

Neurons and Neural Transmission

Part I / IV

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Nervous system before 20th century

- *Ancient Egypt*: heart and soul
 - Trepanation medicine
- *Aristotle*: brain “cools” the heart
- *Descartes*: spirits acting through nerves
- *19th century*: brain is the center of intelligence
 - A “magical” interconnected mesh
 - Qualitatively different from normal cells
 - Brain tissue not resolved in microscope
- *1890's*: C. Golgi's silver chromate cell staining



Santiago Ramon y Cajal (1852-1934)

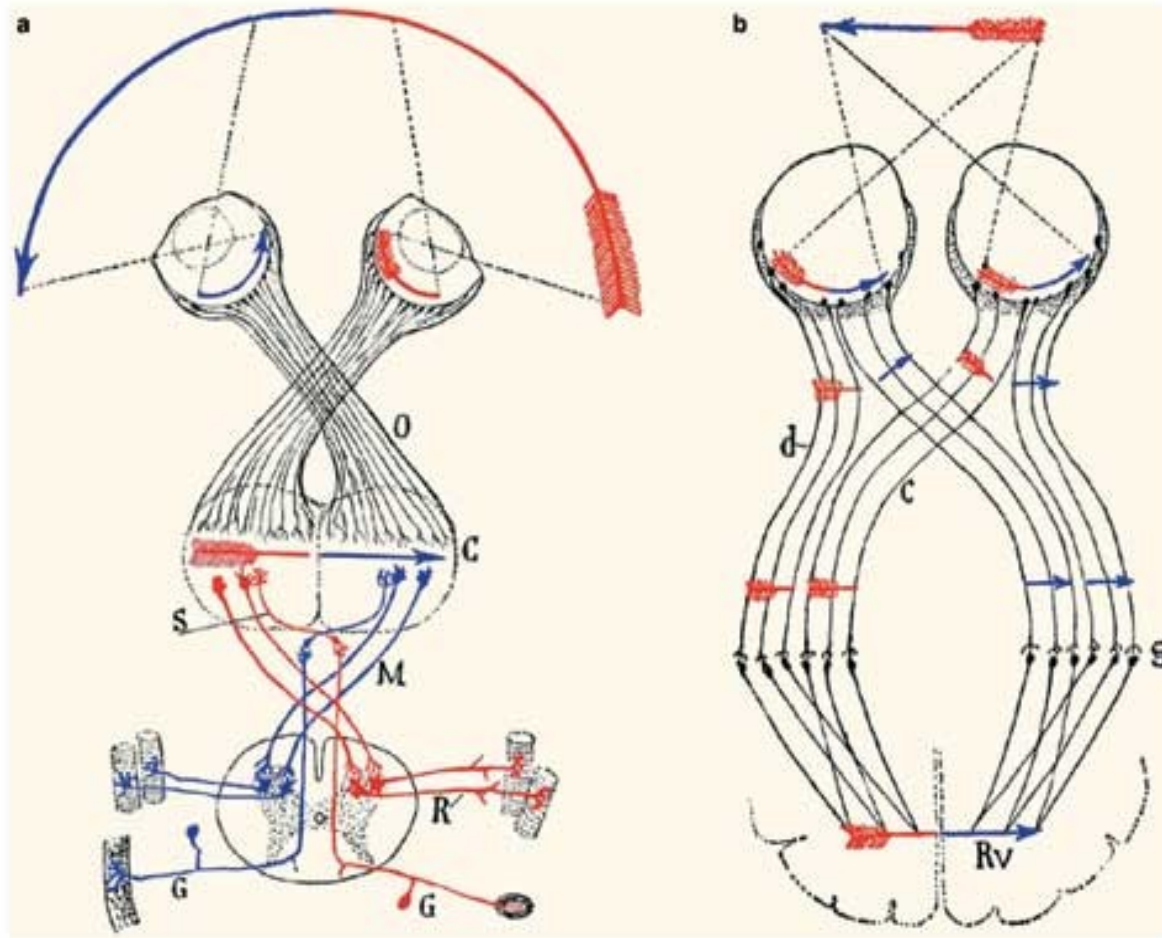
“Father of modern neuroscience”

- Spanish physician
- Anti-authoritarian attitude
- Avid painter
- Nobel Prize in 1906
- Accomplishments:
 - Structure of neurons
 - Classification of neurons
 - Neuron Doctrine



Ramon y Cajal's eye diagram

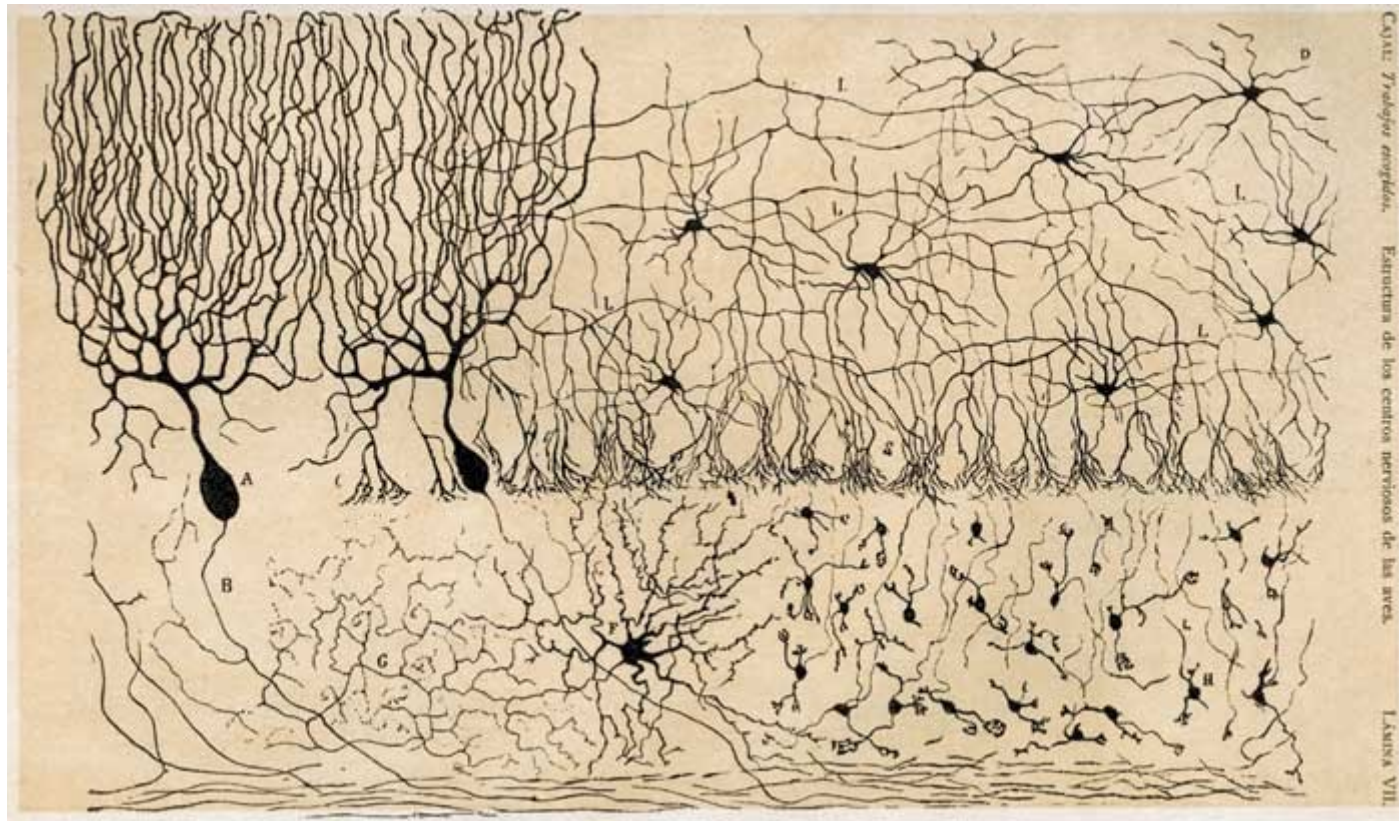
Visual system of lower vertebrates (a) and humans (b)



Different degrees of crossing of optical nerve

Ramon y Cajal's neurons

Chicken cerebrum (from microscopic observations)

