



Introduction to Cognitive Neuroscience

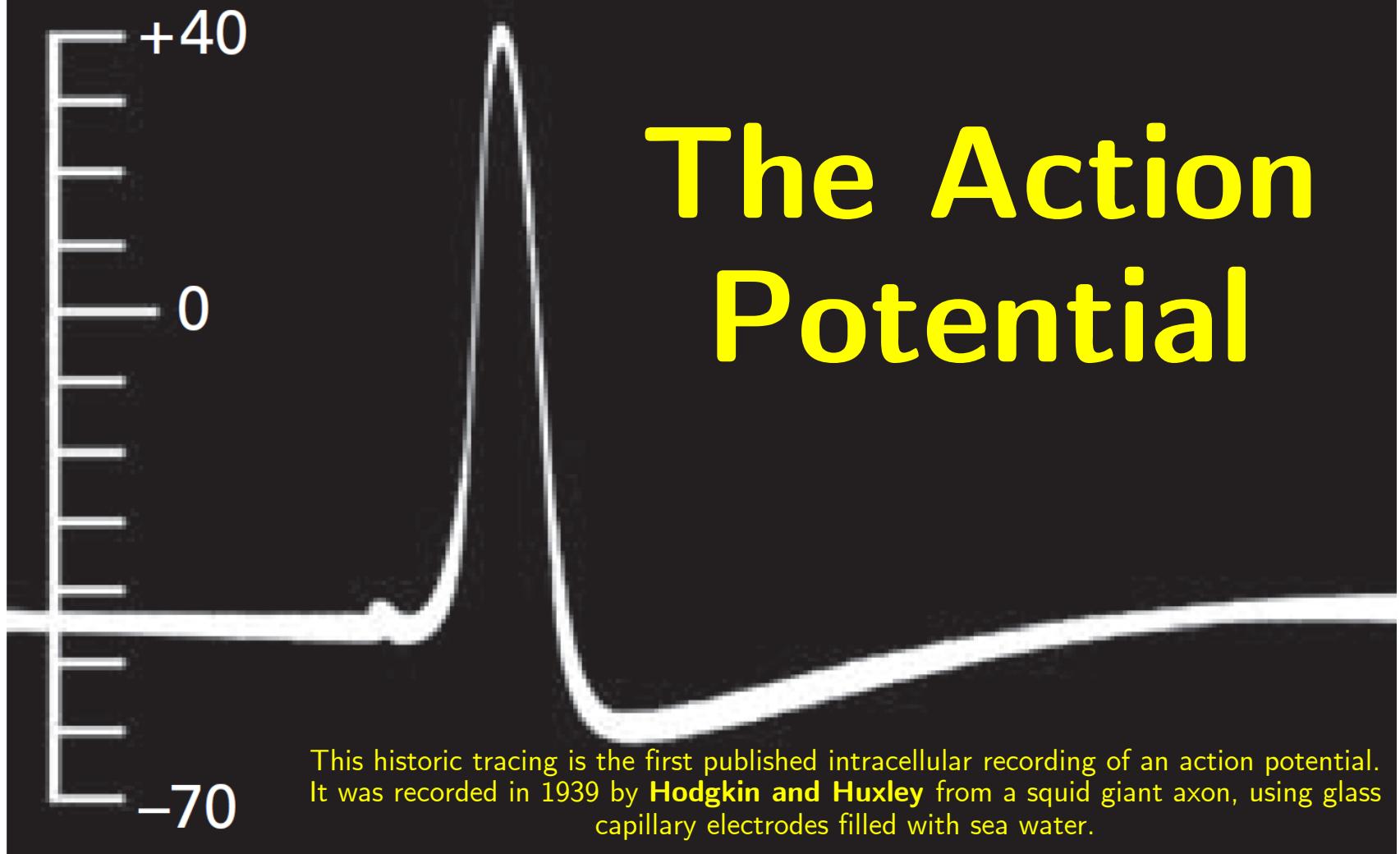
Lecture 6 The Action Potential

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The Action Potential



Introduction; what is the AP?

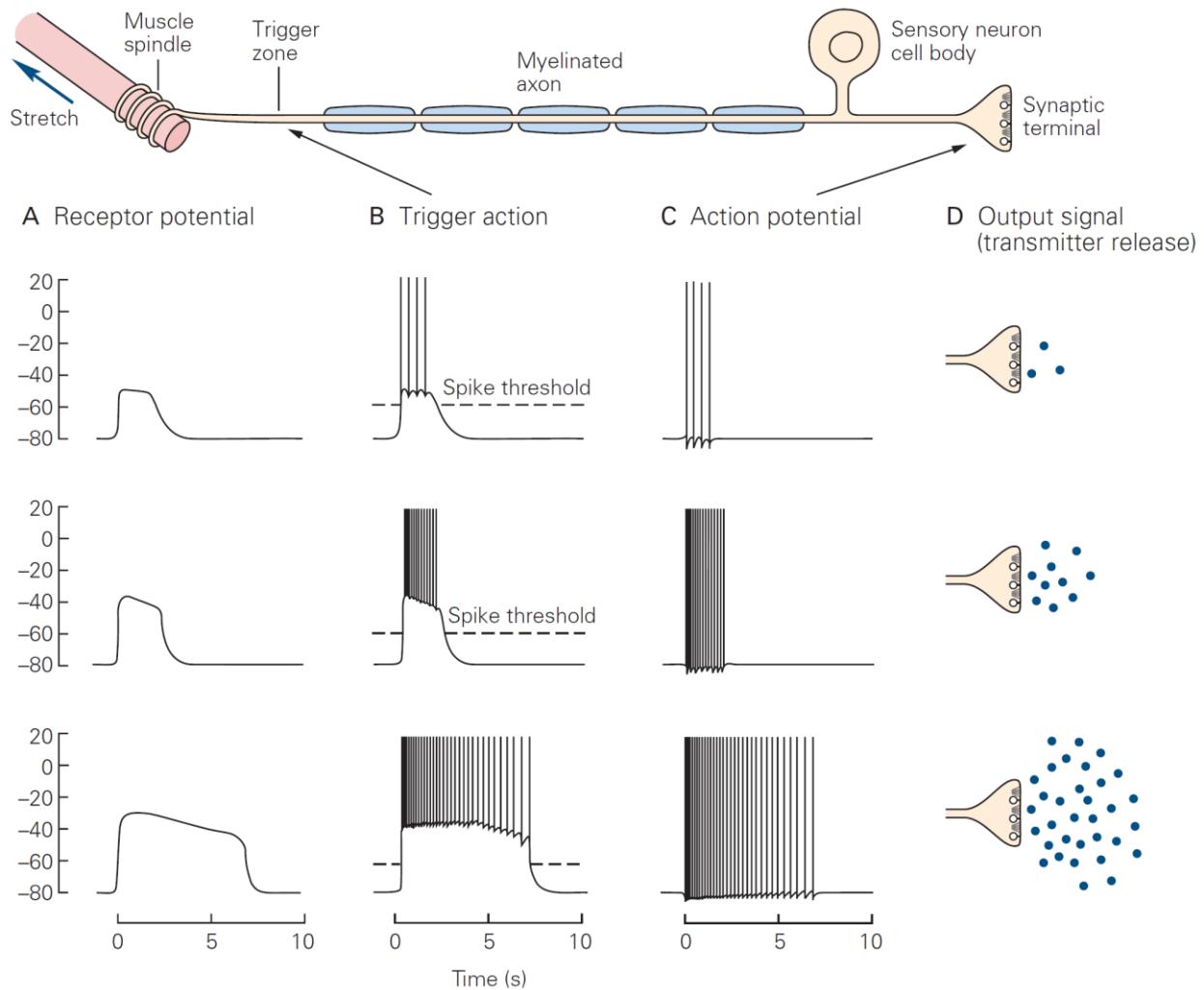


- Cytosol in the neuron at rest is **negatively charged** with respect to the extracellular
- The action potential is a **rapid reversal** of this situation
- It names: **spike**, a **nerve impulse**, or a **discharge**
- The action potentials generated by a cell are all similar in **size** and **duration**, and they **do not diminish** as they are conducted down the axon
- **All-or-none**



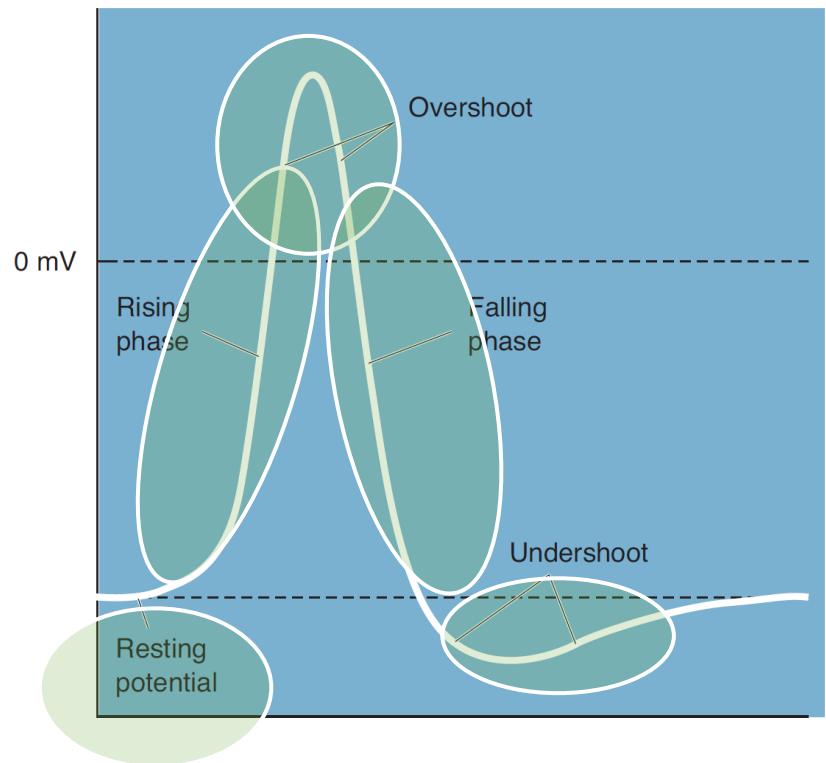
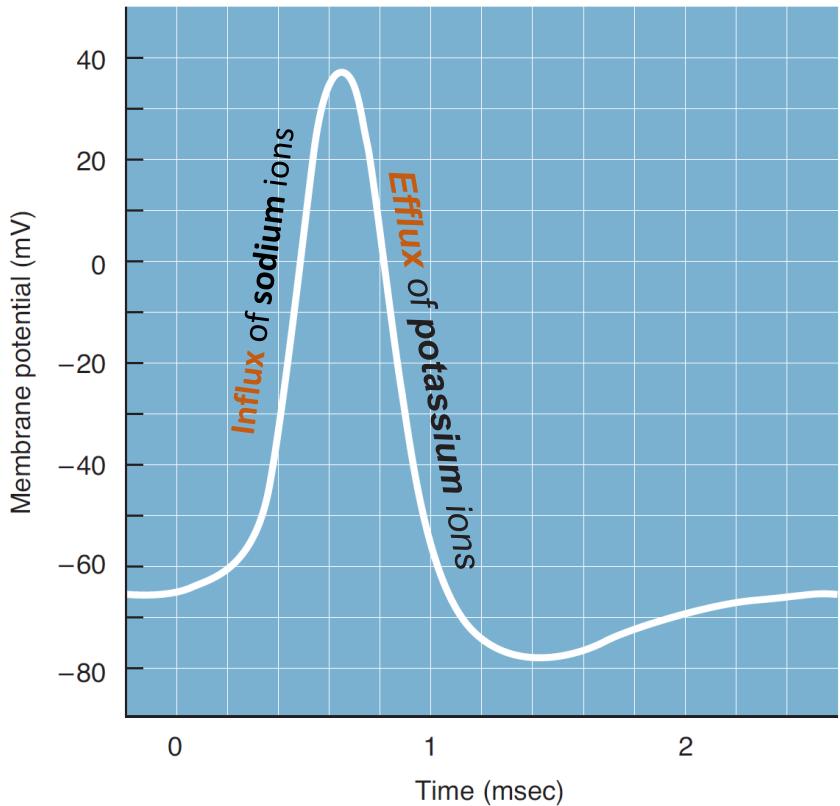
Big picture

The **frequency** and **pattern** of action potentials constitute **the code** used by neurons to transfer information from one location to another

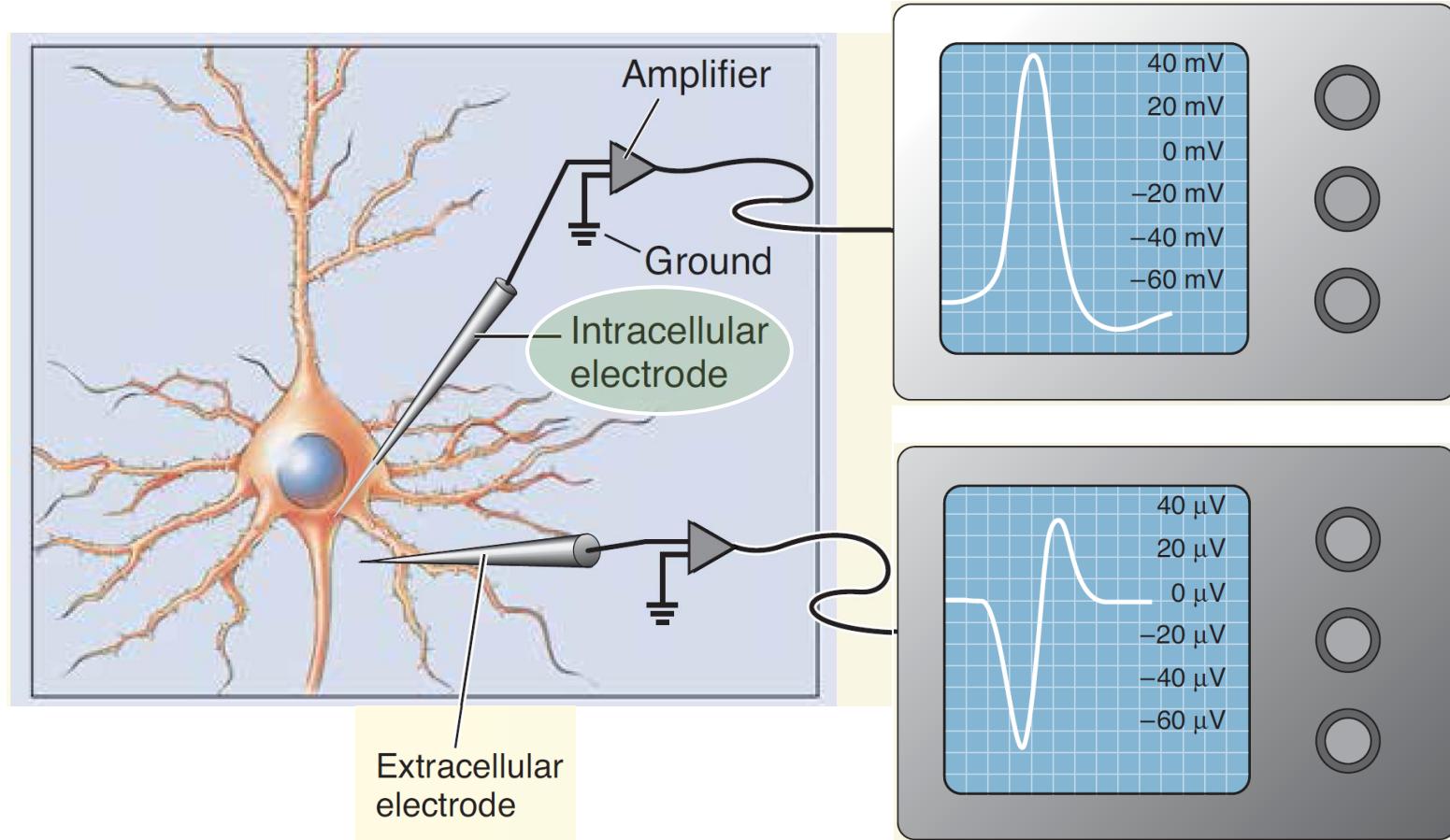




The ups and downs of an action potential



Methods of recording action potentials

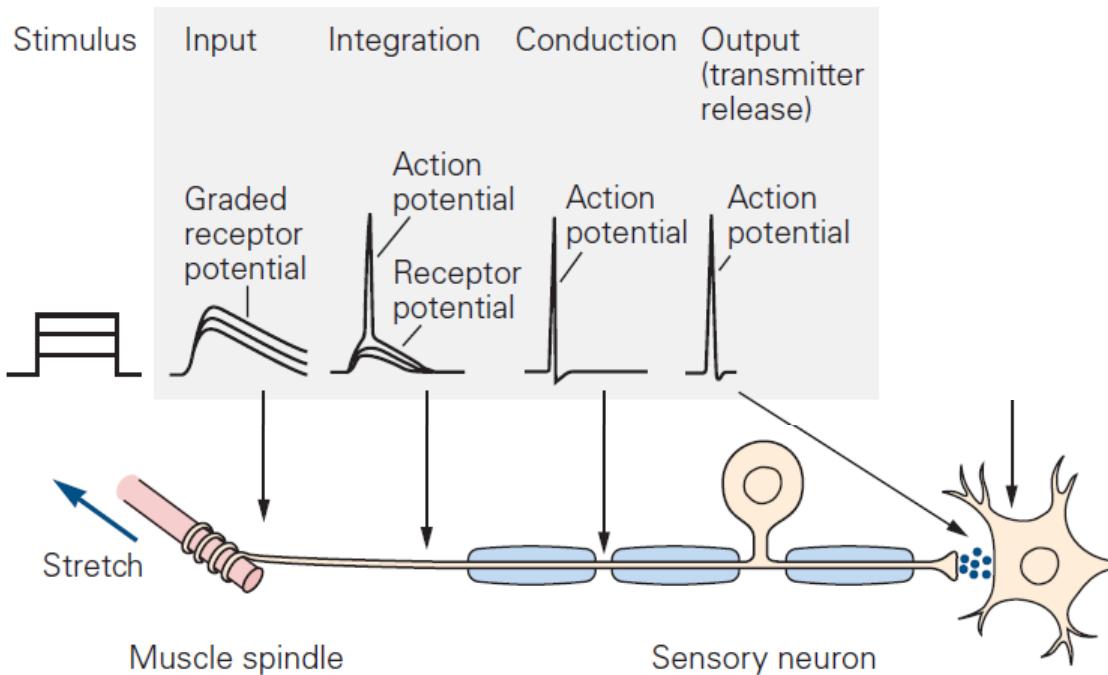




Action potentials initiation I

Entry of Na^+ through specialized ion channels that were sensitive to one physical event (e.g. membrane stretching)

