



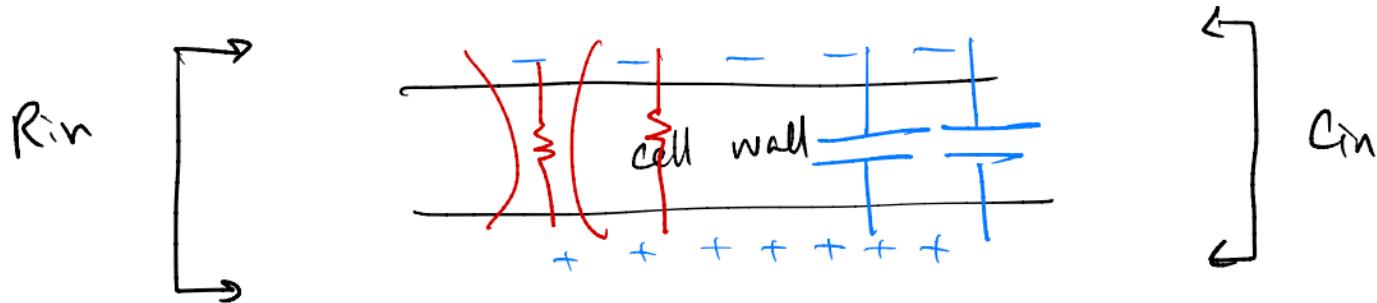
Lecture 5: Action potentials and firing rate statistics

Announcements.

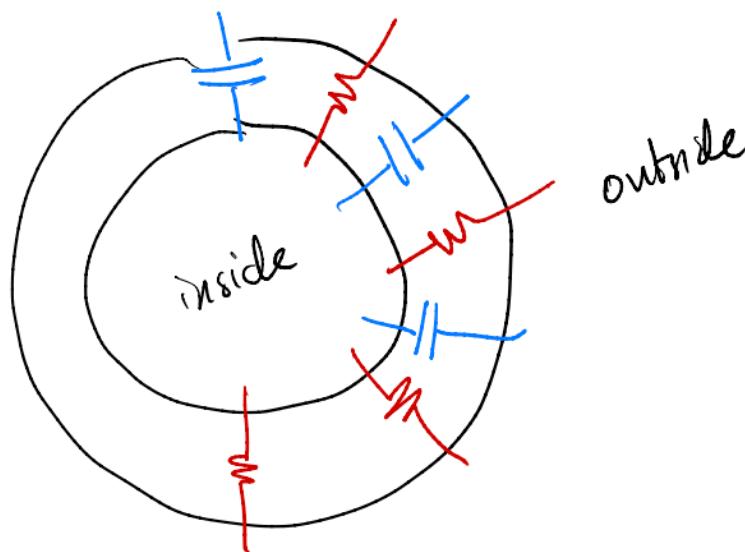
1. HW #1 is uploaded to Bruin Learn and is due Wednesday, April 13, by 11:59pm, uploaded to Gradescope.
2. Readings: PNS passive properties (ch 8), PNS action potential (ch 7)
3. HW #2 will be uploaded today, due Friday, April 22, 2022.
Has a Python component.



How quickly can V_m change?



Spherical Neuron w/ radius a

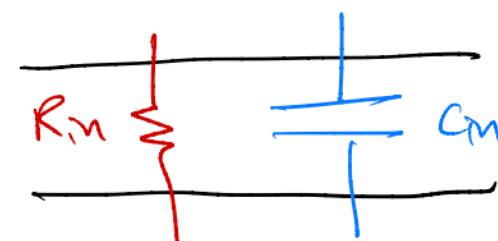


$$R_m = \frac{R_m}{4\pi a^2}$$

$$C_m = C_m \cdot 4\pi a^2$$

$R_m [=] \Omega \text{ cm}^2$

$C_m [=] \frac{\mu F}{cm^2}$



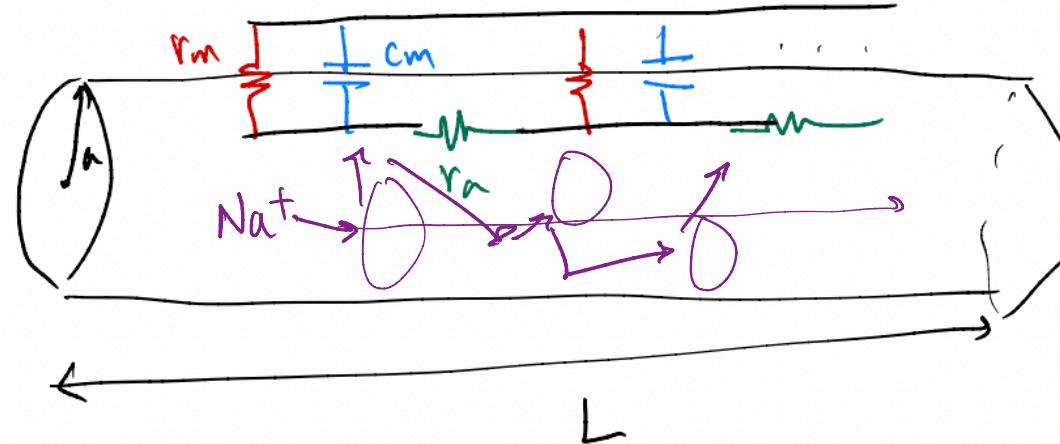
V_m changes as quickly as

22

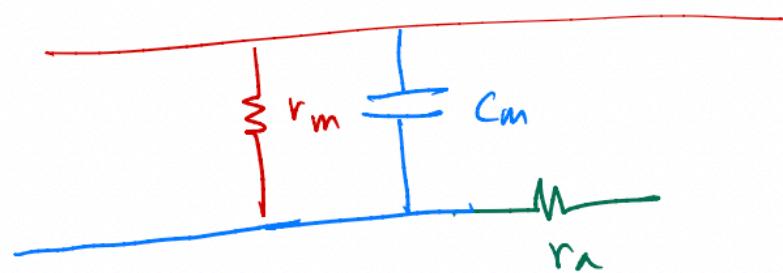
$$\tau = R_m C_m = R_m C_m$$



How far can voltage propagate (distance)?



$$\text{Area} = 2\pi a L$$



$$r_m = \frac{R_m}{2\pi a} [=] \Omega \cdot \text{cm}$$

$$C_m [=] \frac{\mu F}{\text{cm}}$$

$$r_a [=] \frac{\Omega}{\text{cm}}$$

$$\lambda = \sqrt{\frac{r_m}{r_a}} = \sqrt{\frac{\Omega \cdot \text{cm}}{\Omega/\text{cm}}} = \sqrt{\text{cm}^2} = \text{cm}$$



Action Potential Velocity

- It is important to have fast action potentials.
- Action potential speed $\propto \frac{1}{r_a c_m}$
- Two mechanisms have evolved to increase speed:

- Increase diameter of axon core:

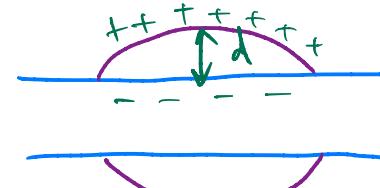
$$r_a \propto \frac{1}{\text{diameter}^2} \text{ and } c_m \propto \text{diameter}$$

thus $r_a c_m \propto \frac{1}{\text{diameter}} \rightarrow \text{speed} \propto \text{diameter}$.

- Myelination of the axon (glial cell wrapping) effectively increases membrane thickness (up to 100x).

$$c_m \propto \frac{1}{\text{thickness}}$$

thus $r_a c_m \propto \frac{1}{\text{thickness}} \rightarrow \text{speed} \propto \text{thickness}$.



$$C = \frac{\epsilon A}{t}$$

Nodes of Ranvier

- For neurons w/ myelinated axon, action potentials (APs) triggered at nonmyelinated segment of membrane at axon hillock.
- This current can discharge capacitance of myelinated axon segment ahead of it.
- Myelin sheath interrupted every 1-2 mm by bare patches (~2 μm in length).
- These Nodes of Ranvier are dense in voltage-gated Na^+ channels → boost amplitude of APs and keep them from dying out.
- Multiple sclerosis is caused by demyelination.

