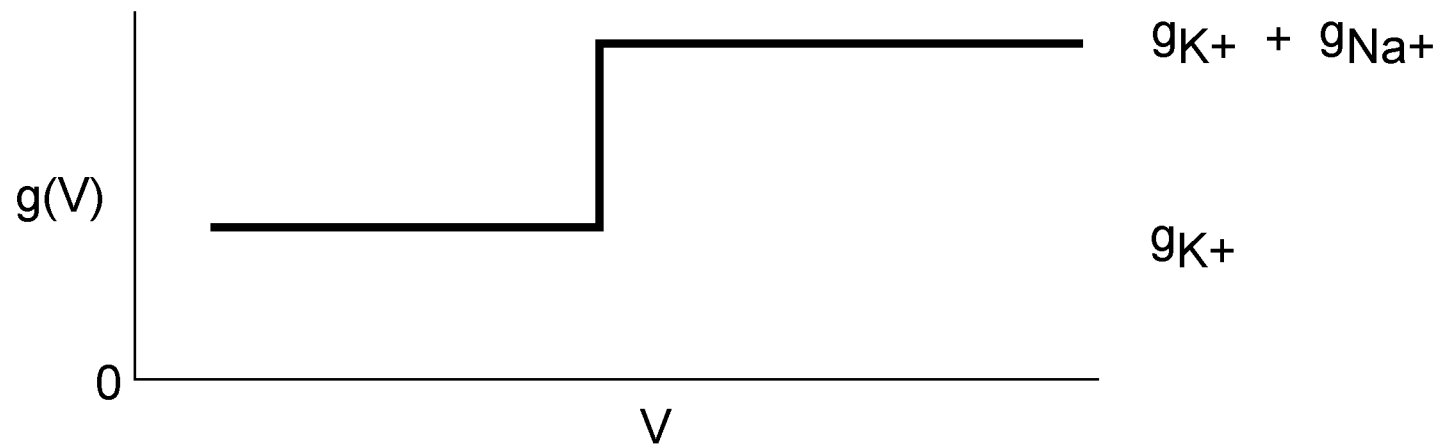


$$C \frac{dV_m}{dt} = I_{inj} + \frac{V_m - V_r}{R}$$

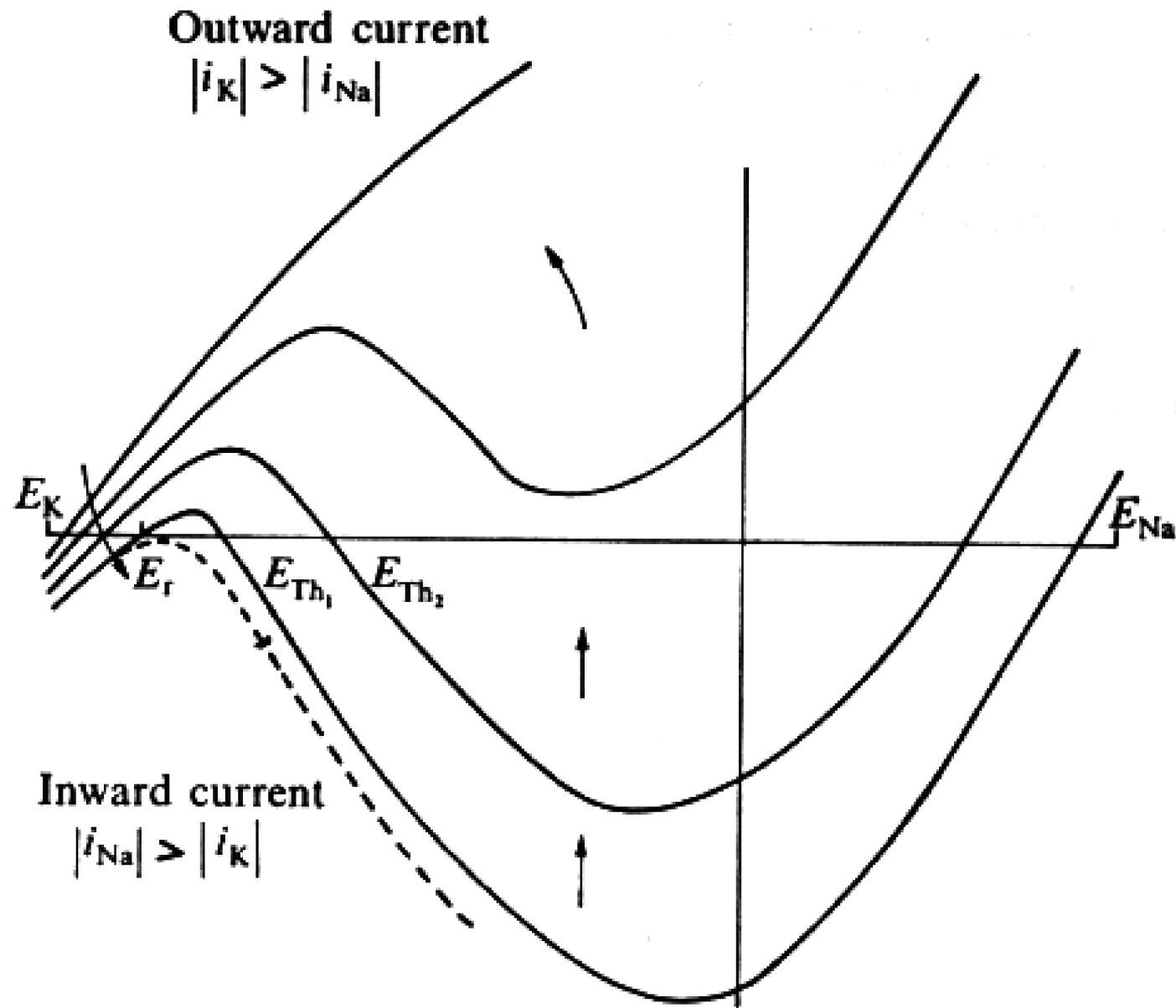


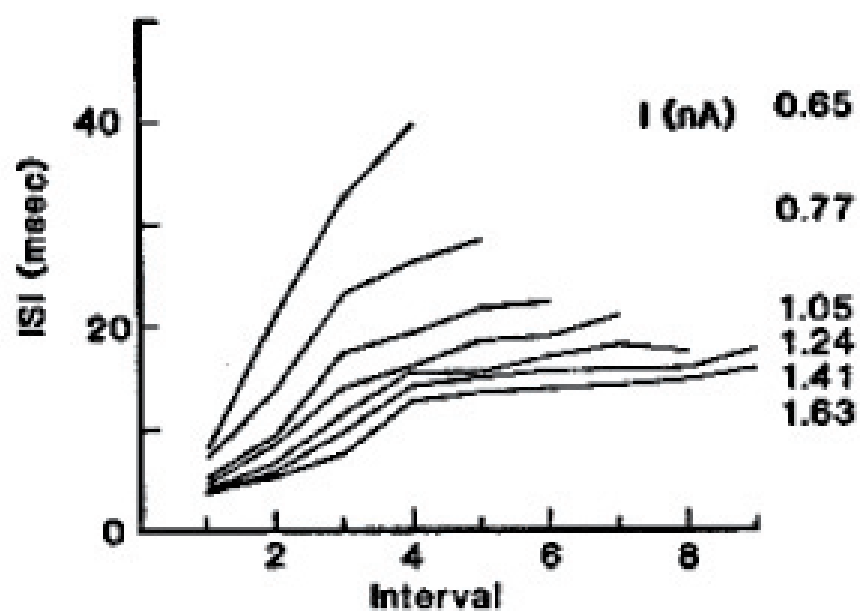