Threshold: The critical level of depolarization that must be reached in order to trigger an action potential is called

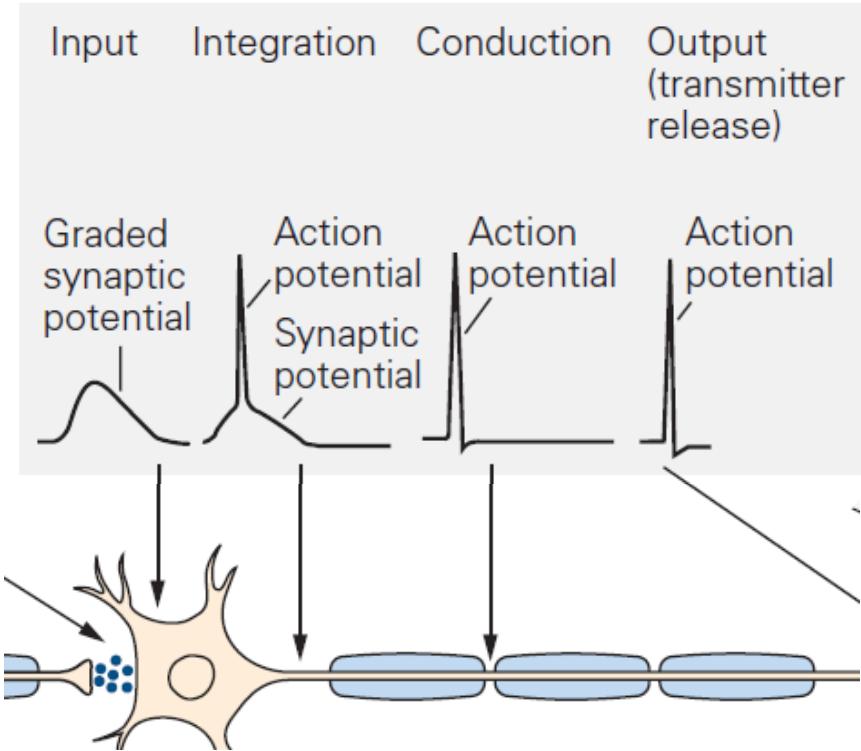


Sensory signals

Action potentials initiation II

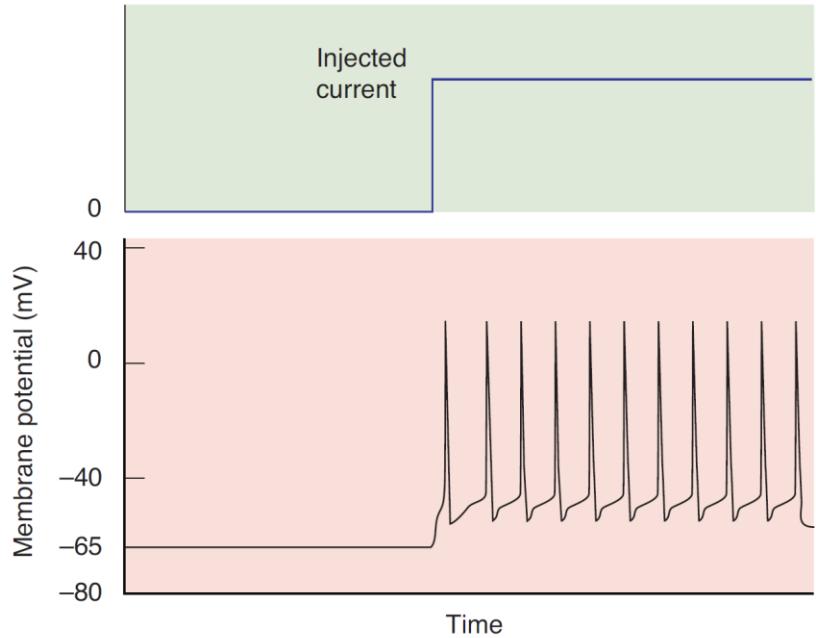
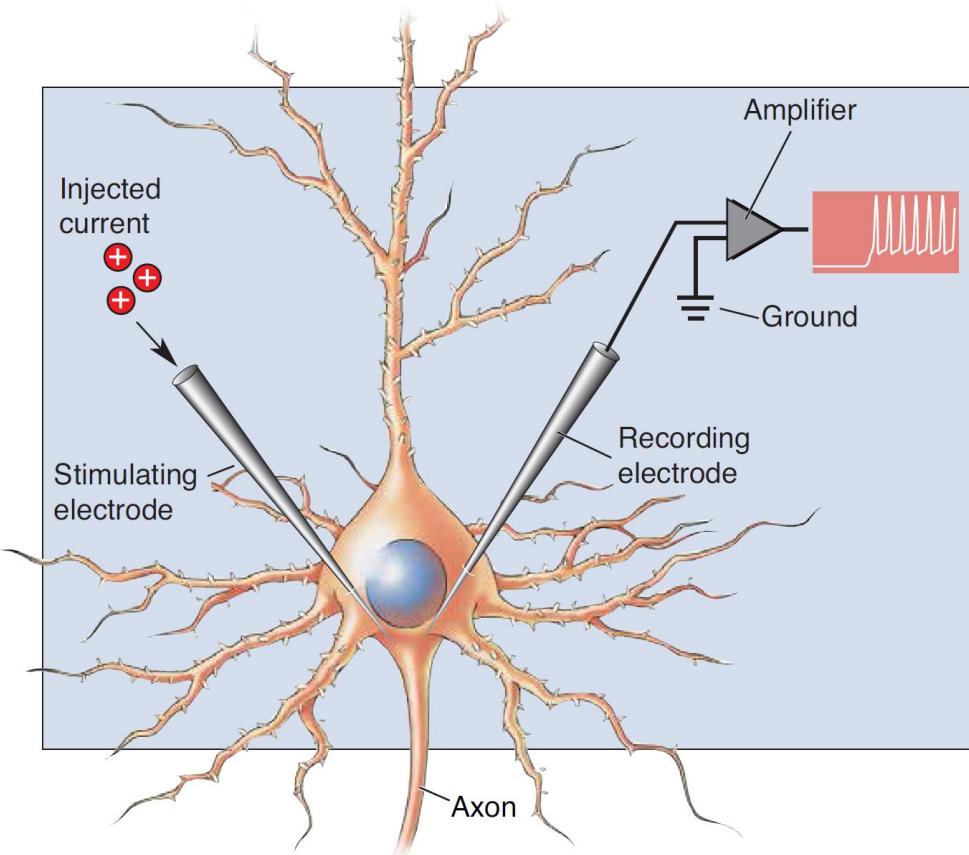


Through **channels** that
are sensitive to
neurotransmitters



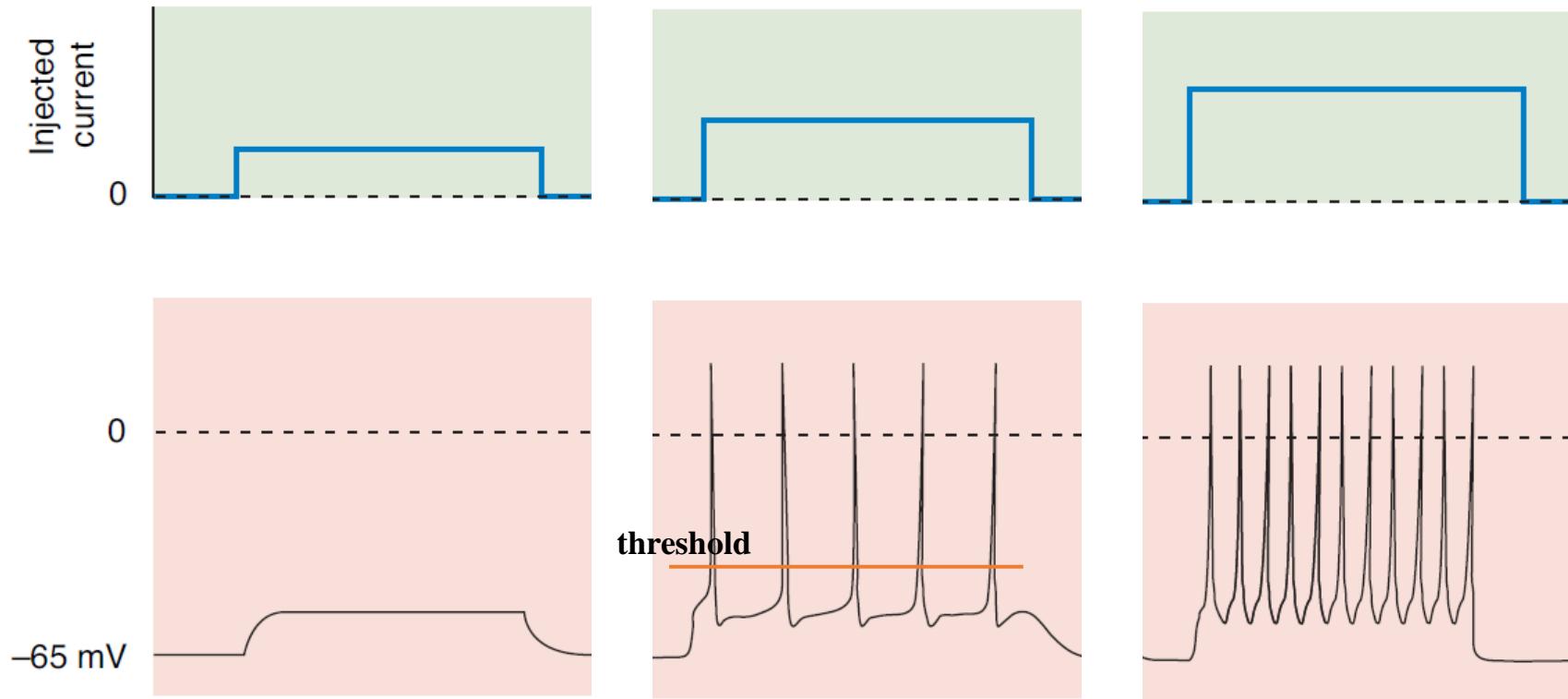


Action potentials initiation III





Firing frequency of action potentials reflects the magnitude of the depolarizing current



Refractory periods

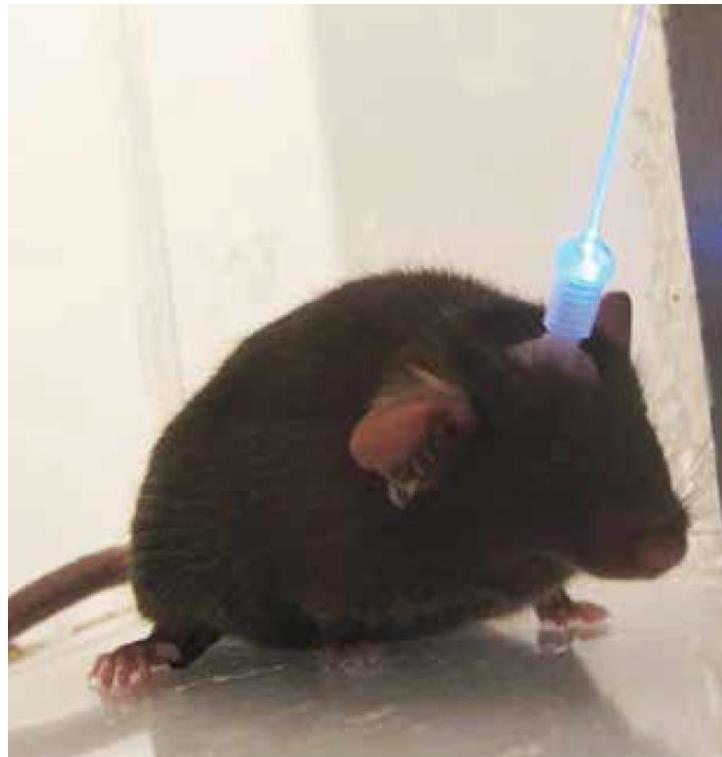


- **Absolute refractory period:**
 - It is impossible to initiate another for about 1 msec (max firing rate: 1K hertz)
- **Relative refractory period:**
 - Relatively difficult to initiate another action potential for **several milliseconds** after the end



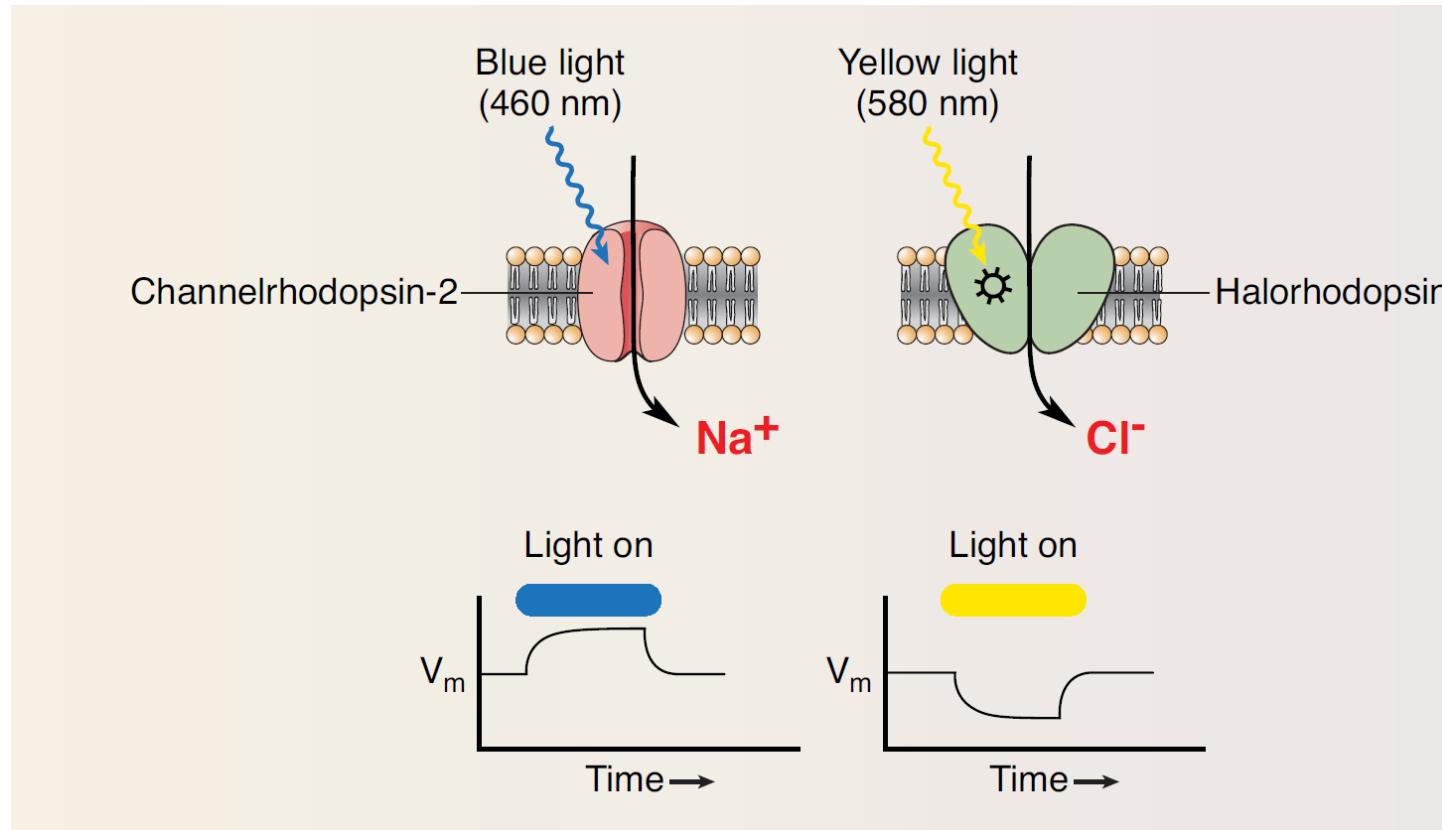
Optogenetics: Controlling neural activity with light

- Neuroscientists historically have had to use **microelectrodes** to **inject** electrical current
- **Optogenetics** introduces into neurons **foreign genes** that express membrane ion channels that open in **response to light**





