The action potential

25 Aug, 2016

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- Voltage gated channels
- Hodgkin and Huxley’s experiments
- Properties of the action potential

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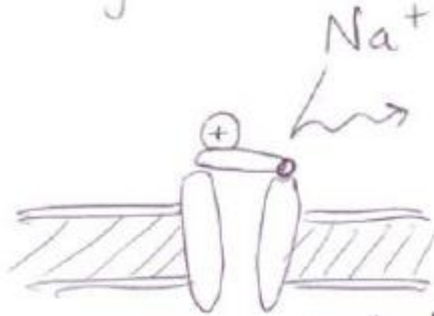
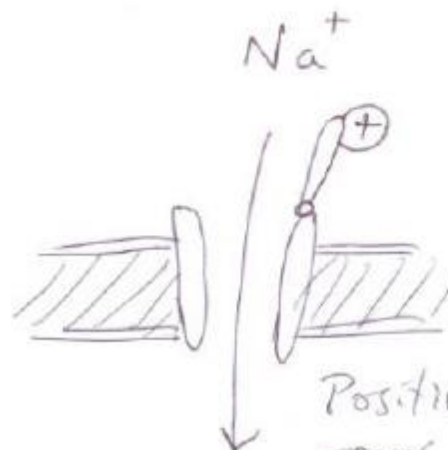
Some ion channels are voltage gated:



Negative potential inside cell closes gate



Positive potential opens gate

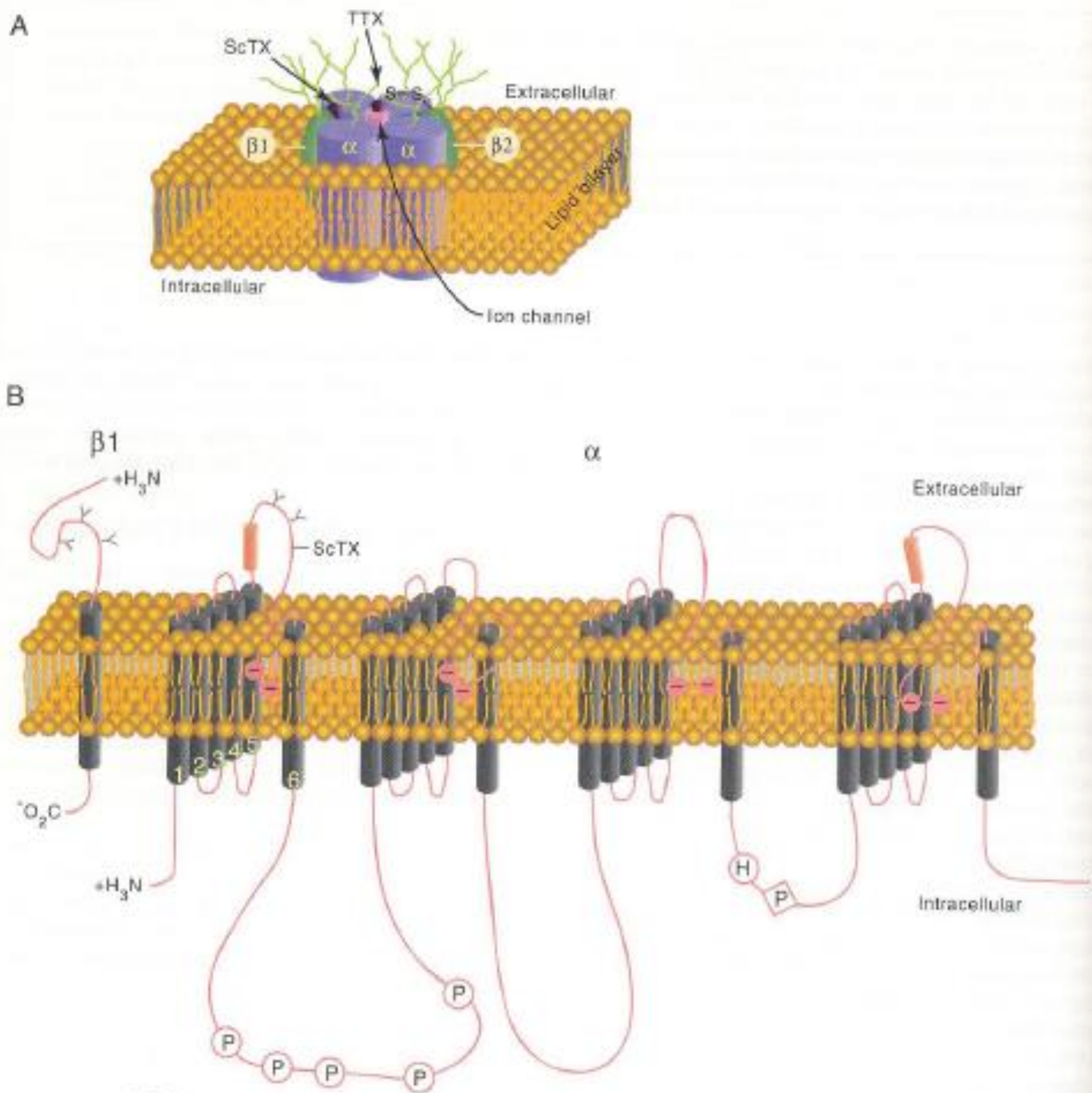
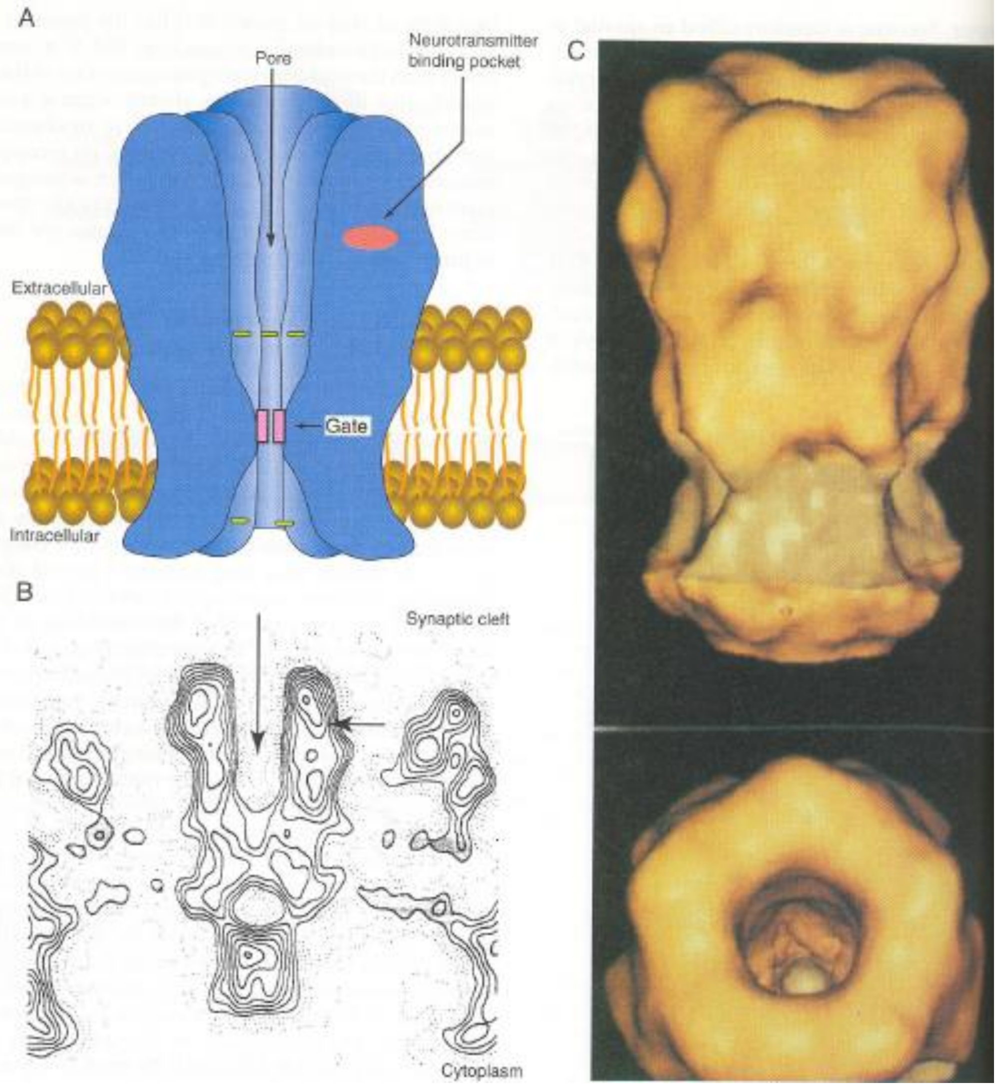
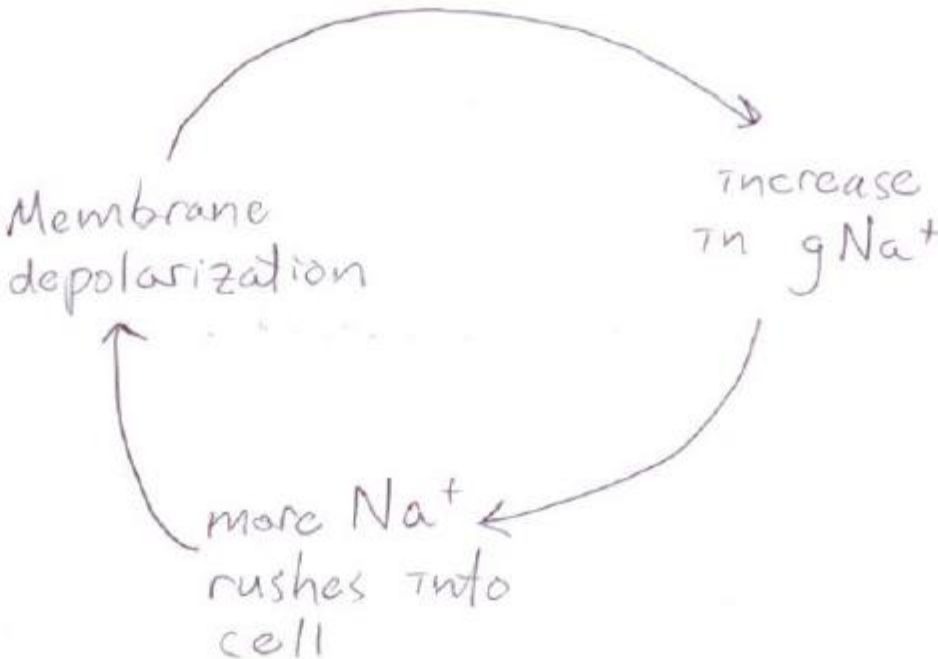


FIGURE 6.9 Structure of the sodium channel. (A) Cross section of a hypothetical sodium channel consisting of a single transmembrane α subunit in association with a $\beta 1$ subunit and a $\beta 2$ subunit. The α subunit has receptor sites for α-scorpion toxins (ScTX) and tetrodotoxin (TTX). (B) Primary structures of α and $\beta 1$ subunits of sodium channel illustrated as transmembrane folding diagrams. Cylinders represent probable transmembrane α-helices.

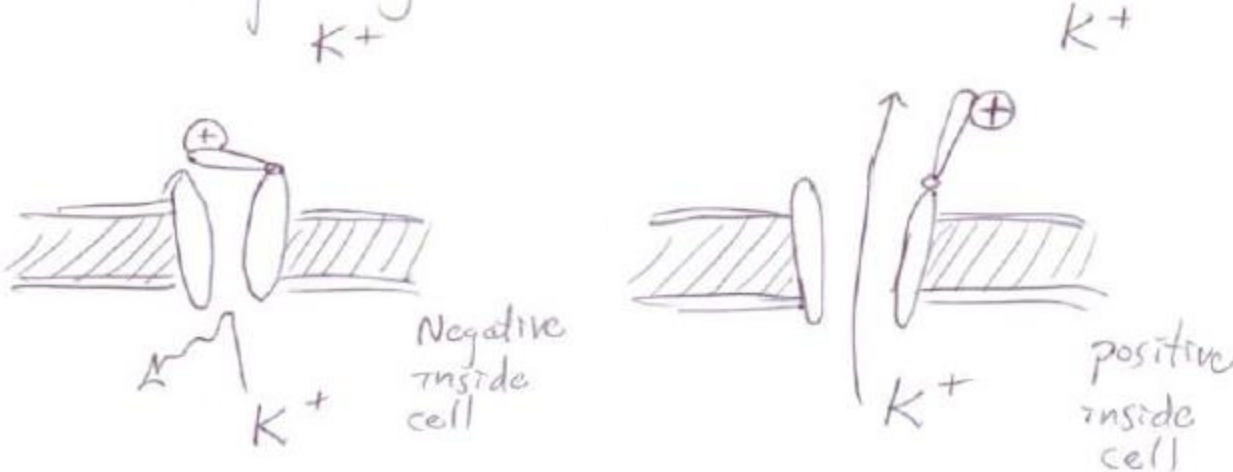

A
Pore
Neurotransmitter
binding pocket
Extracellular
Gate
Intracellular
B
Synaptic cleft
Cytoplasm
C

This leads to a positive feedback loop:



After allmost all Na^+ channels are opened, they inactivate.

Channels for K^+ are also voltage-gated:

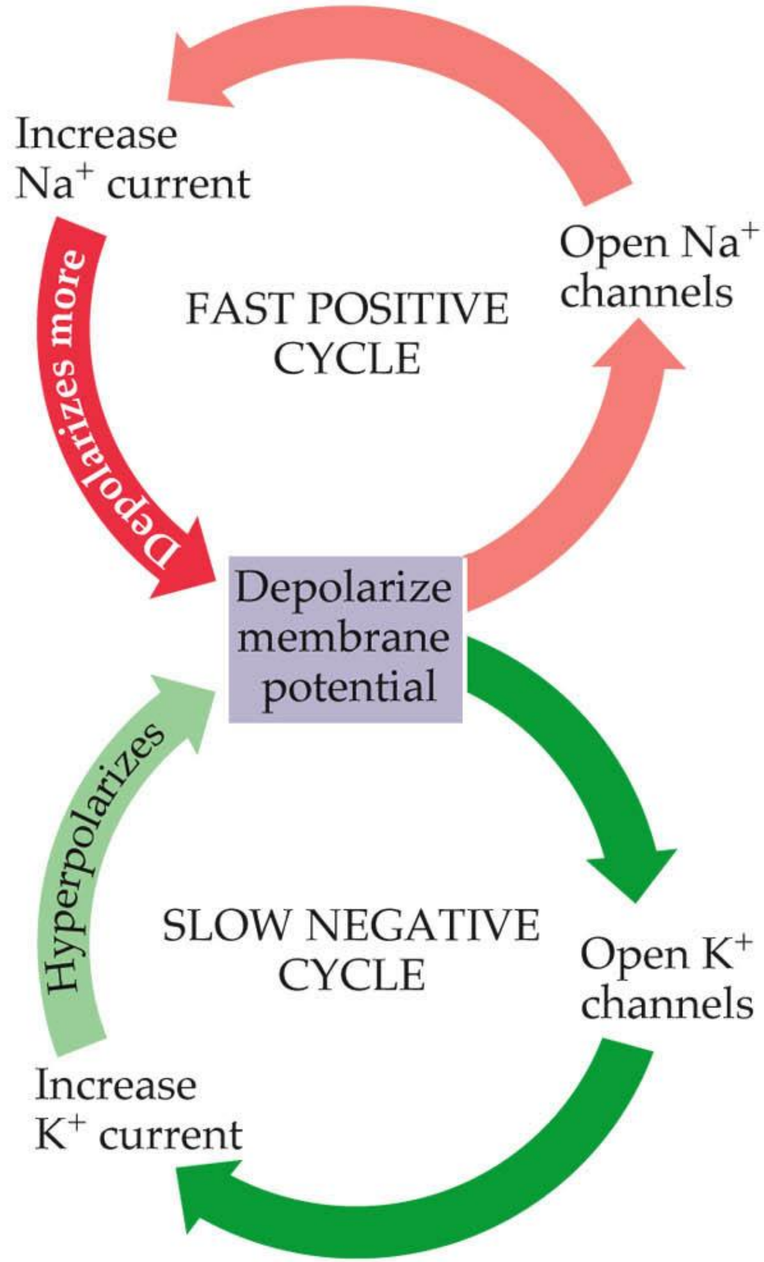


This counteracts the voltage changes caused by Na^+

Membrane depolarization → Increase in gK^+ → K^+ rushes out → Membrane hyperpolarization