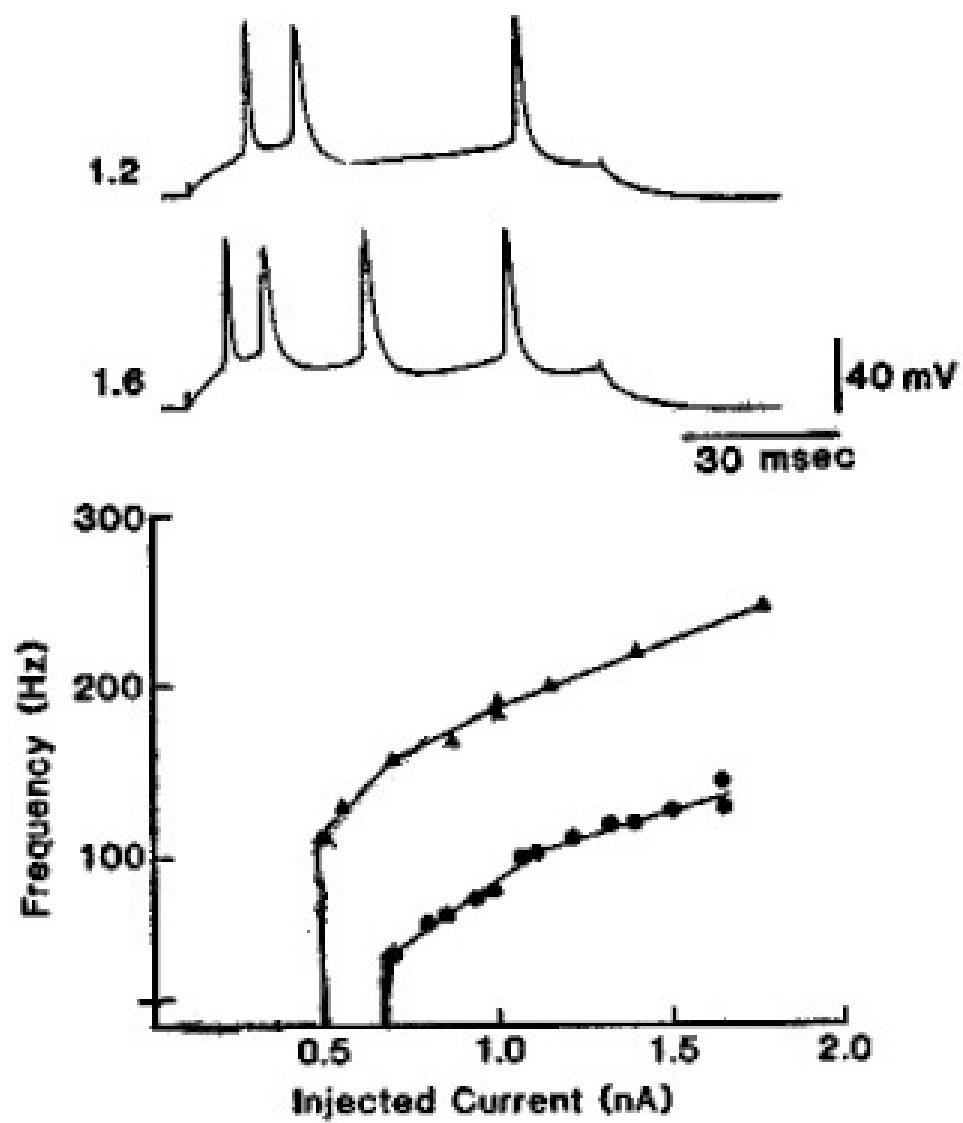
Real Data from Lobster Axon