Channelrhodopsin-2 and halorhodopsin in the plasma membrane





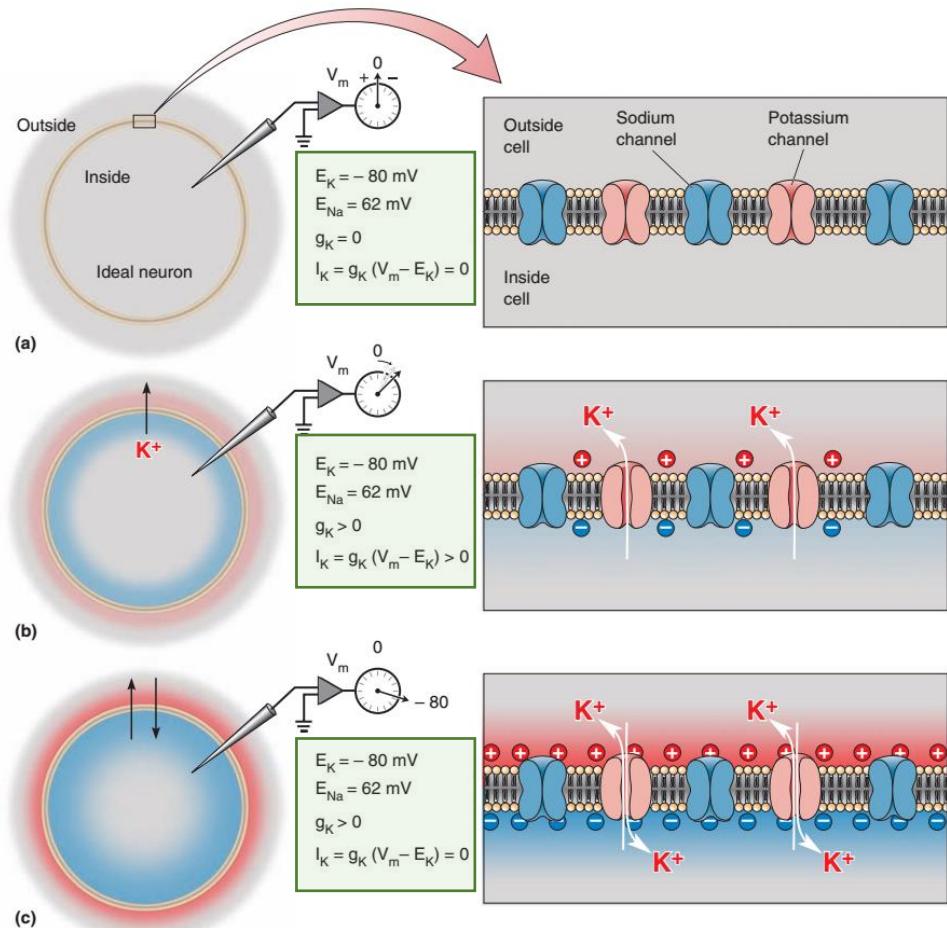
Membrane currents and conductances in ideal neurons

The **pumps** establish ionic **concentration gradients** so that K^+ is concentrated inside the cell and Na^+ is concentrated outside the cell

(a) Initially, all channels are closed

(b) We open the potassium channels

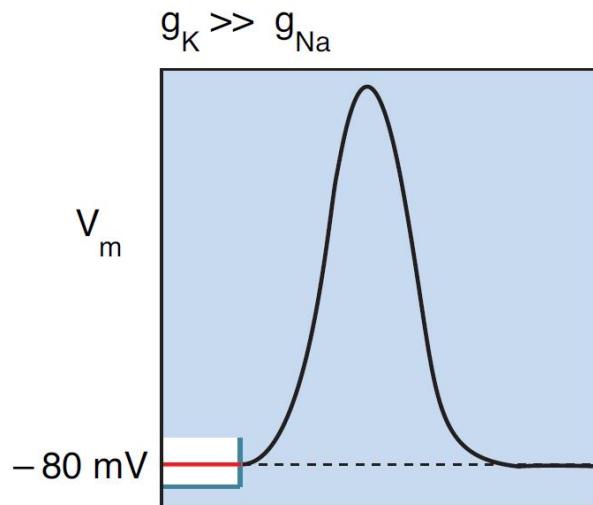
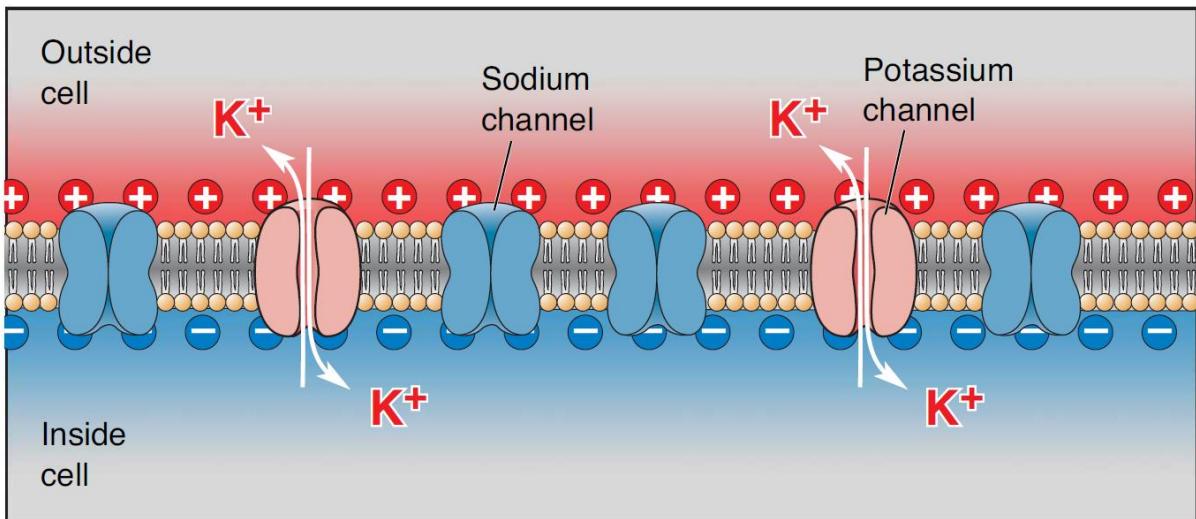
(c) At equilibrium, an equal number of K^+ enters and leaves.



$$I_{ion} = g_{ion} (V_m - E_{ion}).$$



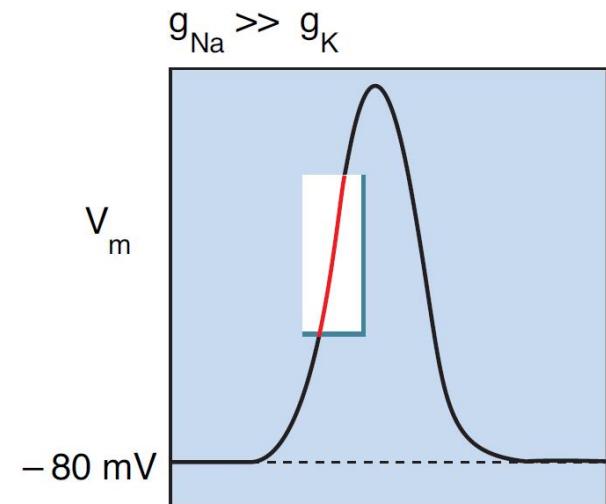
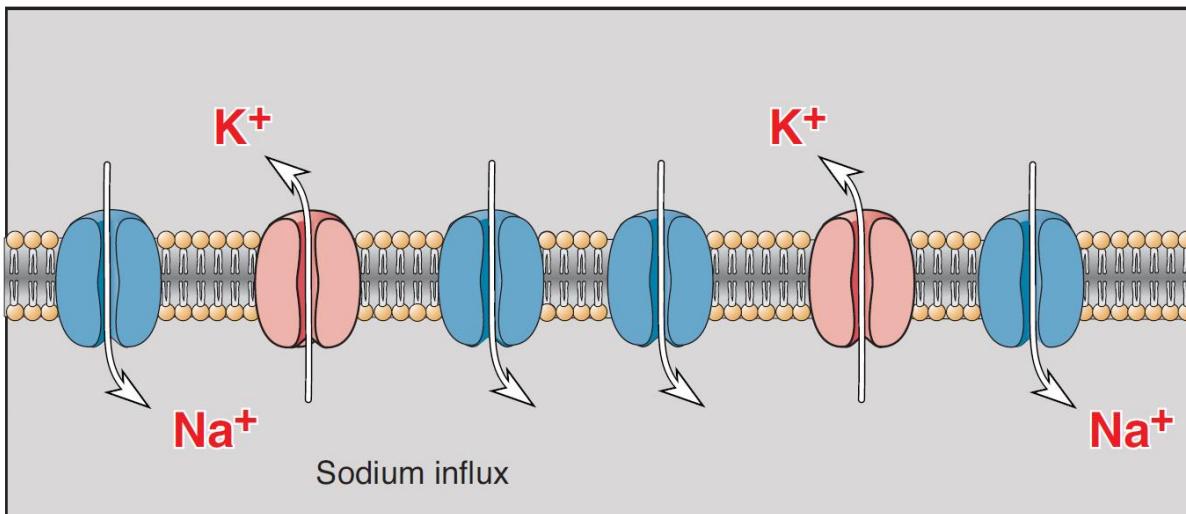
The membrane is permeable only to K and that $V_m = E_K$





Sodium channels open so that $g_{\text{Na}} \gg g_{\text{K}}$

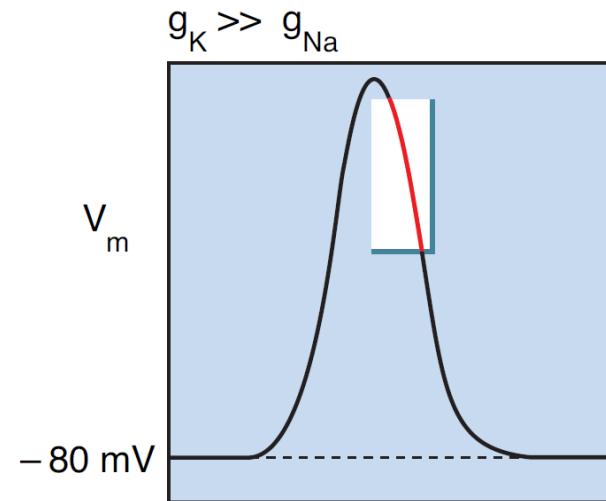
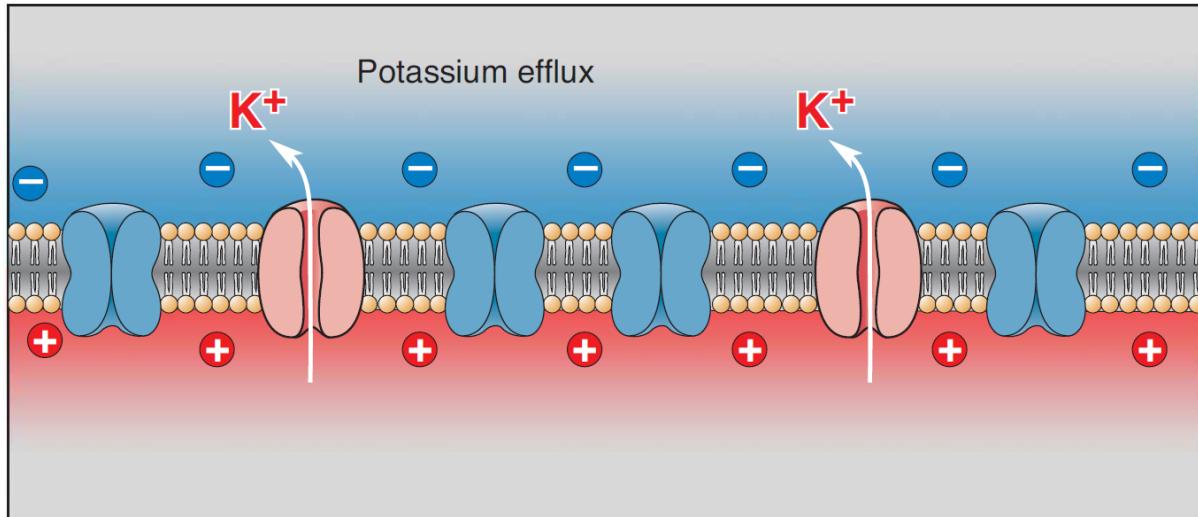
There is a large **driving force** on Na, so Na rushes into the cell, taking V_m toward E_{Na} .



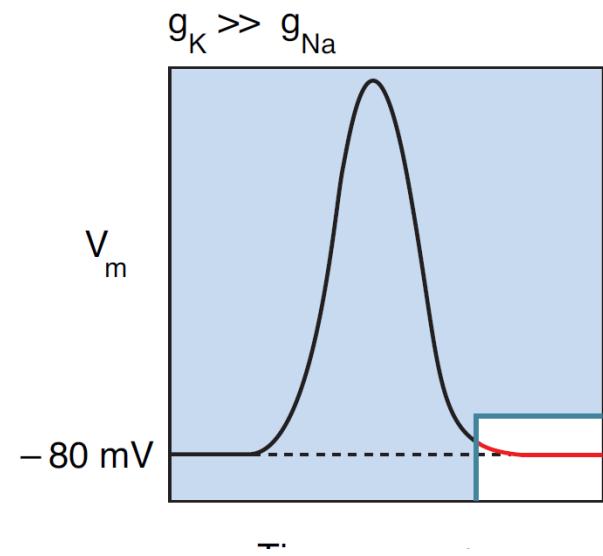
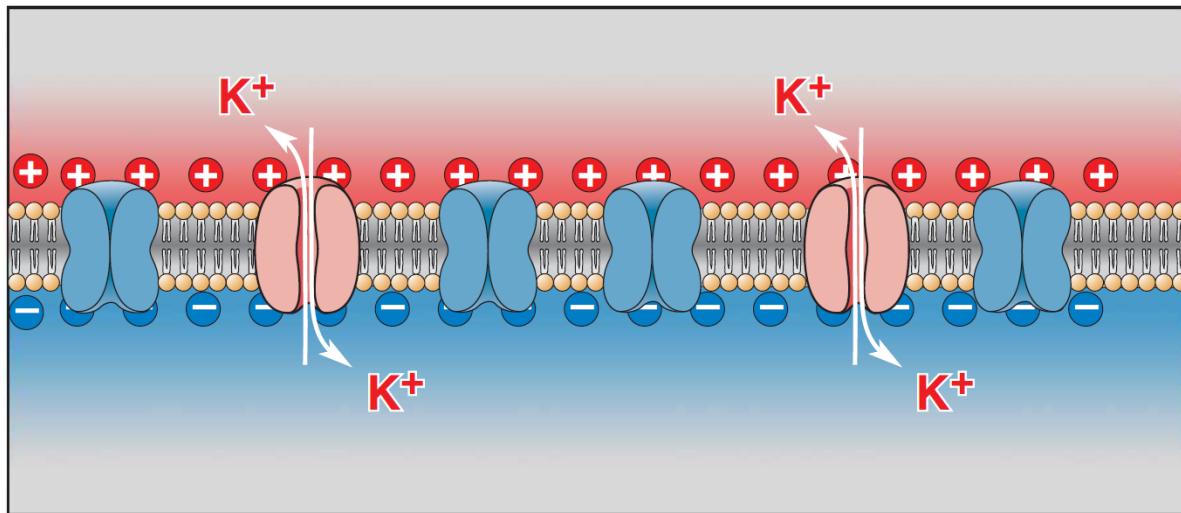
Closing the sodium channels so that $g_K \gg g_{Na}$



Because the membrane potential is positive, there is a **large driving force on K**. The **efflux** of K takes V_m back toward E_K .



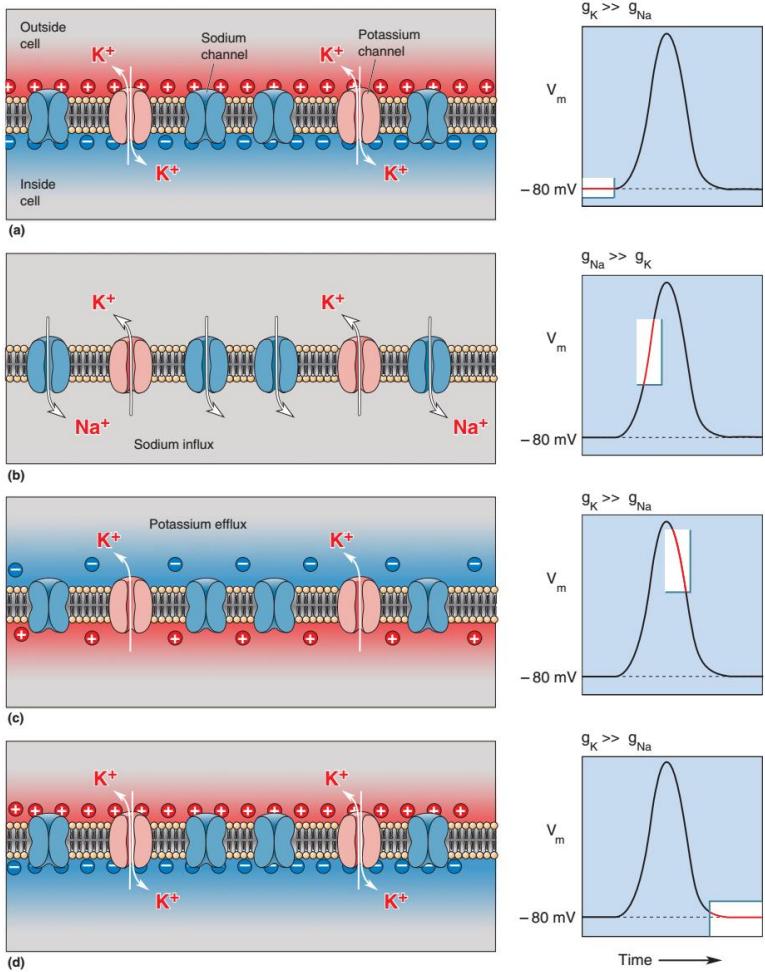
The resting state is restored where $V_m = E_K$



The action potential accounted by the movement of ions through channels that are gated by changes in the membrane potential.