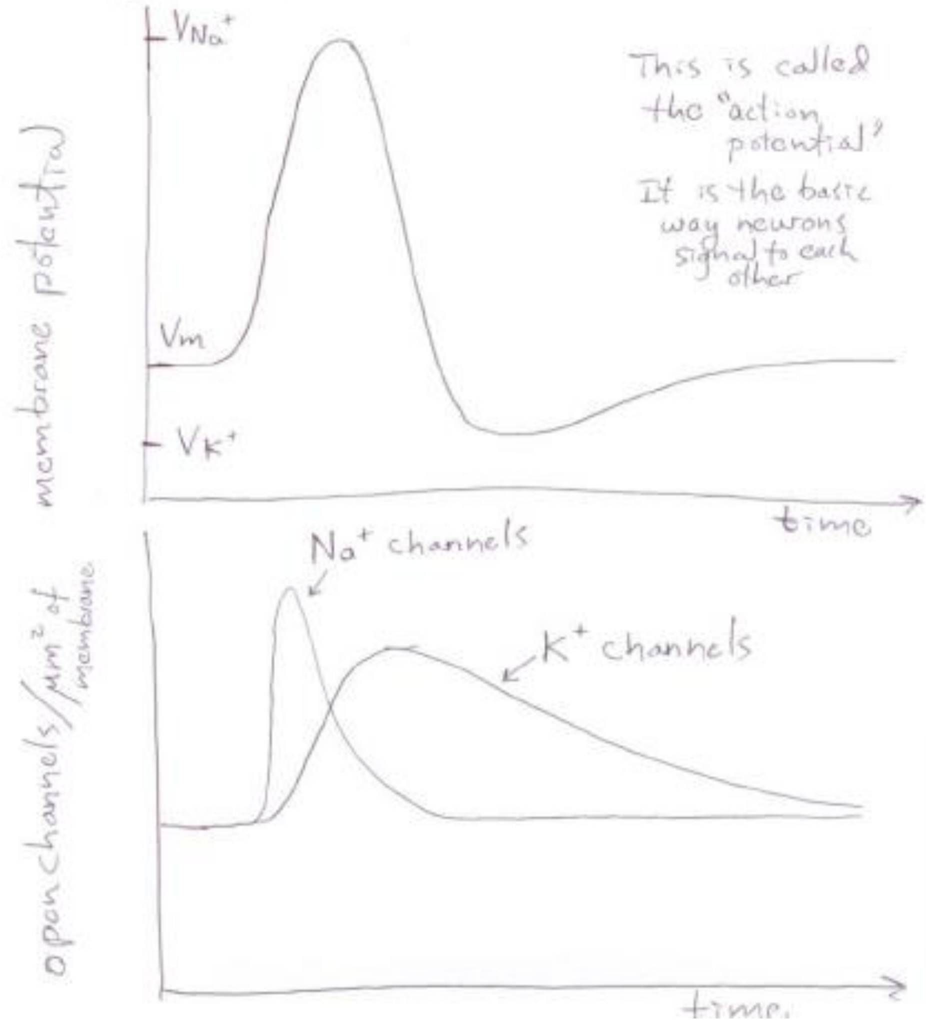
After almost all K^+ channels are opened, they also inactivate.

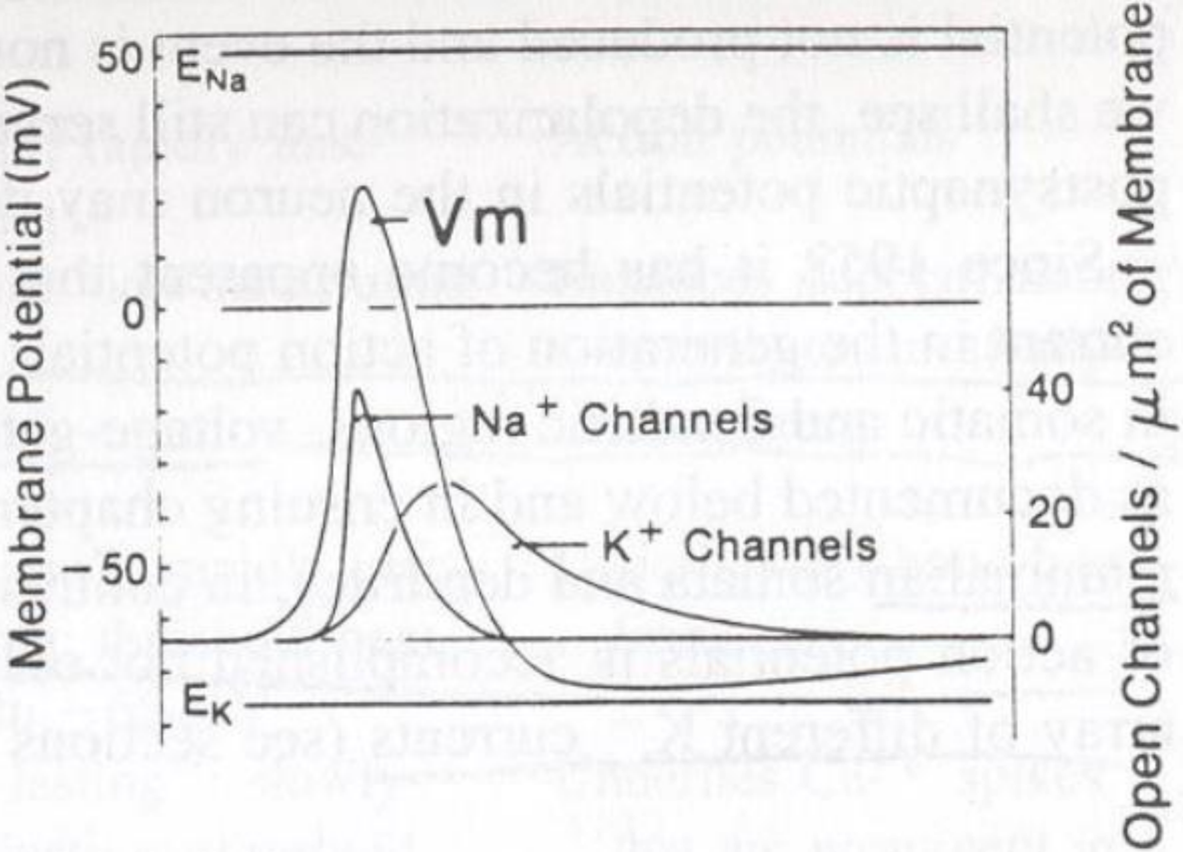
Feedback cycles responsible for membrane potential changes.



NEUROSCIENCE, Third Edition, Figure 3.9 © 2004 Sinauer Associates, Inc.

Both channel types acting together:





Membrane Potential (mV)
50
0
−50
E$_{Na}$
E$_K$
Vm
Na$^+$ Channels
K$^+$ Channels
40
20
0
Open Channels / μm^2 of Membrane

Goldman-Hodgkin-Katz (GHK)

In the presence of several different ions, the equilibrium of the cell depends on the relative permeability of the ions. For this, we use the Goldman-Hodgkin-Katz equation:

$$V_{rest} = \frac{RT}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}} \quad (2)$$

Permeability of an ion is dependent on a number of factors such as the size of the ion, its mobility, etc. During rest in the squid giant axon, the permeabilities have the ratio P_K:P_{Na}:P_{Cl} = 1:0.03:0.1 so that

$$V_{rest} = 58 \log \frac{1(10) + 0.03(460) + 0.1(40)}{1(400) + 0.03(50) + 0.1(540)} = -70mV$$

Since P_K dominates, this is close to E_K.

During an action potential the ratio is P_K:P_{Na}:P_{Cl} =1:15:.1 so that

$$V_m = 58\log\frac{1(10)+15(460)+0.1(40)}{1(400)+15(50)+0.1(540)} = +44mV$$

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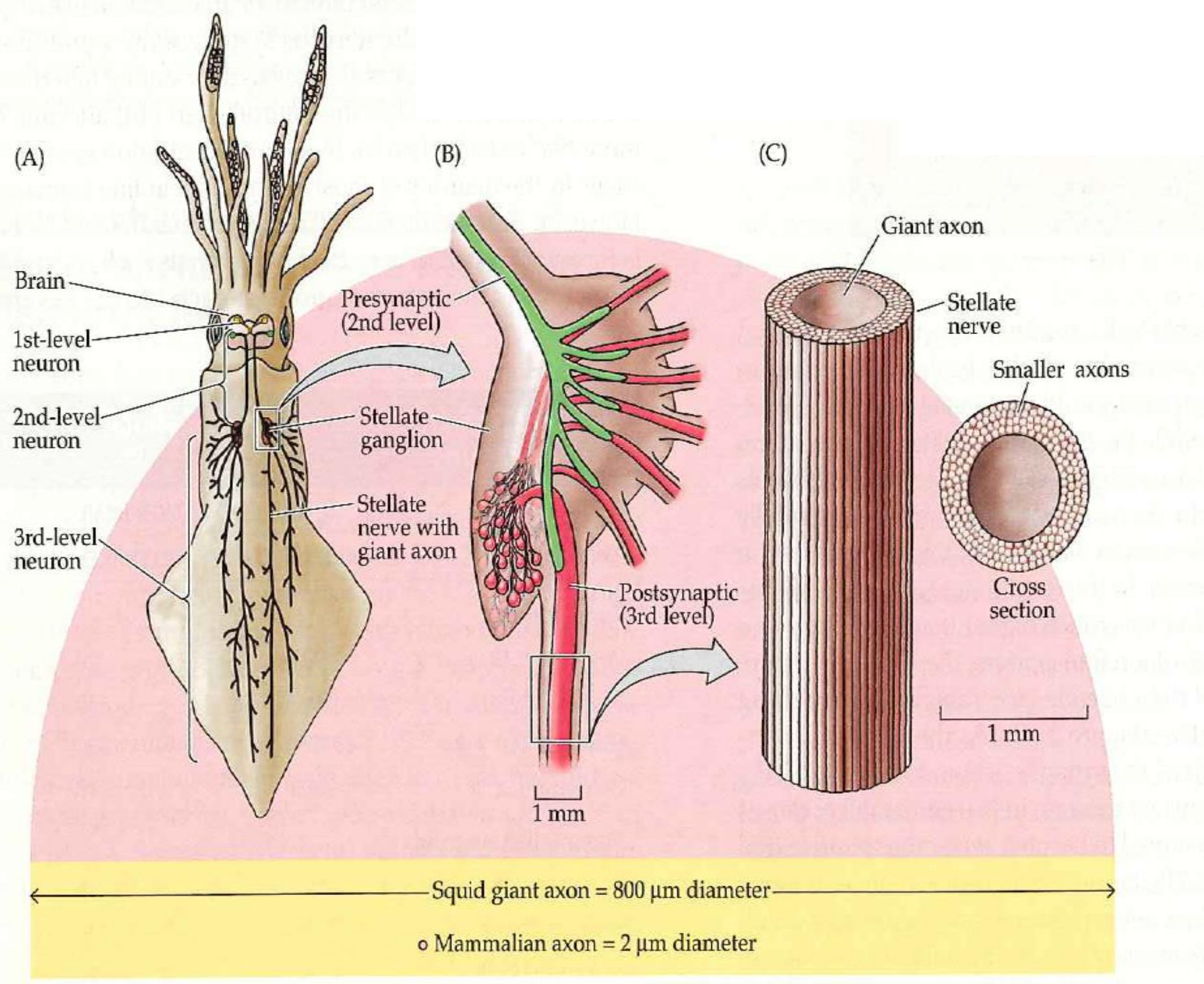
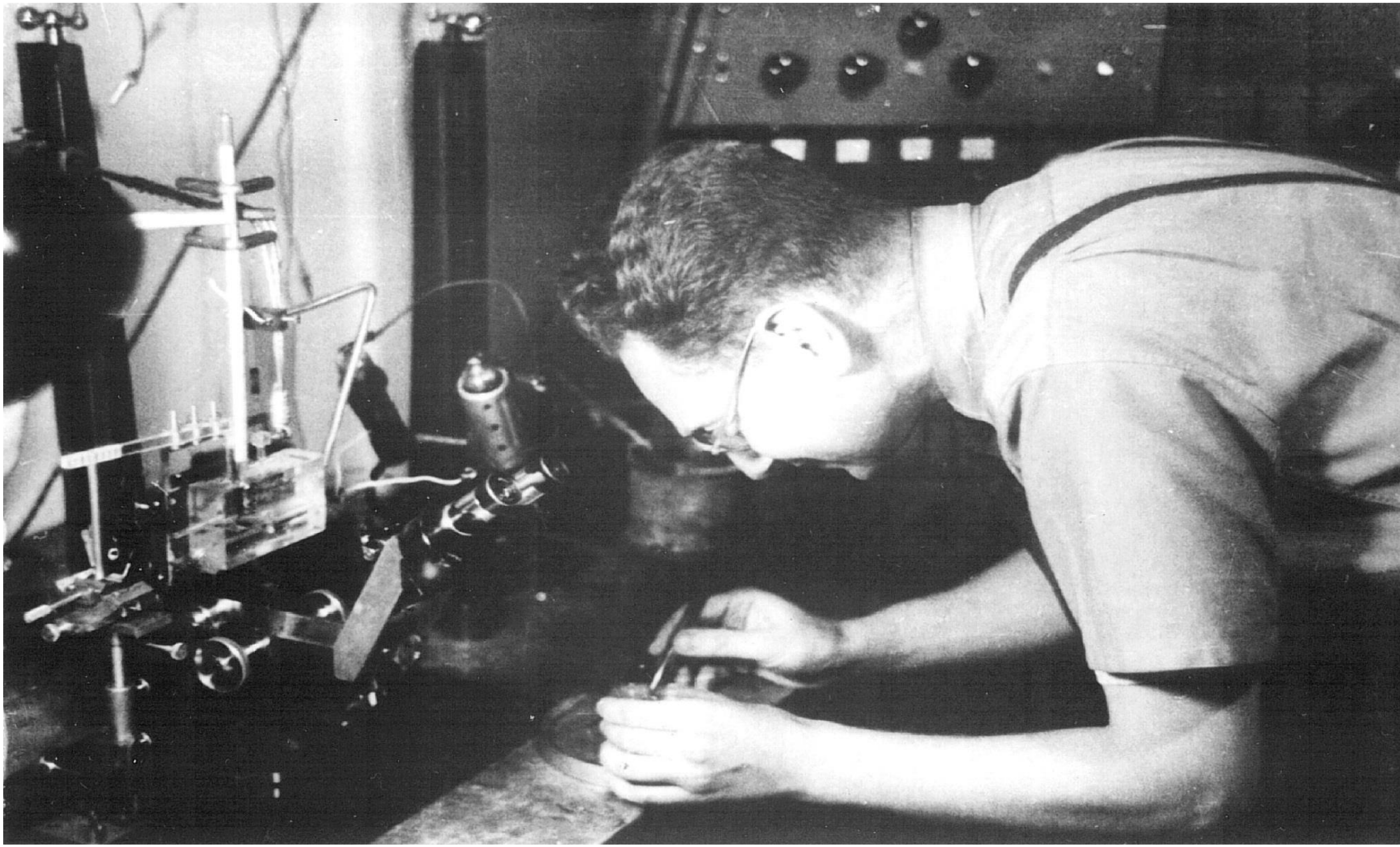
Opti