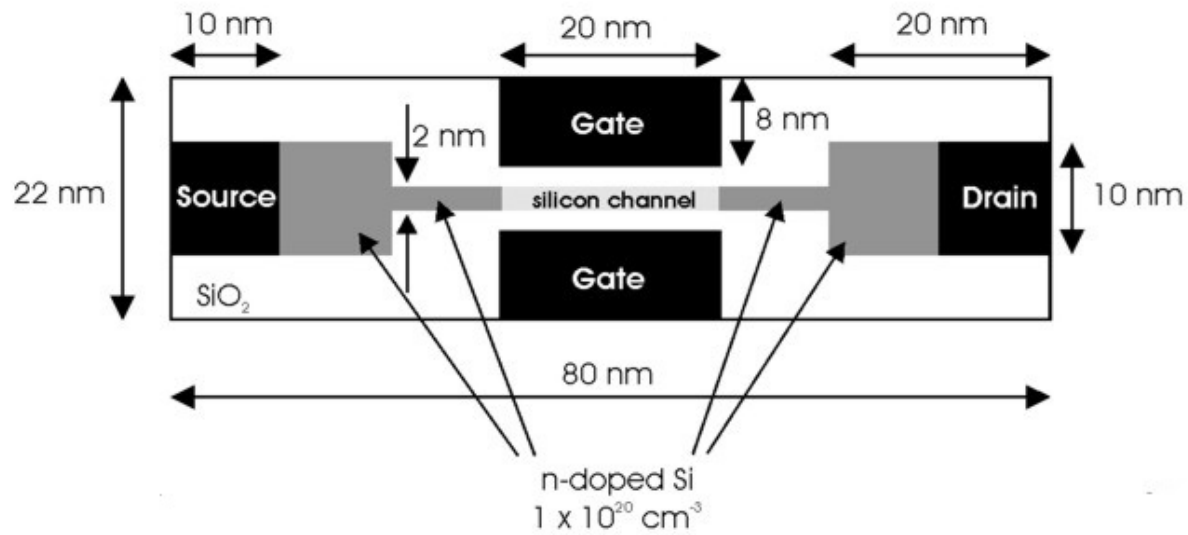




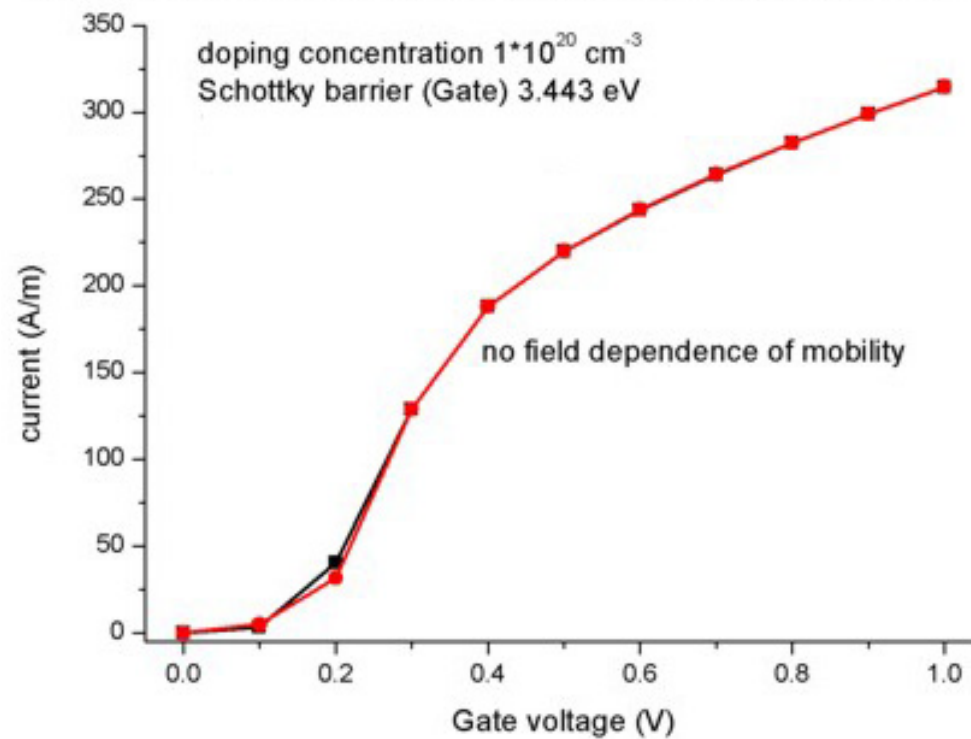
I-V curves for Squid Axon from Action Potential Trigger to Recovery