Flipping the membrane potential by changing the **relative ionic** permeability of the membrane

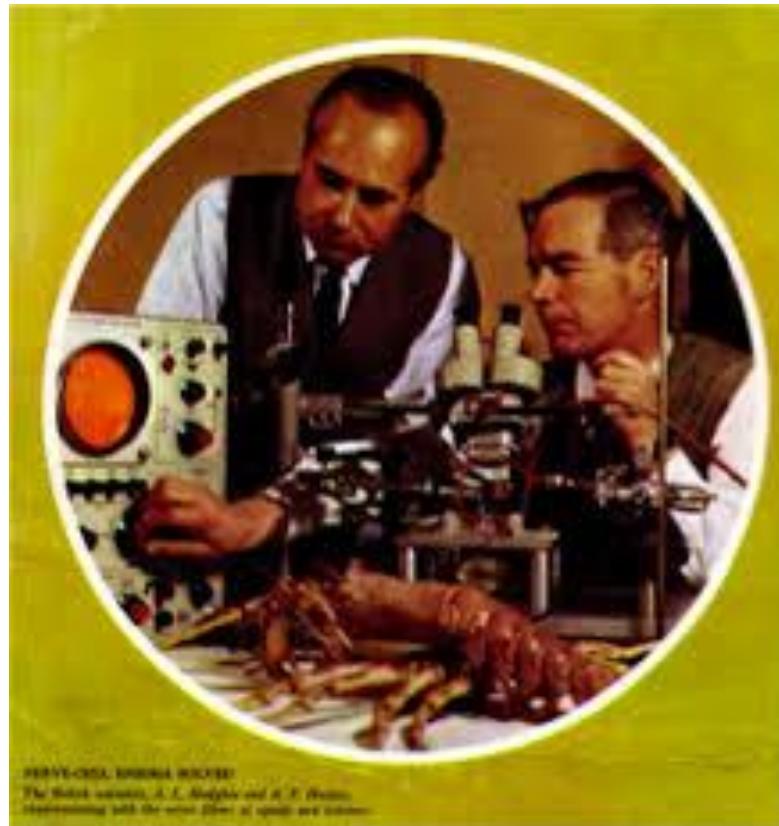
Ion	Concentration outside (in mM)	Concentration inside (in mM)	Ratio Out : In	E_{ion} (at 37°C)
K^+	5	100	1 : 20	-80 mV
Na^+	150	15	10 : 1	62 mV





Voltage clamp; measuring conductance in real world

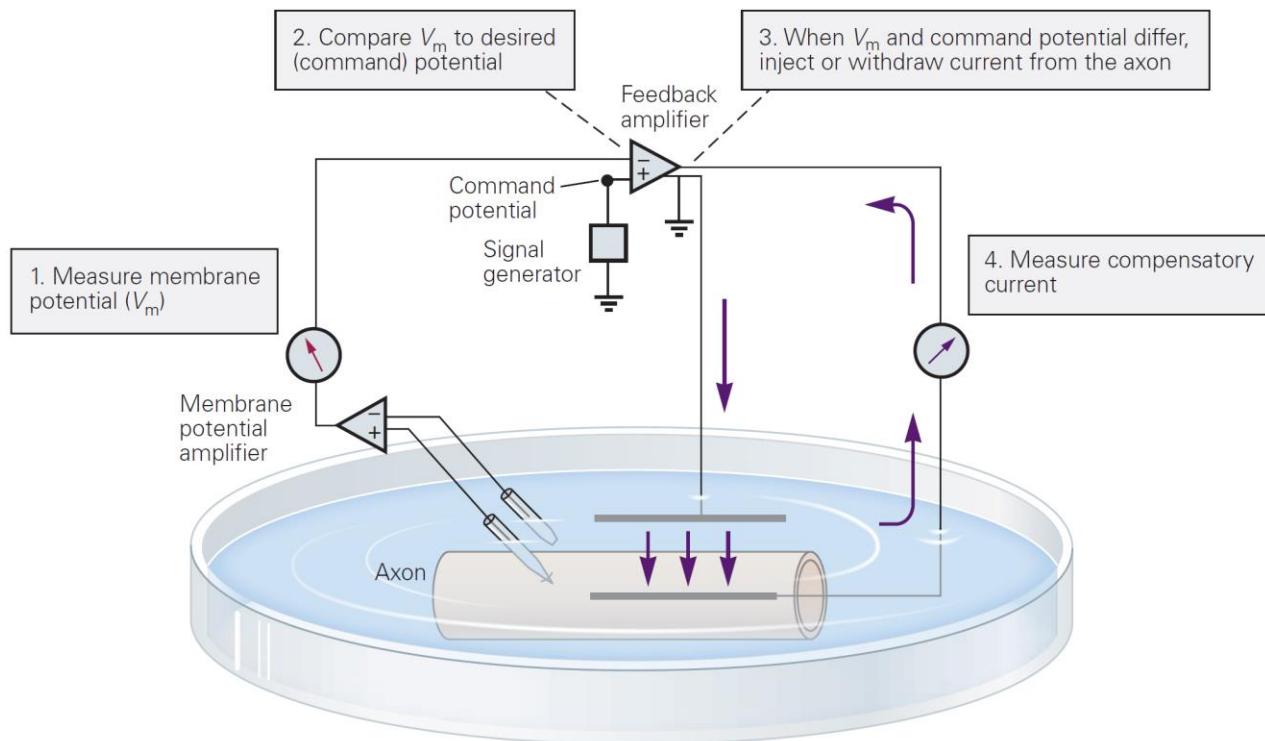
- The key technical **breakthrough** came with a device called a **voltage clamp**, invented by the American physiologist **Kenneth C. Cole** and used in decisive experiments by **Alan Hodgkin and Andrew Huxley around 1950**
- Using this method, they can “**clamp**” the **membrane potential** of an axon at any value they chose and measured the **currents that** flowed **across** the membrane
- They **predicted voltage** dependent gate for K and Na, **20 years before** direct demonstration of voltage gated channels



ALAN HODGKIN AND ANDREW HUXLEY
The British scientists A. F. Huxley and R. E. Huxley
experimenting with the nerve fibers of a frog and a toad.

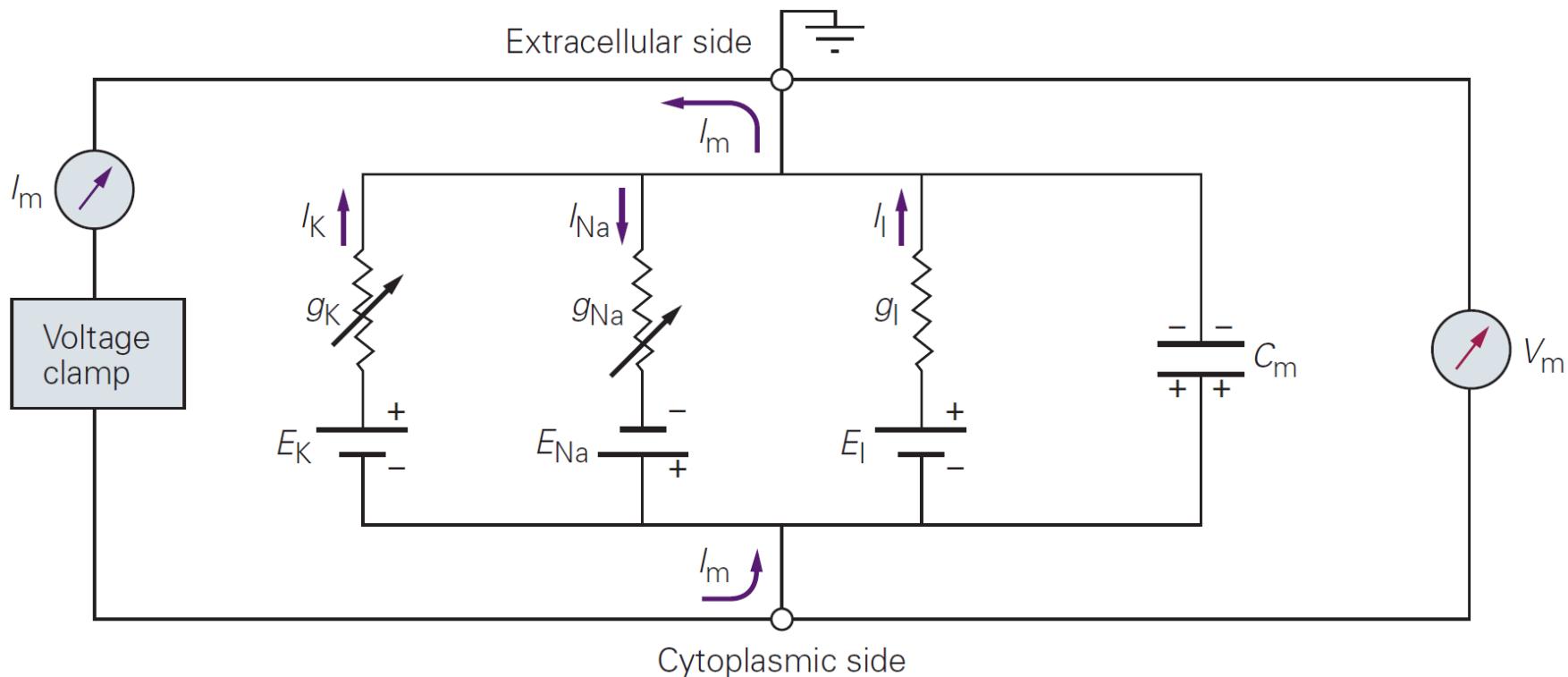


The negative feedback mechanism of the voltage clamp





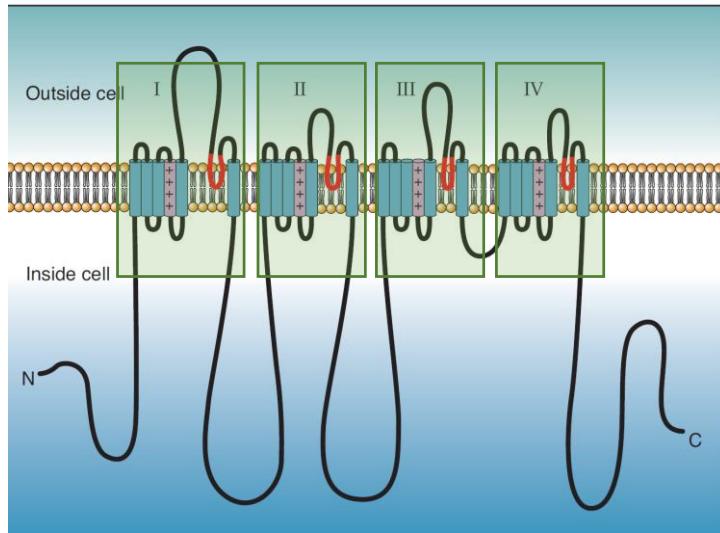
Equivalent circuit of a voltage-clamped neuron



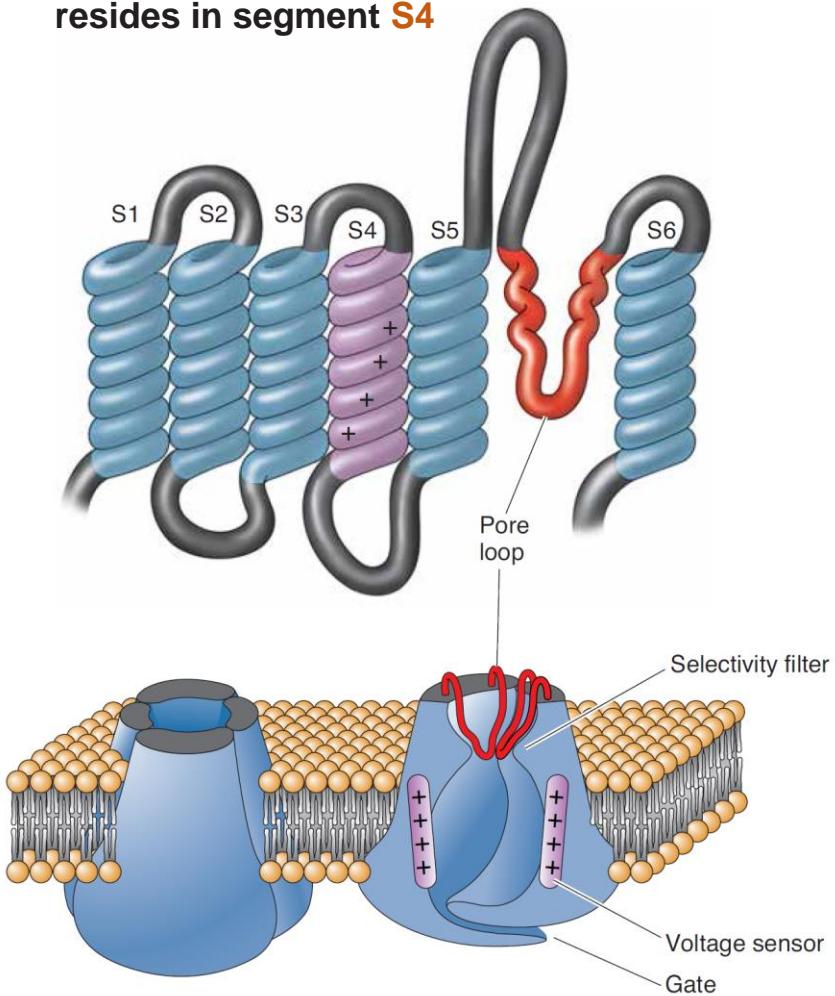


The structure of the voltage-gated sodium channel

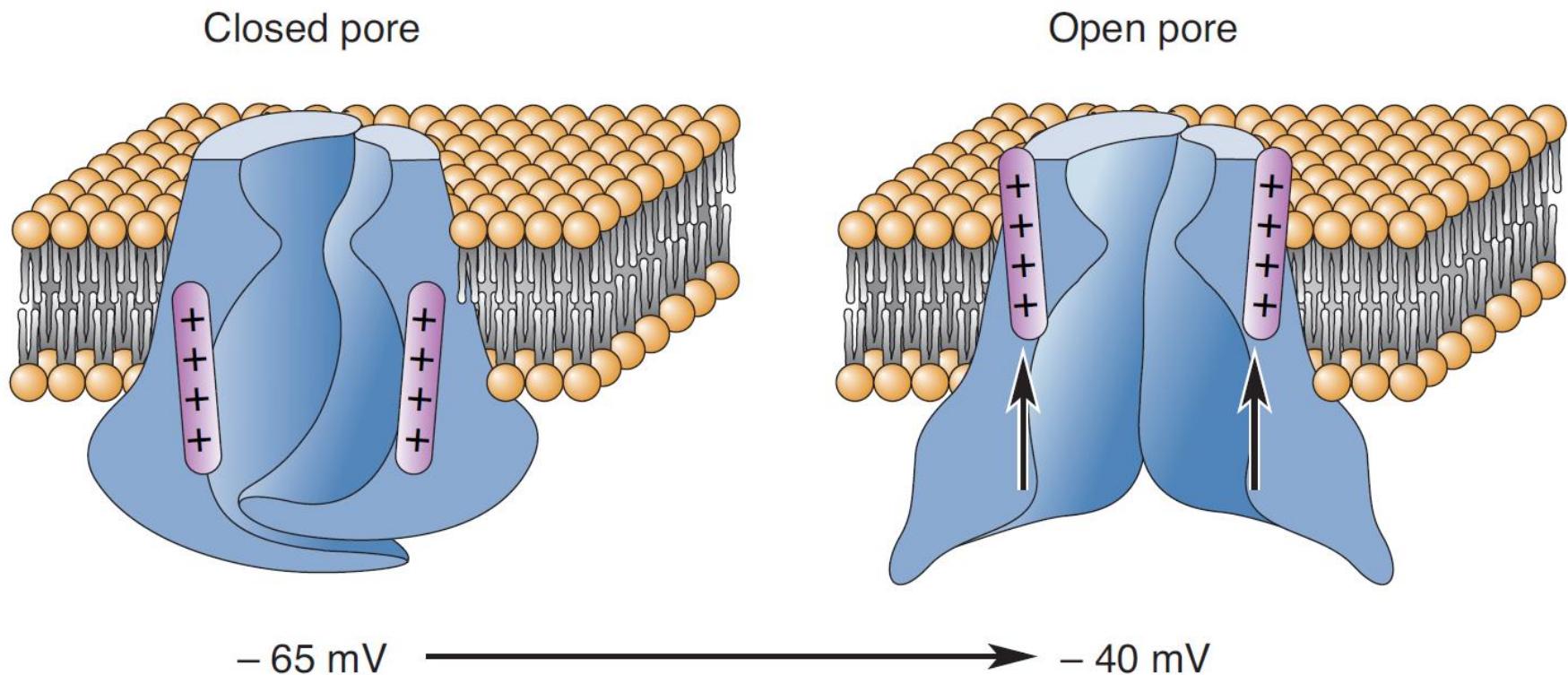
The **protein** forms a pore in the membrane that is highly selective to Na^+ , and the pore is opened and closed by **changes in membrane voltage**.