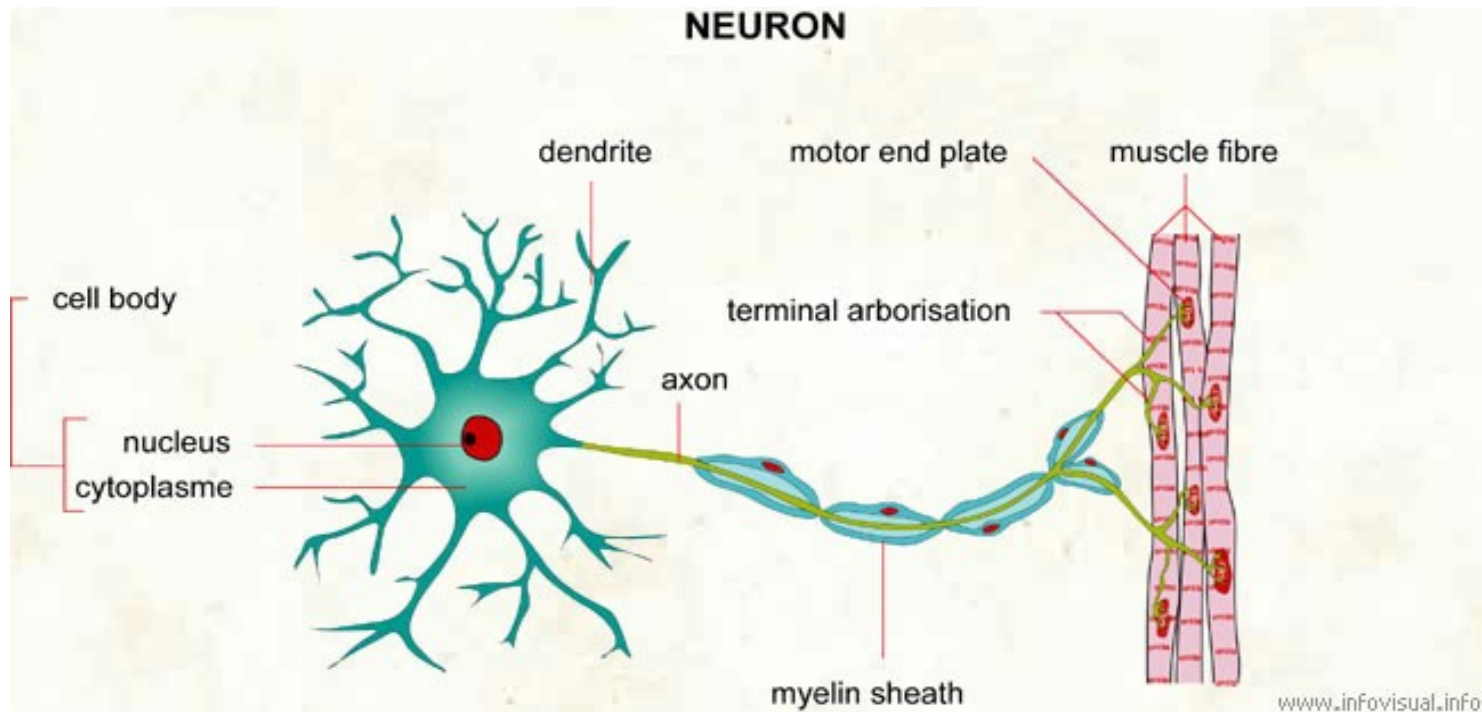


Information in neurons flows in one direction:

“from dendrites through cell body to axons”

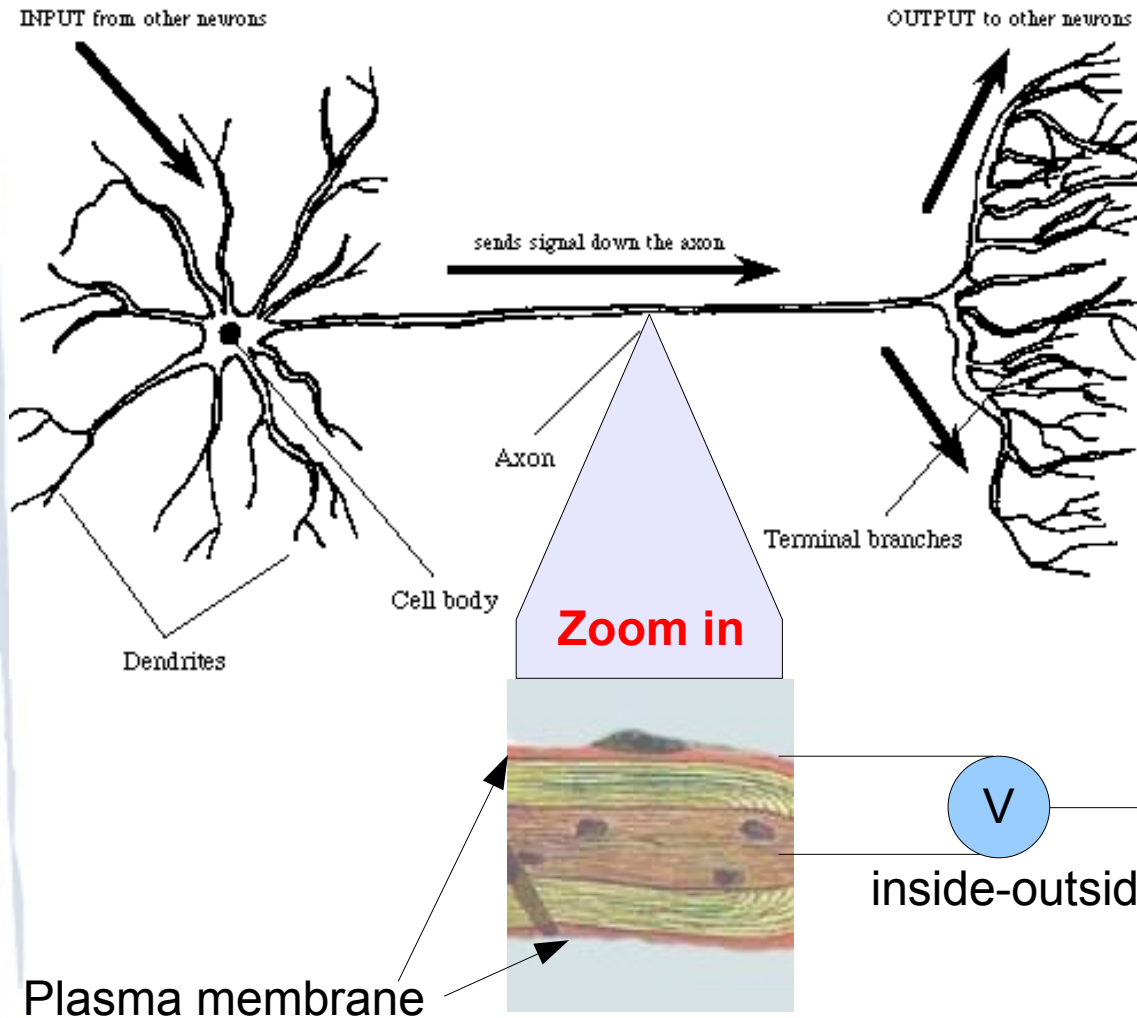
Neuron doctrine

- The fundamental structural and functional unit of the nervous system is a neuron.
- Neurons are discrete cells which are not continuous with other cells.
- The neuron is composed of 3 parts - the dendrites, axon and cell body.
- Information flows along the neuron in one direction via "nervous current".

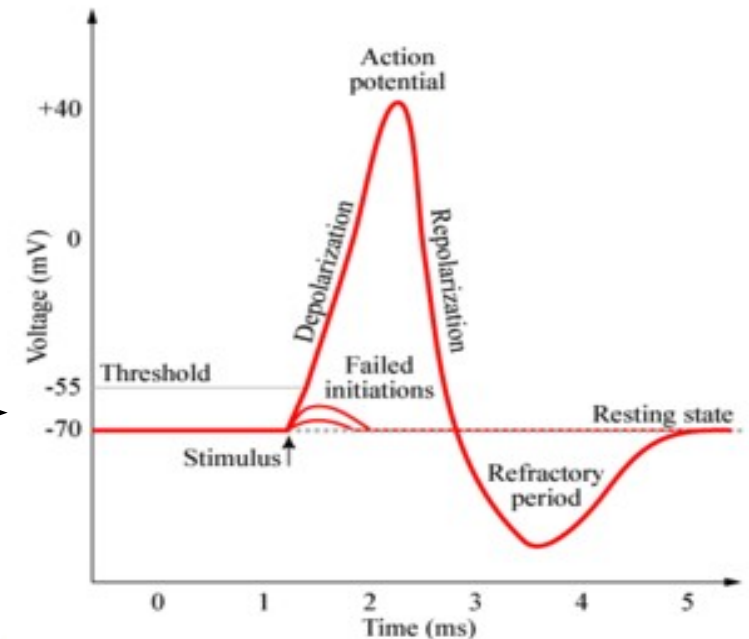


Sneak peek: Action potential

- Electric signal that propagates through axon



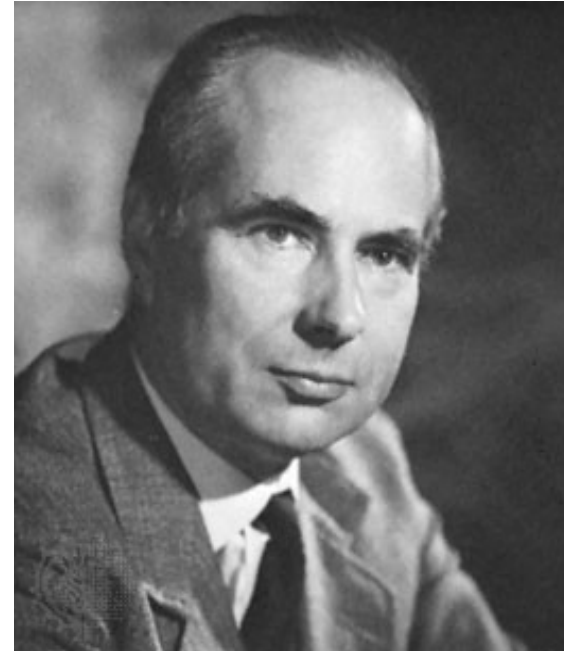
Action potential in a neuron:



Alan Hodgkin (1914 - 1998)



Andrew Huxley (1917 -)