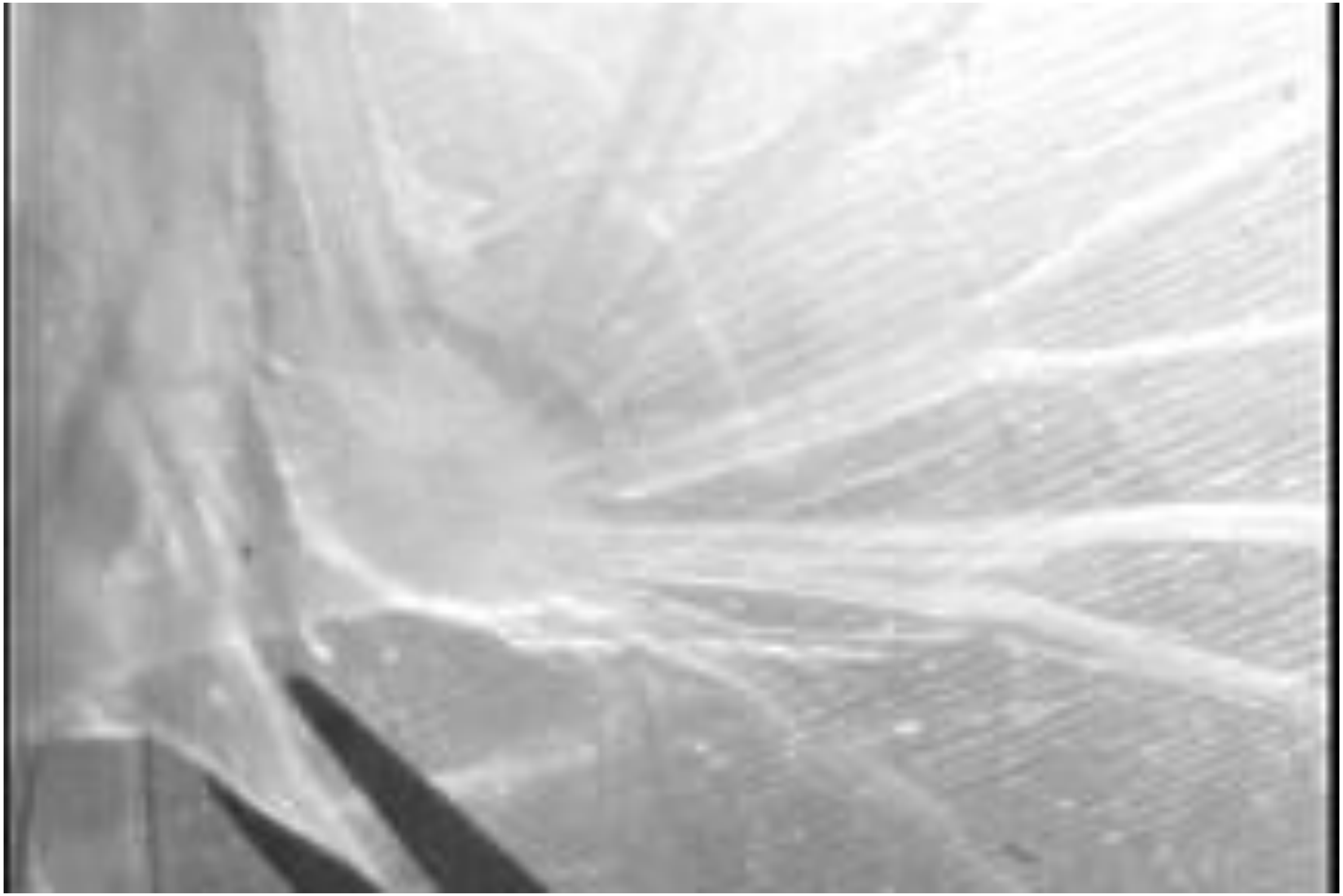
(A)
(B)
(C)
Brain
1st-level neuron
2nd-level neuron
3rd-level neuron
Stellate ganglion
Stellate nerve with giant axon
Presynaptic (2nd level)
Postsynaptic (3rd level)
1 mm
Giant axon
Stellate nerve
Smaller axons
Cross section
1 mm
Squid giant axon = 800 μm diameter
Mammalian axon = 2 μm diameter

Bernard Katz dissecting a squid



Nobel Prize for showing how nerves and muscles interact

Squid nerve cell



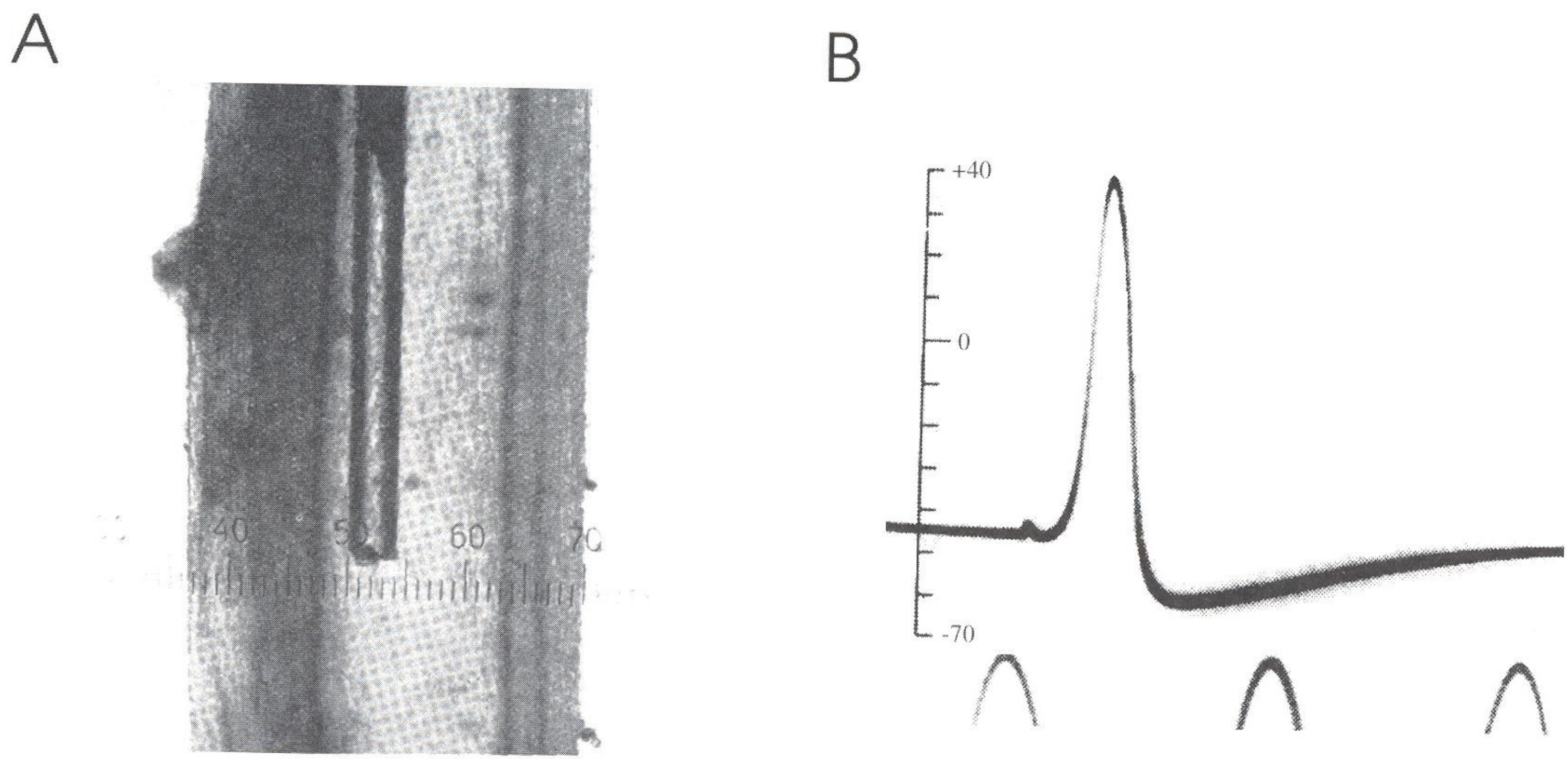
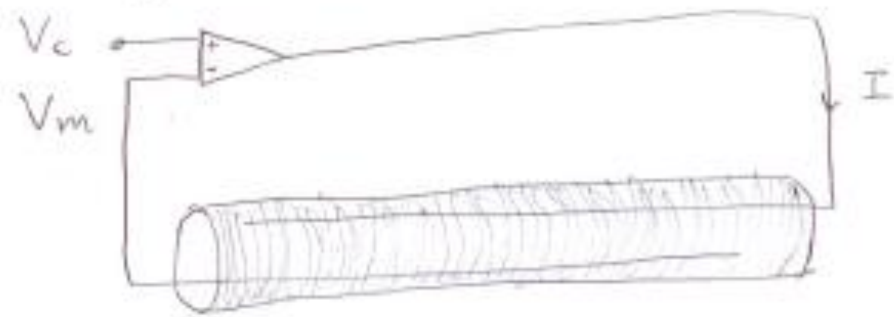


FIGURE 6.1 Intracellular recording of the membrane potential and action potential generation in the squid giant axon. (A) A glass micropipette, about 100 μm in diameter, was filled with seawater and lowered into a squid giant axon that had been dissected free. The axon, about 0.5 mm in diameter, was transilluminated from behind. (B) The nerve action potential. Note that the membrane potential becomes positive at the peak and that the repolarization is followed by an afterhyperpolarization. The sine wave at the bottom provides a scale for timing, with 2 ms between peaks. From Hodgkin and Huxley.[4]

Now lets use this as we examine
Hodgkin + Huxley's experiments
on squid giant axon:



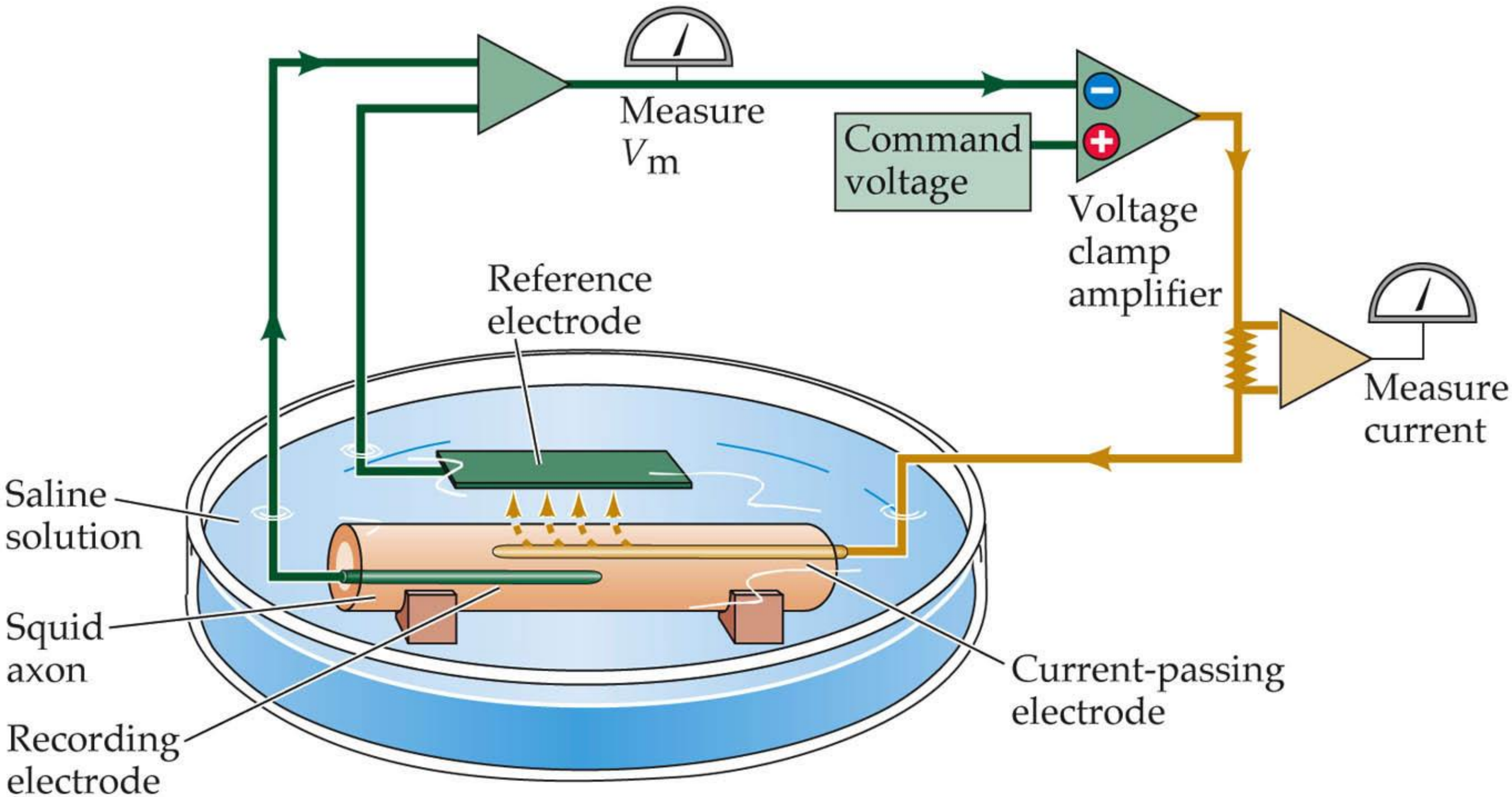
V_c sets the 'command' voltage

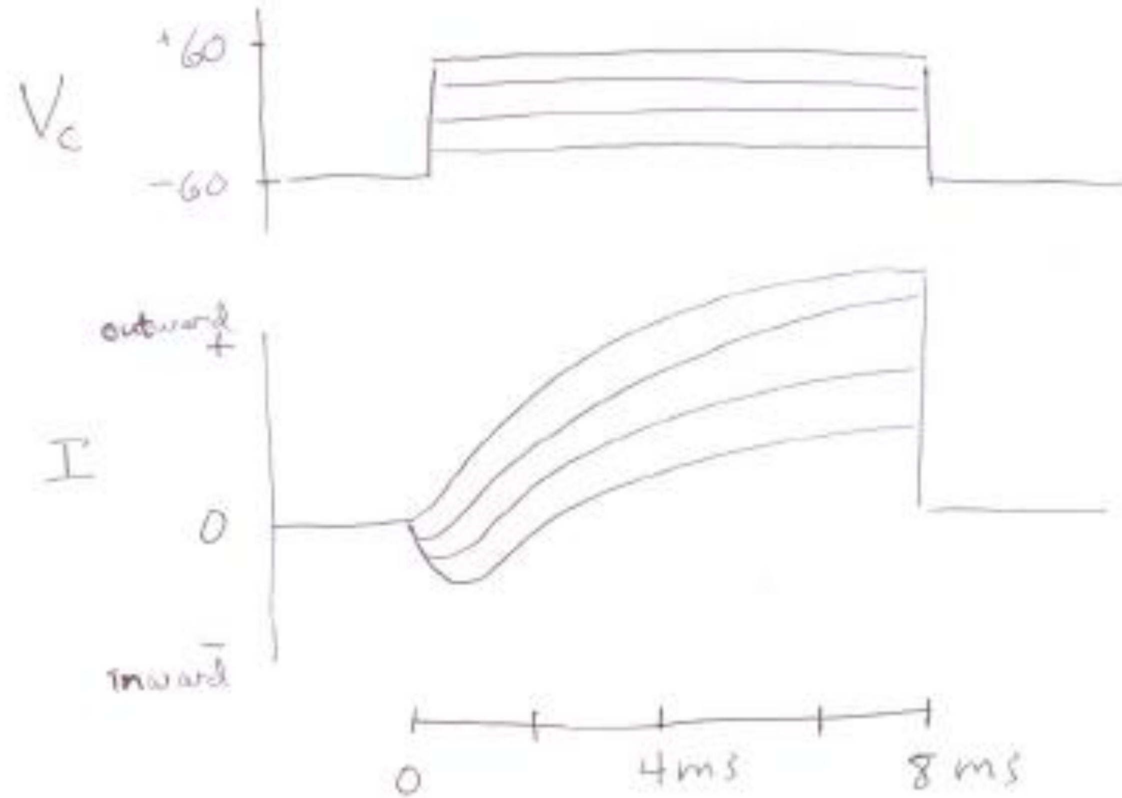
V_m gives the membrane voltage

I is the current injected to
keep V_m close to V_c

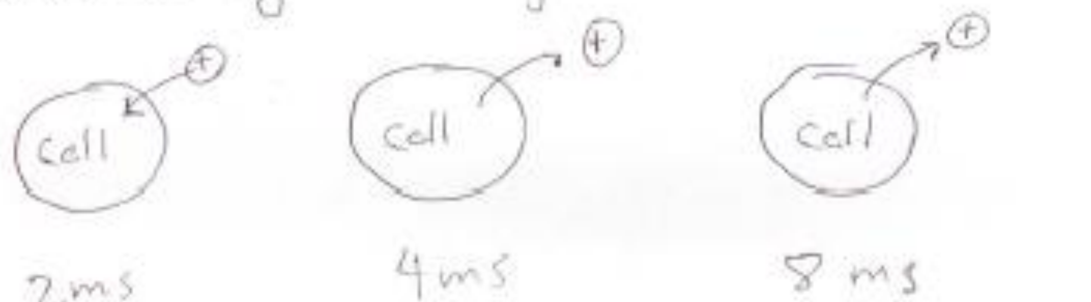
Using this set-up, they could
see the currents flowing into and
out of the axon as they stepped
it to different voltages.