Voltage sensor
resides in segment **S4**

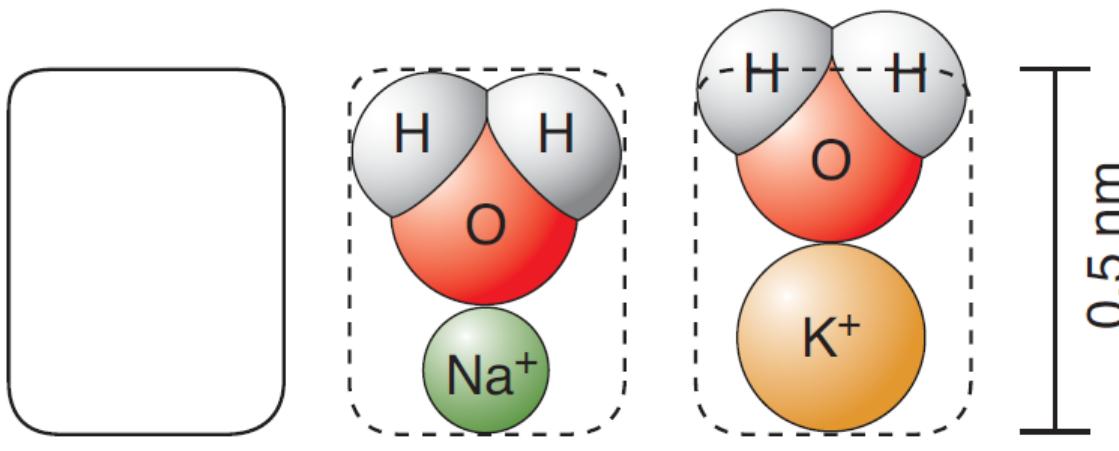


A hypothetical model for changing the configuration of the sodium channel by depolarizing the membrane





Dimensions of the sodium channel selectivity filter

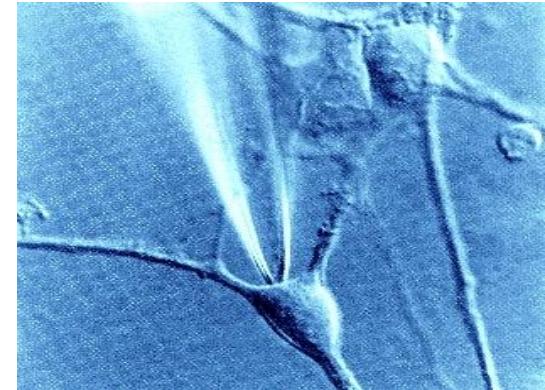
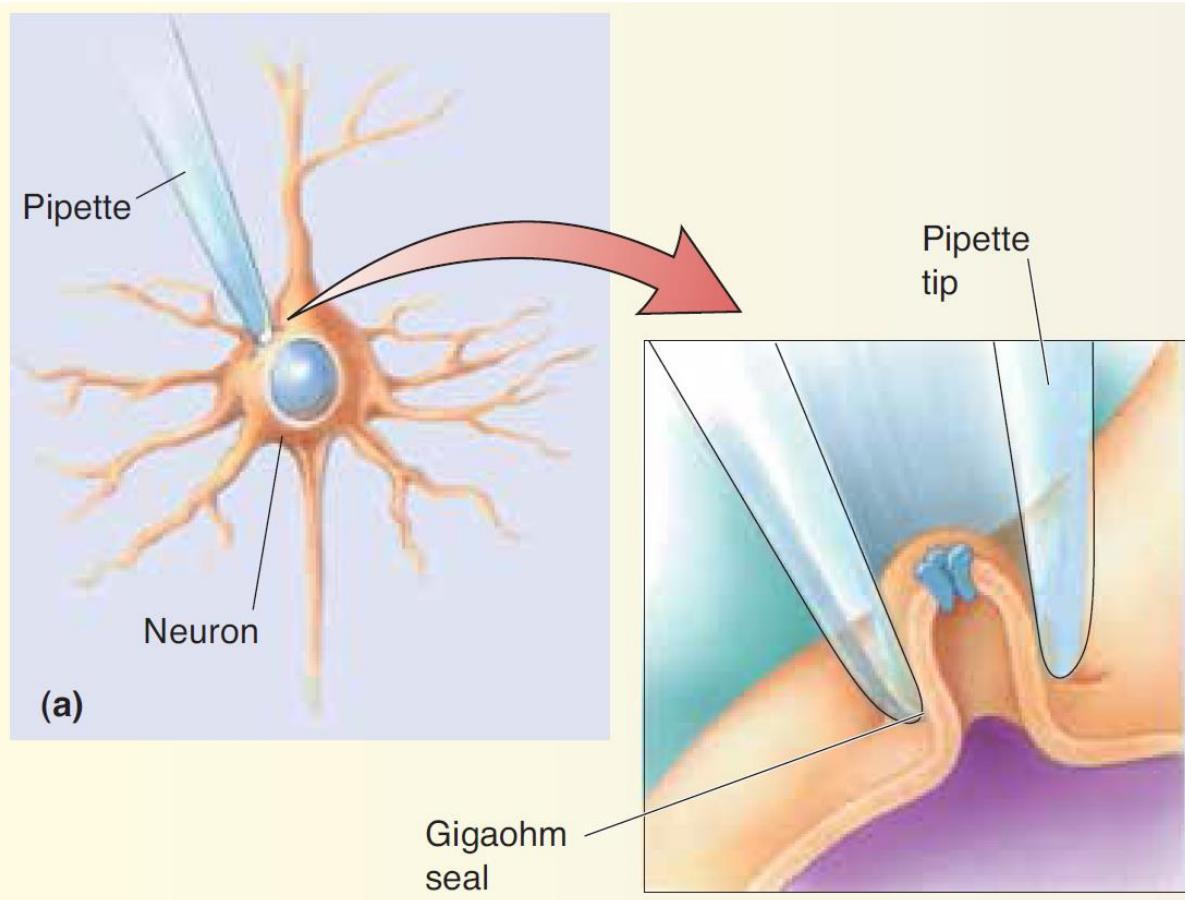


Size of
sodium
channel
selectivity
filter

Size of
partially
hydrated
 Na^+ ion

Size of
partially
hydrated
 K^+ ion

Patch clamp technique



Apply positive pressure ($2\text{-}6 \text{ M}\Omega$)

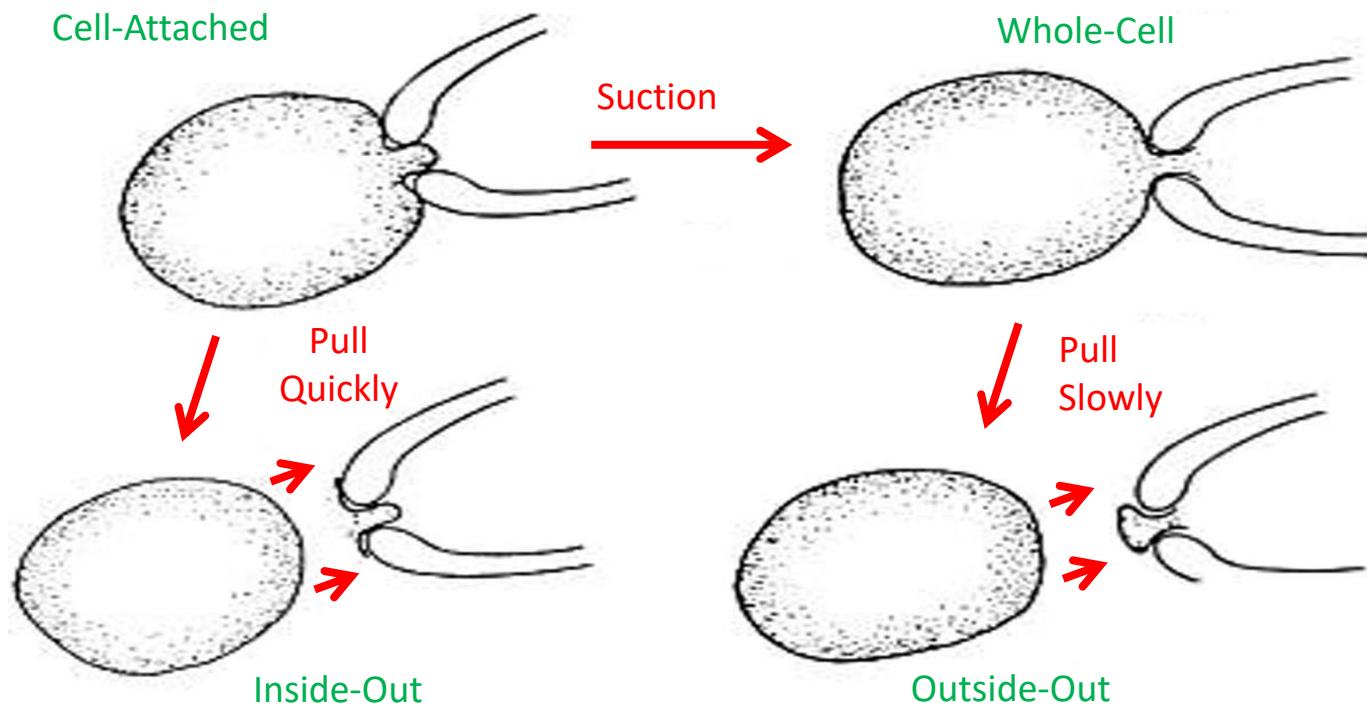
Clear tissue as you move down

Near cell membrane > 'bubble'

Apply negative pressure > suction until $1 \text{ G}\Omega$ seal

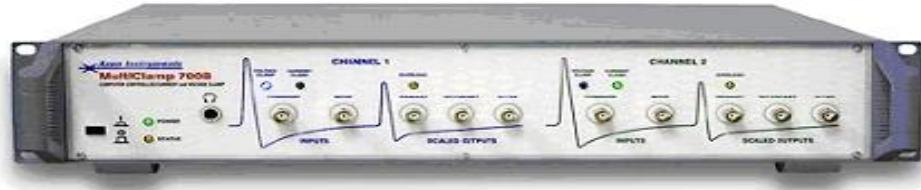
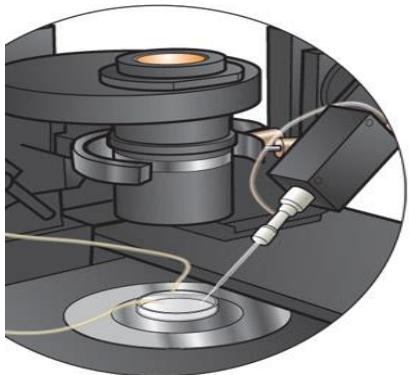


4 Common Patch-Clamp Configurations





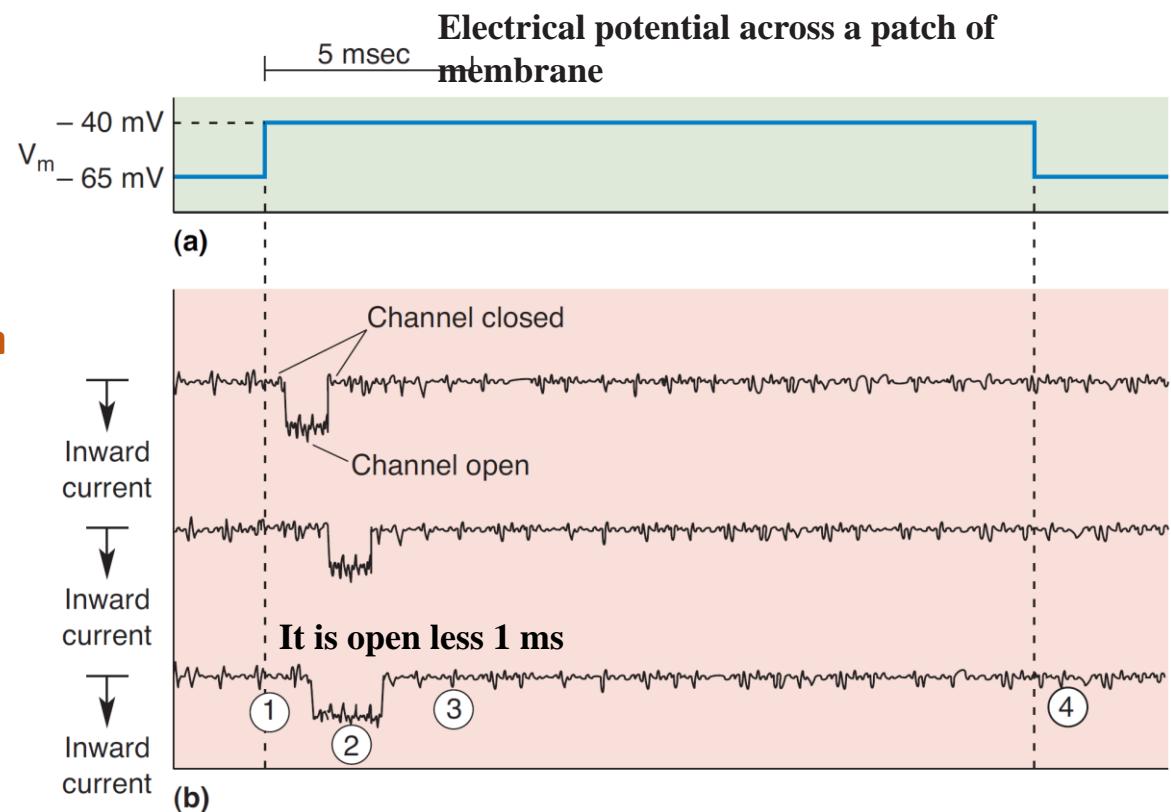
Recording patch devices



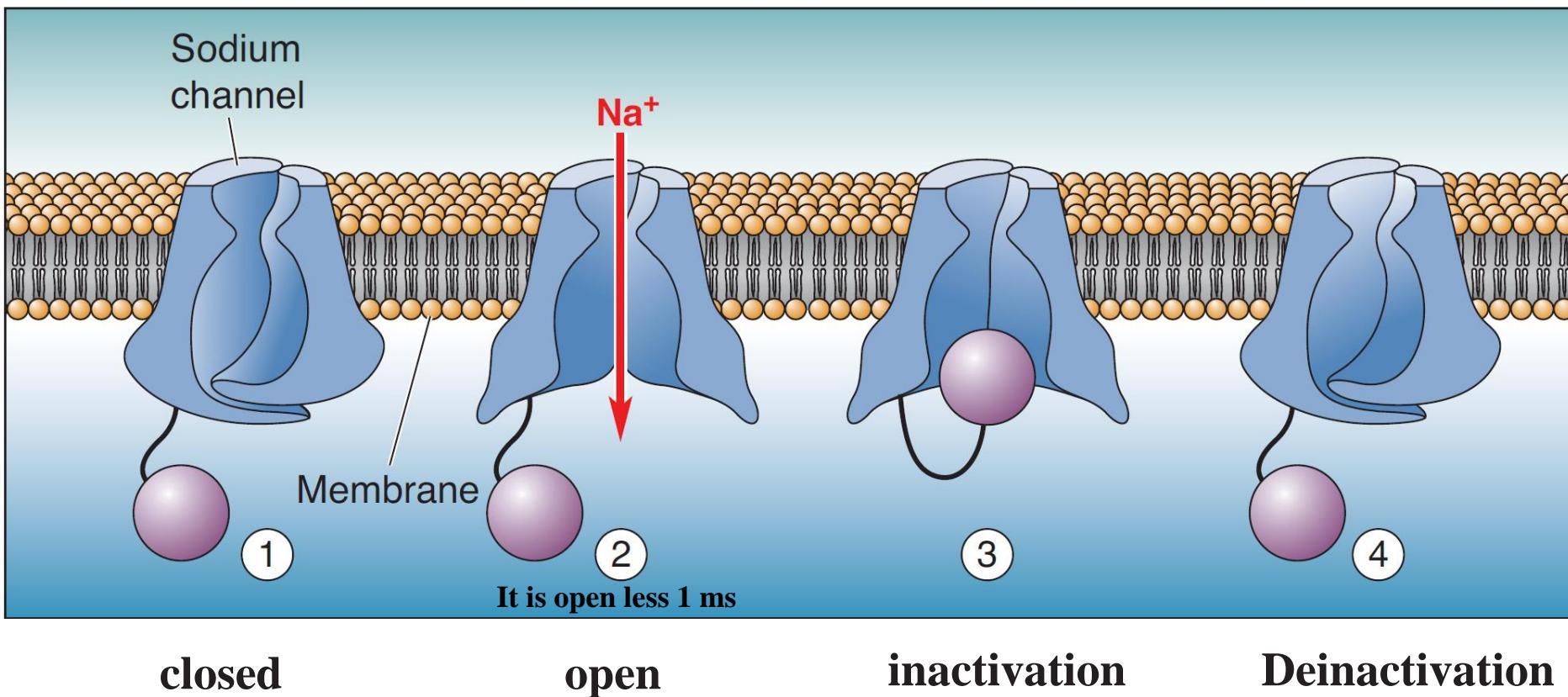


The opening and closing of sodium channels upon membrane depolarization

- Three different channels respond to the voltage
- ① At -65 mV, the channels are **closed**
- ② Membrane is depolarized to -40 mV, the channels briefly **open** and current flows inward
- ③ The closure of the sodium channel is called **inactivation**
- ④ To **deactivate** the channels, the membrane must be returned to -65 mV again.