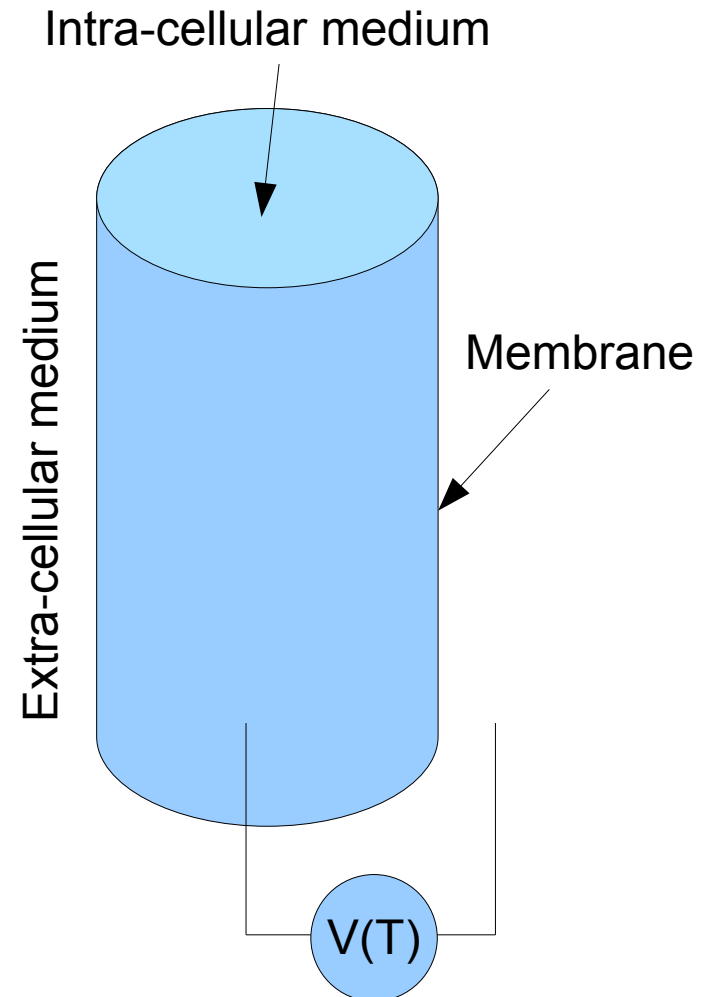


- British biologists
- Worked in Cambridge, and then at Trinity College
- 1952: **5 papers explaining origins of action potential**
- Shared 1963 Nobel Prize
- Both knighted in the 70's

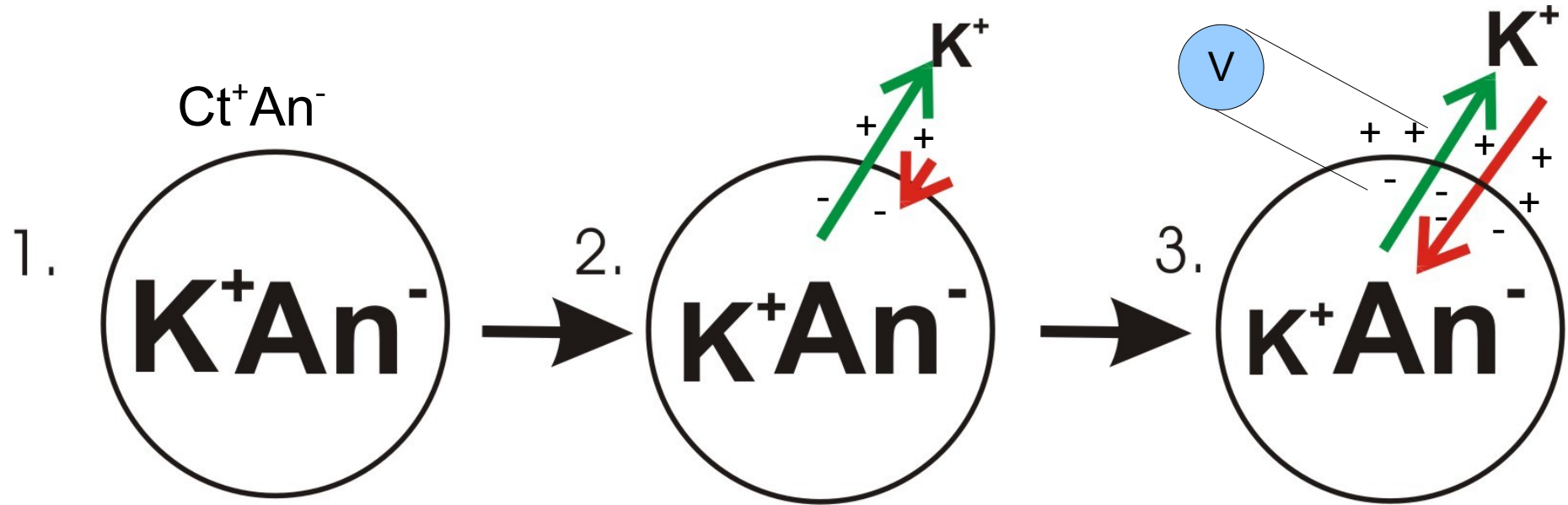
Membrane potential

- Membrane around the cell:
 - Has resistance
 - Can maintain a potential
- Intra- and extra-cellular medium:
 - Ionic liquid
 - Fairly good conductor
- Nerve pulse runs on membrane
 - As voltage wave
- Two ways to study traveling wave:
 - Voltage profile in space
 - **Voltage at a point -vs- T**

A small section of an axon:



Reversal & resting potential

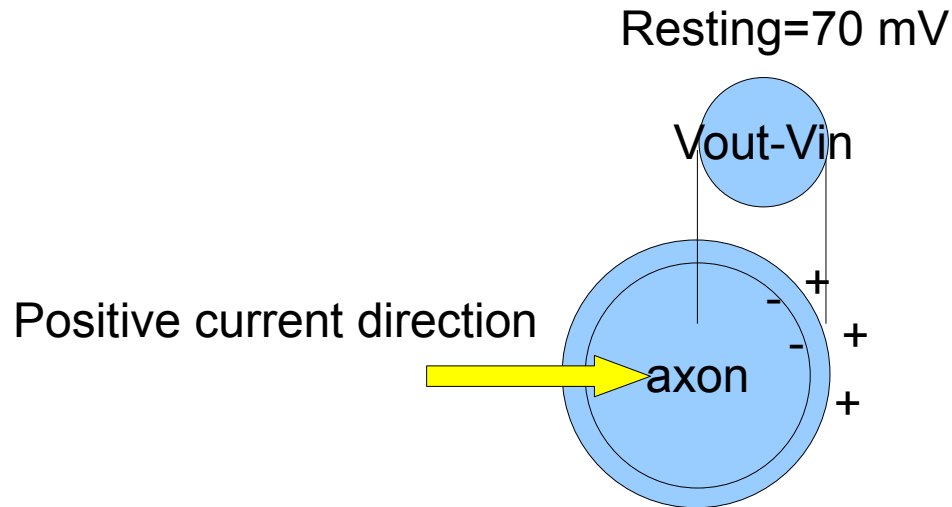


1. Impenetrable membrane with high K^+ concentration
2. K^+ ion channel opens => chemical (diffusive) gradient
3. Electric reversal potential equal to chemical potential

In case different ions can penetrate the membrane, the outside-inside resting potential is a superposition of such processes.

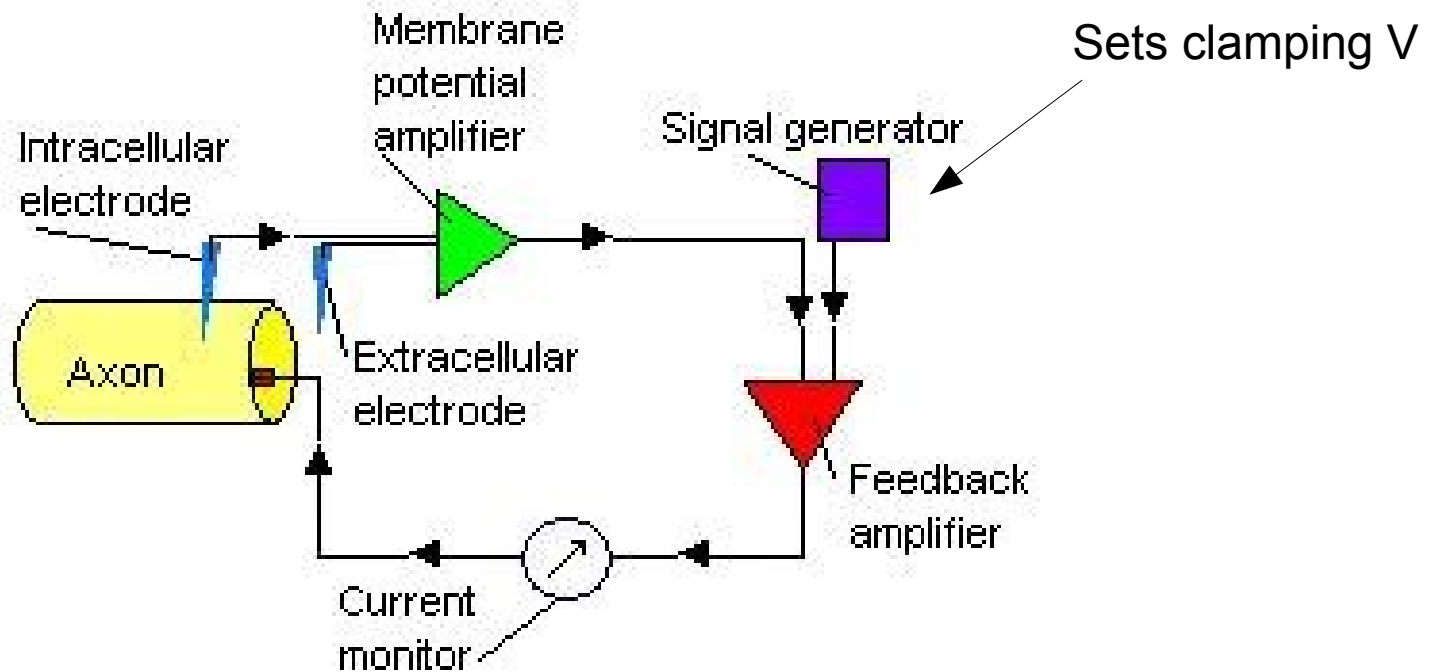
For **unexcited neurons**, only K^+ permeability is large, so the resting potential $\approx \text{K}^+$ reversal potential \approx 70 mV