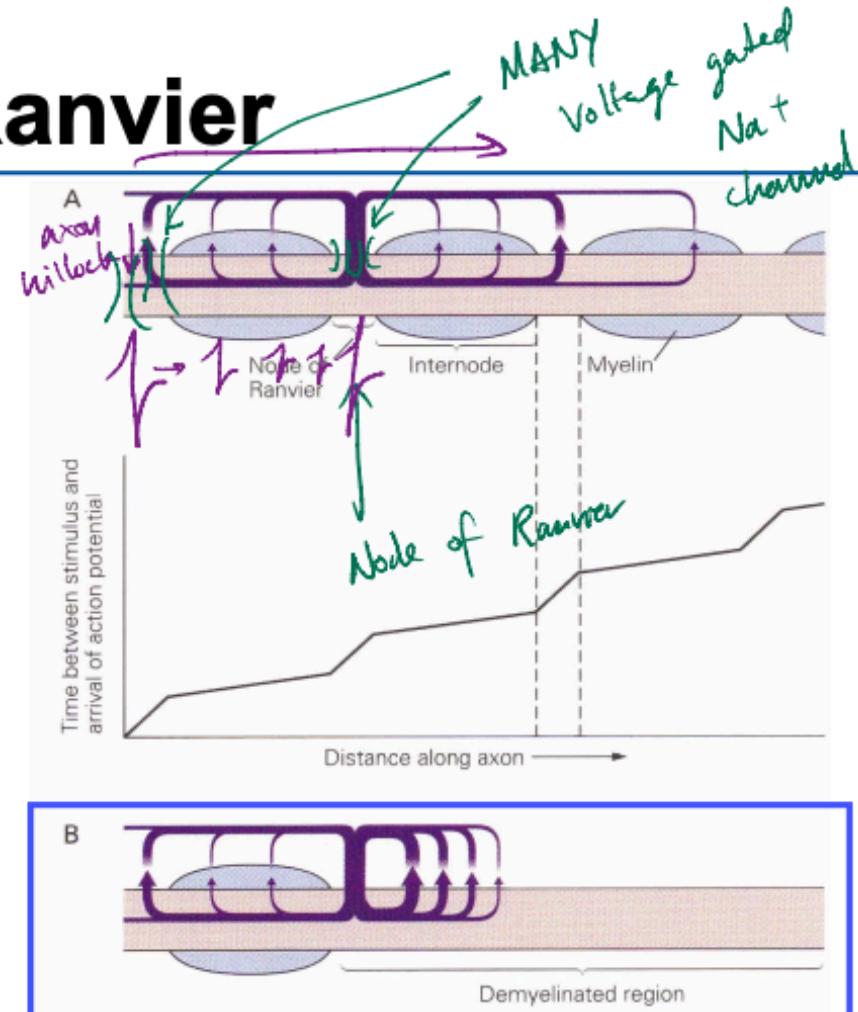


Figure 8-8 Action potentials in myelinated nerves are regenerated at the nodes of Ranvier.

A. In the axon capacitive and ionic membrane current densities (membrane current per unit area of membrane) are much higher at the nodes of Ranvier than in the internodal regions. The density of membrane current at any point along the axon is represented by the thickness of the arrows. Because of the higher capacitance of the axon membrane at the unmyelinated nodes, the action potential slows down as it approaches each node and thus appears to skip rapidly from node to node.

B. In regions of the axon that have lost their myelin, the spread of the action potential is slowed down or blocked. The local-circuit currents must charge a larger membrane capacitance and, because of the low r_m , they do not spread well down the axon.



Propagated Signals – Action Potentials

- Reading assignment from Kandell, Schwartz & Jessell:
 - Chapter 7 – Propagated Signaling: The Action Potential
- Neurons can carry information long distances b/c of action potentials.
- Action potentials (APs or “spikes”) – regenerative electrical signal whose amplitude does not attenuate as it moves down the axon.
 - Chap. 6 – APs arise from sequential changes in membrane’s selectivity for Na^+ and K^+ .
 - Chap. 6 – membrane’s passive properties influence AP propagation speed.
 - **Chap. 7 – here we consider voltage-gated ion channels, which are critical for generating and propagating APs.**



APs and Ion Flow Through Voltage-Gated Channels

- How are APs generated?
- Ion conductance *HIGH* during AP.
- 1st evidence that AP result from change in ion flux through membrane channels.
- But which ions?
- Big clue: if extracellular $[Na^+]$ *LOW*, then AP amplitude *LOW*.
- Thus Na^+ responsible for rising edge of AP.
- Hodgkin's & Katz's data also pointed to K^+ involved w/ falling edge of AP.
✓ ✓ K
- To test these hypotheses, need to measure Na^+ and K^+ conductance as a function of membrane potential (V_m).
- Problem: V_m and ion conductance coupled.
- Solution: The Voltage Clamp.

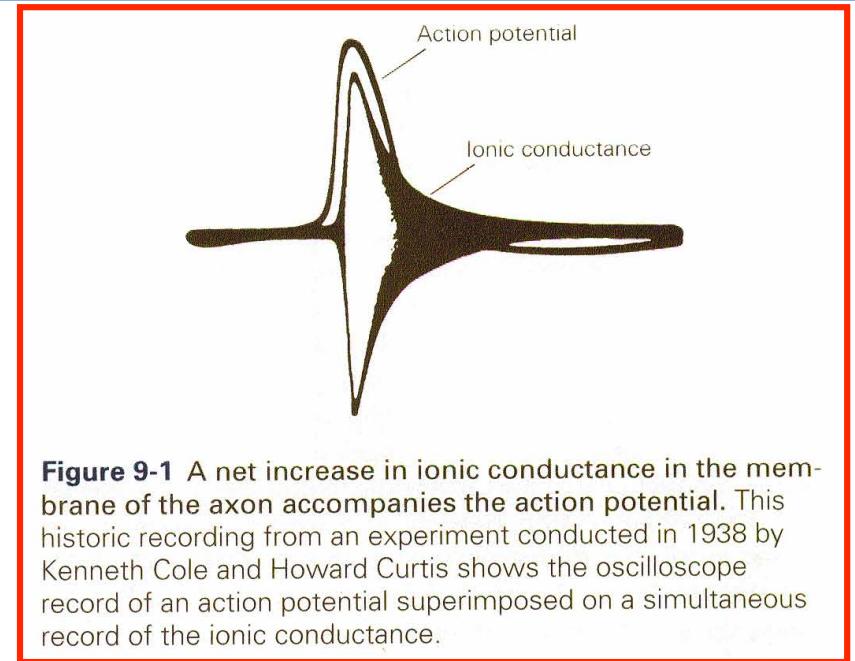
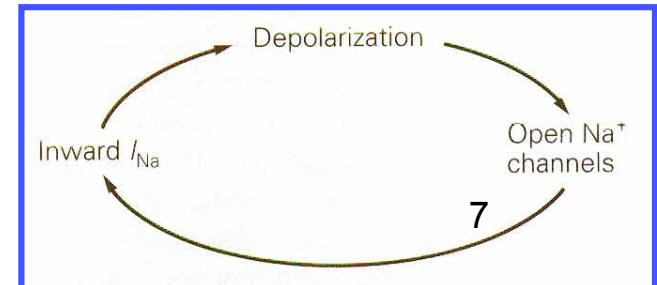


Figure 9-1 A net increase in ionic conductance in the membrane of the axon accompanies the action potential. This historic recording from an experiment conducted in 1938 by Kenneth Cole and Howard Curtis shows the oscilloscope record of an action potential superimposed on a simultaneous record of the ionic conductance.





The Voltage Clamp

- “Voltage clamp” decouples V_m and the opening / closing of voltage-gated ion channels.
- Injects current into axon that is equal and opposite to current flowing through voltage-gated ion channels.
- Thus, membrane charge and V_m do not change.
- The current supplied by the voltage clamp is a direct measure of current flowing across membrane.
- Hodgkin & Huxley used voltage clamp to provide 1st complete description of ionic mechanisms underlying APs.
- A brief aside – How important was this work?
 - The Nobel Prize in Physiology or Medicine 1963, Hodgkin
 - The Nobel Prize in Physiology or Medicine 1963, Huxley
 - The Nobel Prize in Physiology or Medicine 1970, Katz

$$\downarrow \quad V = I R$$

constant



The Voltage Clamp

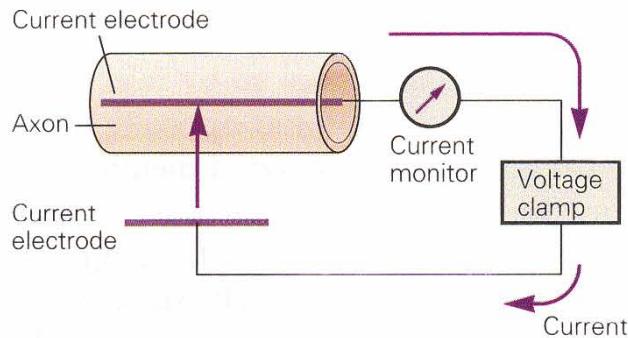


Figure 9-2 A

The voltage clamp is a current generator that is connected to a pair of electrodes. It is used to change the charge separation, and thus the electrical potential difference, across the membrane. Monitoring the additional current that is passed to clamp the membrane potential at its new value then provides a measure of the membrane current passing through the ion channels in the membrane.

- 1) Step V_m to level of depolarization.
- 2) Voltage-gated Na^+/K^+ open.
- 3) V-clamp sources equal and opposite I to maintain V_m .

- Developed by Kenneth Cole (1949).
- Patch clamp similar, but more advanced, allowing measurement of single-channel currents.