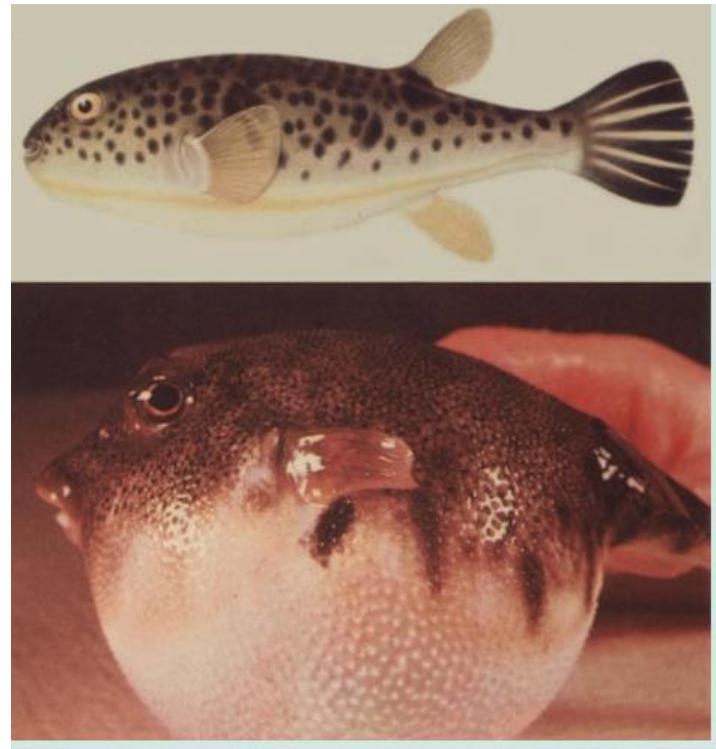
A model for how changes in the conformation of the sodium channel protein might yield its functional properties





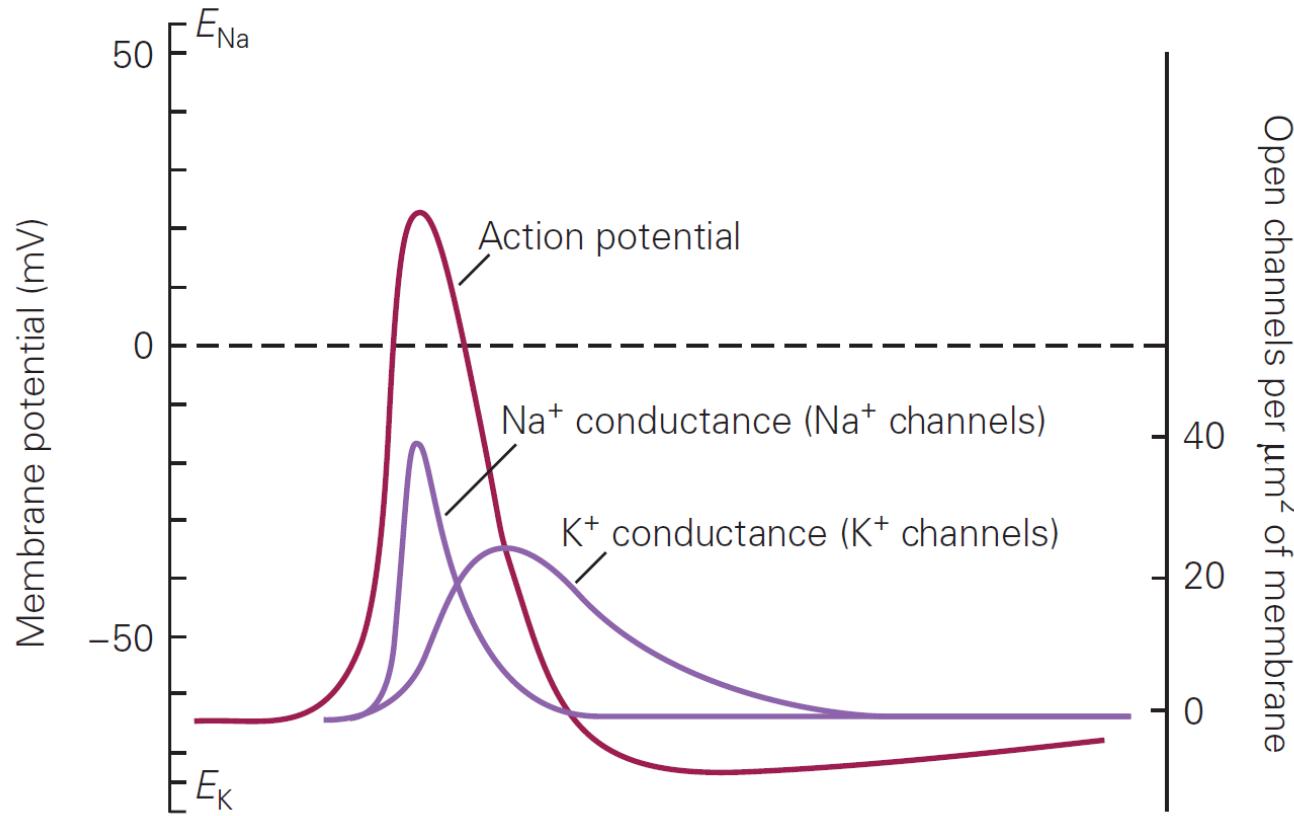
The effects of toxins on the sodium channel

- **Tetrodotoxin (TTX):**
 - A **puffer fish** blows out when irritated
- **Saxitoxin:**
 - Produced by dinoflagellates of the genus *Gonyaulax*
- They can be used as **experimental tools** to study the consequences of blocking action potentials.





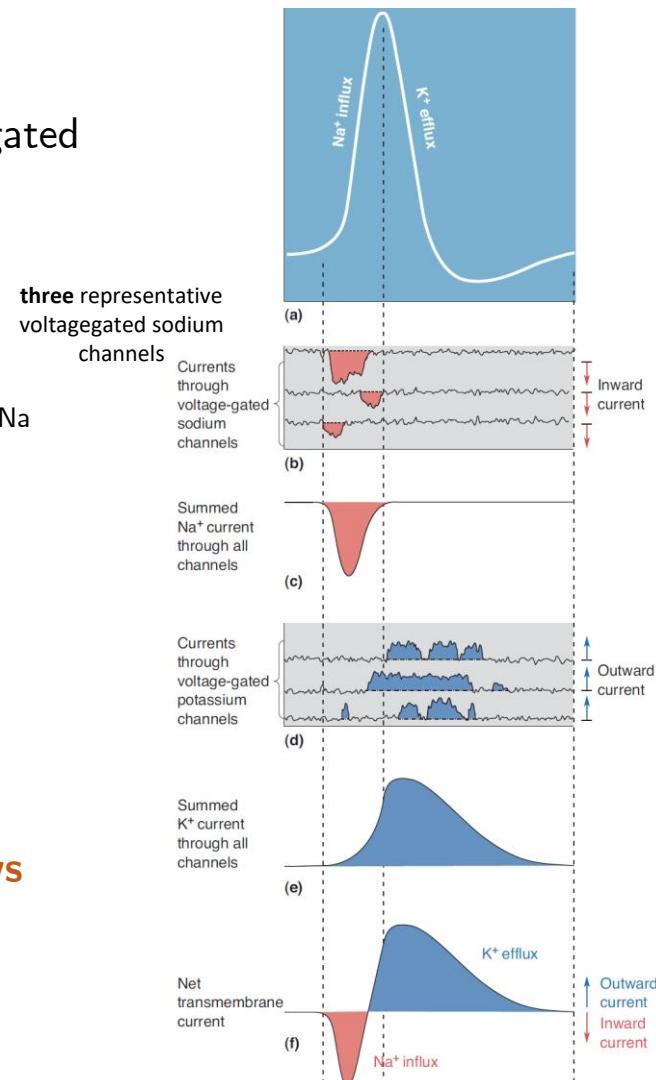
The sequential opening of voltage-gated Na⁺ and K⁺ channels generates the action potential





The molecular basis of the action potential

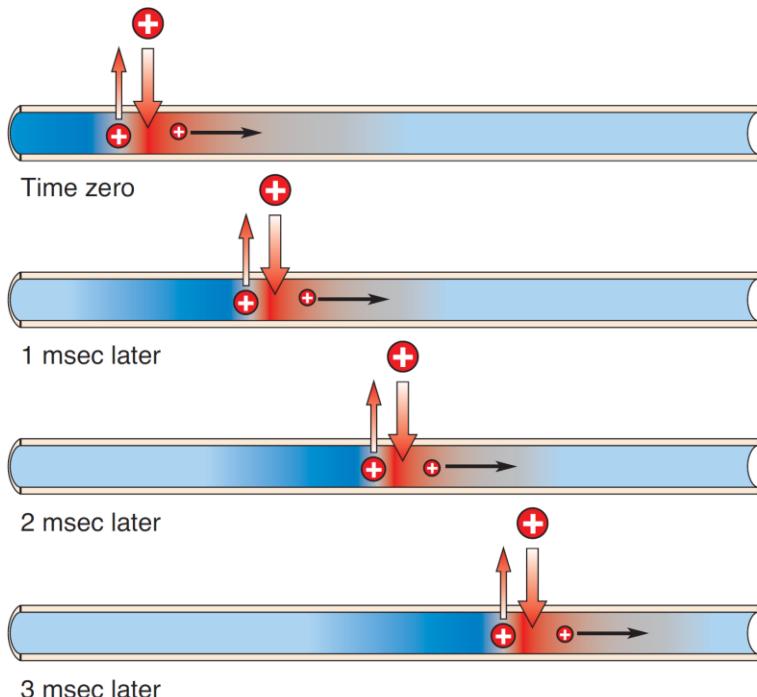
- **Threshold**: membrane potential at which enough voltage-gated sodium channels open
- **Rising phase**:
- **Overshoot**: membrane potential goes to a value close to E_{Na}
- **Falling phase**:
- **Undershoot**: membrane potential goes toward E_K
- **Absolute refractory period** : **Sodium channels inactivate** when the membrane becomes strongly depolarized
- **Relative refractory period** : The **membrane potential stays hyperpolarized** until the voltage-gated potassium channels close
- **Sodium-potassium pump also** is working quietly in the background





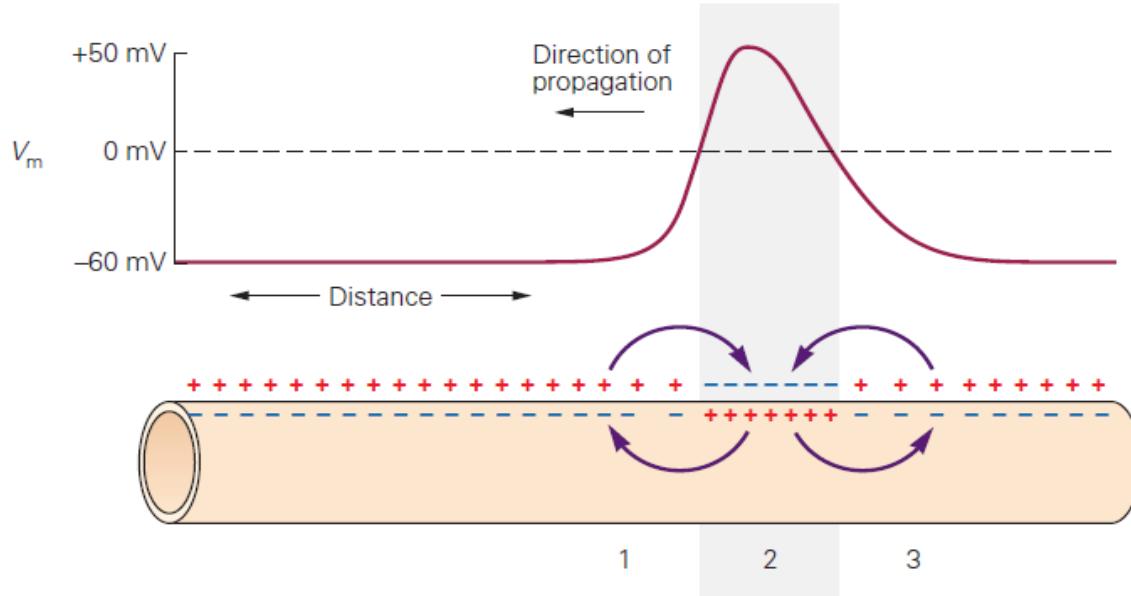
Action potential conduction

- Like the burning of a **fuse**
- Propagates only in **one direction**
 - The membrane just behind it is **refractory** due to **inactivation of the sodium channels**
- **Orthodromic** conduction:
 - From the soma to the axon terminal
- **Antidromic** conduction:
 - Backward propagation, sometimes elicited **experimentally**
- Because the axonal membrane is excitable (capable of generating action potentials) along its entire length, **the impulse will propagate without decrement**





Short circuit to convey charge



The **length of membrane** that is **engaged** in the action potential **at any instant** in time: (Action potential conduction velocities vary, but 10 m/sec is a typical rate)

$$10 \text{ m/sec} \times 2 \times 10^{-3} \text{ sec} = 2 \times 10^{-2} \text{ m.}$$

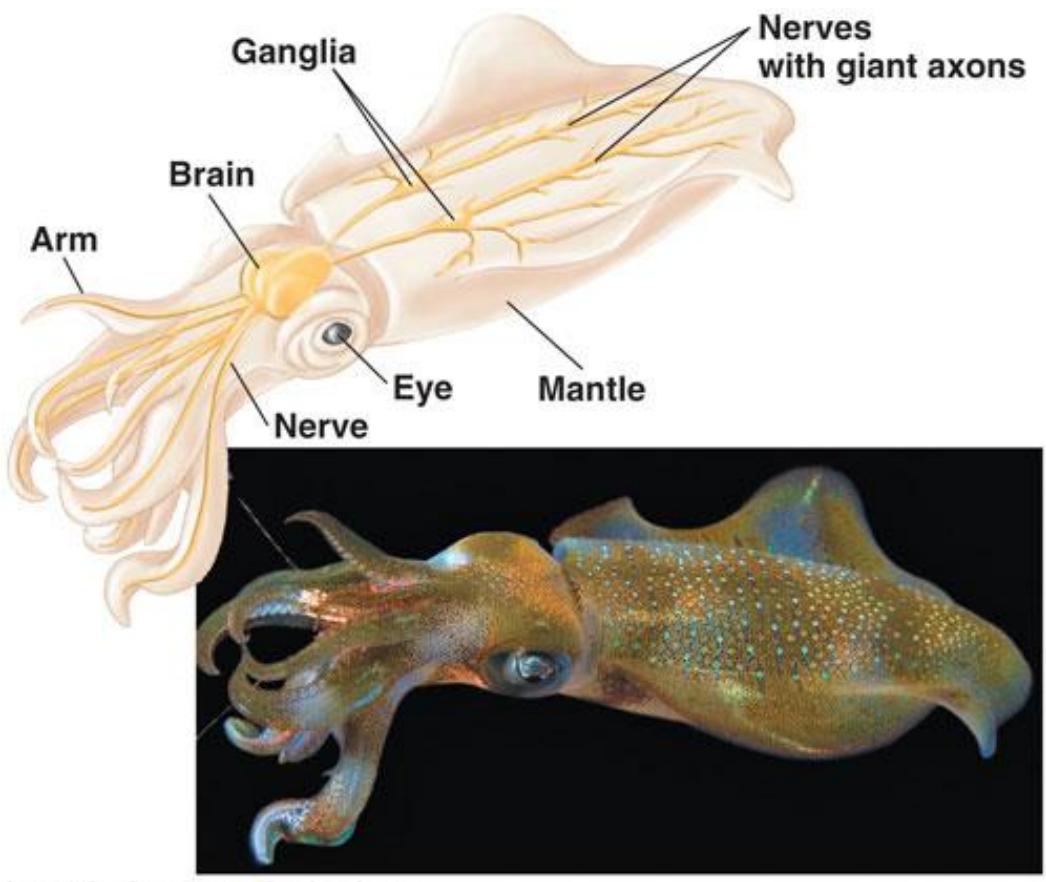


Factors influencing conduction velocity

- **10 m/sec** is a typical rate
- The **speed of action** potential propagates depends on **how far the depolarization ahead** of the action potential spreads
- It depends on **certain physical characteristics of the axon.**
 - If the axon **is narrow** and there are **many open membrane pores**, most of the current will flow out across the membrane
 - **Axonal size**, and the **number of voltage-gated** channels in the membrane
- **Analogy** of water conduction in a **leaky garden hose**
- **Smaller axons require greater depolarization** to reach action potential threshold and are **more sensitive to being** blocked by **local anesthetics** (Lidocaine's mechanism of action)



The **squid giant axon** can be 1 mm in diameter, that mediates an **escape reflex** in response to strong sensory stimulation



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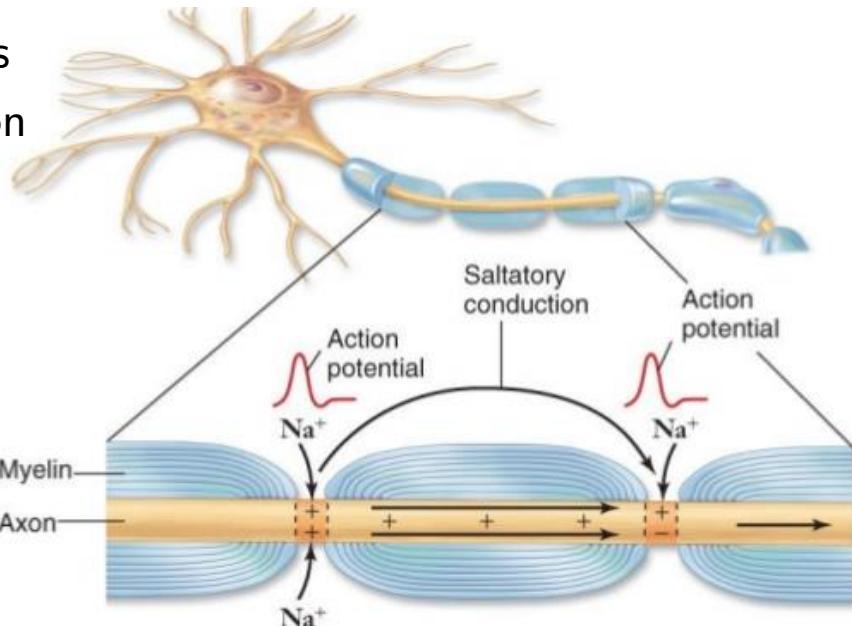


Myelin and Saltatory Conduction

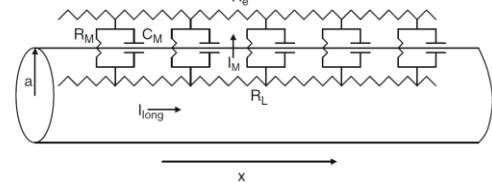
- Instead of **increasing diameter**, vertebrates evolved another solution for increasing action potential conduction velocity:

Wrapping the axon with insulation called **myelin**

- Like **wrapping a leaky garden hose** with duct **tape**
- Voltage-gated sodium channels are concentrated in the **Ranvier nodes**.
- Distance between nodes: **0.2-2.0 mm**
 - fatter axons have larger intermodal distances
- In myelinated axons, action potentials **skip from node to node**
 - It is called saltatory conduction (from the Latin meaning “to leap”)