More definitions



- Membrane Potential: $V_{out} - V_{in}$
- Depolarization: shift of membrane potential from resting value
 - Occurs naturally during action potential
 - Can also be induced by applying voltage across $V_{out}-V_{in}$
- Repolarization: return of membrane potential to resting value
- Idea: study membrane by measuring I at fixed (imposed) V : $R=V/I$

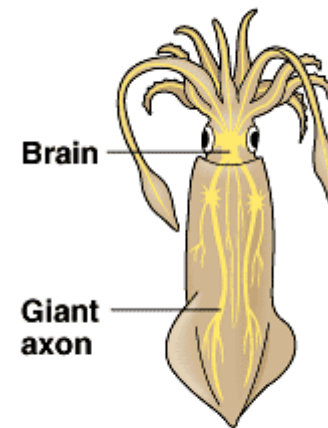
Voltage Clamping



- **Green amp** measures membrane potential
- **Red amp** compares it to clamp voltage
 - If unequal, sends current through membrane
 - Current causes voltage to approach clamp V

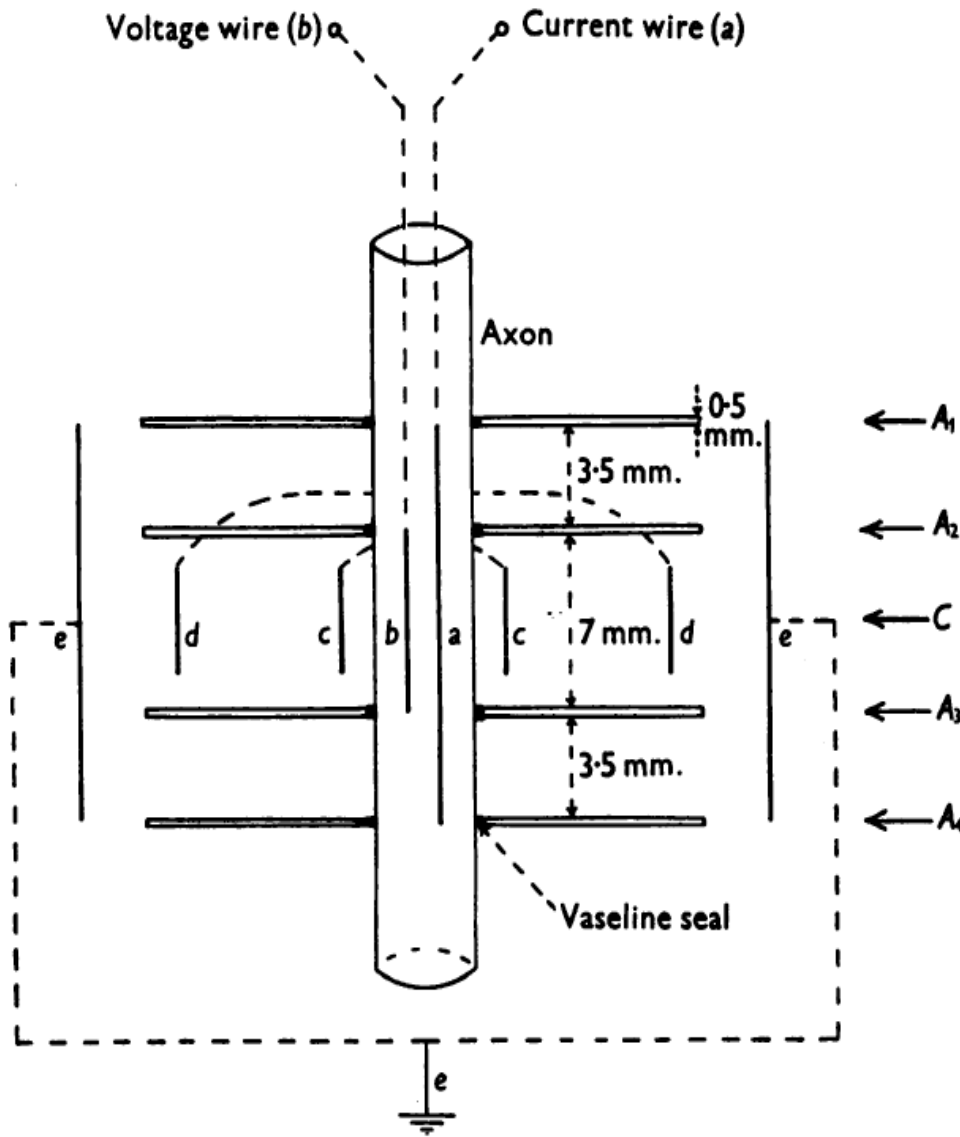
Giant Squid

- Deep-ocean squid
- Up to 40 ft long
- Giant Squid Axon
 - Controls jet propulsion
 - Long (a few inches)
 - Thick: 0.4 – 0.8 mm
 - Pulse speed: ~25 m/s
 - Can be separated

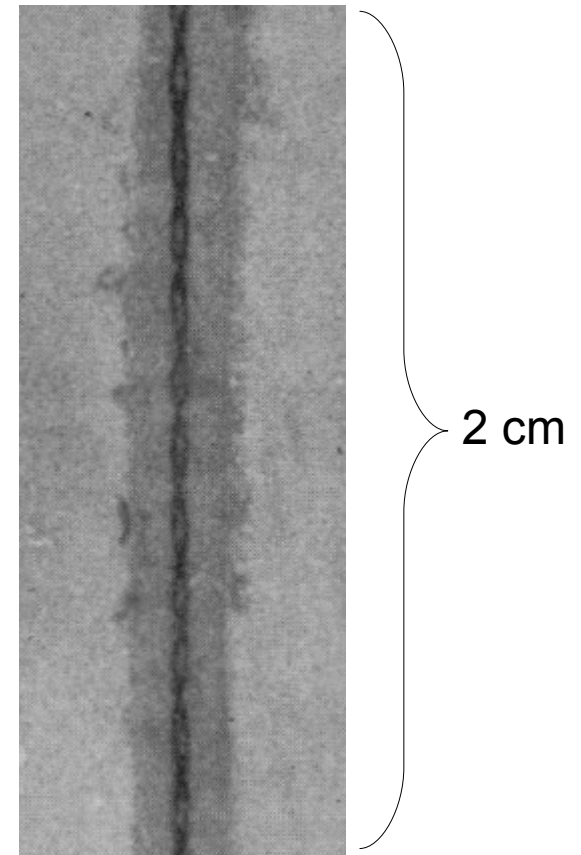


(g) Squid (mollusk)

Experimental setup & V clamping



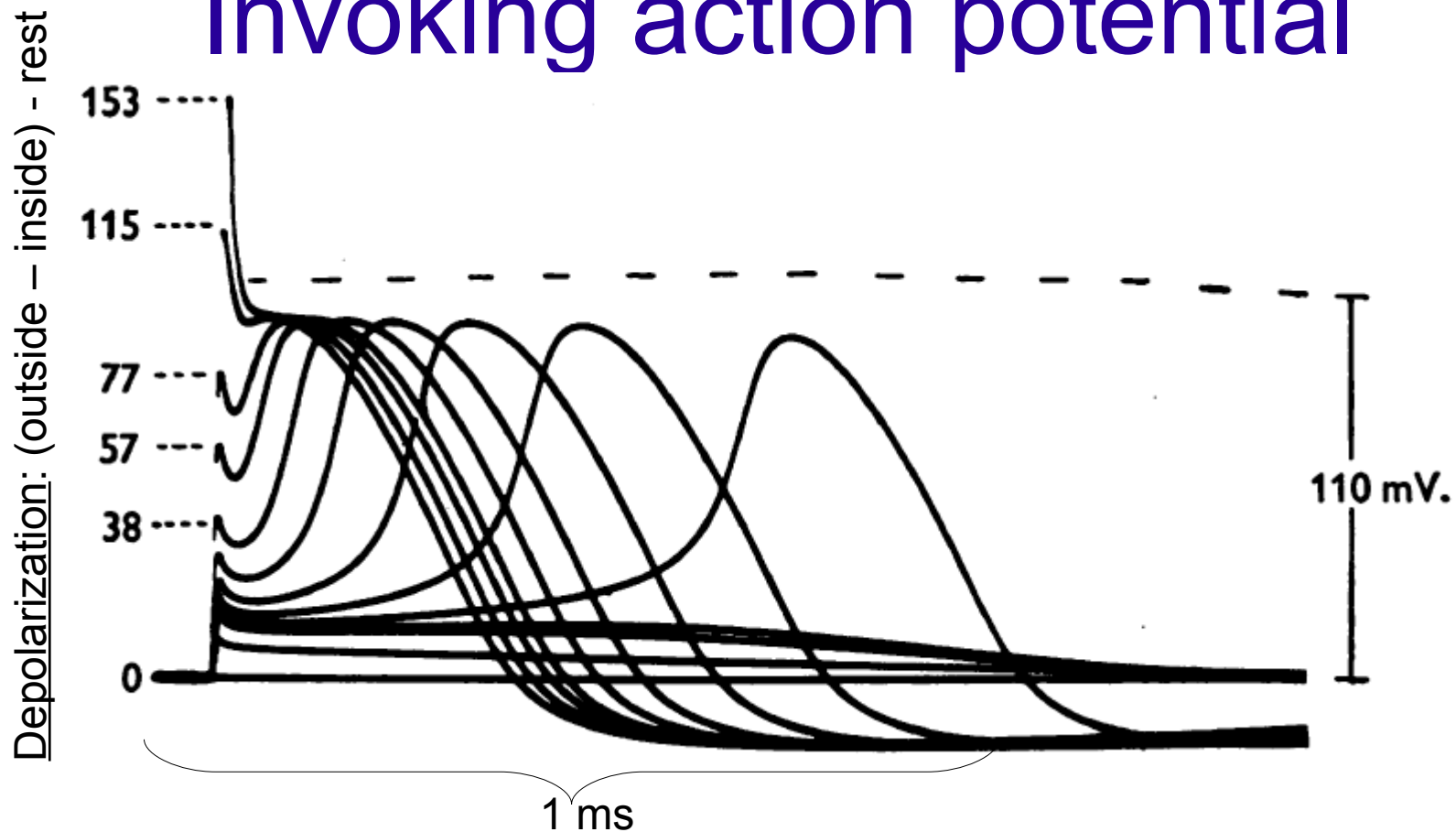
1. Drill a hole using glass capillary
2. Insert two twisted wires:
(voltage and current)