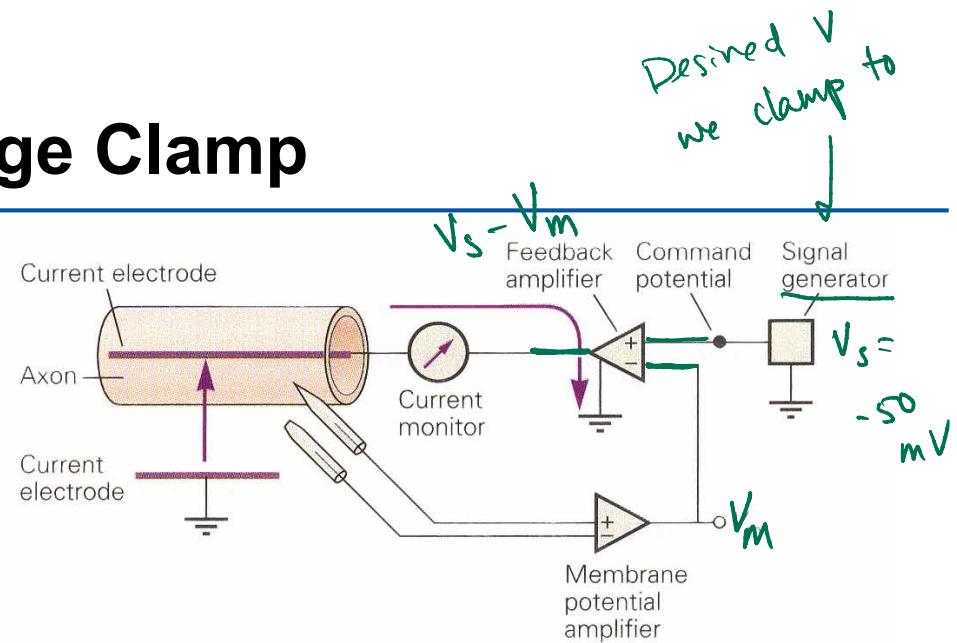


Figure 9-2 B

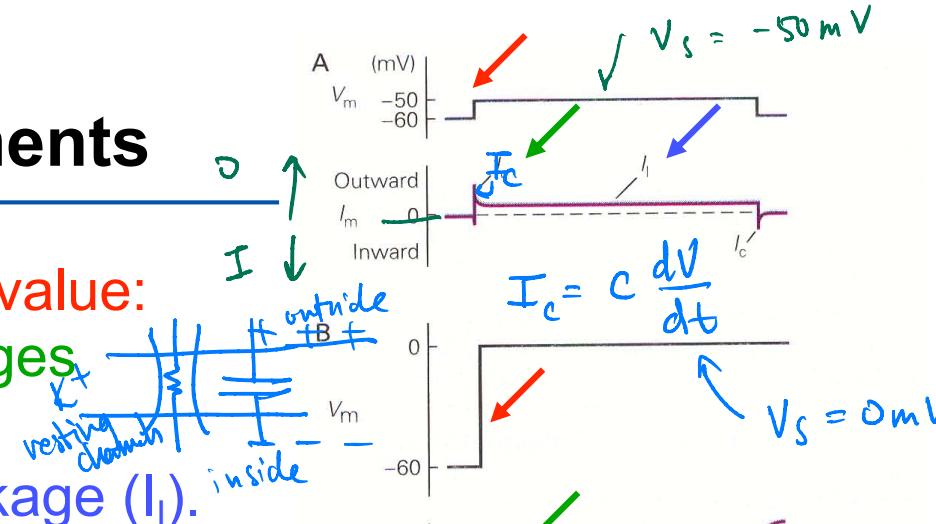
The negative feedback mechanism by which the voltage clamp operates. Membrane potential is measured by one amplifier connected to an intracellular electrode and to an extracellular electrode in the bath. The membrane potential signal is displayed on an oscilloscope and is also fed into one terminal of the "feedback" amplifier. This amplifier has two inputs, one for membrane potential (V_m) and the other for the command potential. The command potential, which comes from a signal generator, is selected by the experimenter and can be of any desired amplitude and waveform. The feedback amplifier subtracts the membrane potential from the command potential. Any difference between these two signals is amplified several thousand times at the feedback amplifier. The output of this amplifier is connected to a current electrode, a thin wire that runs the length of the axon. To accurately measure the current-voltage relationship of the cell membrane, the membrane potential must be uniform along the entire surface of the axon. This is achieved by using a highly conductive current electrode, which short circuits the axoplasmic resistance, reducing the axial resistance to zero (see Chapter 8). This low-resistance pathway within the axon eliminates all potential differences along the axon core.



Voltage Clamp Experiments

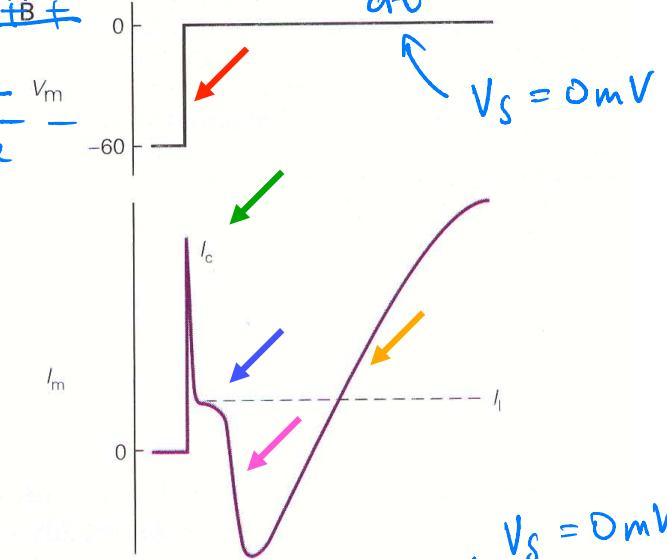
A) 10 mV depolarizing step w.r.t. resting value:

- Brief capacitive current (I_c) discharges membrane capacitance.
- Sustained ionic current termed leakage (I_l).



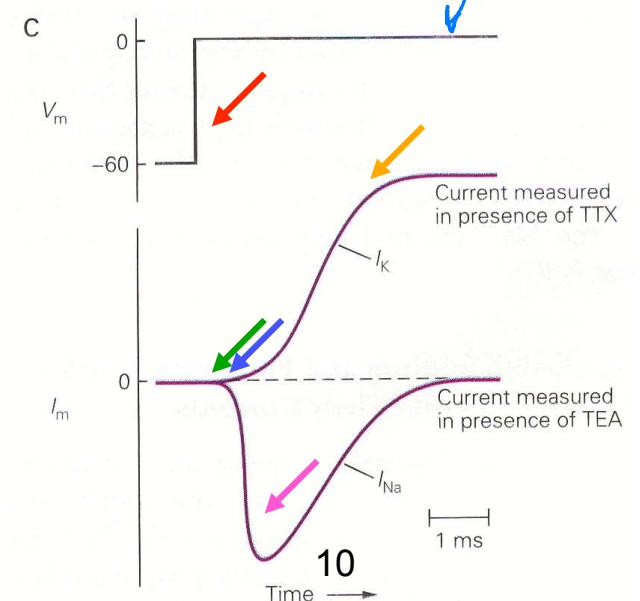
B) 60 mV depolarizing step w.r.t. resting value:

- Larger I_c and I_l now.
- Short time later, large inward current.
- Shortly after that, large outward current.



C) 60 mV depolarizing step w.r.t. resting value:

- Subtract stereotyped I_c and I_l from traces.
- Tetraethylammonium (TEA) blocks voltage-gated K⁺ channels, revealing I_{Na} component.
- Tetrodotoxin (TTX) blocks voltage-gated Na⁺ channels, revealing I_K component.





$$V = IR \Rightarrow R = \frac{V}{I}$$

$$g = \frac{1}{R}$$

Channel Conductance Kinetics

- Repeat V-Clamp experiments – step to a range of V_M 's.
- Na^+ and K^+ conductance **similarities**:
 - Depolarizing V_M steps → channels open ($g \uparrow$).
 - Larger depolarizing steps → probability and rate of opening increases (rise times \mathcal{DOWN}).
- Na^+ and K^+ conductance **differences**:
 - Rates of opening: $\text{Na}^+ > \text{K}^+$.
 - Responses to prolonged depolarization: Na^+ opens and closes (*inactivation*); K^+ stays open.

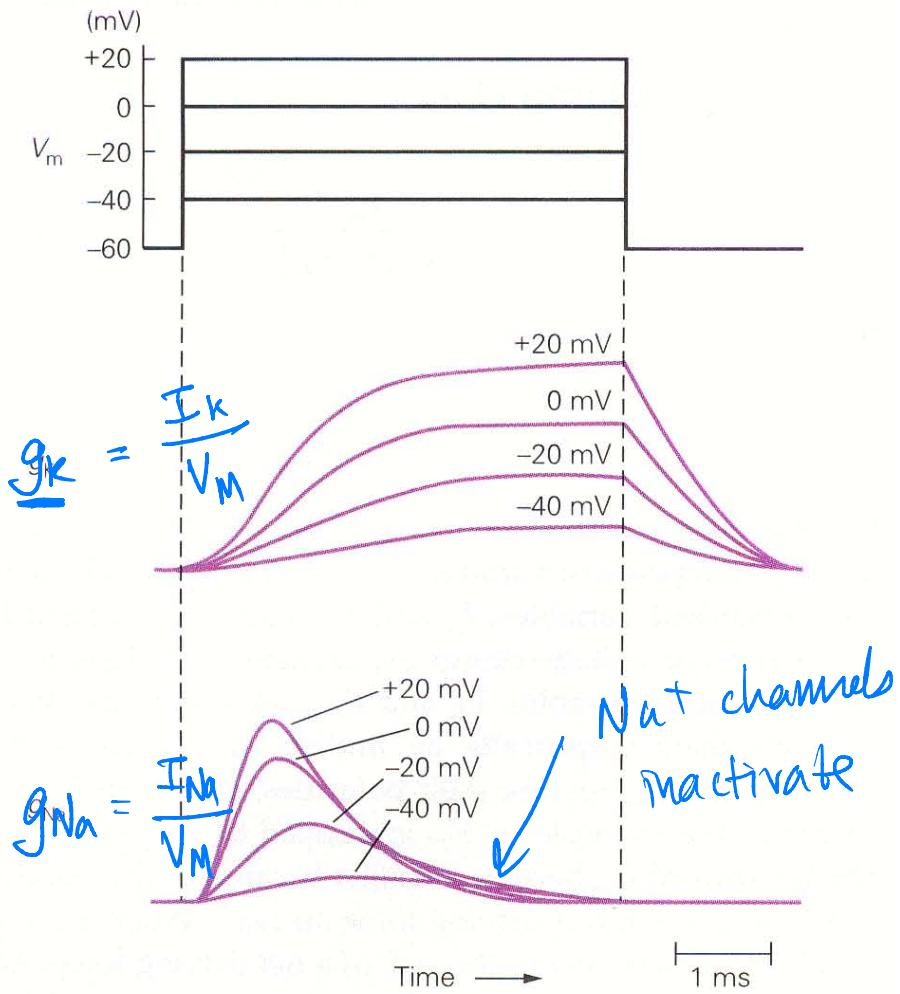


Figure 9-6 Voltage-clamp experiments show that Na^+ channels turn on and off more rapidly than K^+ channels over a wide range of membrane potentials. The increases and decreases in the Na^+ and K^+ conductances (g_{Na} and g_K) shown here reflect the shifting of thousands of voltage-gated channels between the open and closed states. 11



Short-term vs. Long-term Depolarization

a) Short-term depolarization allows Na^+ and K^+ channels to return to their resting states.

b) Long-term depolarization cause Na^+ channels to enter inactive state.