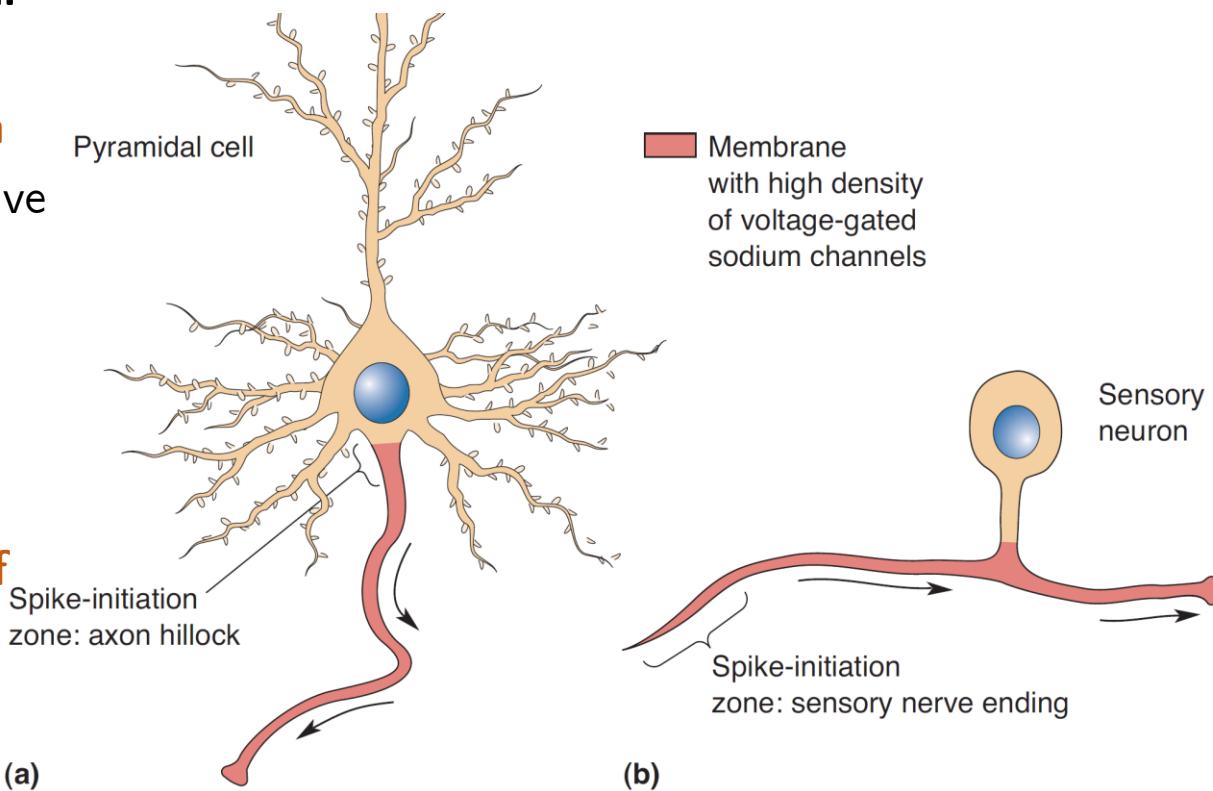
$$\lambda = \sqrt{\frac{ar_M}{2r_L}}$$





Spike-initiation zone; The region of membrane where action potentials are normally generated

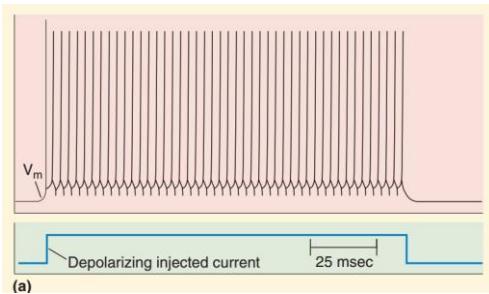
- As a rule, the membranes of **dendrites** and neuronal **cell bodies** do not generate **sodium-dependent action potentials** because they have very few **voltage-gated sodium channels**
- Axonal membrane can be identified at the **molecular level** by its high **density of voltage-gated** sodium channels.



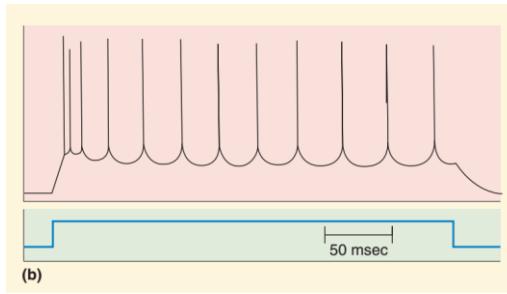


The Electric Behavior of Neurons

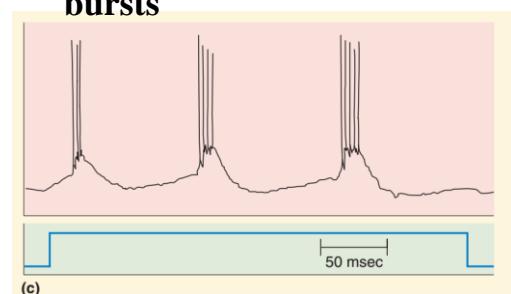
Steady frequency



Adaptation



Rhythmic, repetitive bursts



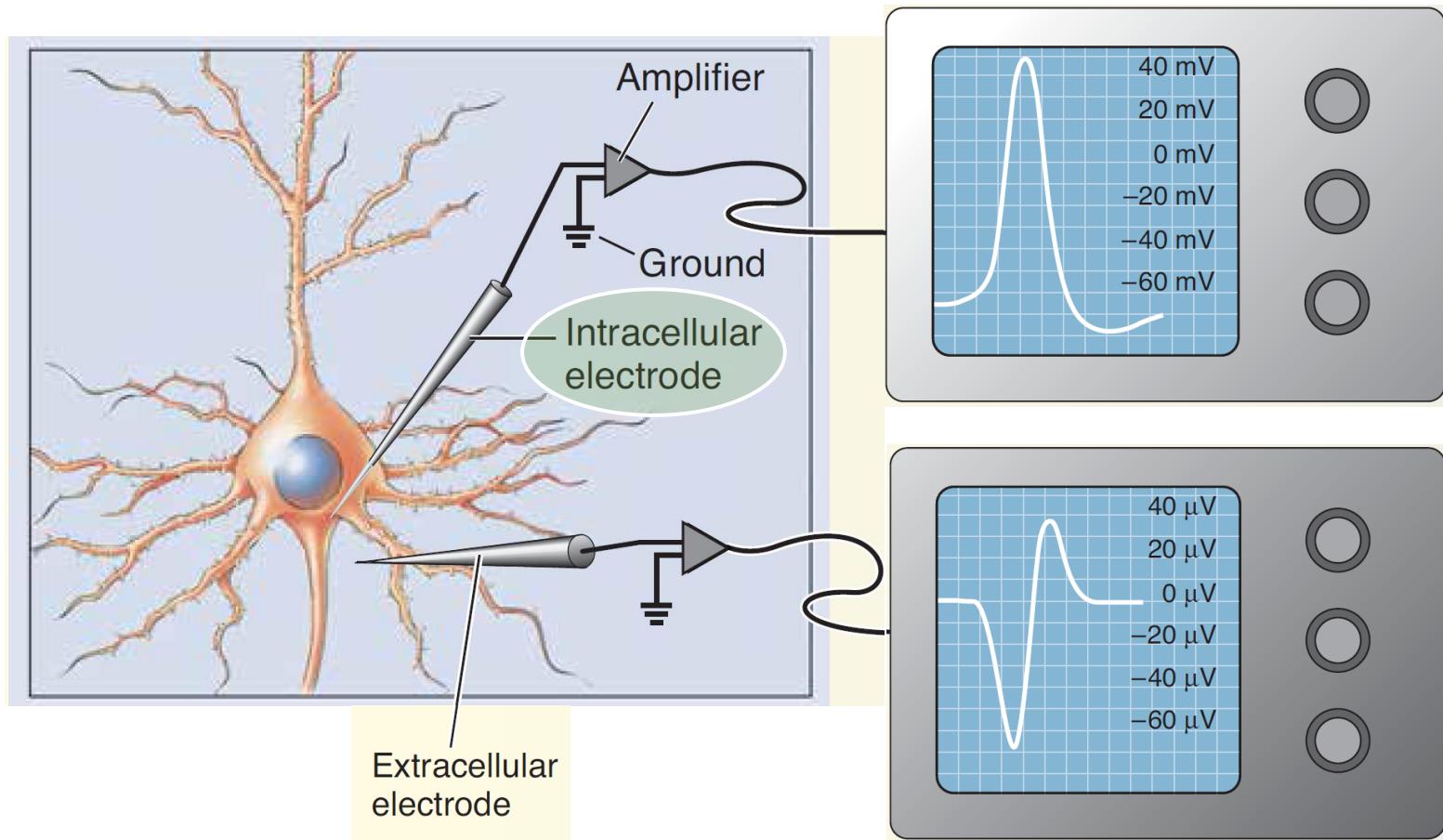
Stellate cell

Pyramidal cells

Subtype of large pyramidal neuron cell

Complex interactions of multiple ion channels that create the eclectic signature of each class of neuron

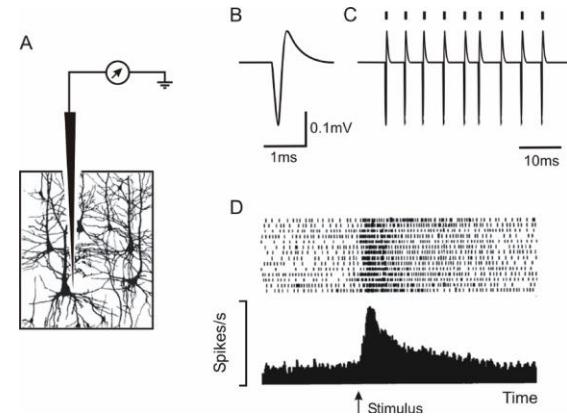
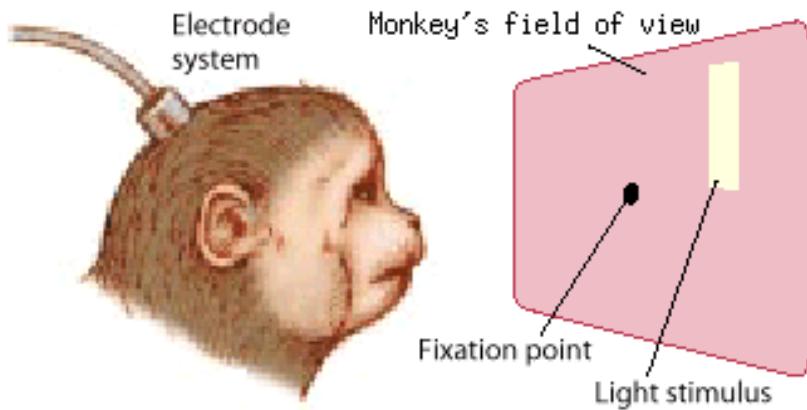
Methods of recording action potentials



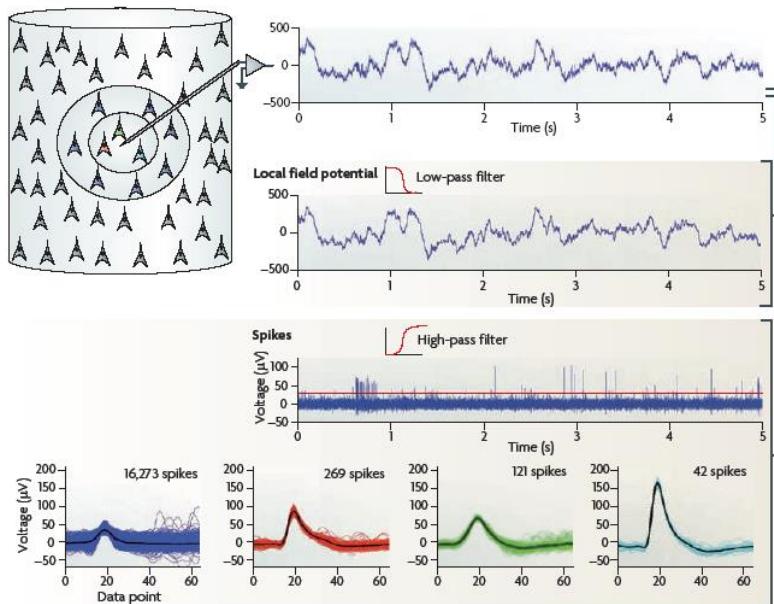
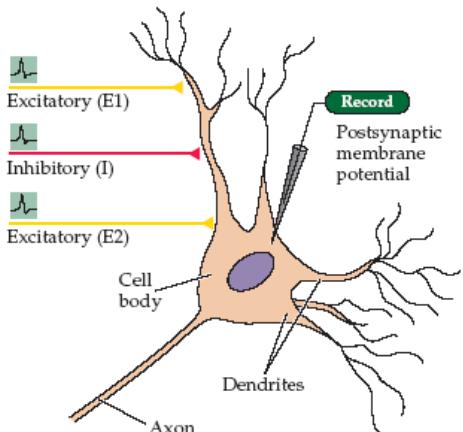
Single cell recording in the 1960s and 1970s



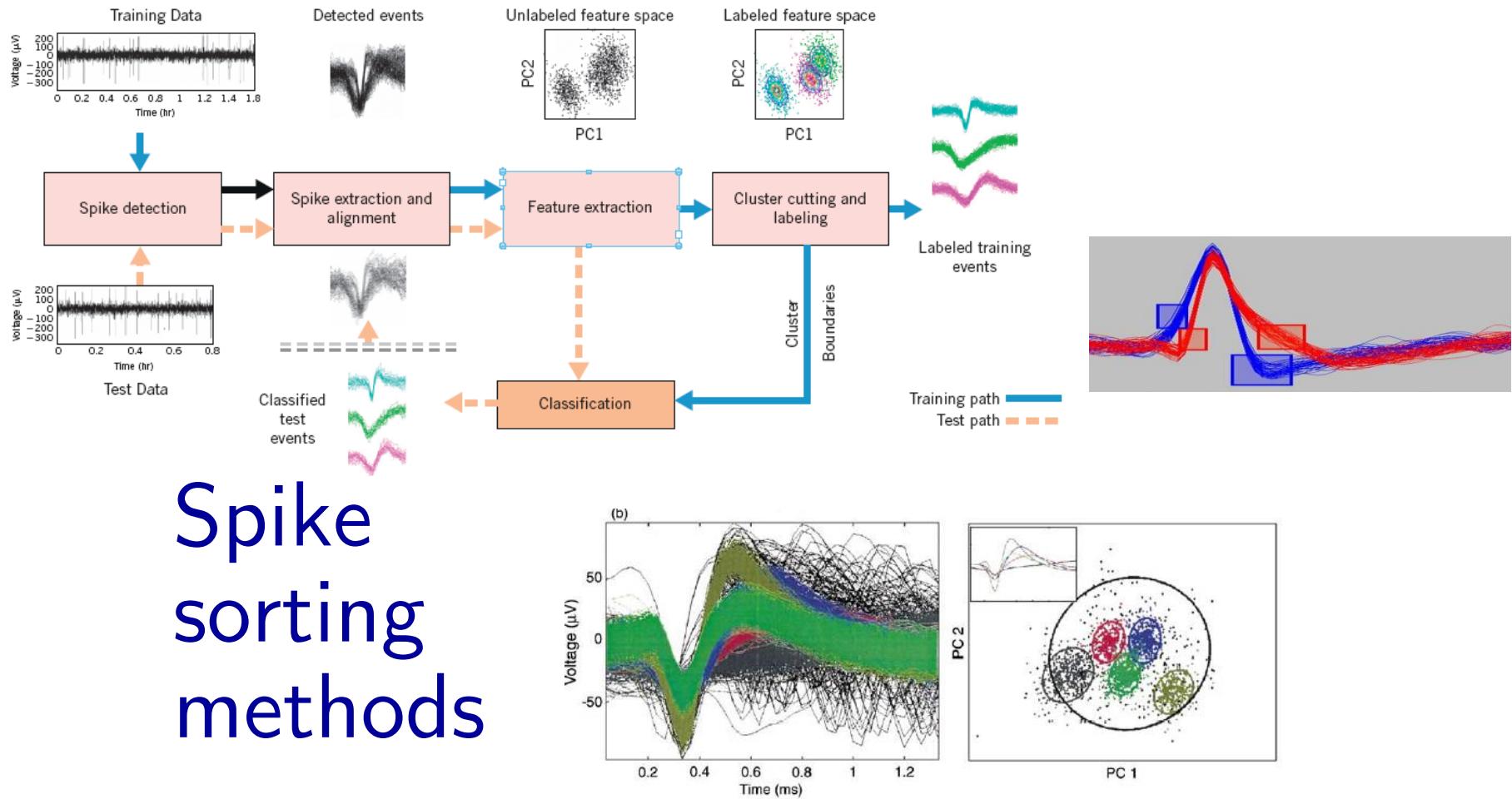
Robert Wurtz Edward Evarts



Intra and extracellular recording



http://www.zoology.ubc.ca/~gardner/chemical_synapses%20-%20postsynaptic.htm

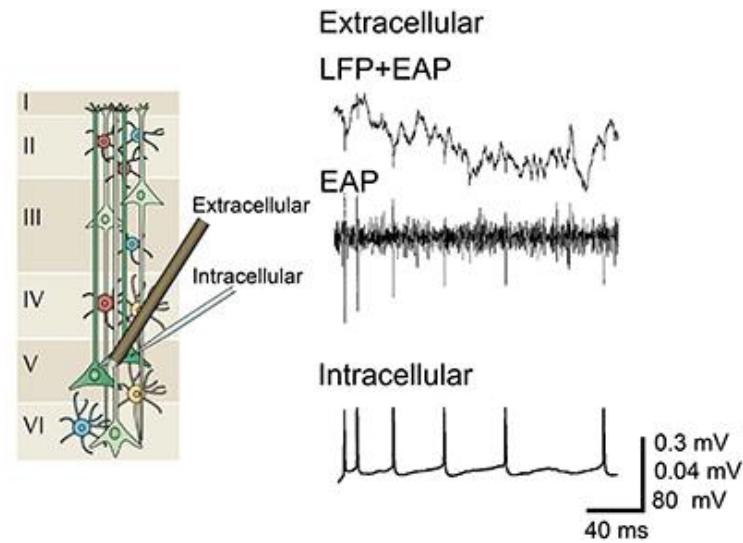
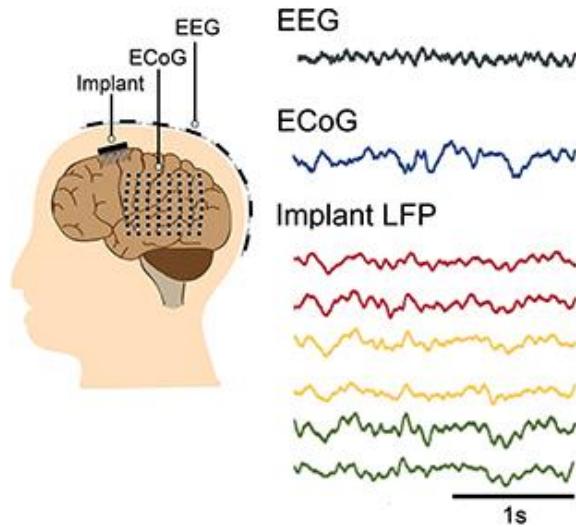