Two 20 μm wires
inside a 600 μm axon

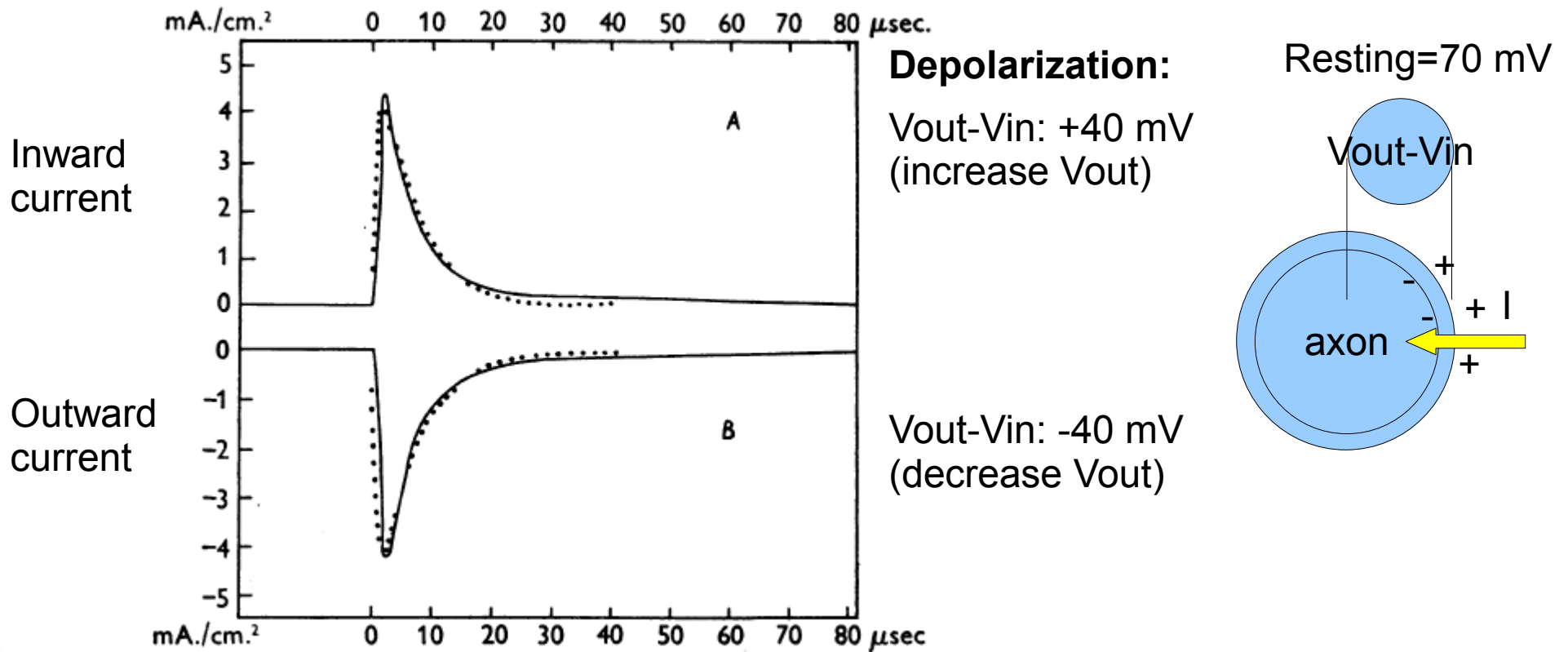
Solid lines = exposed wires; dashed lines = isolated wires

Invoking action potential



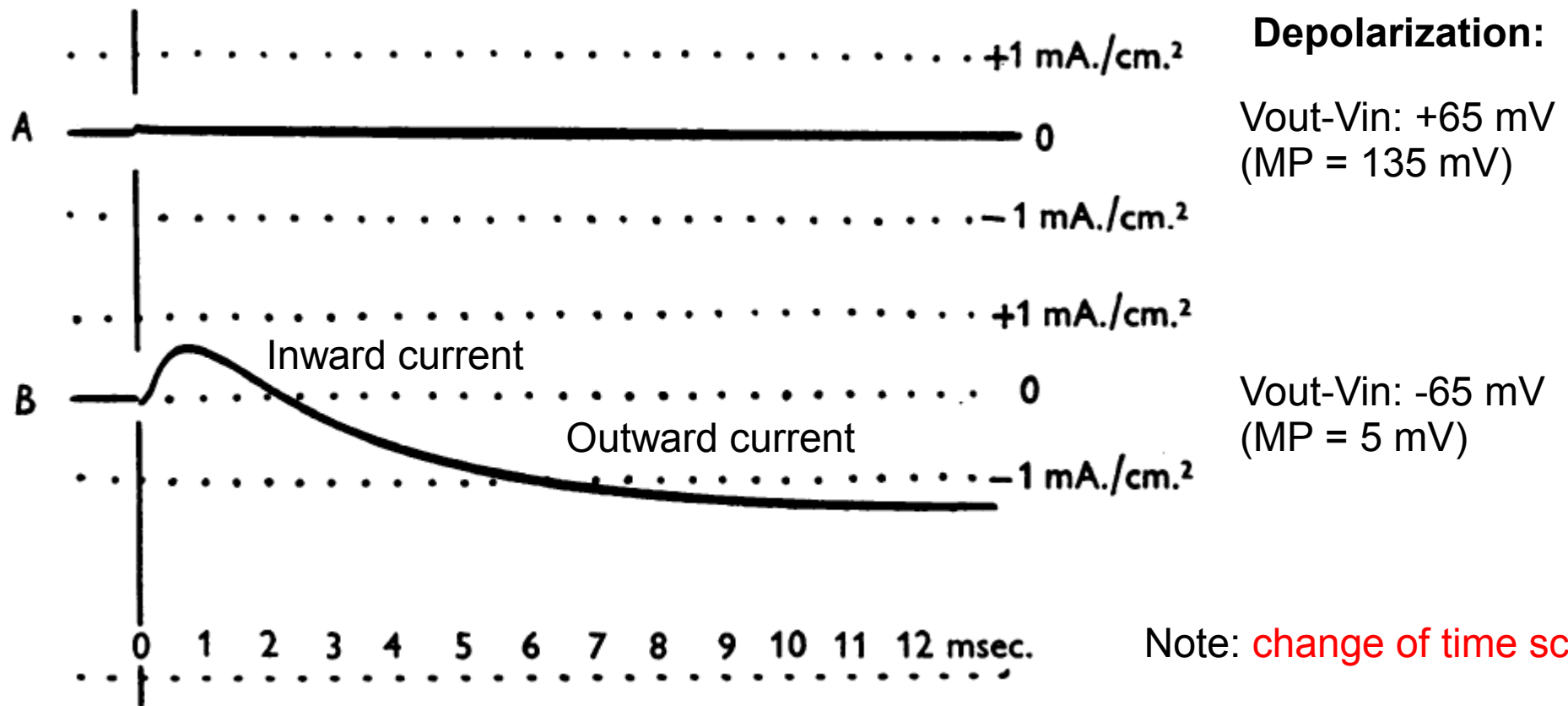
- Send a short pulse through current wire (no clamping)
- Membrane is quickly depolarized (depending on pulse strength)
- If depolarization is $>10-15\text{mV}$, action potential is generated
 - Such a neuron is good, and will be used for further tests

Voltage clamp: short times



- After suddenly depolarizing in either direction, there is a current spike
- This is consistent with charging a capacitor
- Estimated membrane capacitance = 0.9 μF/cm² (from the fit)

Voltage clamp: long times



- **Case A:** inward current of 30 μA, pretty steady in time, slow decay
- **Case B:** inward current of 600 μA, followed by outward of -1300 μA
 - That's interesting: the current changes direction!