Box A Voltage Clamp Method





They saw a brief inward current followed by a longer outward current



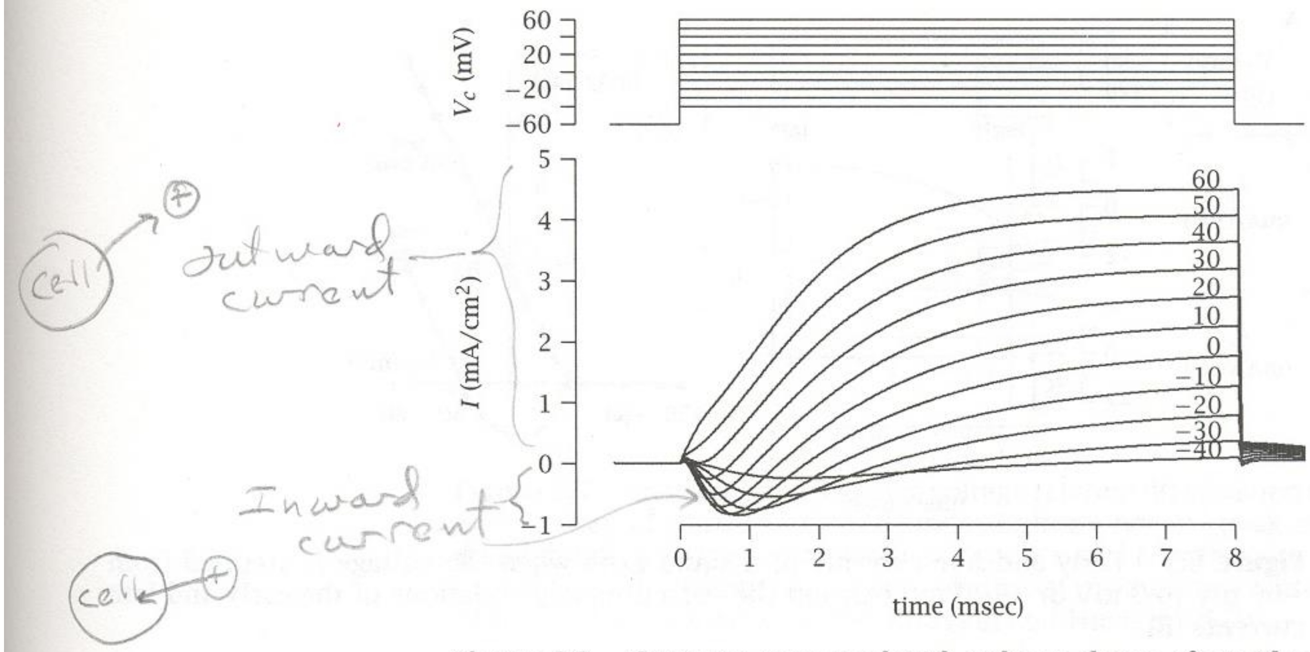
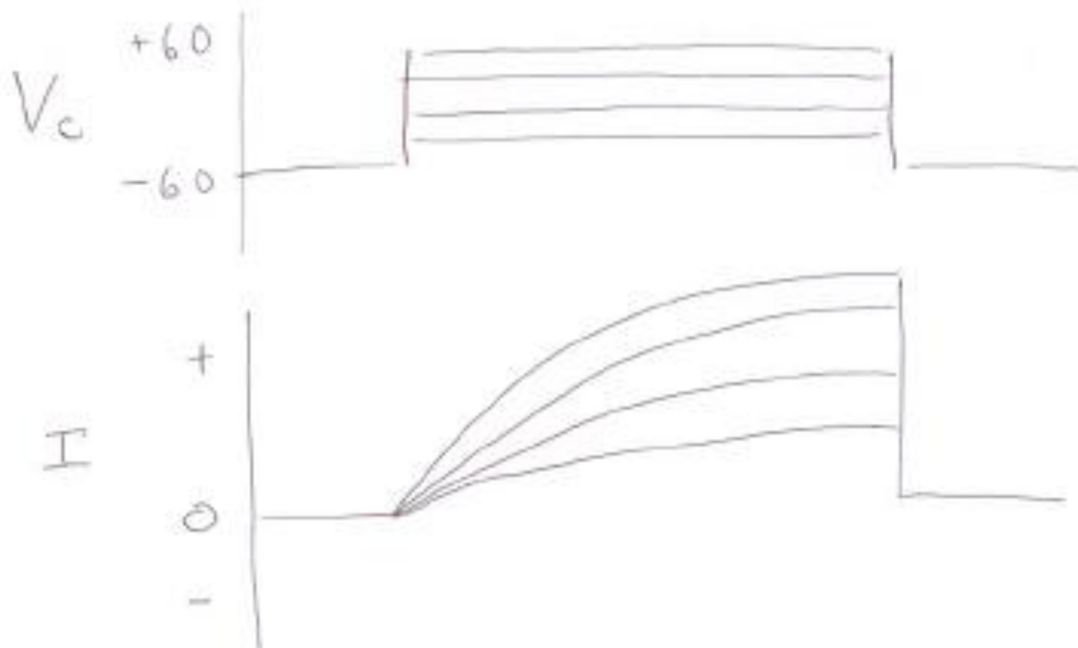


Figure 6.2 Currents measured with voltage clamp of squid axon. Membrane potential was held at −60 mV and then stepped (at 0 msec) to various potentials (shown at the right of each trace) for 8 msec before stepping back to −60 mV.

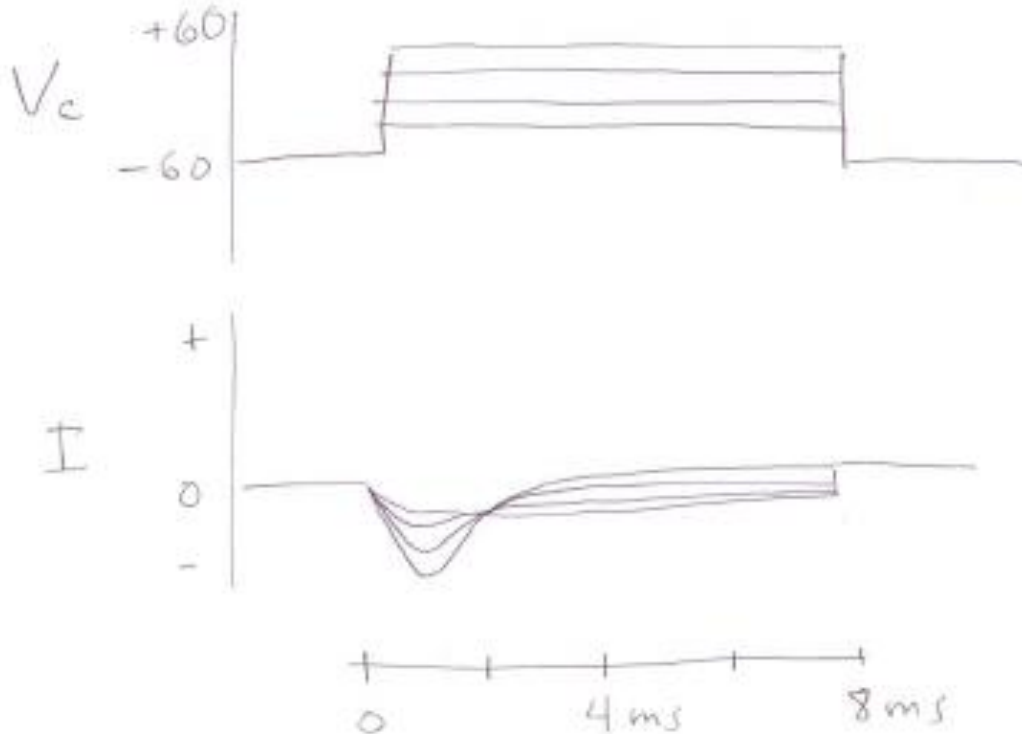
They could separate these currents using TTX and TEA

TTX blocks Na^+ channels:



Revealing only an outward, later current.

And TEA blocks K^+ channels, revealing a rapid, transient inward current:



So the membrane current was made up of Na^+, K^+ movement.

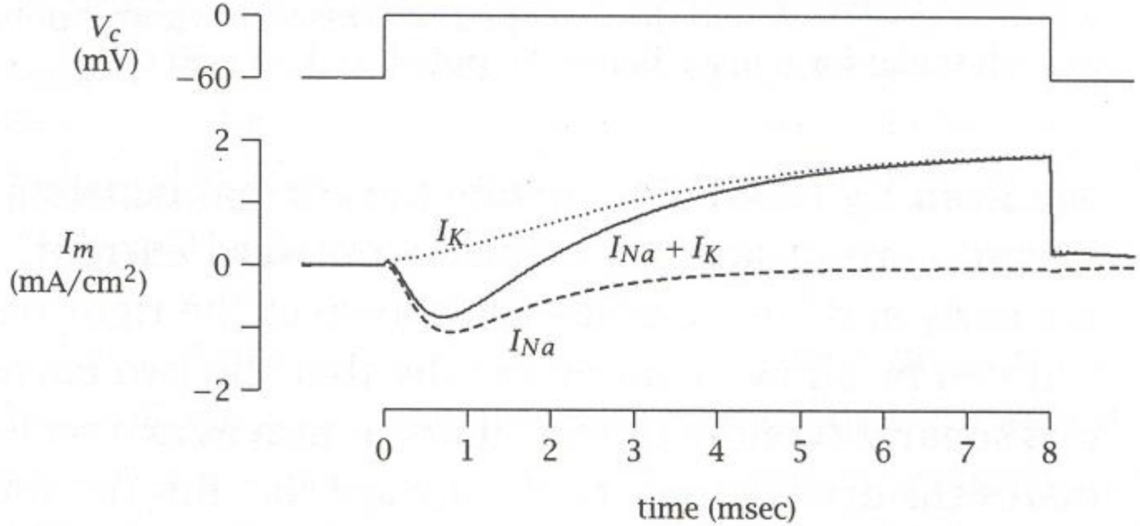


Figure 6.4 Separation of membrane current (solid trace) into Na^+ (dashed trace) and K^+ (dotted trace) currents. I_K is obtained in the presence of TTX or when $[Na^+]_{out} = 0$; I_{Na} is obtained in the presence of TEA. The voltage is stepped from −60 mV to 0 mV for 8 msec.

- **Electrical conductance** is a measure of the ease of flow of current between two points. The conductance between two electrodes in salt water can be increased by adding more salt, or by bringing the electrodes closer together.

- Conductance is measured in units called **siemens** (abbreviated **S,** and formerly called "mhos") and is defined by Ohm's law in simple conductors:

$$I = g\,E$$

$$I = g\,E$$

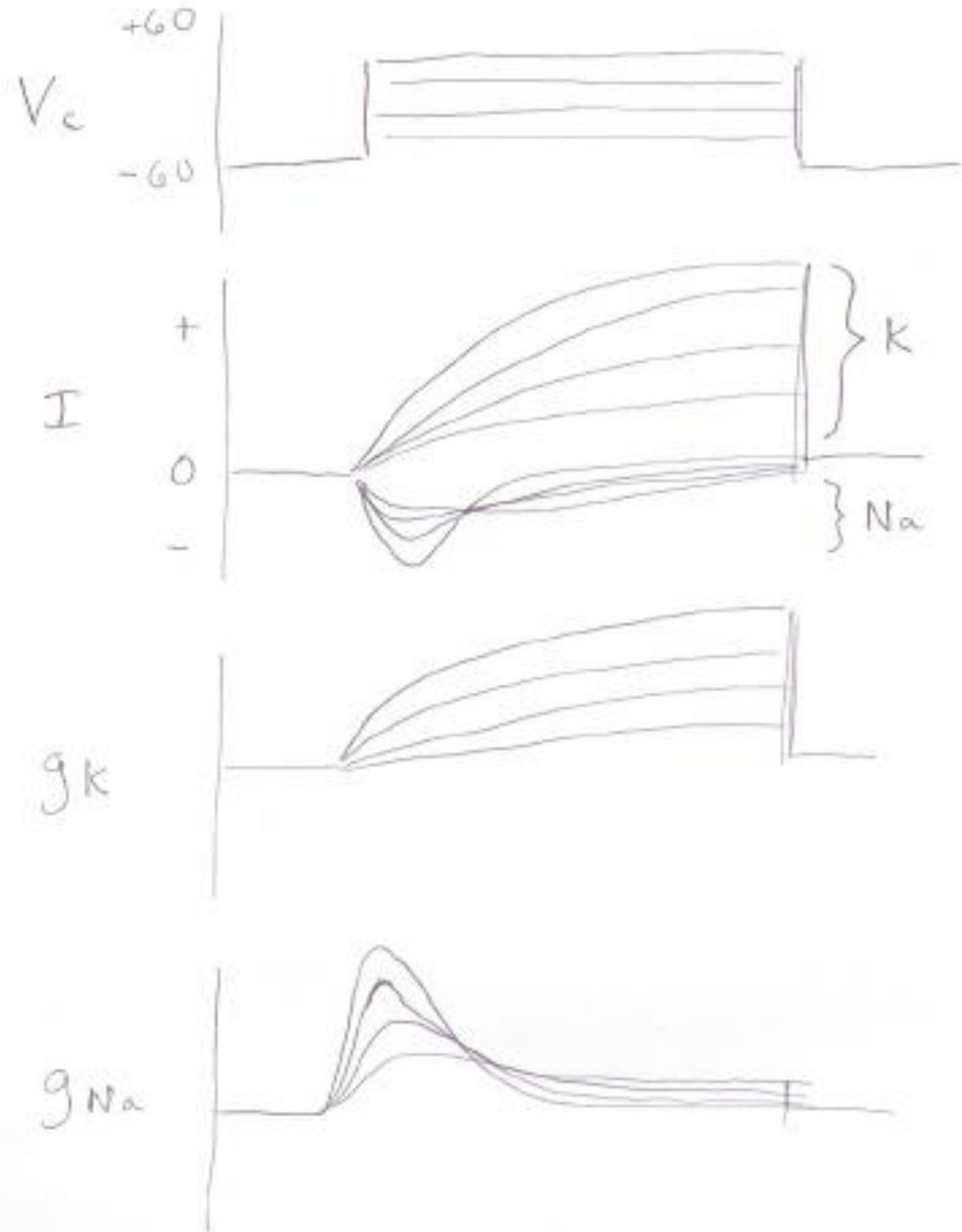
This equation says that current (***I,*** in amps) equals the product of conductance (***g,*** in siemens) and the voltage (***V,*** in volts) difference across the conductor. The reciprocal of conductance (***1/g***) is termed **resistance** (***R)*** and is measured in **ohms.**

Ohm's law can thus be re-written as:

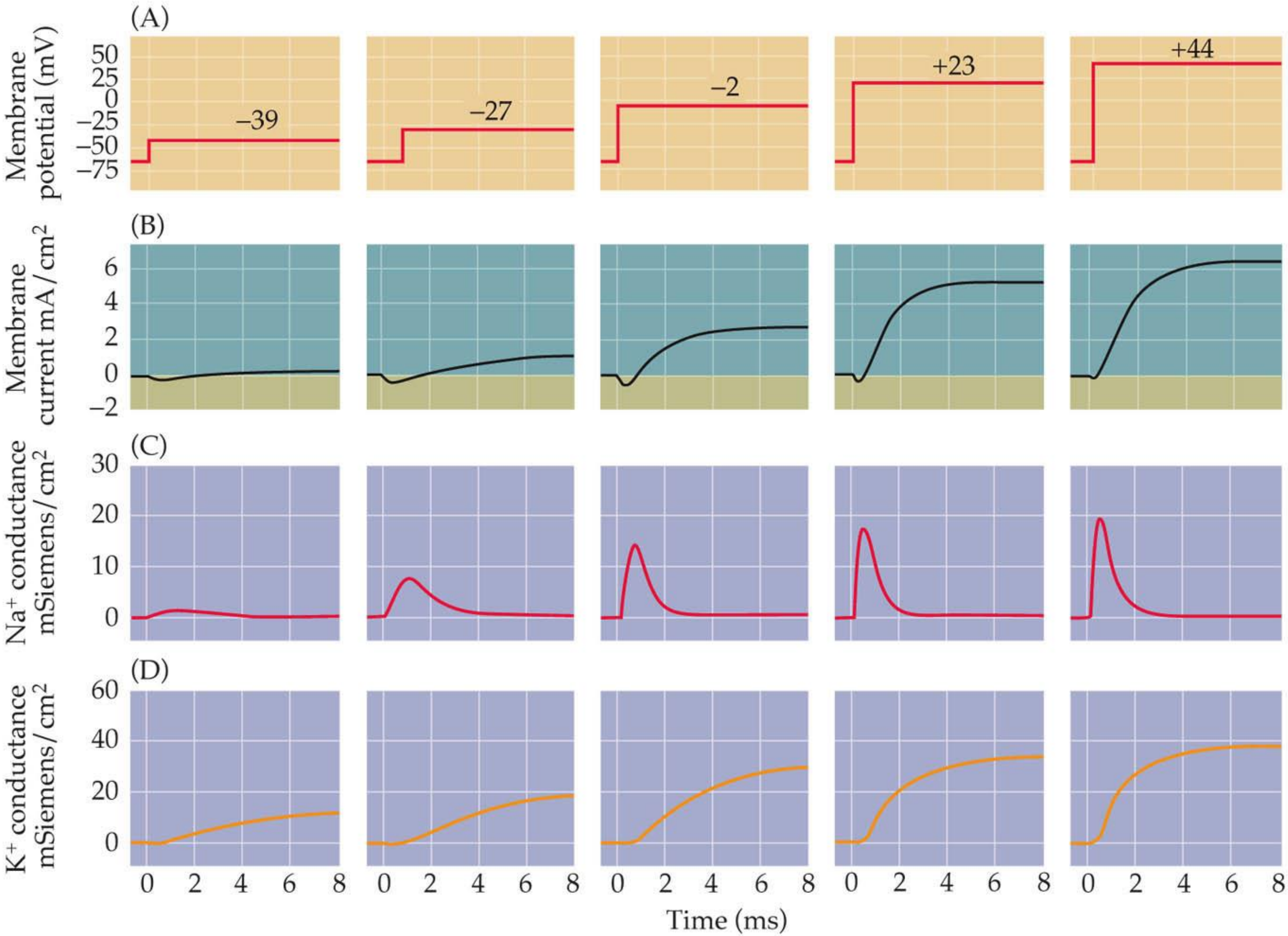
$$E = I\,R$$

Using Ohm's law, they could determine the conductances g_K, g_{Na}

$$g_K = \frac{I_K}{(V - E_K)} \qquad g_{Na} = \frac{I_{Na}}{(V - E_{Na})}$$

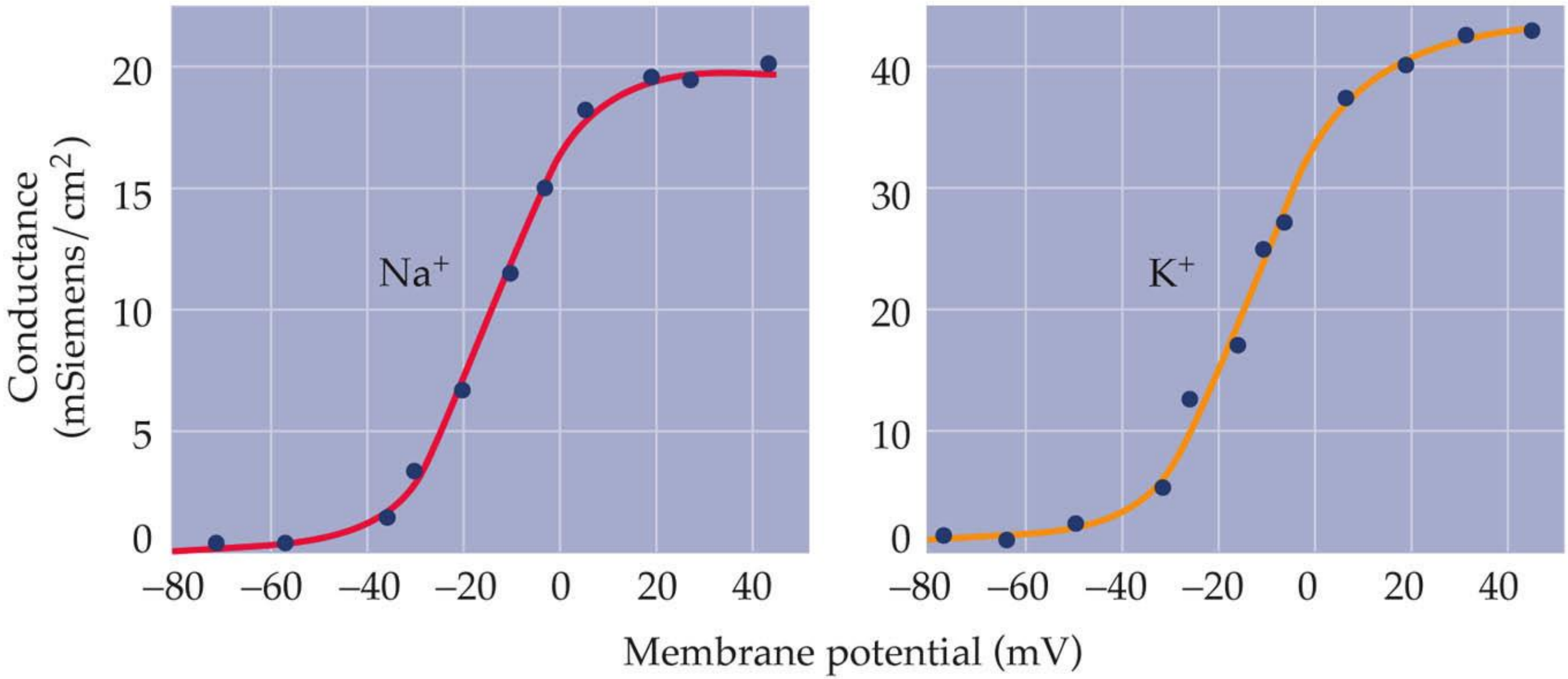

+60
V_c
-60
+
I
0
-
K
Na
gK
gNa

Membrane conductance changes are time- and voltage-dependent.

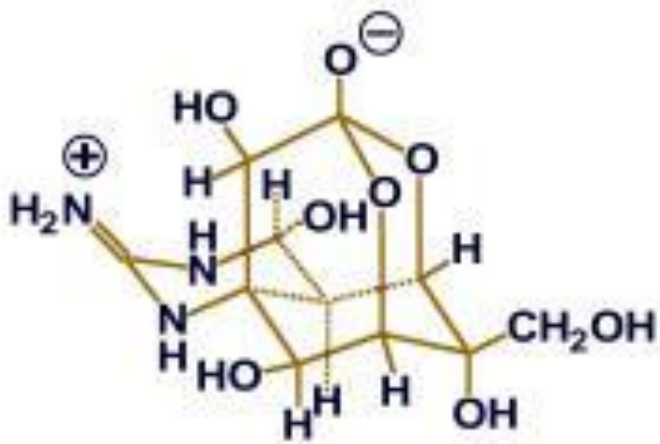


NEUROSCIENCE, Third Edition, **Figure 3.6**

Depolarization increases Na^+ and K^+ conductances of the squid giant axon.

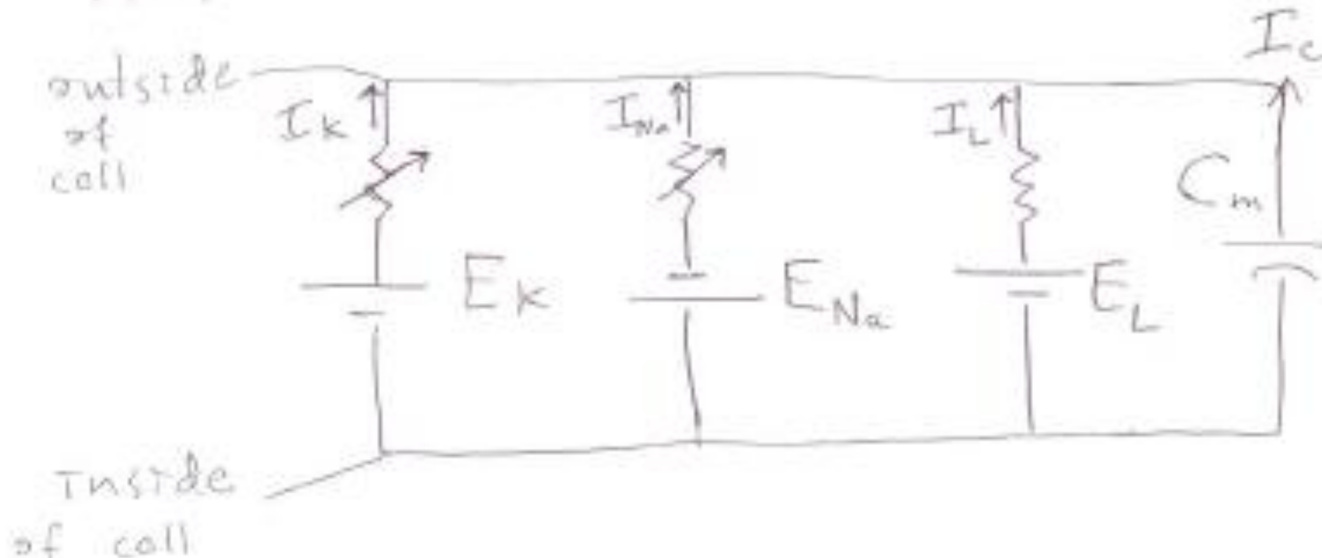


Tetrodotoxin, Japanese puffer fish (fugu), and fugu sashimi



- Poisoning with the neurotoxin tetrodotoxin (TTX) occurs after ingestion of various species of puffer fish. The flesh of the puffer fish (ie, fugu) is considered a delicacy in Japan. It is prepared by chefs specially trained and certified by the government to prepare the flesh free of the toxic liver, gonads, and skin. Despite these precautions, many cases of tetrodotoxin poisoning are reported each year in patients ingesting fugu.
- Poisonings usually occur after eating fish caught and prepared by uncertified handlers.
- Tetrodotoxin also is found in the gastropod mollusc; in the eggs of horseshoe crabs; in newts of the genus *Taricha*; in the skin of Atelopid frogs; and in the skin and viscera of porcupine fish, globefish, balloon fish, blowfish, sunfish, toadfish, blue-ringed octopus, and some species of salamanders.

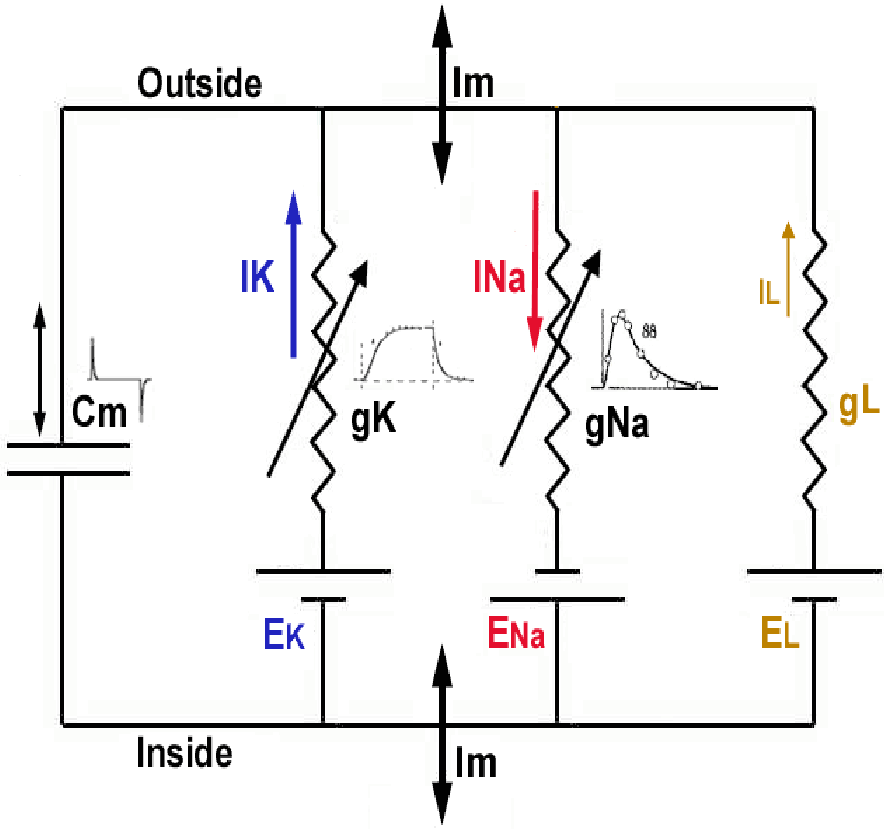
Their model of the membrane had these conductances:



Membrane current is given by:

$$I_m = C_m \frac{dV}{dt} + g_K(V,t)(V - E_K) + g_{Na}(V,t)(V - E_{Na}) + g_L(V - E_L)$$

Equivalent Circuit for Hodgkin-Huxley Equation



- From left to right, the current paths are:
  - through the capacitance (Cm)
  - through the K conductance (gK)
  - through the Na conductance (gNa)
  - through the leak conductance (gL).

- **Variable resistors and batteries**

- The voltage-sensitive conductances, gNa and gK, are diagrammed by a resistor that is variable because of the voltage sensitivity of the channels. That is, the value of these resistors depends on the voltage--in series with a battery representing the driving force on the ion through that channel. The polarity of the K battery is inside-negative because at EK the voltage across the membrane is negative inside with respect to outside. The polarity of the Na battery is the reverse because at ENa the voltage across the membrane is positive inside with respect to outside.

- **Conductance and current waveforms**

- To the right of each element (except for the leak conductance) is a diagram showing current (for Cm) or conductances (for gK and gNa) as a function of time **in response to a voltage step** under voltage clamp.

$$\underset{\text{Total current}}{I} = \underbrace{C_M \frac{\mathrm{d}V}{\mathrm{d}t}}_{\text{Capacitive current}} + \underbrace{\bar{g}_{\mathrm{K}} n^4 (V - V_{\mathrm{K}})}_{\text{Potasssium current}} + \underbrace{\bar{g}_{\mathrm{Na}} m^3 h (V - V_{\mathrm{Na}})}_{\text{Sodium current}} + \underbrace{\bar{g}_l (V - V_l)}_{\text{Leakage current}},$$

Hodgkin-Huxley equation

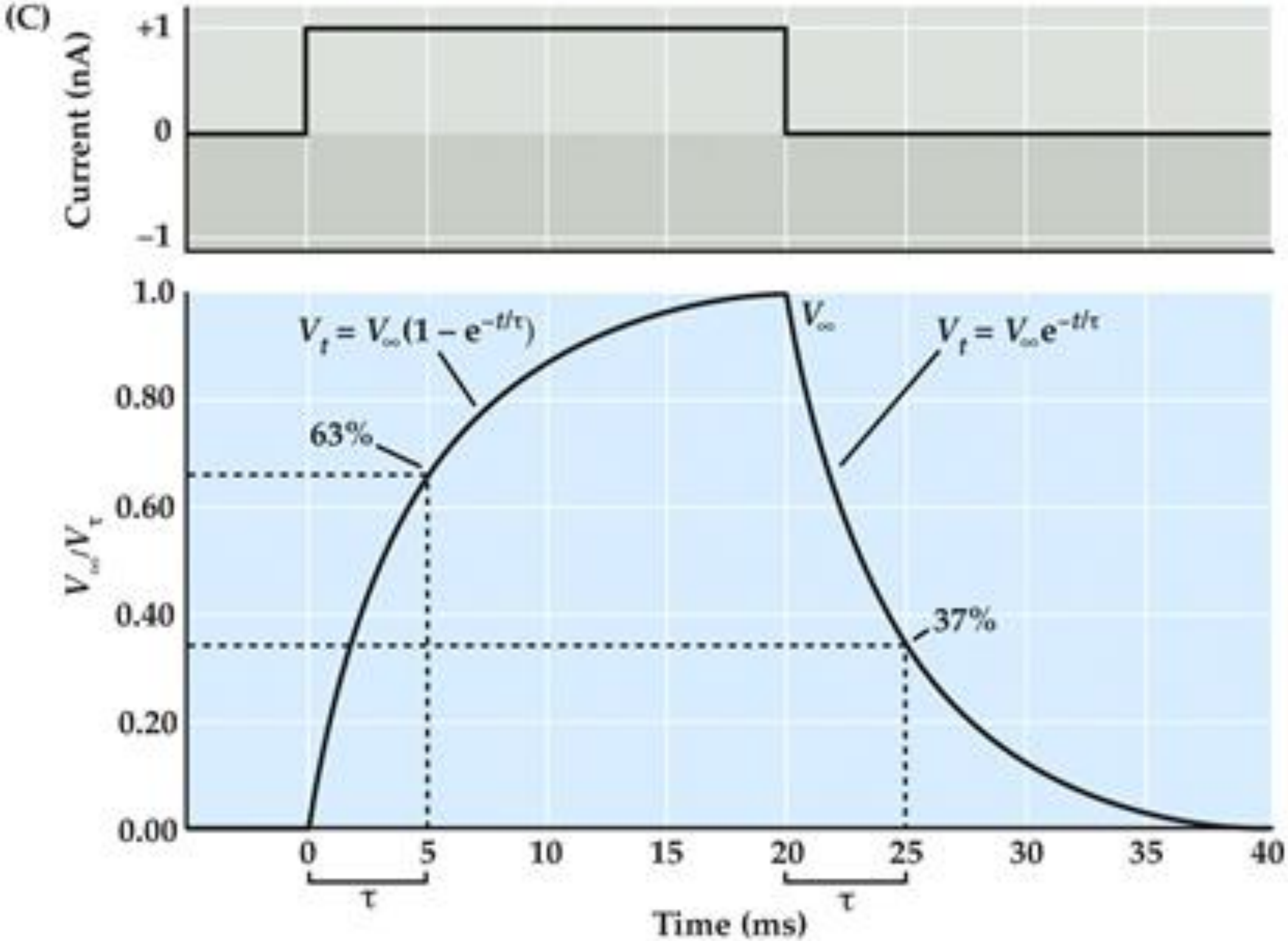
The Hodgkin-Huxley equation expresses the total current flowing through a membrane in terms of the four current components. The terms of the equation are represented in the same order (left to right) in the diagram on the next slide by a corresponding element.