Shoham, S., Fellows, M. R., & Normann, R. a. (2003). Robust, automatic spike sorting using mixtures of multivariate t-distributions. *Journal of Neuroscience Methods*, 127(2), 111–122.
doi:10.1016/S0165-0270(03)00120-1



Five Common Electrophysiology Approaches:

- EEG
- Extracellular/Local Field Potentials
- Intracellular – Sharp Electrode
- Patch-Clamp Configurations
- Multi-Unit Array Recordings

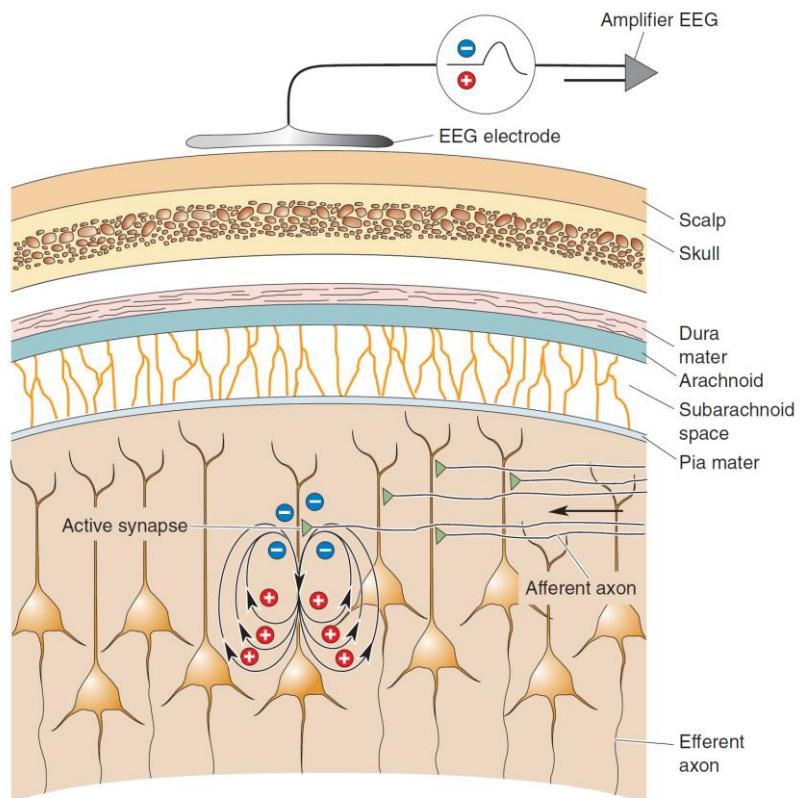


EEGs

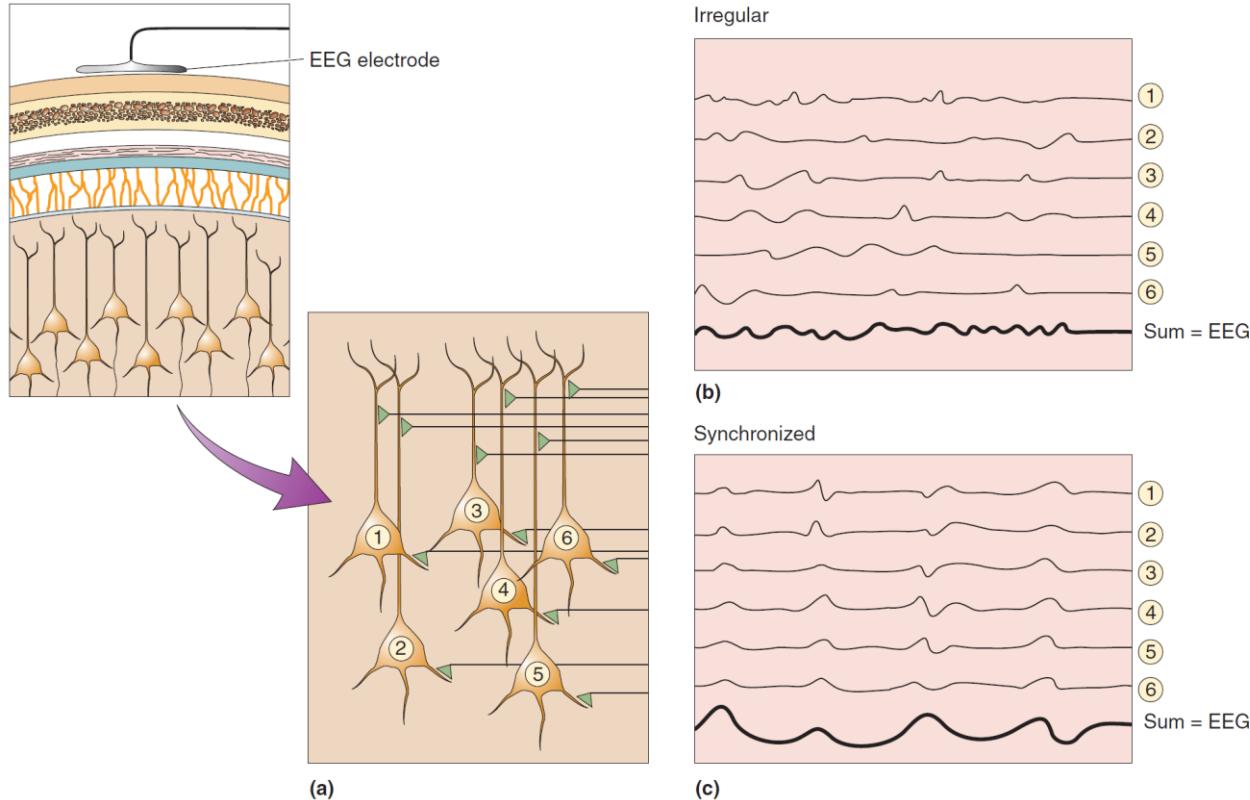
- Recording spontaneous brain (voltage volume conductance) activity from the scalp, described in rhythmic activity: Delta (<4 Hz), theta (4-7 Hz), Alpha (8 – 13 Hz), Beta (14 – 30 Hz), gamma (30-100 Hz)

- **Clinical Neuroscience:** epilepsy, coma, tumors, stroke, focal brain damage, depth of anesthesia

- Coordinate cortical activity = high contribution
Deep structure activity = low contribution



Many **neurons need to sum their activity** in order to be detected by EEG electrodes. The **timing** of their activity is crucial. **Synchronized neural** activity produces larger signals.

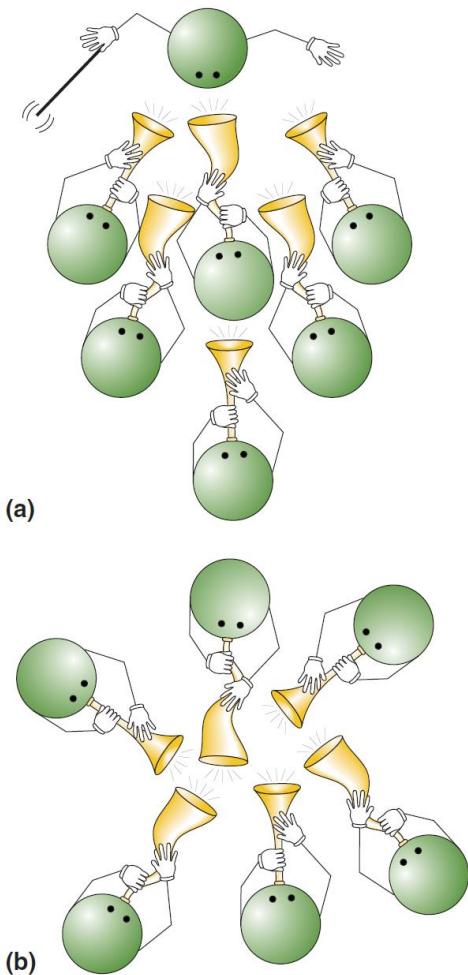


Two ways of generating synchronicity



a) Pacemaker

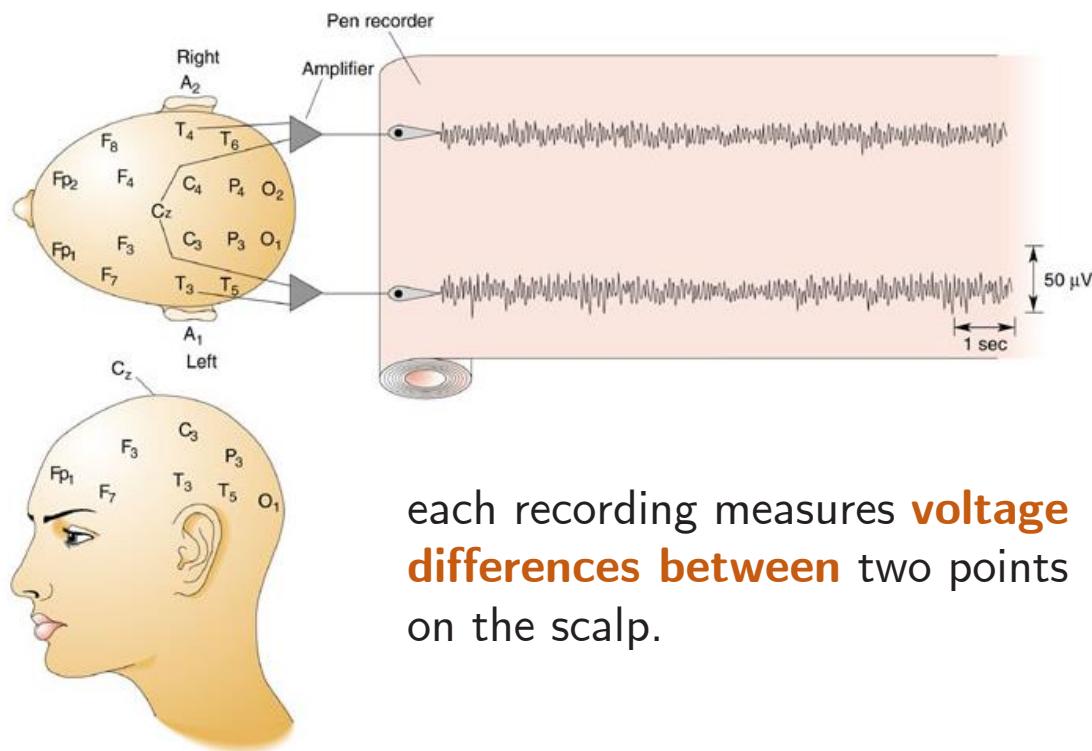
b) mutual coordination: collective behavior of all participants





Standard placements of electrodes on the human scalp

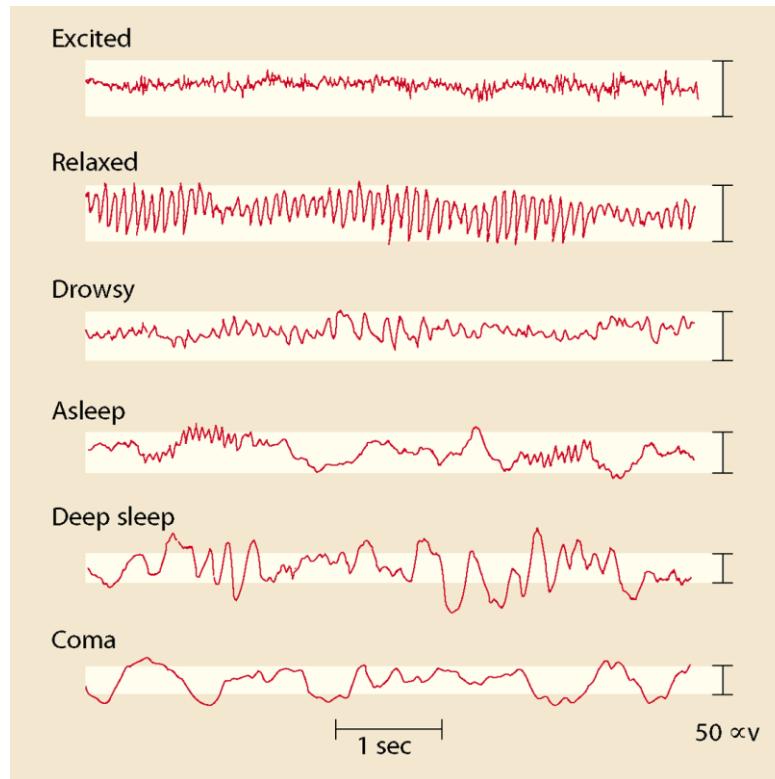
- A, auricle;
- C, central;
- F, frontal;
- F_p, frontal pole;
- O, occipital;
- P, parietal;
- T, temporal.



each recording measures **voltage differences between** two points on the scalp.

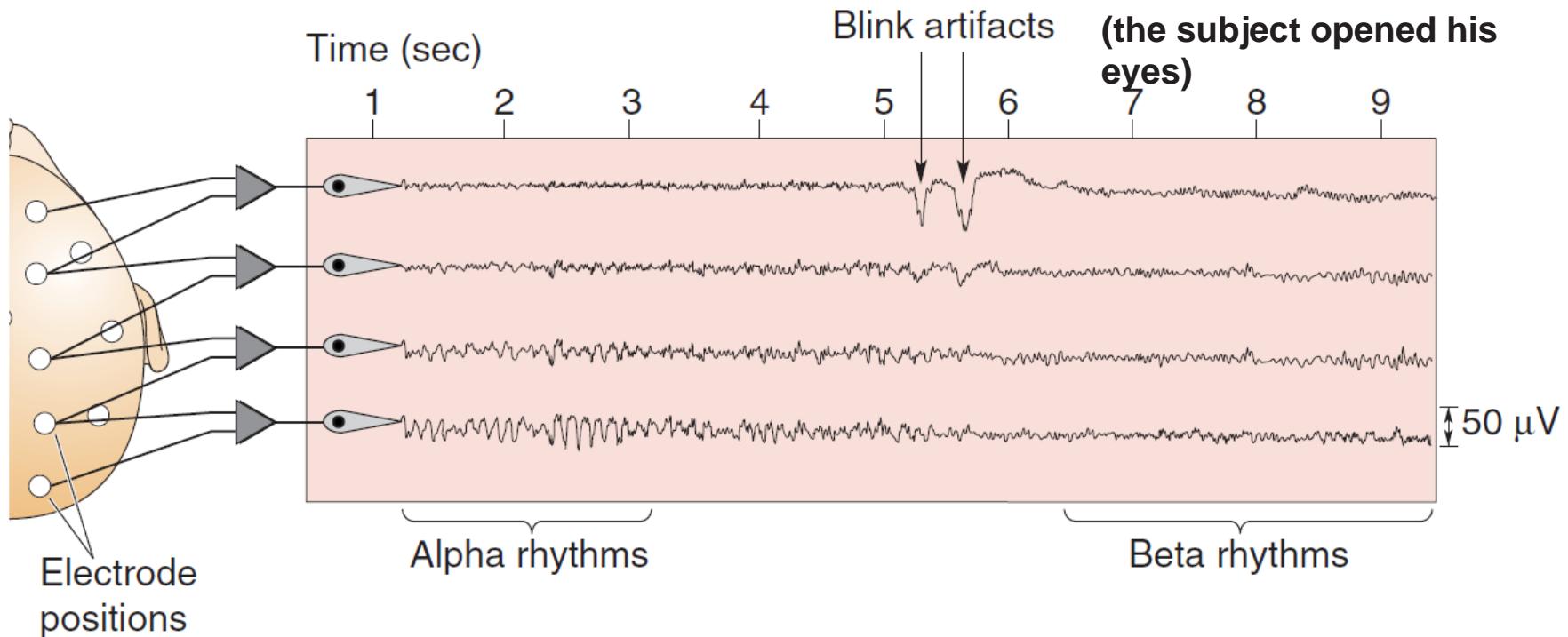


Good indicators of global brain state; EEG waves often display rhythmic patterns at characteristic frequencies





A normal EEG





Event related potential

ERP's are obtained after **averaging EEG** signals obtained over multiple trials (trials are aligned by stimulus onset).