AC (capacity) and DC (ion) currents

- Current under voltage clamp flows on two scales:
 - Short scale (30 μ s), for both polarizations
 - Long scale (10 ms), with extra structure
- Total current through membrane can be modeled as:

$$I = C_M \frac{\partial V}{\partial t} + I_i$$

Capacitance current Ionic current

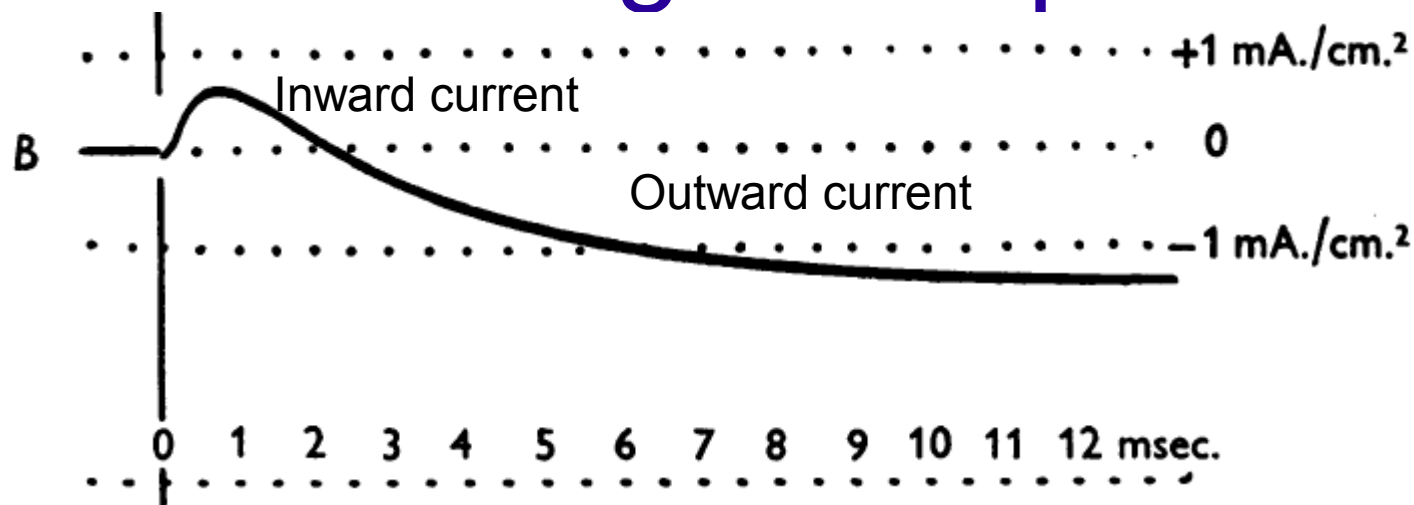
Changes in the ion density
at the outer and inner
surfaces of the membrane

Very short-lived, since voltage
change is near-instantaneous

Physical movement of
charged ions through the
membrane

Could be long-lived, depending
on ionic conductance

Voltage clamp: case B



$V_{out} - V_{in}$: -65 mV

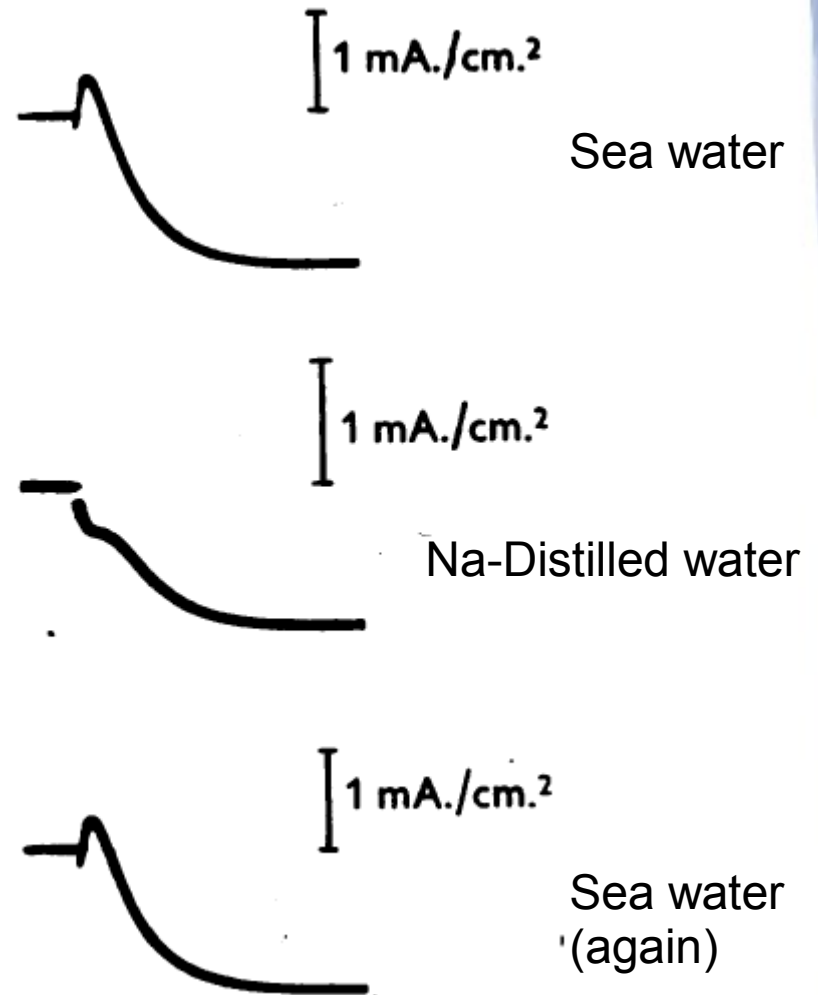
V_{in}, mV	V_{out}, mV
Before:	
0	70
After:	
0	5

- **Case B:** inward current of $600 \mu\text{A}$, followed by outward of $-1300 \mu\text{A}$
- The outside is now at a lower potential than it was at rest
 - We'd expect the current to flow towards low V => outward
 - But: we observe inward current! Something new happened.
- If voltage wasn't clamped during inward-current phase:
 - Inward current will reduce $(V_{out} - V_{in})$ more
 - Estimated rate $\approx 750 \text{ V/sec}$
 - Compatible with raising edge of action potential

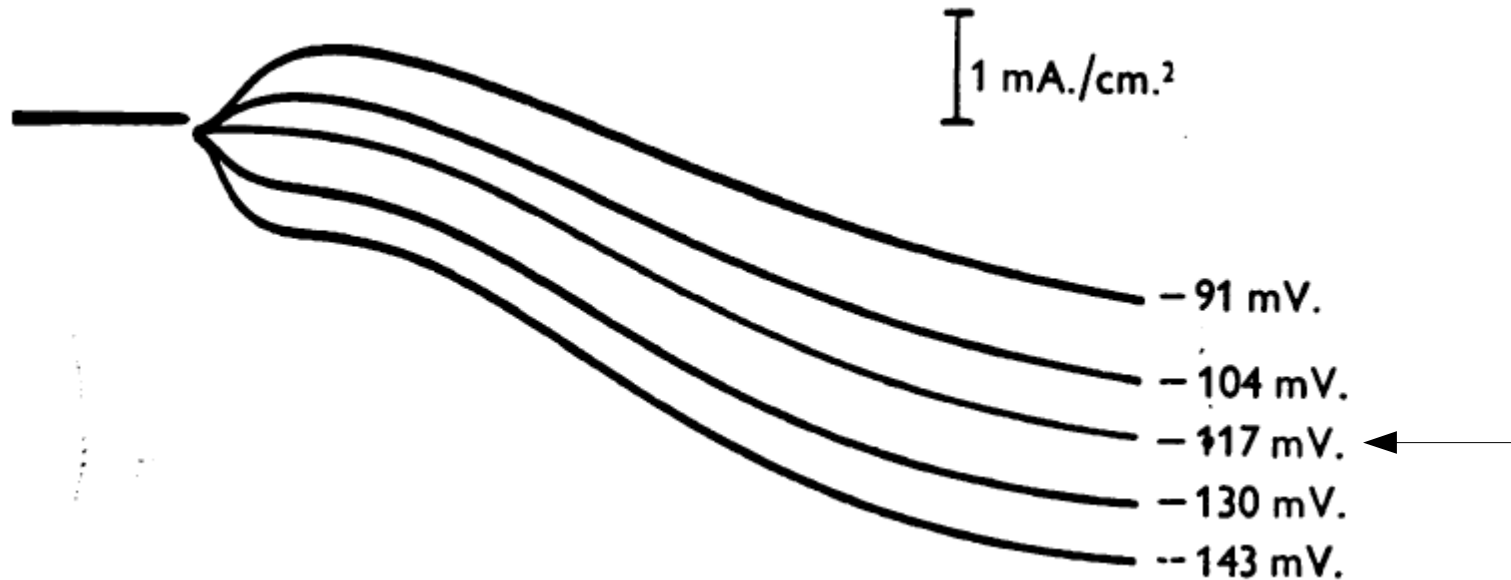
Inward current: entry of sodium

- Extra-cellular space rich in Na^+
- At resting potential, membrane is impenetrable to Na^+
- If depolarization > 15 mV:
 - Na^+ channels open in membrane
- Na^+ ions provide inward current
- Subsequent outward current is independent of Na^+ concentration
 - Carried by K^+ ions instead