- Once inactivated, repolarization required to transit Na^+ channels back to resting state.
- This takes some time.

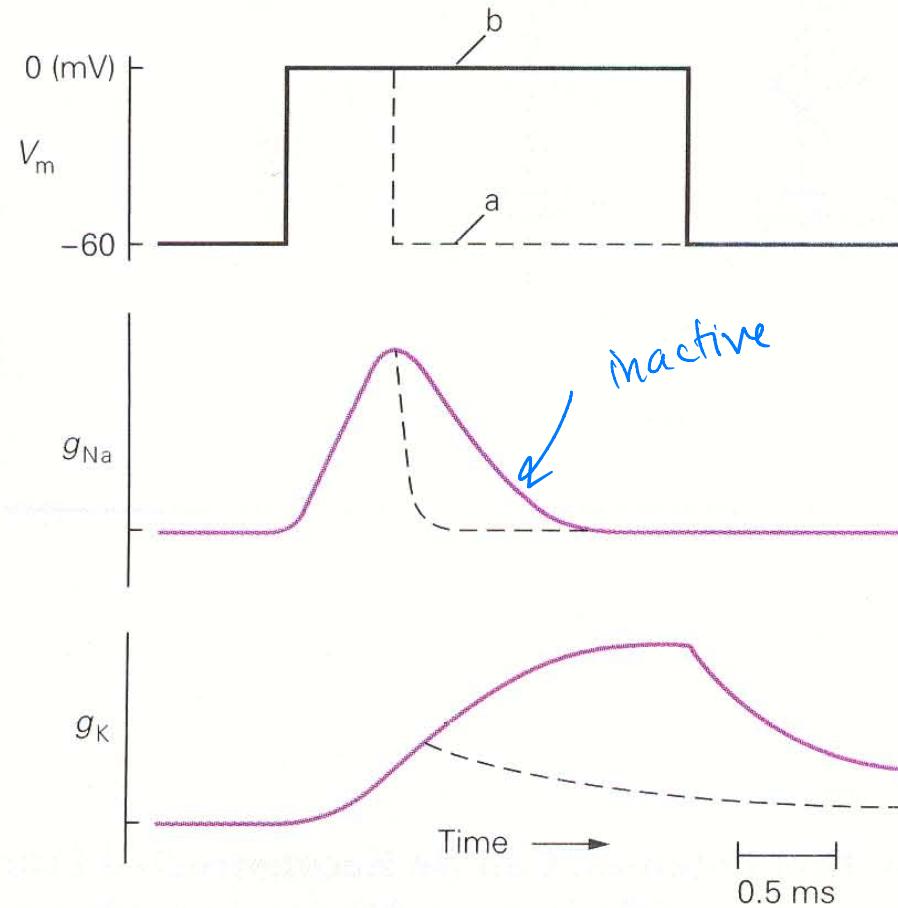


Figure 9-7 Sodium and potassium channels respond differently to long-term depolarization. If the membrane is repolarized after a brief depolarization (line a), both g_{Na} and g_K return to their initial values. If depolarization is maintained (line b), the Na^+ channels close (or inactivate) before the depolarization is terminated, whereas the K^+ channels remain open and g_K increases throughout the depolarization.



Na⁺ Channel Inactivation Timecourse

- Once inactivated, Na⁺ channels must be repolarized for a few ms in order to return to the resting state.
- If the membrane is depolarized prematurely, g_{Na} will not increase appreciably (channel still inactivated).
- Inactivation timecourse underlies the *refractory period*.

"Absolute Refractory Period"
up to 2-4ms

"Relative "
up to 15ms

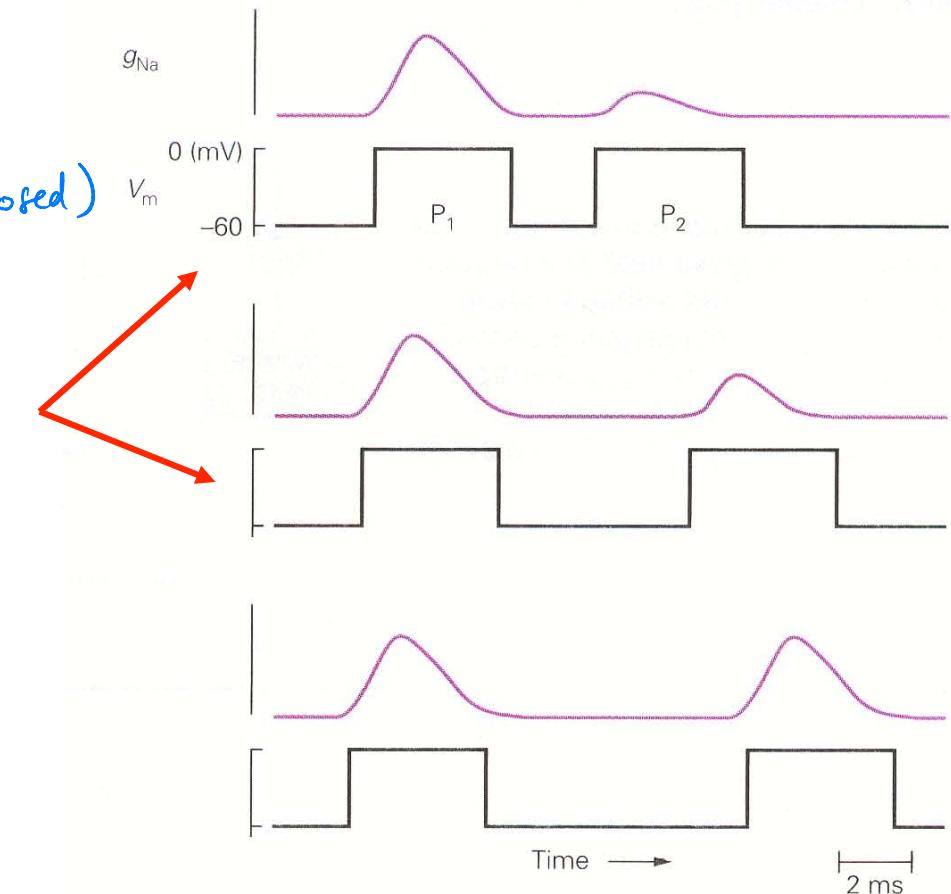


Figure 9-8 Sodium channels remain inactivated for a few milliseconds after the end of a depolarization. Therefore if the interval between two depolarizing pulses (P₁ and P₂) is brief, the second pulse produces a smaller increase in g_{Na} because many of the Na⁺ channels are inactivated. The longer the interval between pulses, the greater the increase in g_{Na} , because a greater fraction of channels will have recovered from inactivation and returned to the resting state when the second pulse begins. The time course of recovery from inactivation contributes to the time course of the refractory period.



Hodgkin-Huxley Measurements & Model Explain APs

- 1) Depolarization event.
- 2) Na^+ channels open fast (g_{Na} UP).
- 3) Inward Na^+ current.
- 4) Further depolarization.
- 5) Further Na^+ channels open.
- 6) Positive feedback continues...
- 7) $V_m \rightarrow E_{\text{Na}}$.
- 8) Na^+ channels inactivate (g_{Na} DOWN).
- 9) K^+ channels start opening (g_{K} UP).
- 10) Outward current decreases V_m .
- 11) $V_m \rightarrow E_{\text{K}}$. Hyperpolarizes beyond resting potential (after potential).
- 12) Absolute refractory period (due to Na^+ inactivation). *up to 4ms*
- 13) Relative refractory period (due to increased opening of K^+).