The action potential

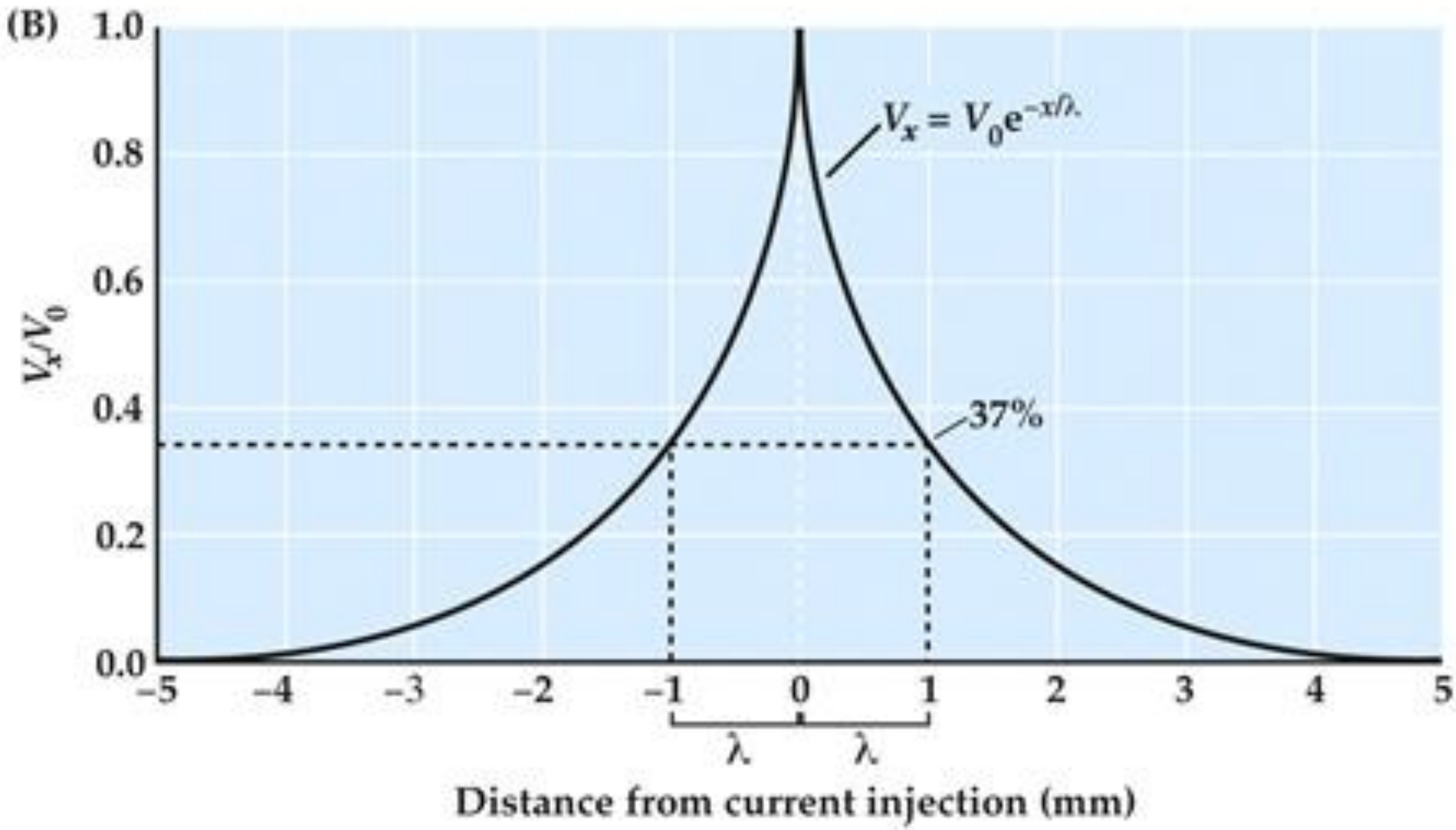
- Voltage gated channels
- Hodgkin and Huxley's experiments
- **Properties of the action potential**

What are passive membrane properties again?

Box 2A Passive membrane properties (Part 3)



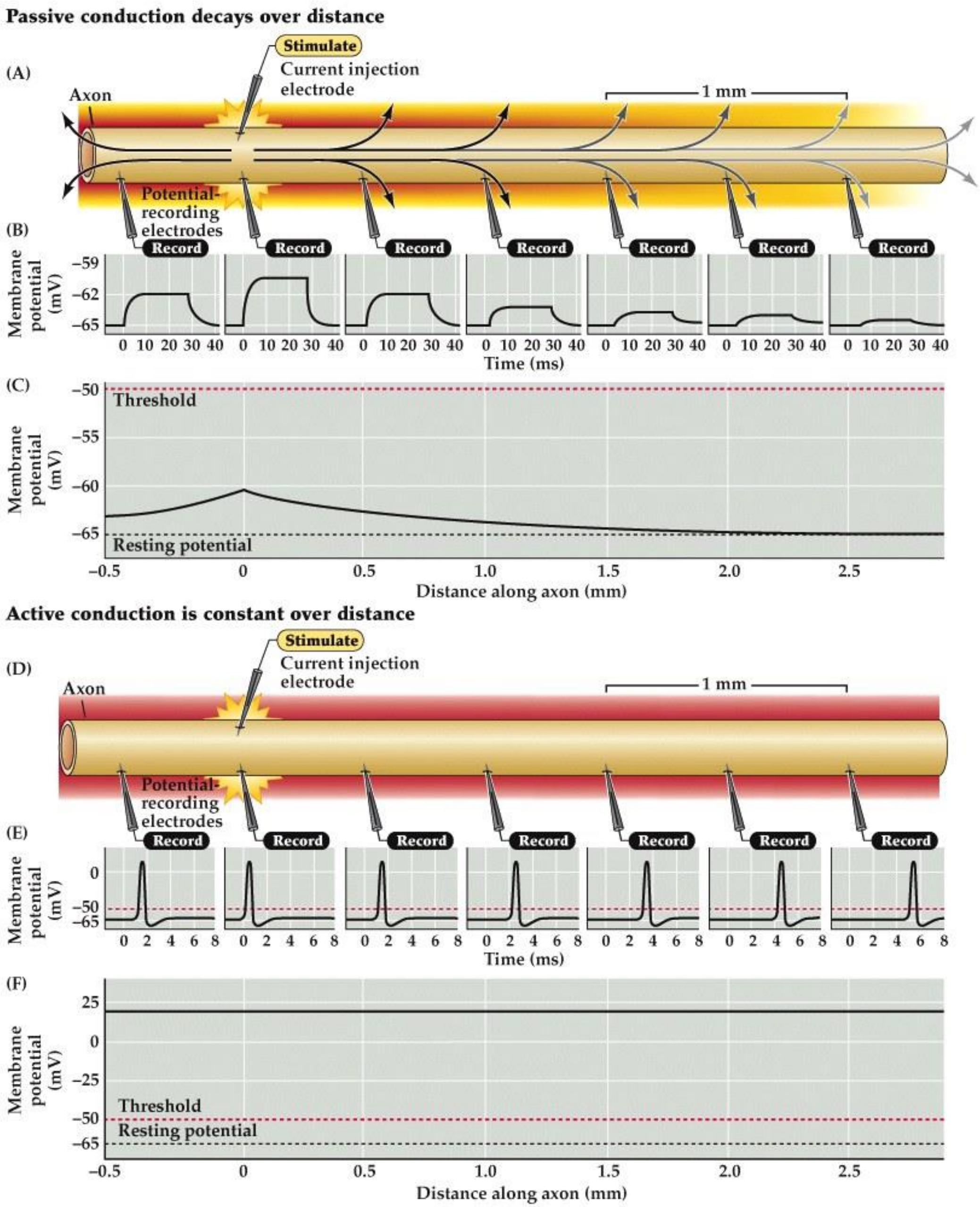
NEUROSCIENCE 5e, Box 2A (Part 3)



NEUROSCIENCE 5e, Box 2A (Part 2)

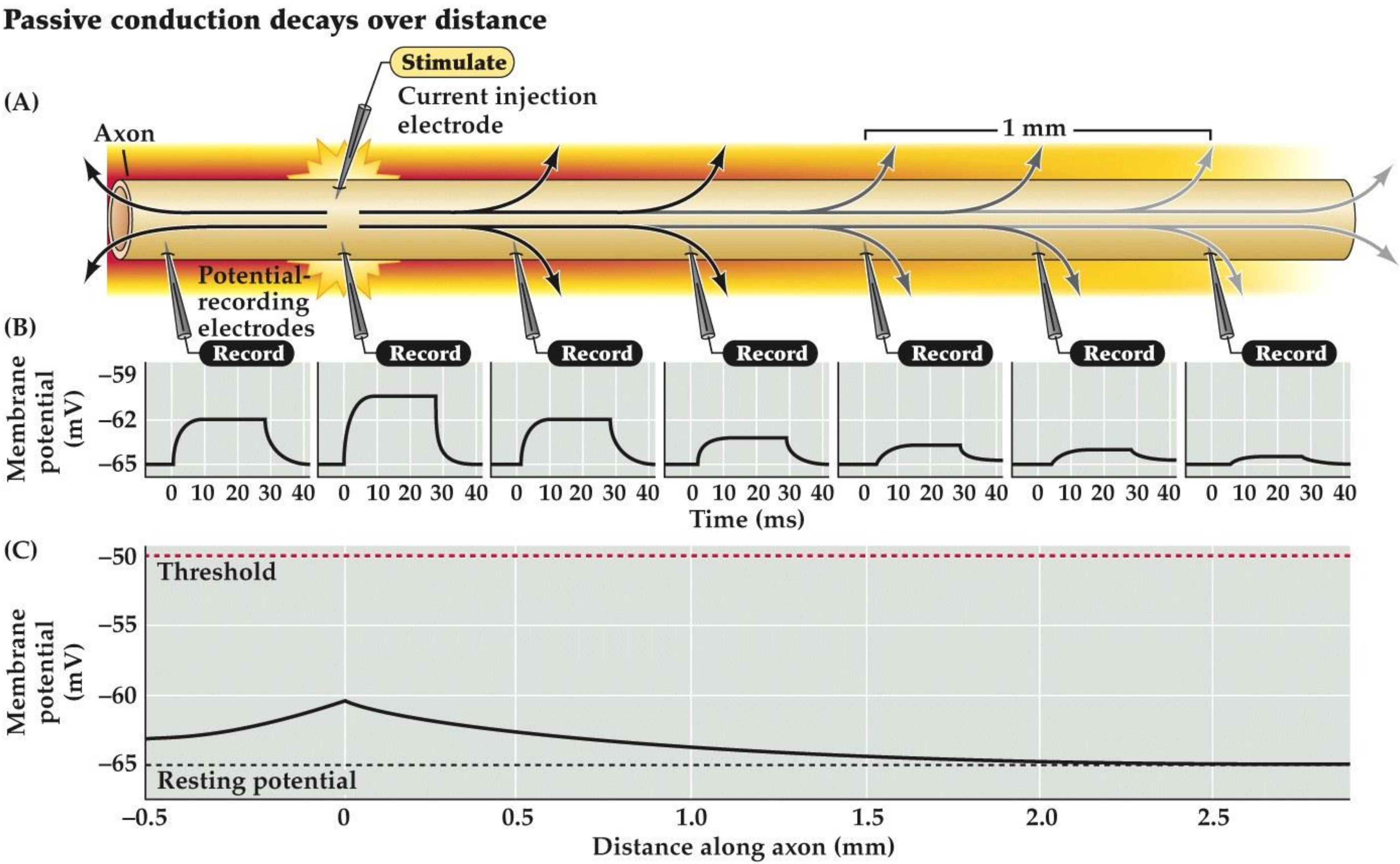
How do passive and active membrane properties compare?

Figure 2.3 Passive and active current flow in an axon



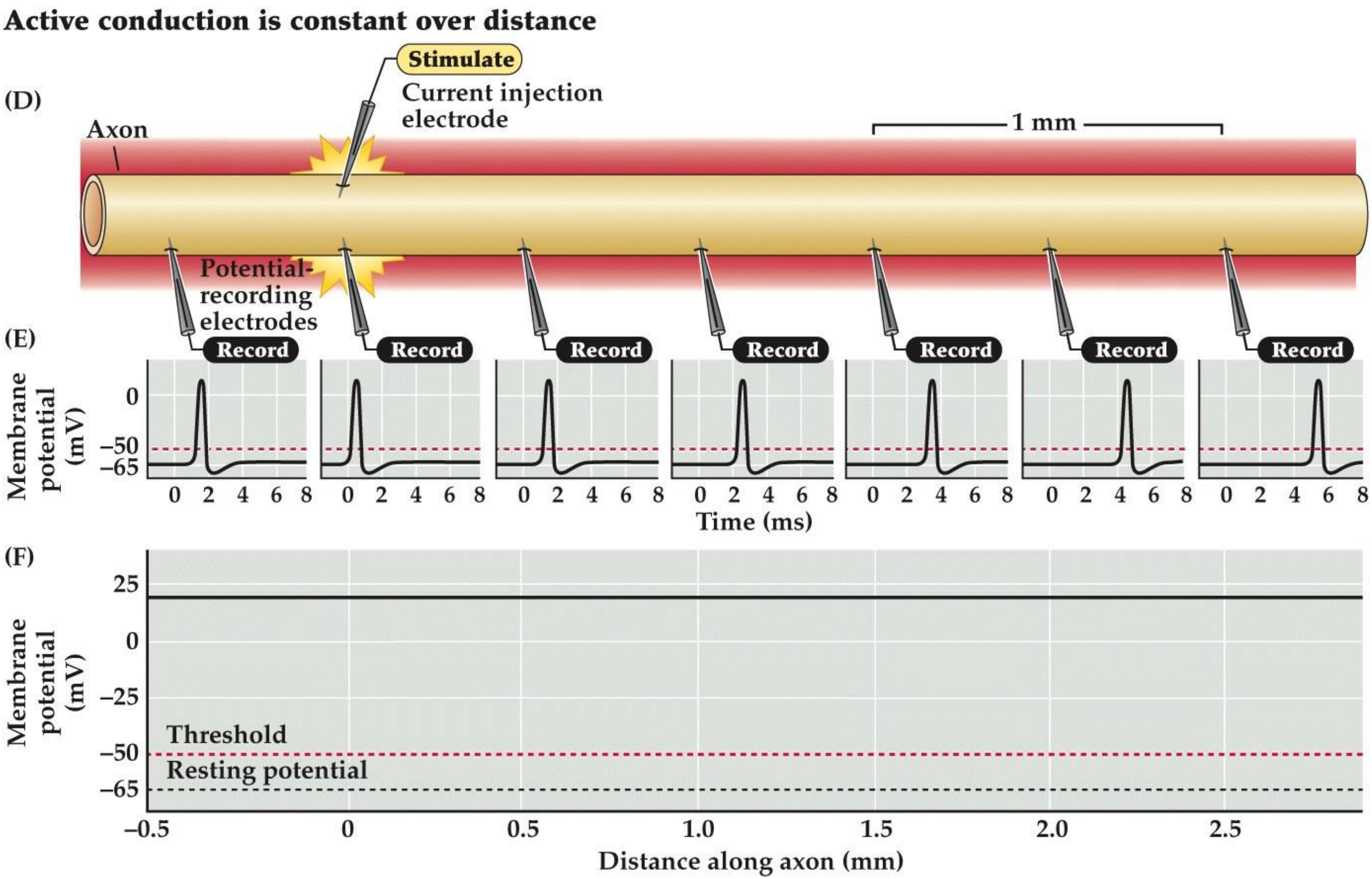
NEUROSCIENCE 5e, **Figure 2.3**

Figure 2.3 Passive and active current flow in an axon (Part 1)