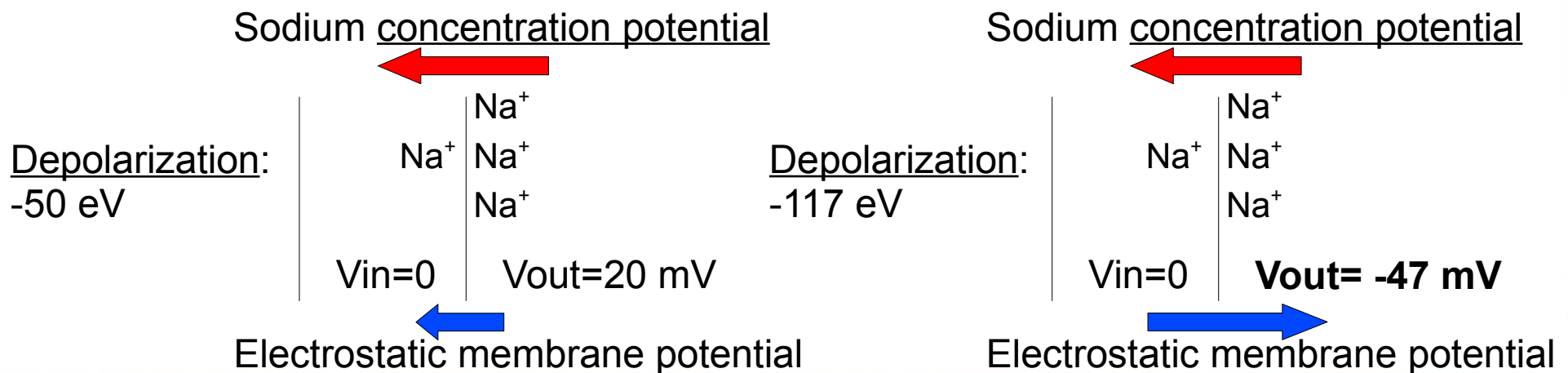
Depolarization: 65 mV



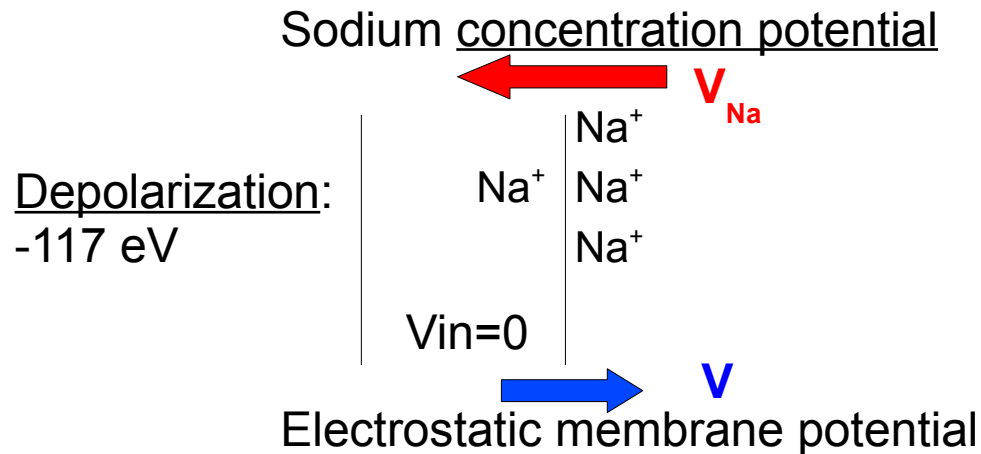
Voltage clamp: high depolarizations



- At -117 mV, the inwards Na^+ current disappears:



Modeling ionic current



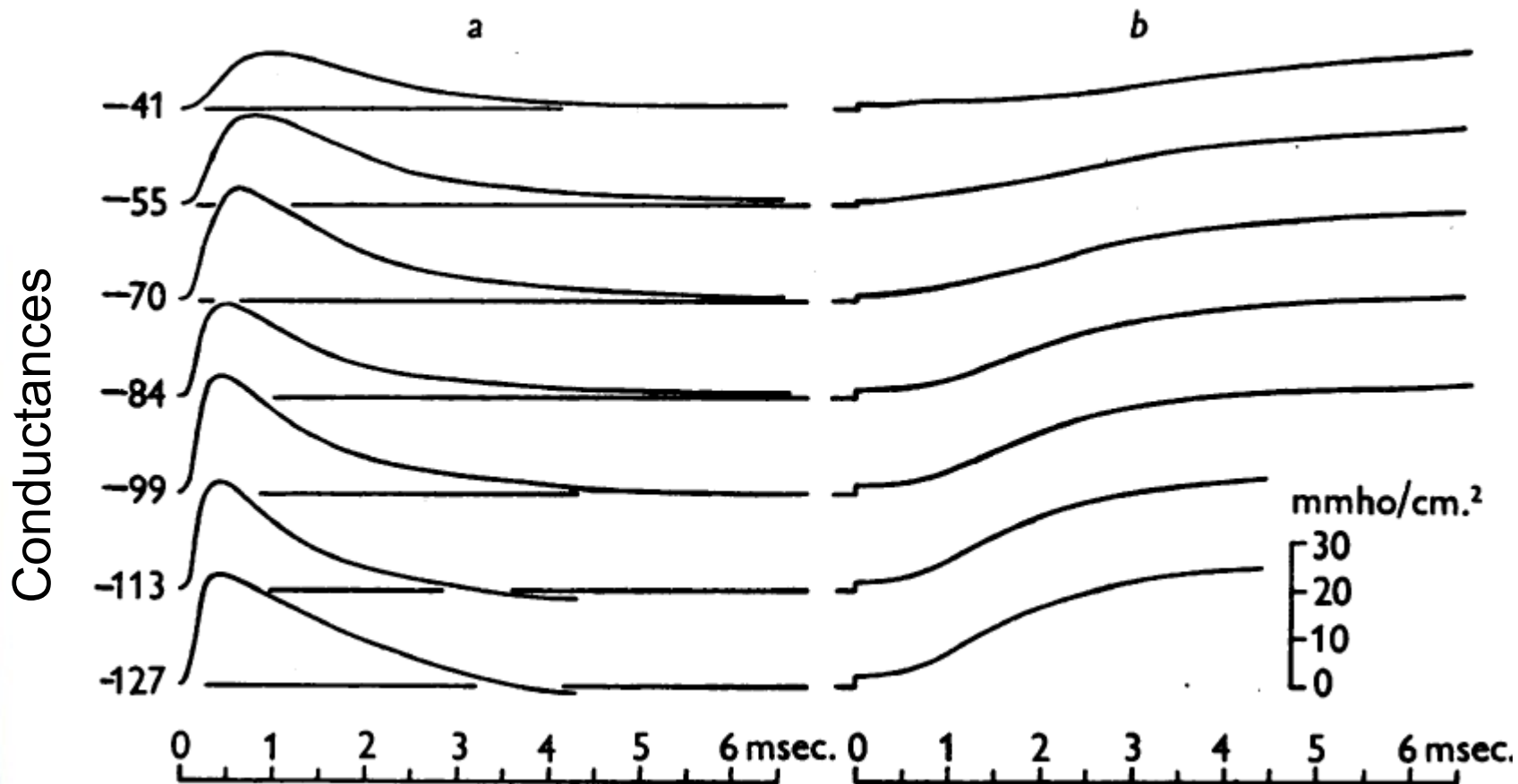
- V – clamped depolarization voltage
- V_{Na} – equilibrium potential of sodium
 - Depends on relevant concentrations inside and out
 - These concentrations are fairly constant for all V
- Current also depends on membrane permeability to Na^+
 - Quantify it via a “conductance” term

$$I_{Na} = g_{Na} (V - V_{Na}) \quad - \text{ and similarly for potassium}$$

K and Na conductances

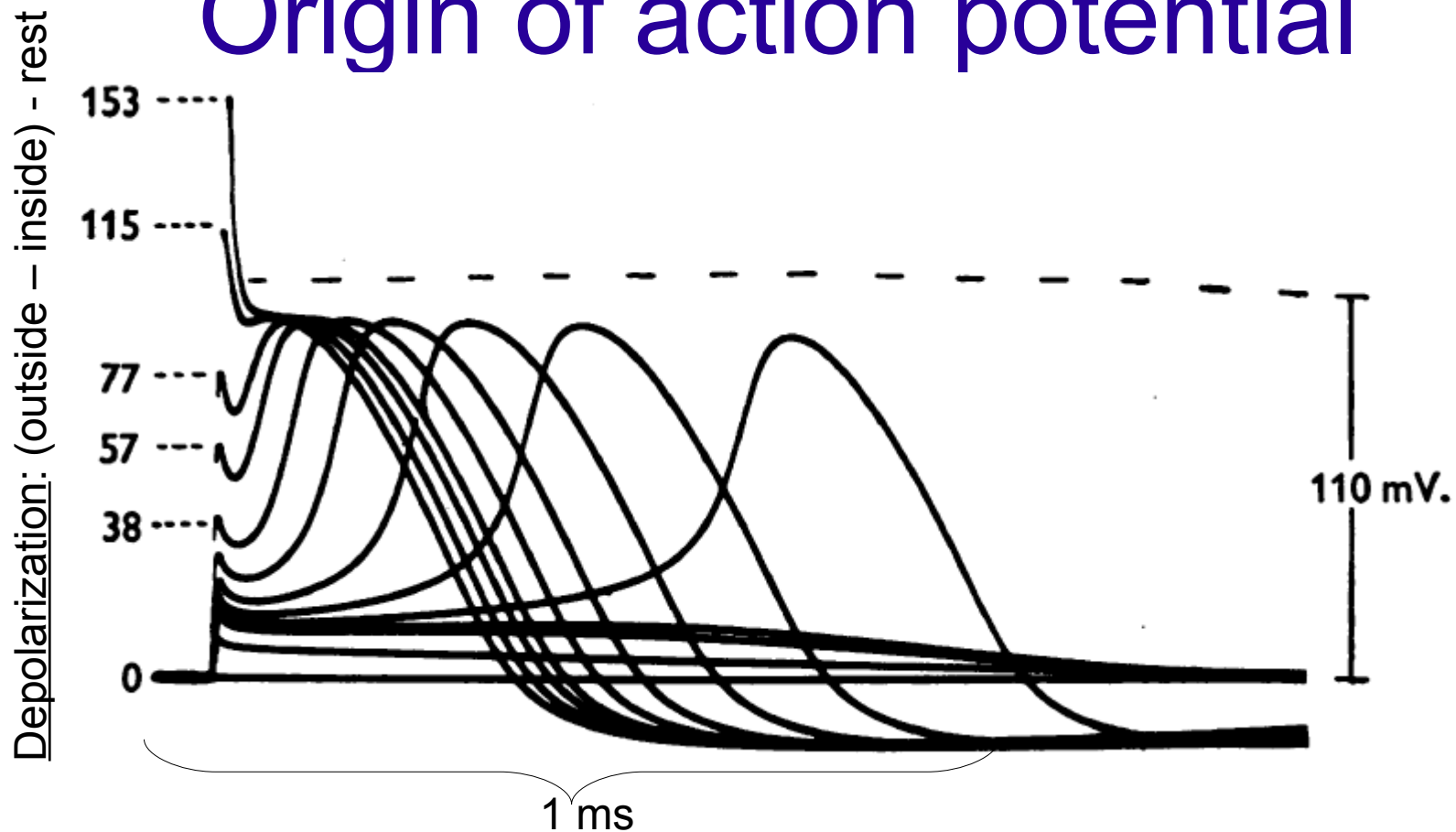
$$I_{\text{Na}} = g_{\text{Na}} (V - V_{\text{Na}})$$

$$I_{\text{K}} = g_{\text{K}} (E - E_{\text{K}})$$



- First few msec (inward current) show increased g_{Na}
- Prolonged outward current associated with increased g_{K}