up to 15ms

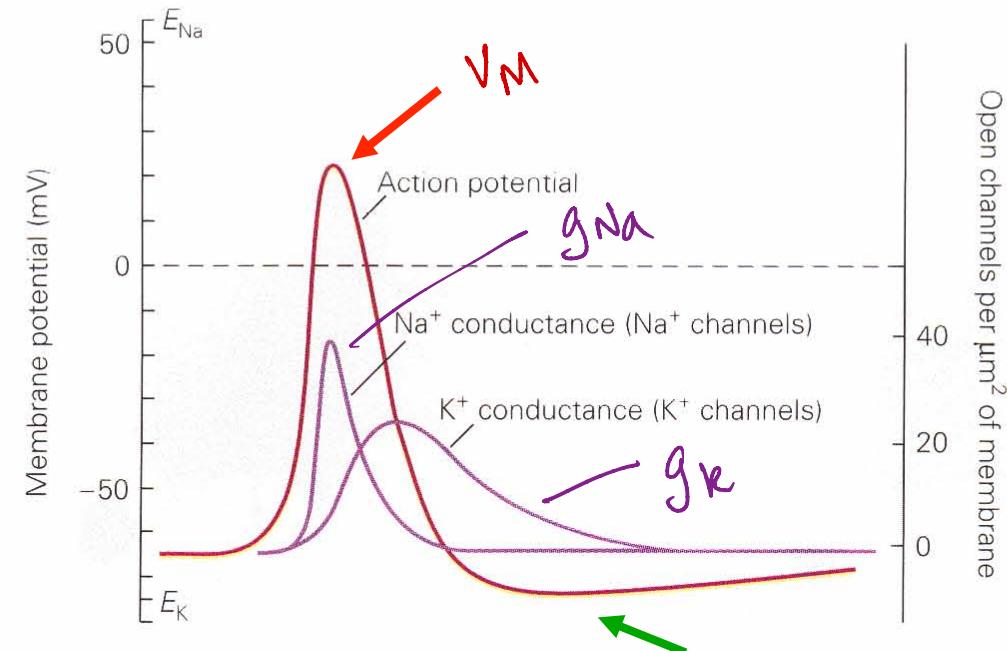
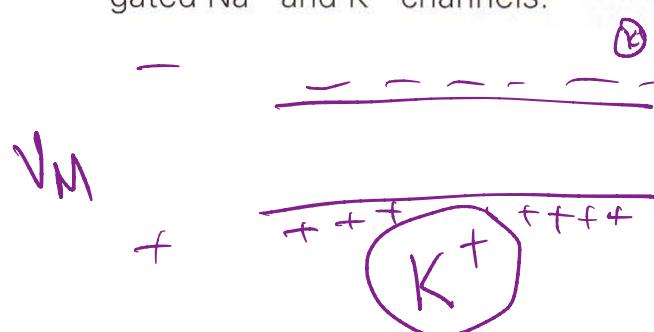


Figure 9-10 The sequential opening of voltage-gated Na^+ and K^+ channels generates the action potential. One of Hodgkin and Huxley's great achievements was to separate the total conductance change during an action potential, first detected by Cole and Curtis (see Figure 9-1) into separate components attributable to the opening of Na^+ and K^+ channels. The shape of the action potential and the underlying conductance changes can be calculated from the properties of the voltage-gated Na^+ and K^+ channels.





Further Notes on Action Potentials

- All-or-nothing behavior of APs:
 - Once V_m depolarization crosses a particular value (threshold)...
 - Positive feedback takes over and ...
 - The rest of the AP waveform unfolds.
- APs in the giant squid axon result from just two type of voltage-gated channels, but many other types of voltage-gated channels are found in the nervous system:
 - Voltage-gated Ca^{2+} , Cl^- channels.
 - Fast / very-slow voltage-gated K^+ channels.
 - This channel variety increases complexity of possible neural information processing.
 - Beyond the scope of this course.
- Ca^{2+} influx is important (e.g., can modulate gating of K^+ channels).
 - Beyond the scope of this course.



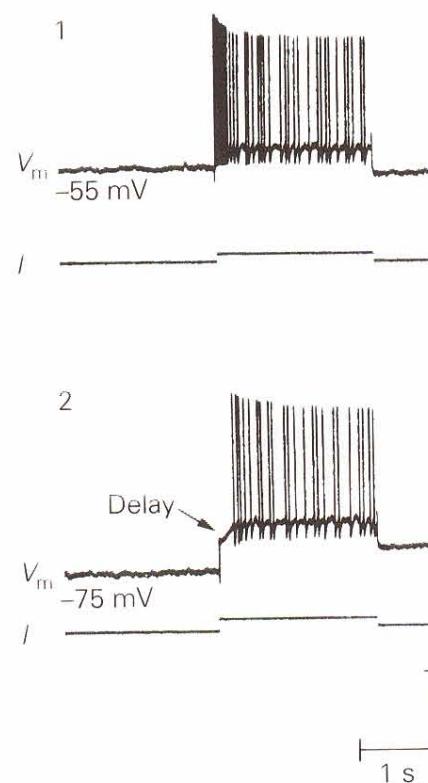
Further Notes on Action Potentials

- Different regions of the neuron perform specific signaling tasks, e.g.:
 - Axon – carries signals over long distances (relay line).
 - Input, integrative regions – lots of complex computations (processor).
 - These functions depend on the particular set of ion channels present.
- Excitability properties vary among neurons:
 - Computing power greater w/ range of functional properties.
 - It's still true that neural function is largely determined by its connectivity, the biophysical properties of cells also critical.
 - How a neuron responds to synaptic input depends on different types and proportions of voltage-gated channels in integrative and trigger zones.
 - Same input could result in single AP, constant frequency train of APs or even accelerating/decelerating train of APs.
 - Some examples are shown on next slide; we'll look at specific response characteristics when we study specific sensory or motor regions of the brain.

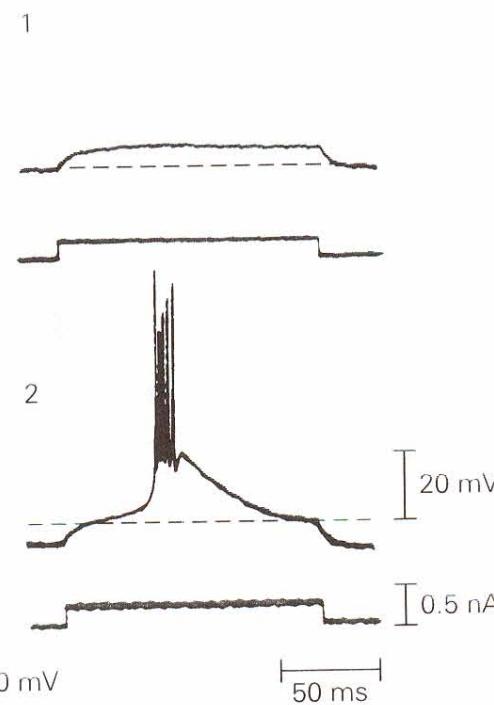


Different Voltage-Gated Channels → Different Firing Properties

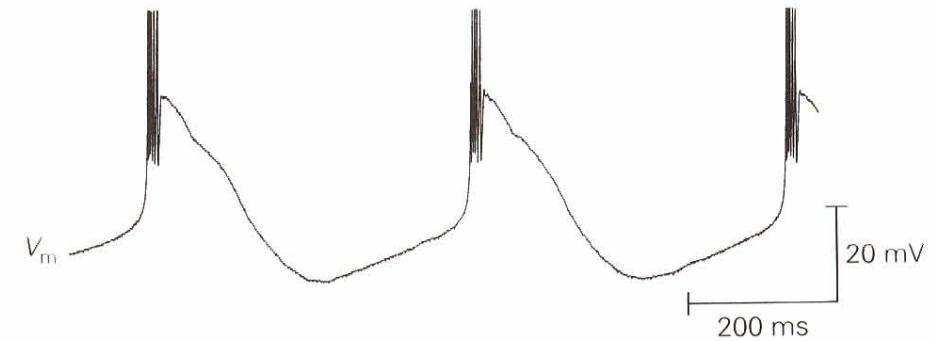
A Delayed firing



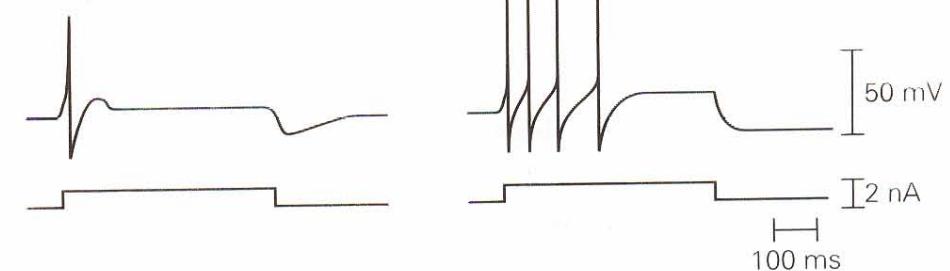
B Potential-dependent excitability



C Bursting neuron



D Spike accommodation





Rest of Chapter 7

- We've covered topics in Chapter 7 up to, but not including, the section titled, "Genes encoding the potassium, sodium, and calcium channels stem from a common ancestor."
- We will not cover this section or beyond.
- Feel free to read if you are interested in learning more.