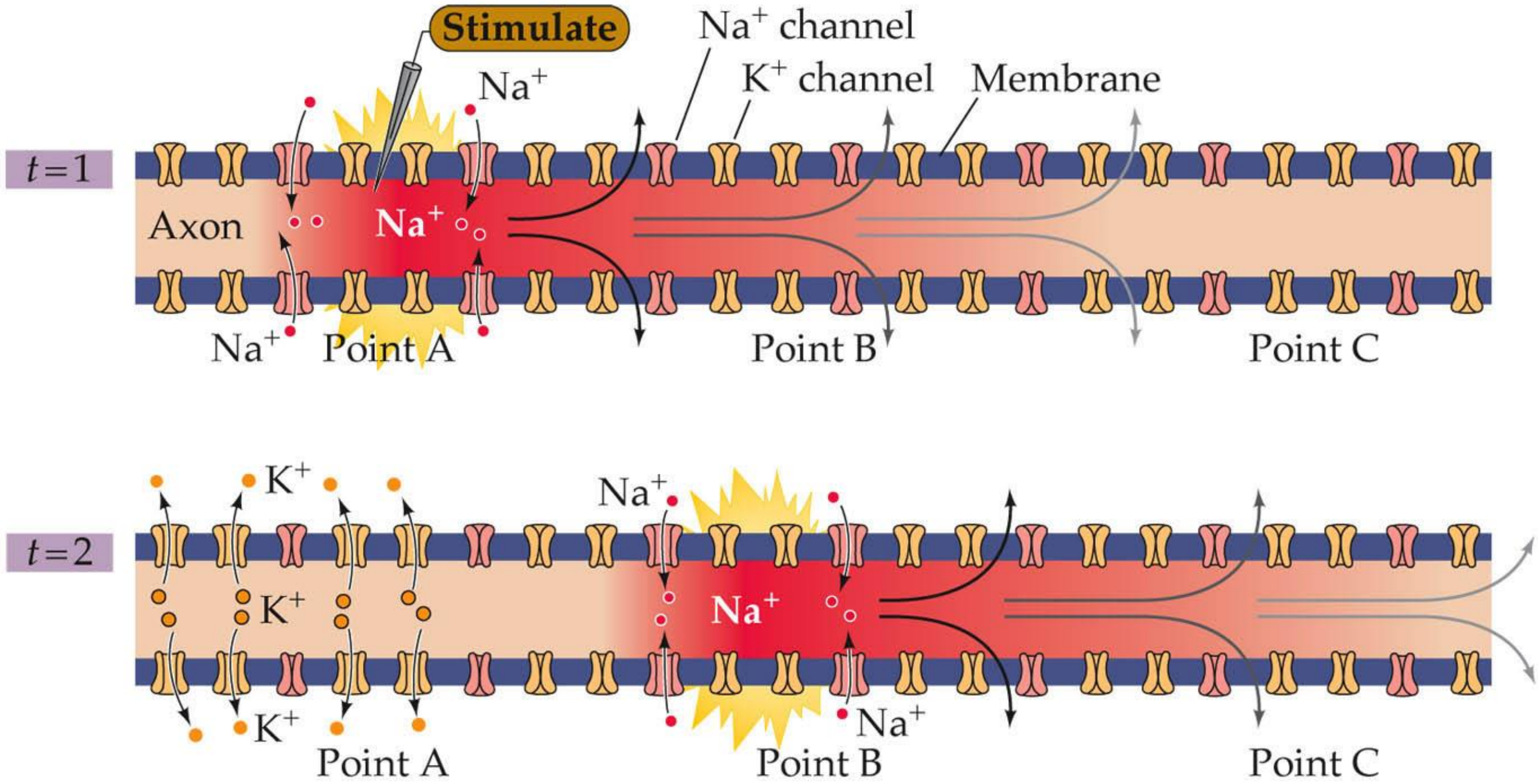
***NEUROSCIENCE 5e*, Figure 2.3 (Part 1)**

Figure 2.3 Passive and active current flow in an axon (Part 2)

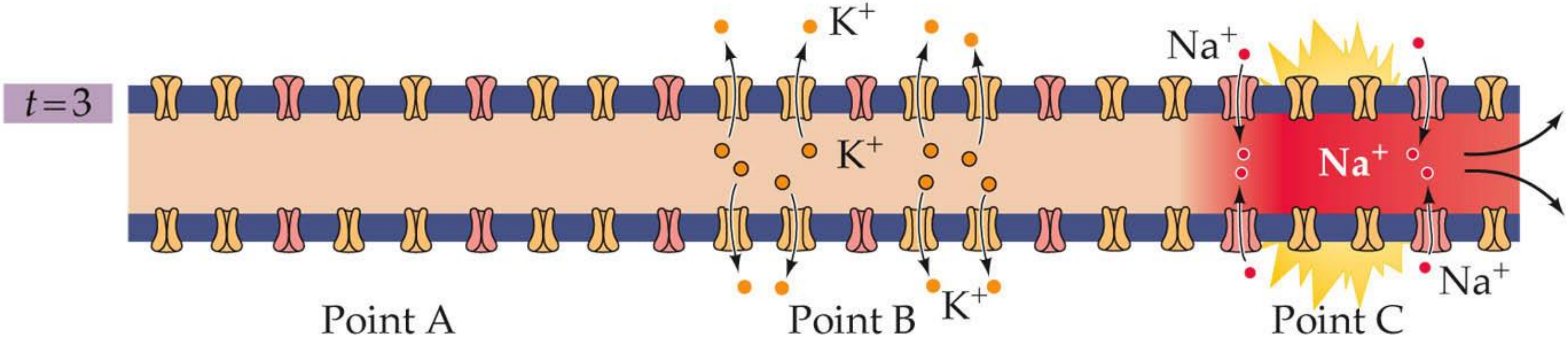


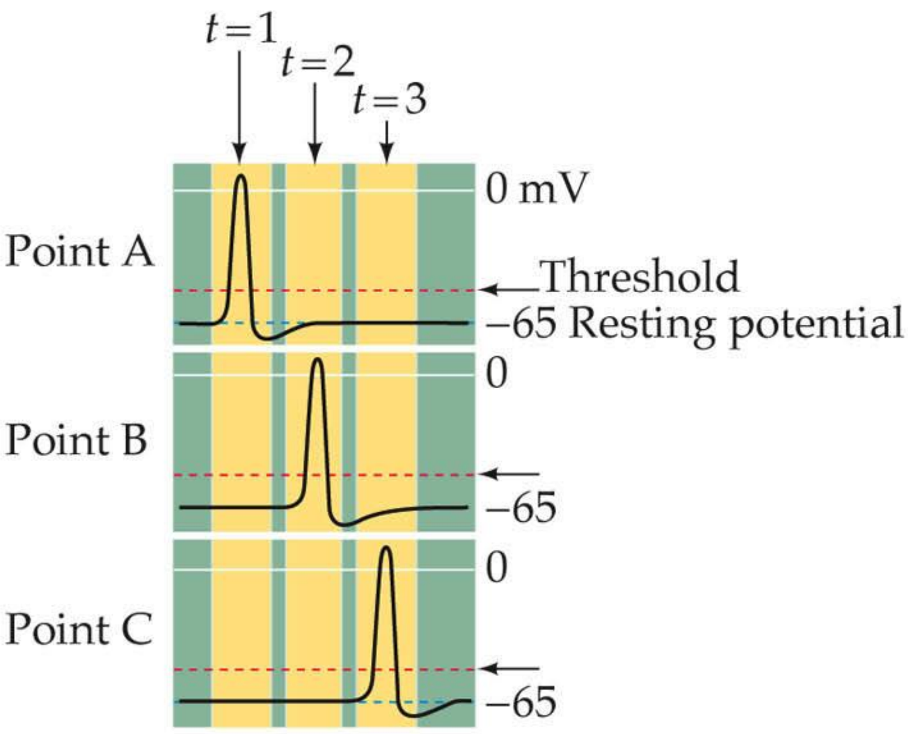
NEUROSCIENCE 5e, **Figure 2.3 (Part 2)**

Action potential conduction requires both active and passive current flow. (Part 1)

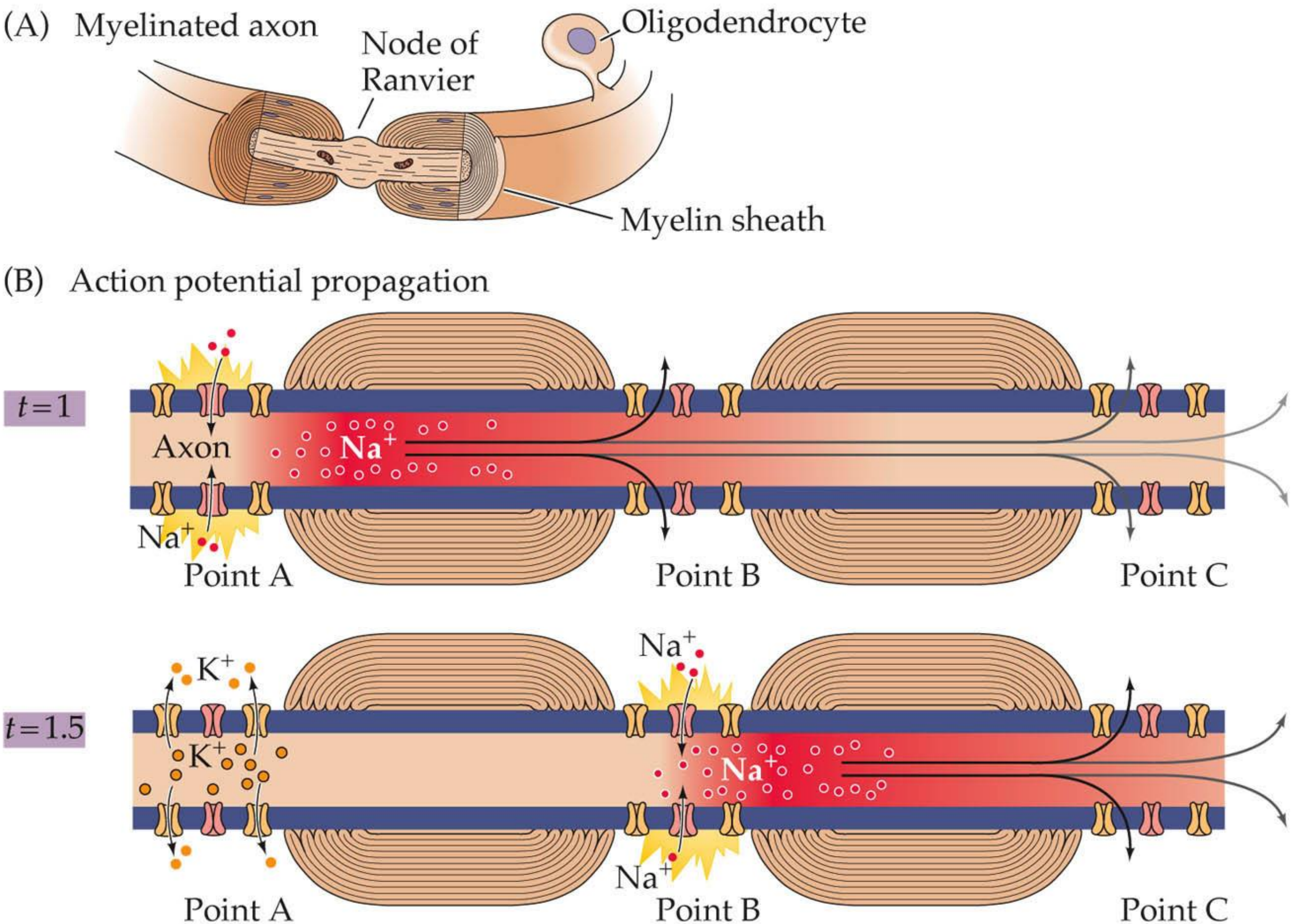


Action potential conduction requires both active and passive current flow. (Part 2)