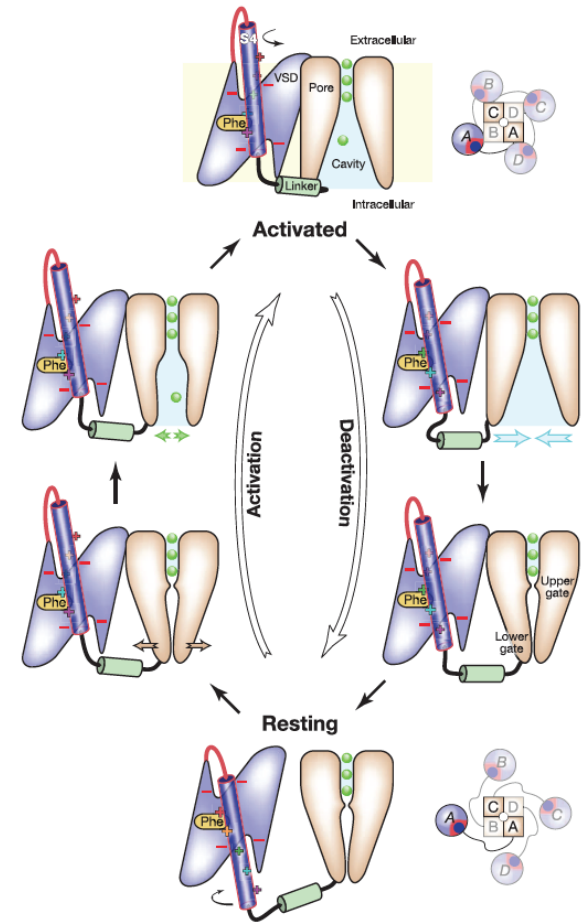
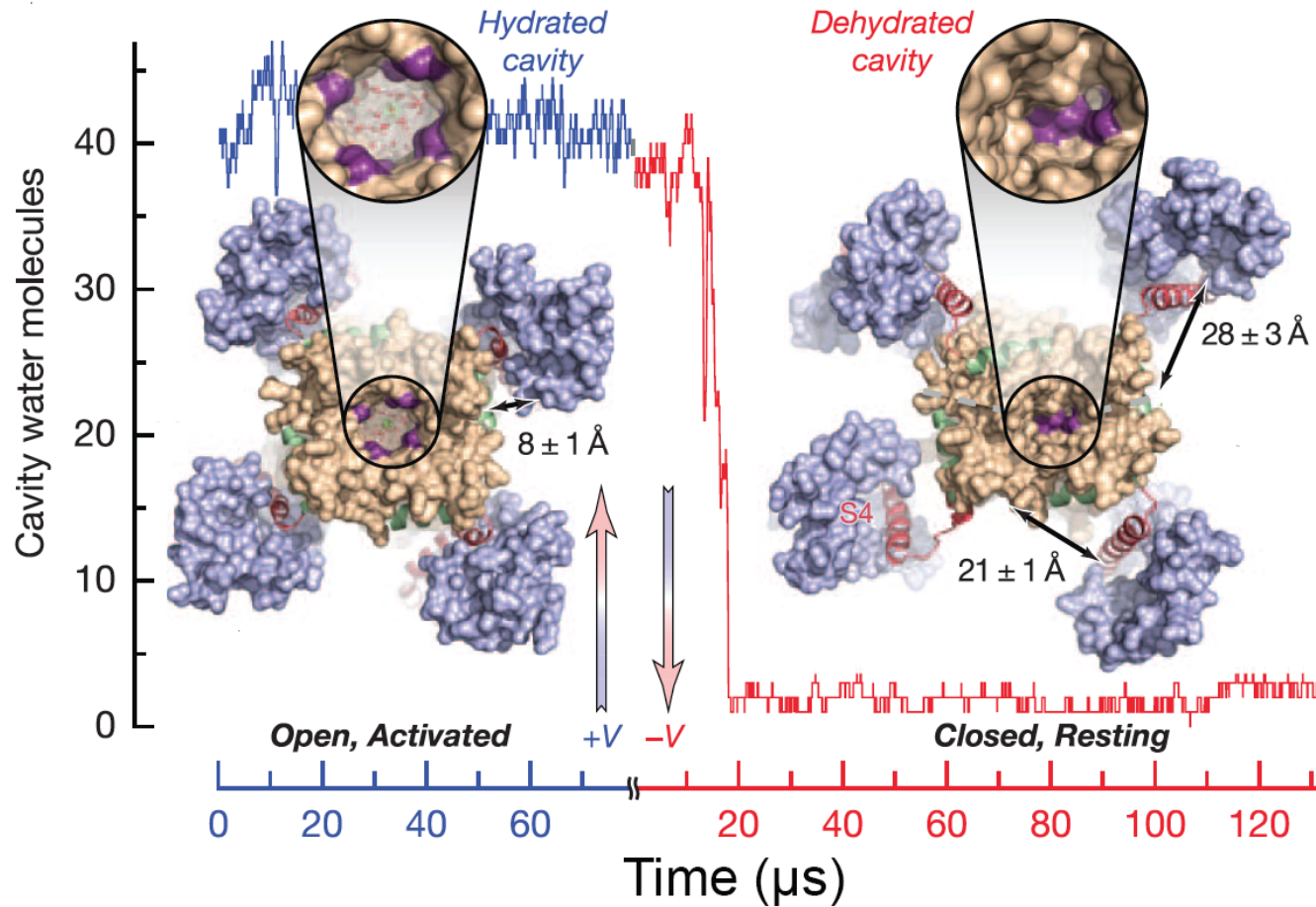


Current-voltage (I-V) characteristic of a 2 nm Si Double Gate MOSFET



Voltage gated Potassium Channel

Early Deactivation: Dewetting & Gate Closure



Analysis of MacKinnon data by Shaw

N-type calcium current in presynaptic terminals initiates synaptic vesicle fusion