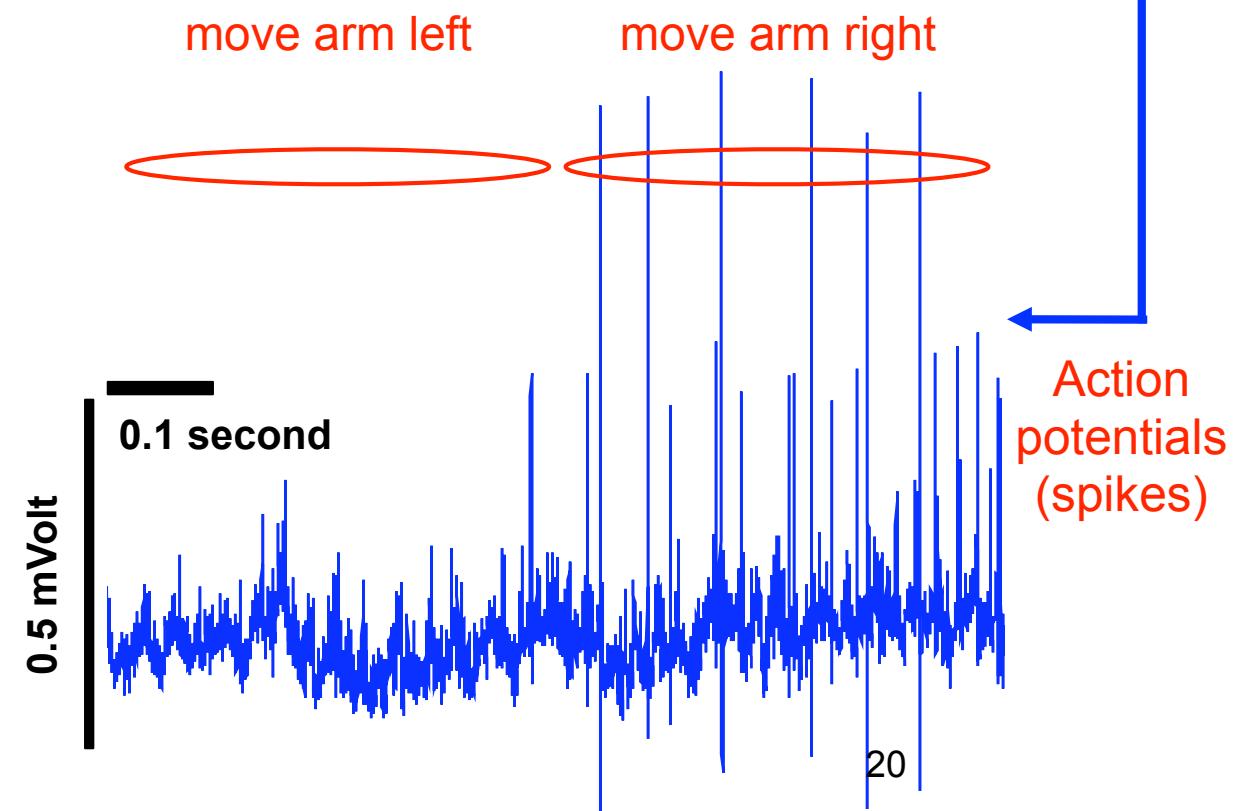
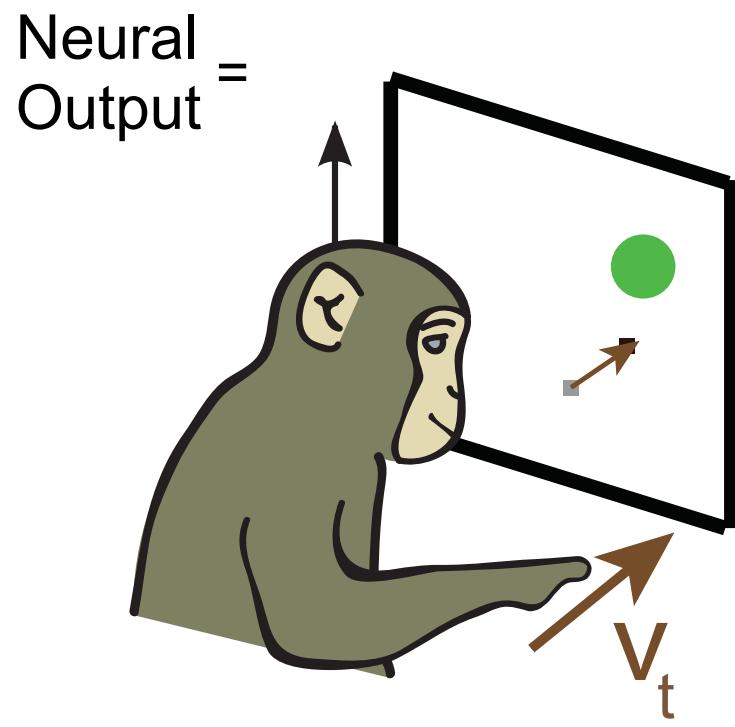
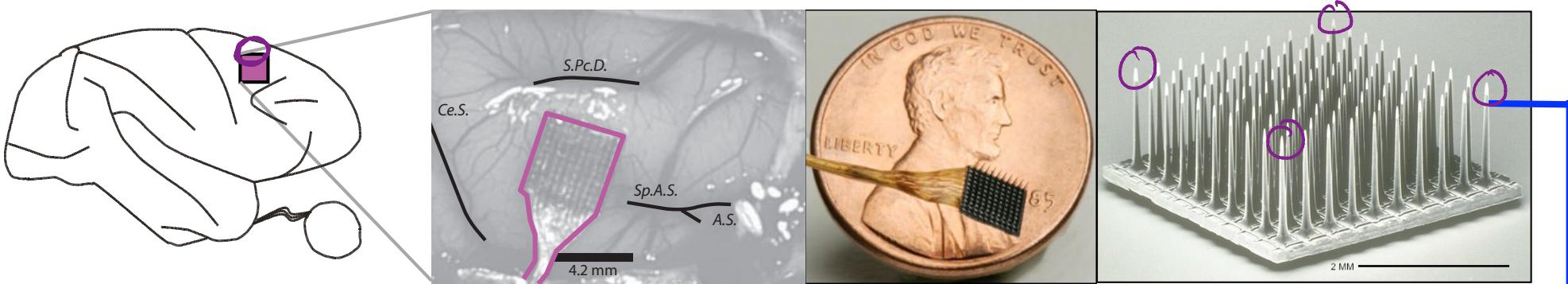


Firing Rates and Spike Statistics

- Reading assignment from Dayan & Abbott:
 - Chapter 1 – Neural Encoding I: Firing Rates and Spike Statistics
 - p. 12-28 of PRML.
- We now know quite a bit about the electrical properties of neurons, including a first-principles understanding of:
 - Ion channels
 - Membrane potential
 - Action potential generation
 - Action potential propagation
- As discussed in class, we could continue learning about various fundamental neuroscience topics including neurotransmitters, synapses, development, genetics, etc...
- Though this would (hopefully!) be interesting and fun, it would constitute a course in neuroscience – not a course in “NeuroEngineering”.



Neural Recordings Encode Arm Movements

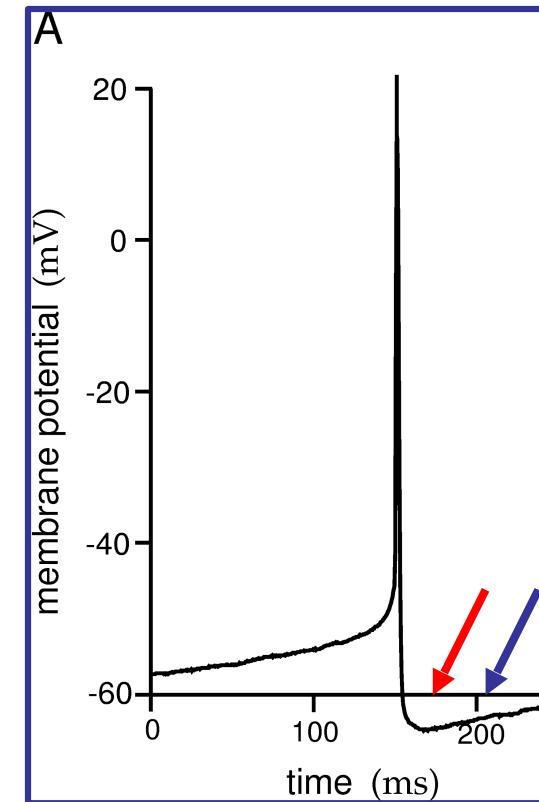
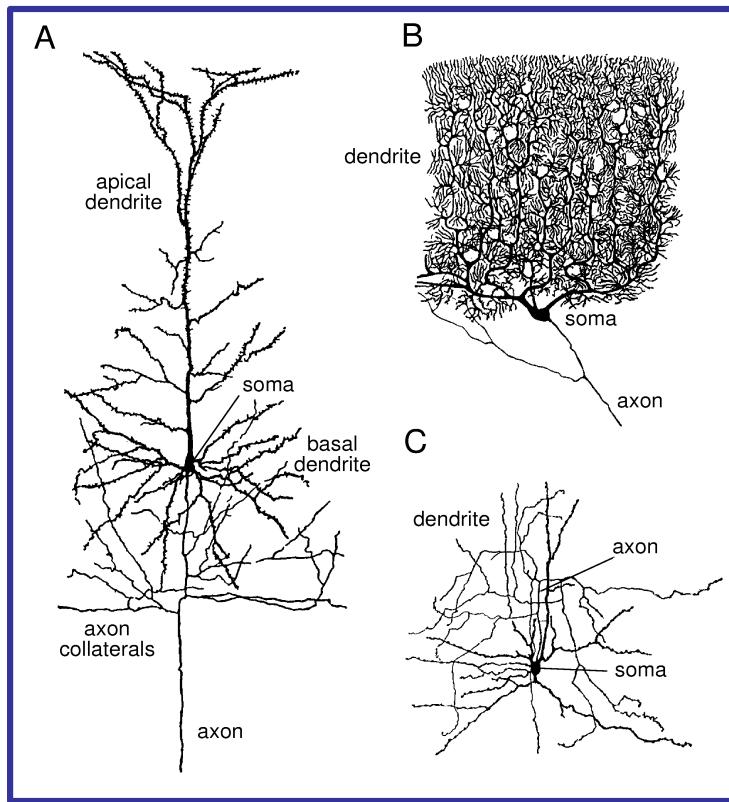