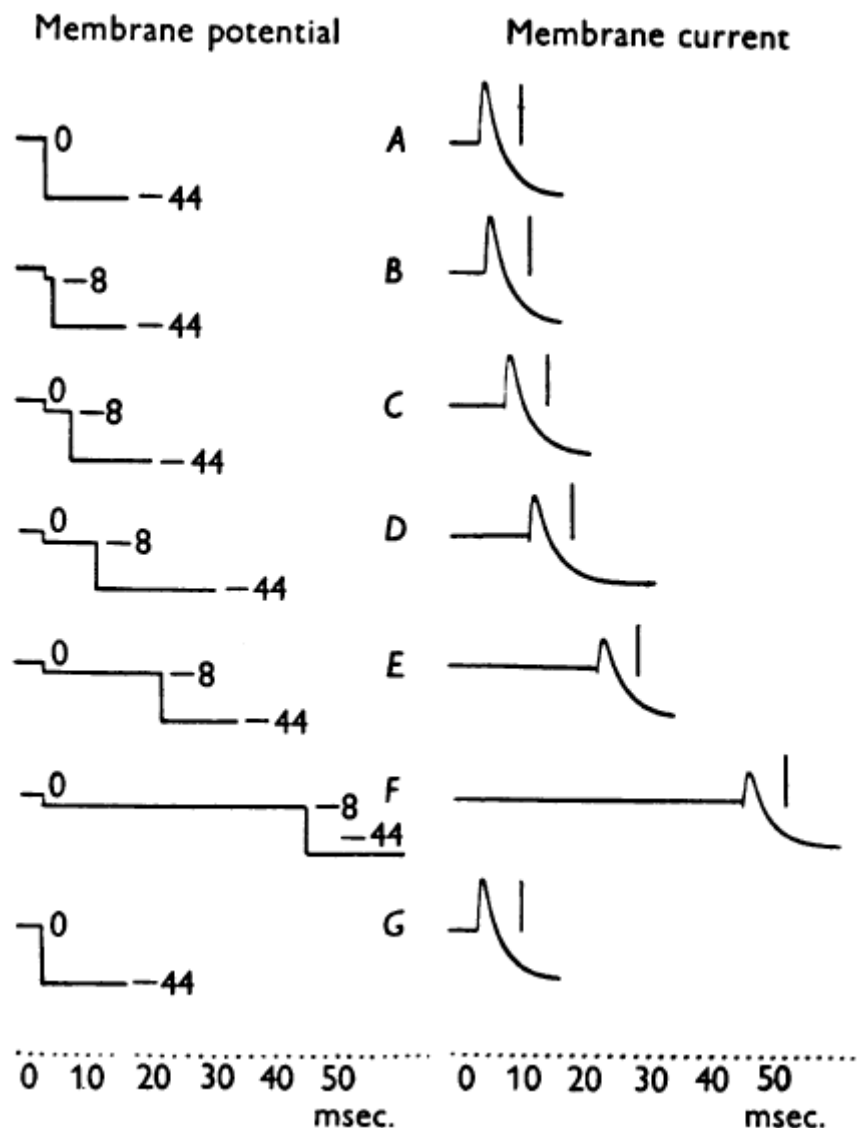
Origin of action potential



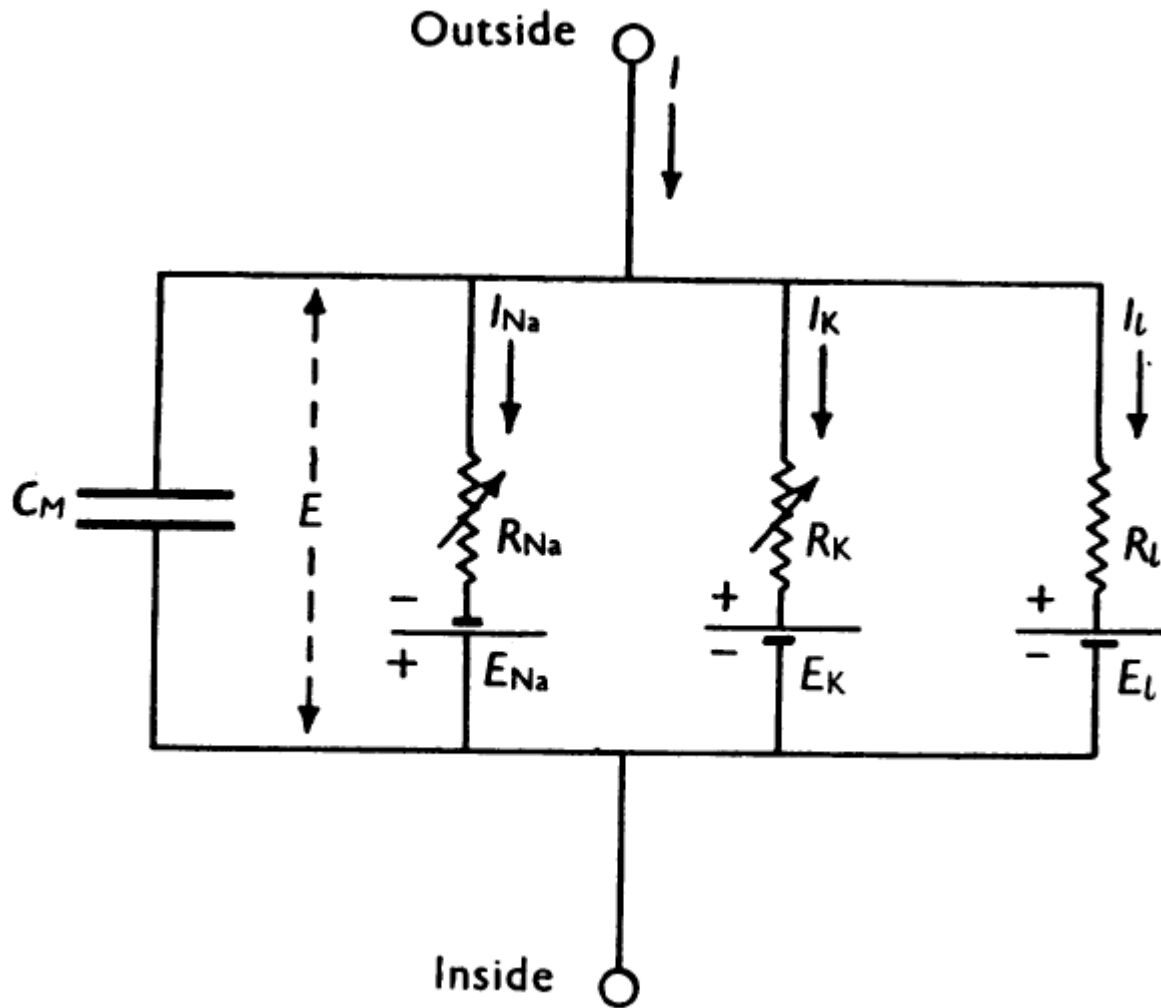
- Current from neighboring region depolarizes membrane
- Sodium conductance channels open, and inward Na current flows
 - This increases original depolarization
- Potassium channels open, and K current flows outside

Sodium inactivation

- Real nerves have refractory period
 - Inability to re-excite
- This can be seen in double-pulse
- The inward sodium current is greatly reduced if there was another depolarization pulse
- Thus, sodium membrane channels have three distinct states:
 - Closed
 - Open
 - Inactivated



Complete model



The Four Papers

- 1951 – clamp experiments + setup
 - Capacitance current + resistance
- 1952a – resolution into two ionic channels
 - Ionic conductance
- 1952b – sudden changes in potential
- 1952c – inactivation: falling edge of the spike
- 1952d – detailed model of action potential

Some references

- <http://neurophilosophy.wordpress.com/2006/08/29/the-discovery-of-the-neuron/>
- <http://www.nature.com.proxy.uchicago.edu/nrn/journal/v4/n1/full/nrn1011.html#B2>
- <http://www.swarthmore.edu/NatSci/echeeve1/Ref/HH/BioWriteUp.htm>
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- http://en.wikipedia.org/wiki/Action_potential#Resting_potential
- http://en.wikipedia.org/wiki/Hodgkin-Huxley_model
- http://www.neuroengineering.upenn.edu/curriculum/be519/Lecture04_files/frame.htm
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- <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1392219>