Neurons and Action Potentials

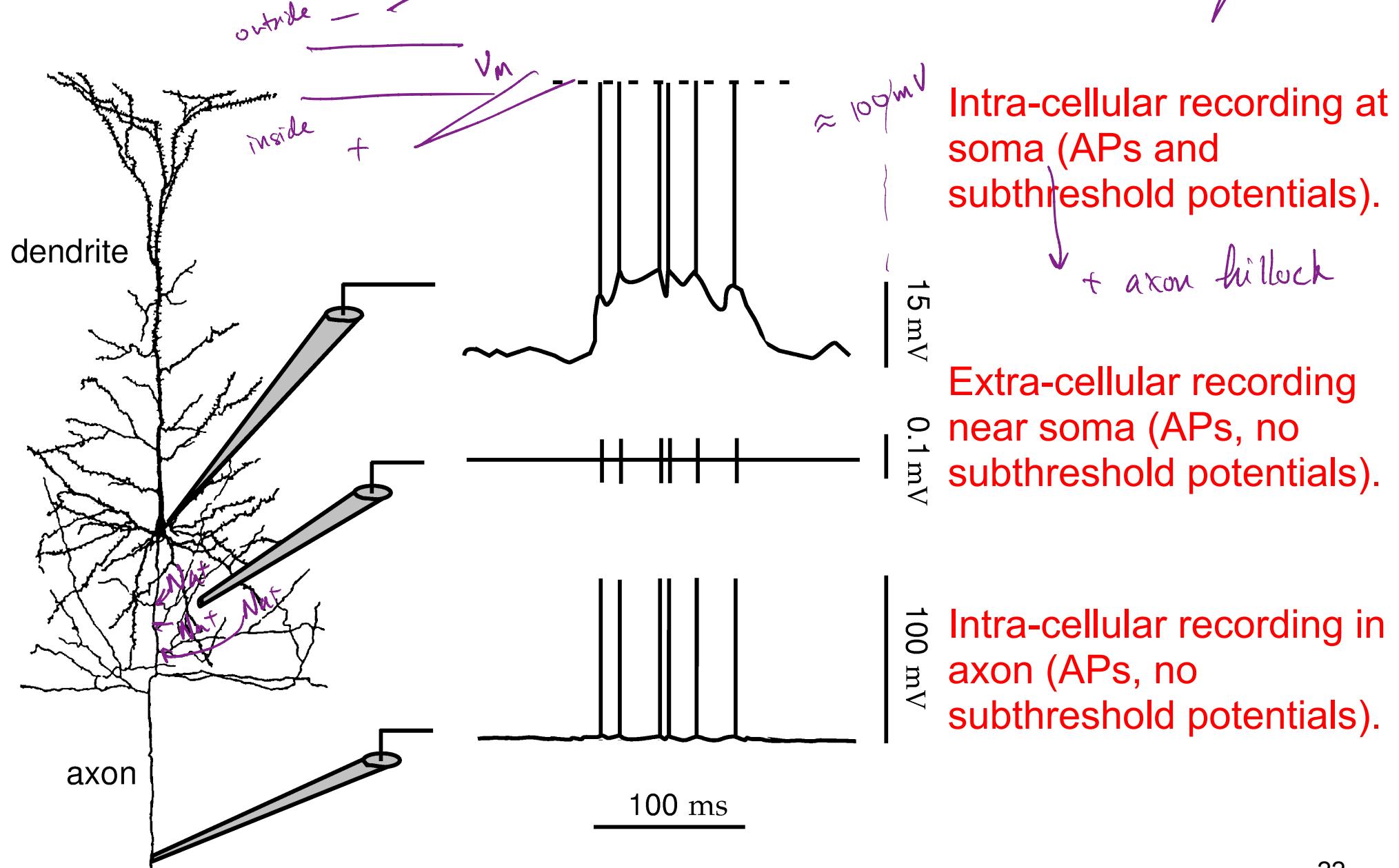
As discussed in previous lectures:

- Neuron morphology varies considerably, and influences function.
- Action potential are V_m deflections (~ 100 mV, ~ 1 ms).
- **Absolute refractory period lasts a few ms.**
- Relative refractory period lasts a few 10's of ms.





Intra- & Extra-Cellular Recordings





Question on extracellular recordings

Poll Question:

143 - 0411 - 1

pw: nemoh

Question:

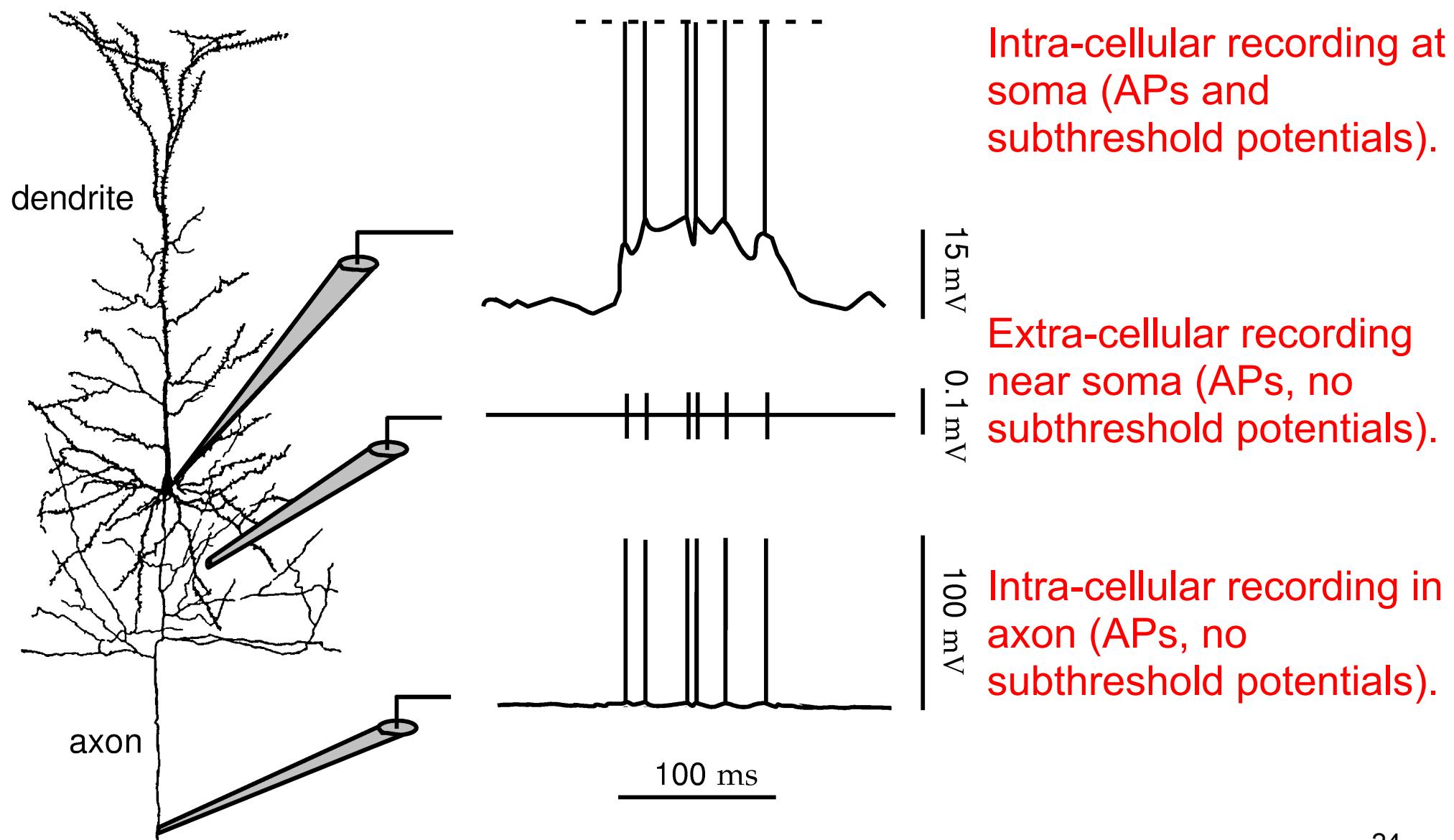
onlinerpoll.ucla.edu

A colleague is running an experiment for the first time and records action potentials. He notices the spike amplitudes are on the order of 100 uV. From this information, select all the following true statements:

- A) The recordings are extracellular, with both electrodes outside the cell.
- B) The recordings could be intracellular, with one electrode inside the cell and one electrode outside.
- C) The recordings will measure subthreshold membrane potential.
- D) The recordings will not measure subthreshold membrane potential.
- E) The action potential waveform will increase to a positive voltage and then decrease back to the resting potential.
- F) The action potential waveform will decrease to a negative voltage and then increase back to resting potential.
- G) It's possible that spikes could be coming from different neurons.
- H) The spikes only come from one neuron.

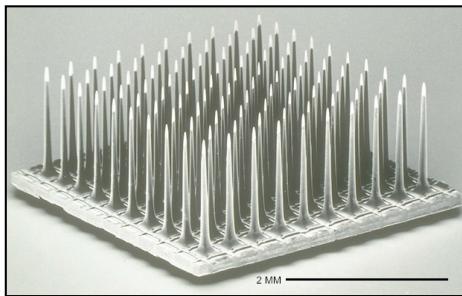


Intra- & Extra-Cellular Recordings





Spike & LFP Processing



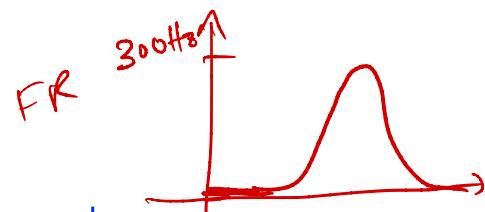
0.5 mVolt

0.1 second

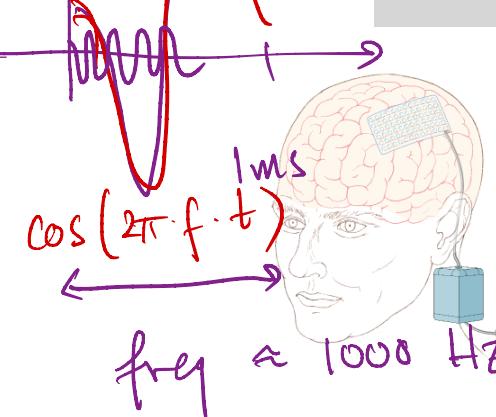
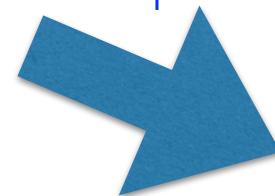
Sampled ~30 kHz
with 7.5 kHz low-pass
(anti-aliasing) filter

local field potential (LFP)

> ~600 Hz



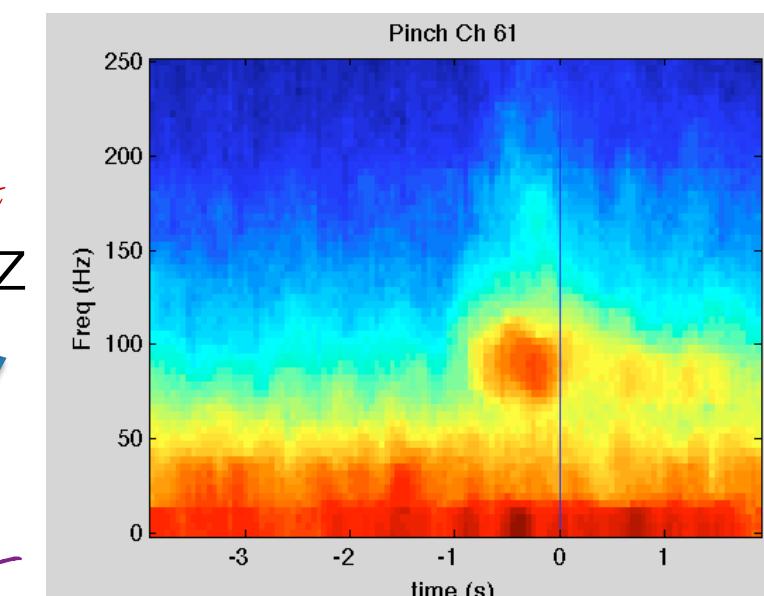
< ~200 Hz



Action Potential (Spike) Times



25

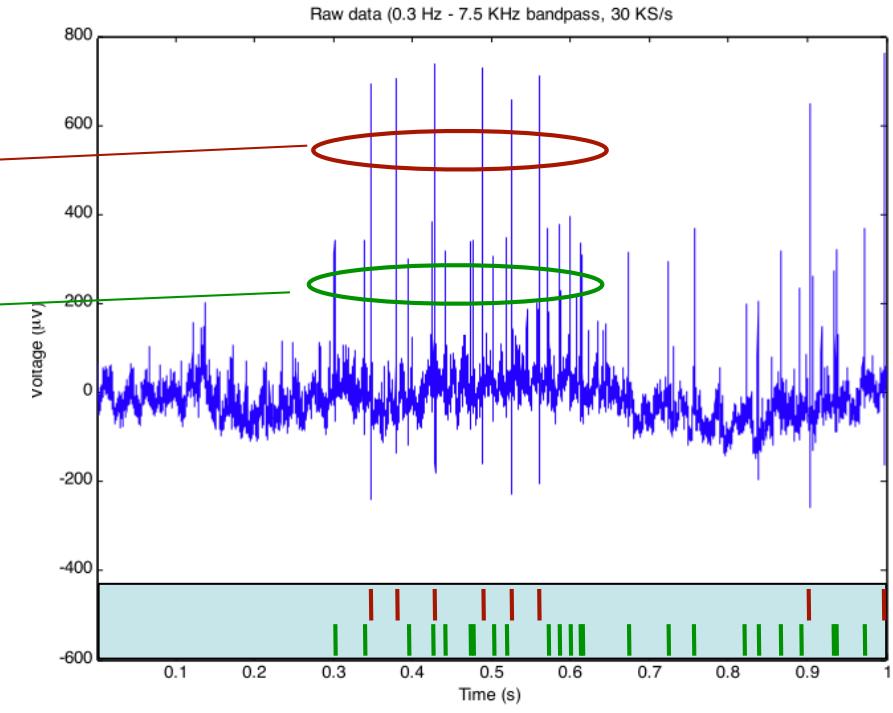
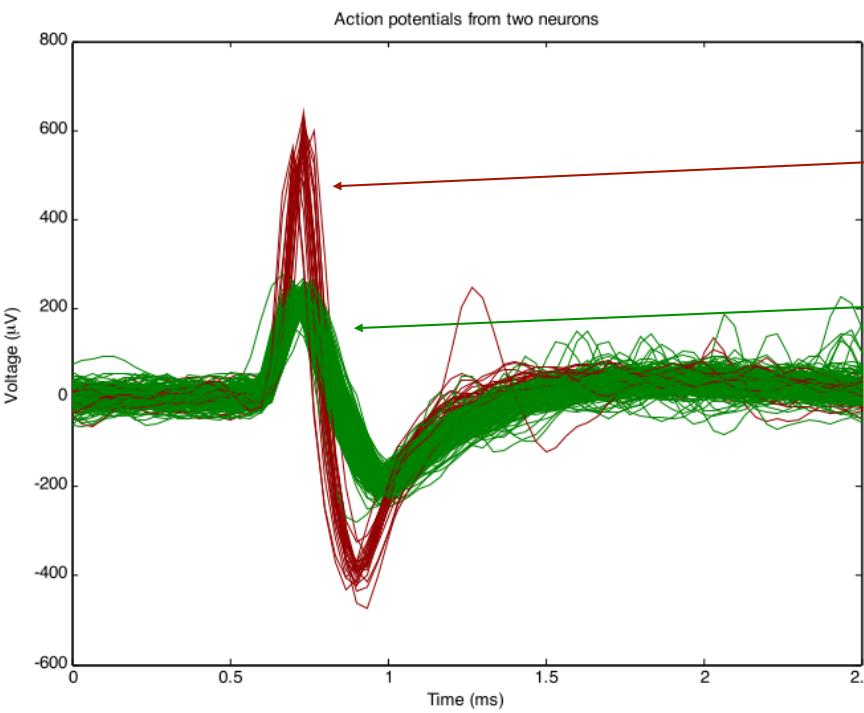
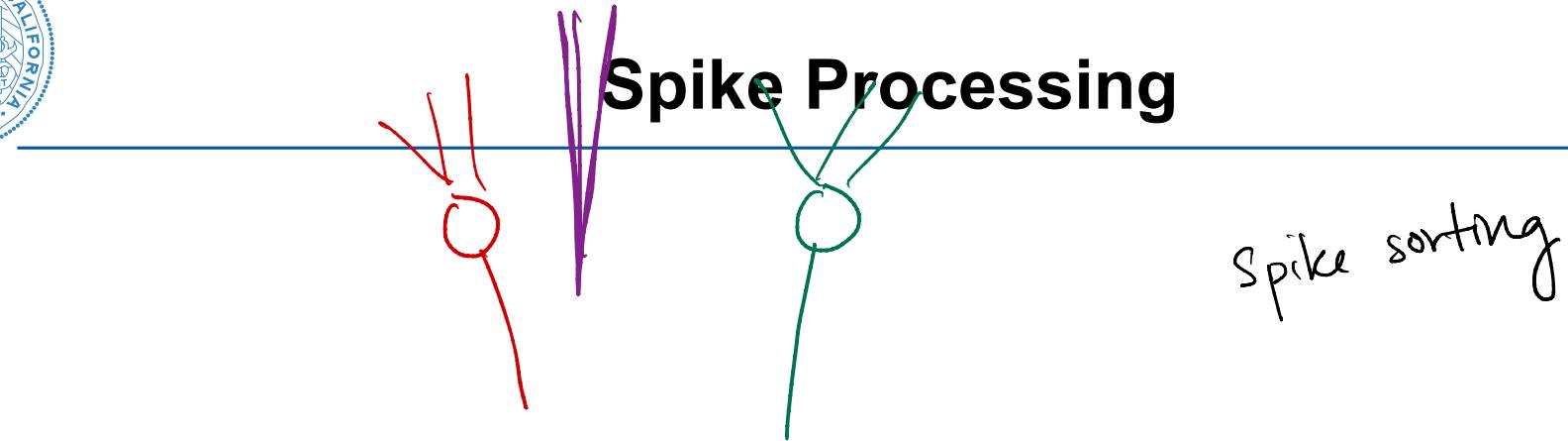


LFP
w/EEG & ECoG





Spike Processing



Can sort shapes to identify individual neurons



Virtual lab tour

- We will be looking at various representations of spikes (full AP waveform, rasters, histograms, etc.) but it is useful have a “look and feel” in mind.
- Thus, a virtual lab tour including listening to action potentials stream in:

**RHESUS MONKEY WITH 100 ELECTRODE ARRAY
(George, implanted 30 October 2003)**

Santhanam, Yu, Ryu, Howard & Shenoy

**Neural Prosthetic Systems Lab
Department of Electrical Engineering
Stanford University**

19 November 2003