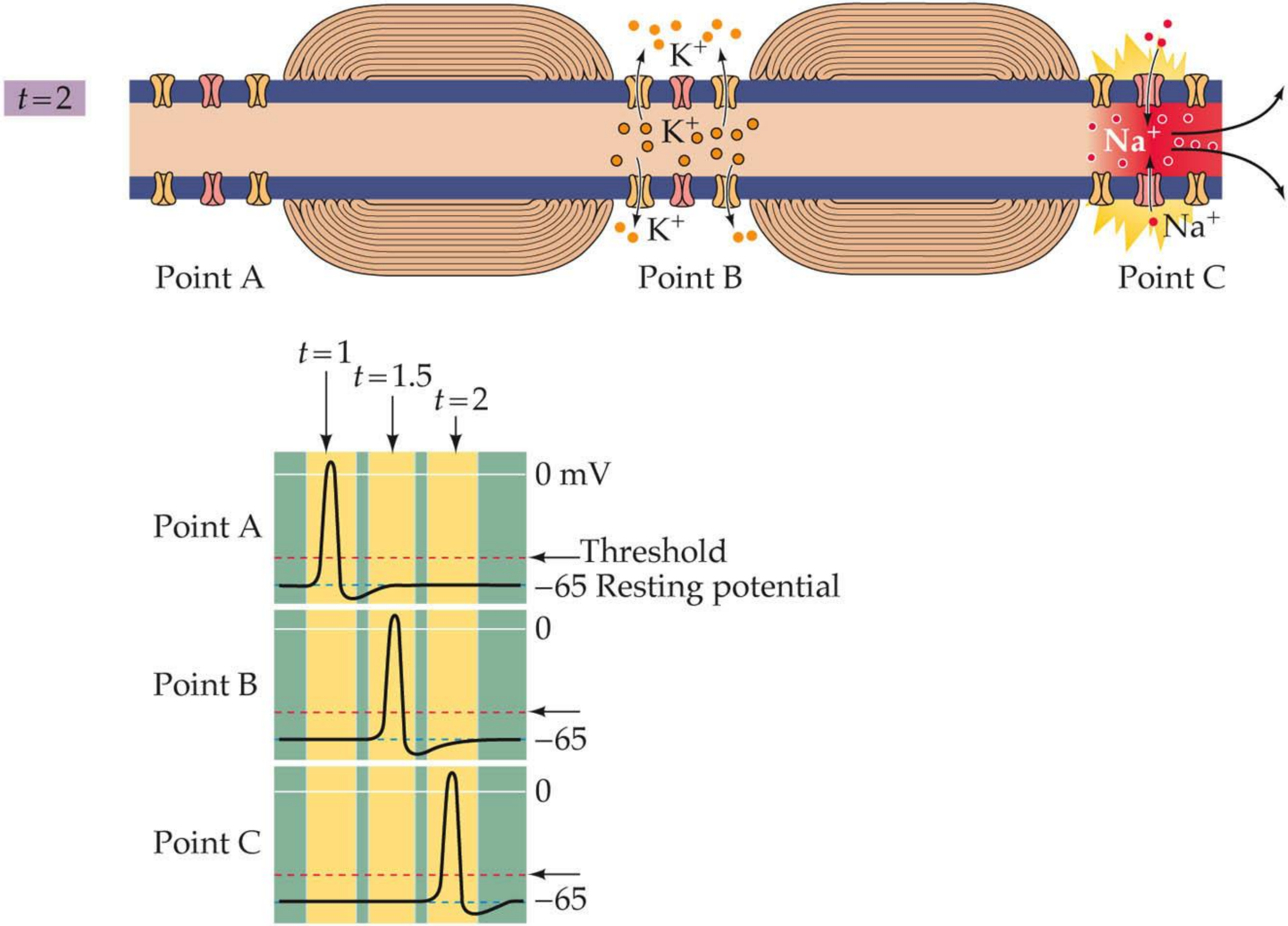




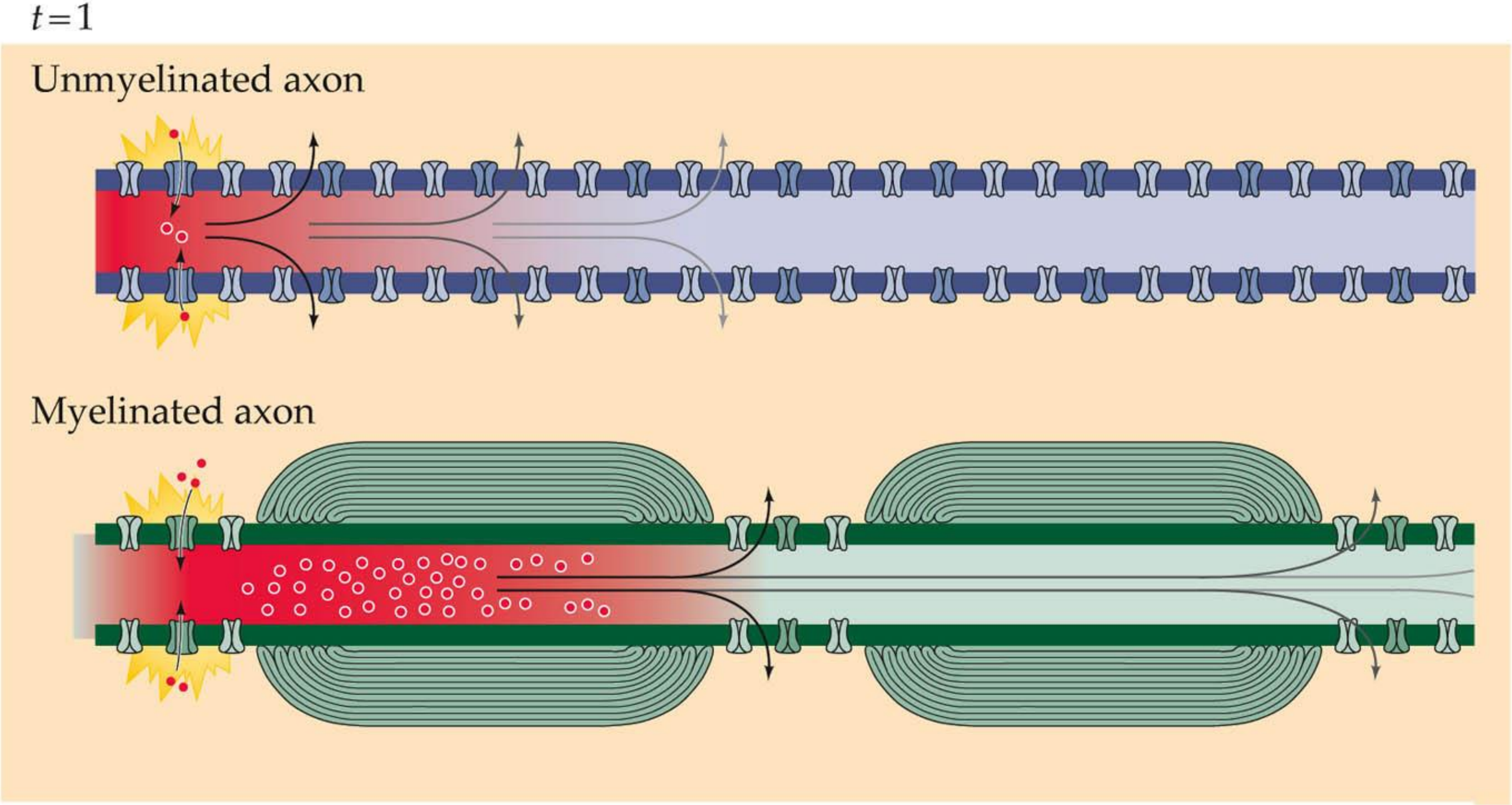
3.13 Saltatory action potential conduction along a myelinated axon. (Part 1)



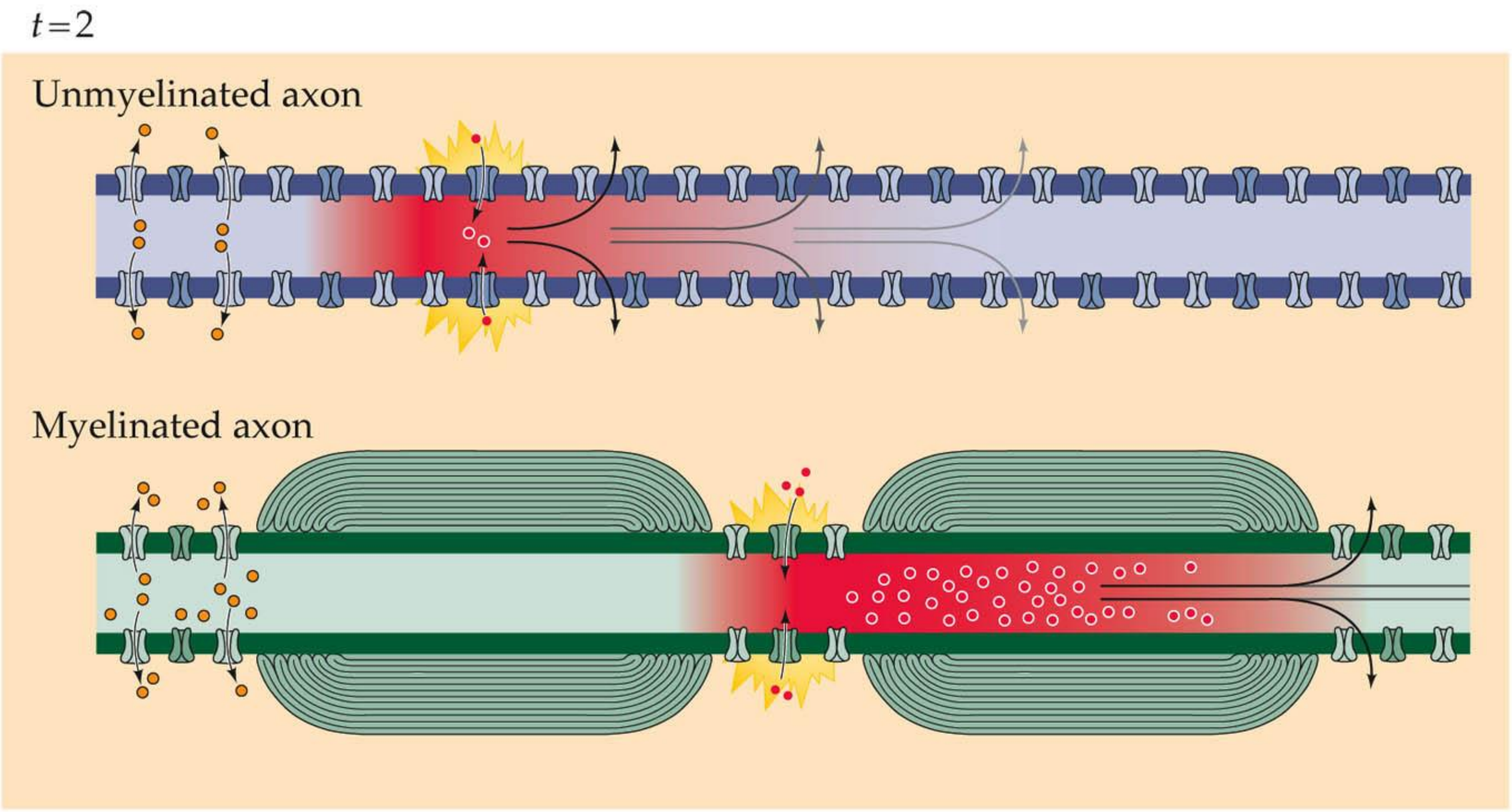
Saltatory action potential conduction along a myelinated axon. (Part 2)



Speed of action potential conduction in unmyelinated and myelinated axons. (Part 1)

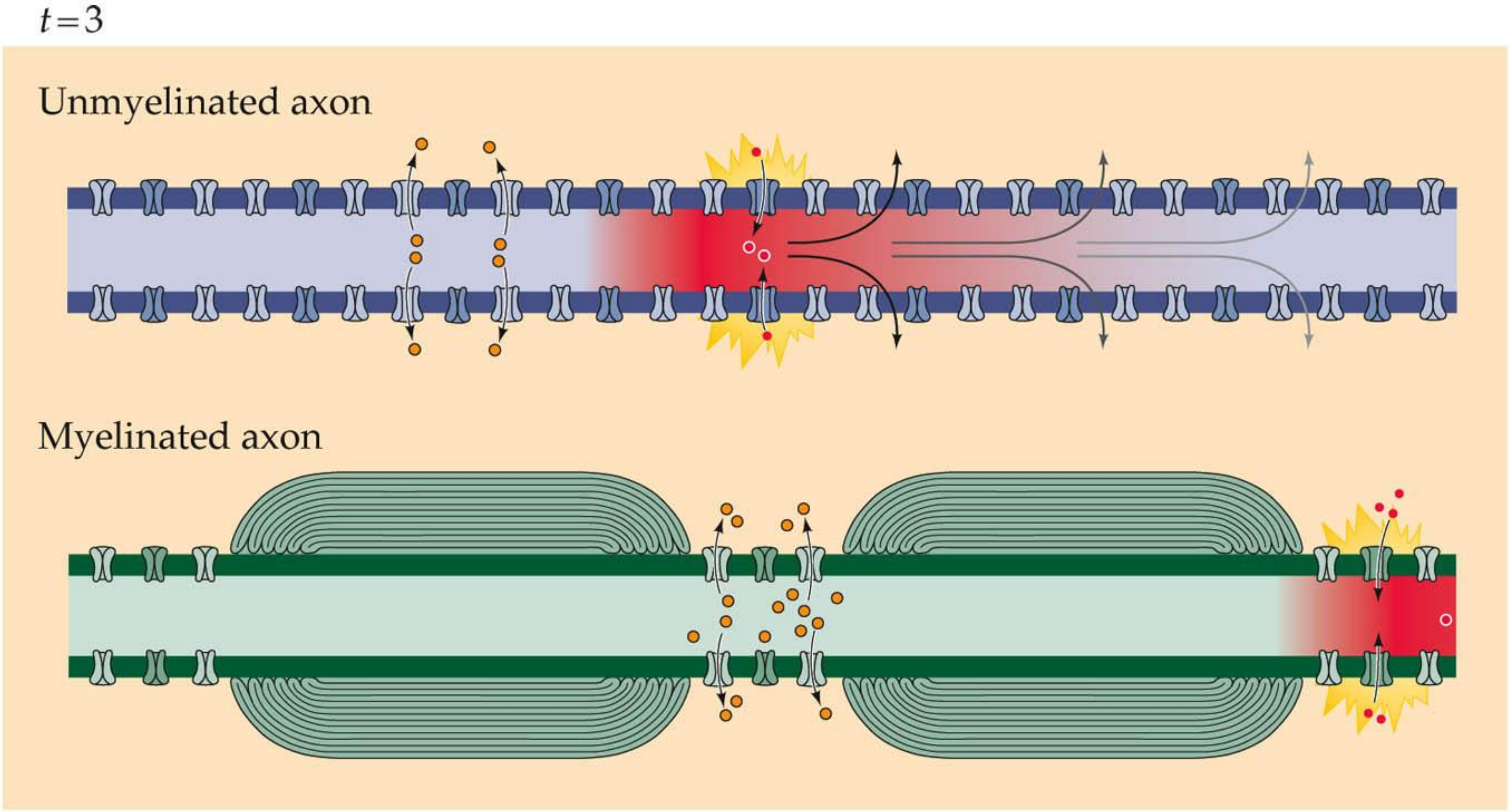


Speed of action potential conduction in unmyelinated and myelinated axons. (Part 2)

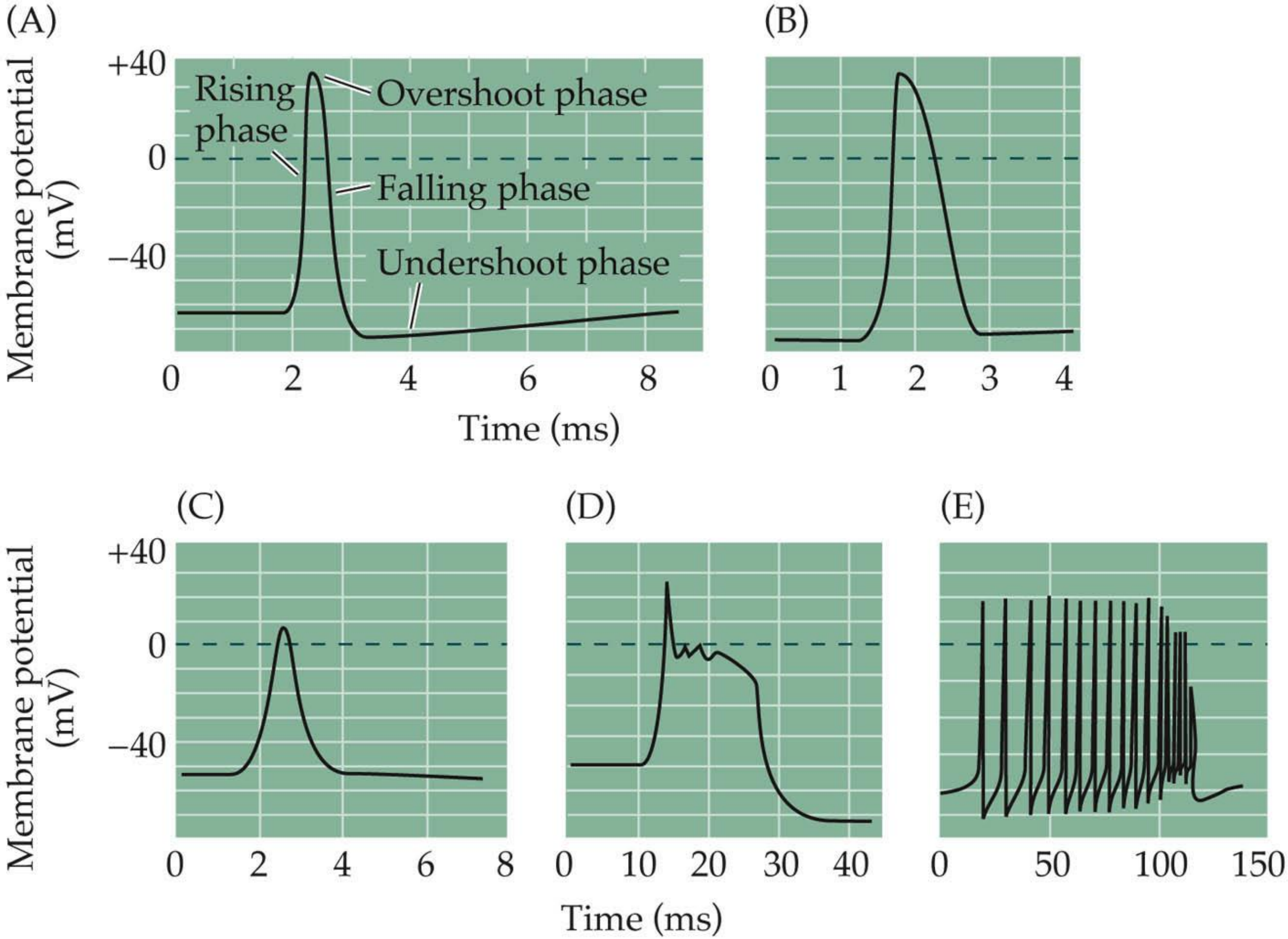


NEUROSCIENCE, Third Edition, Figure 3.14 (Part 2)

Speed of action potential conduction in unmyelinated and myelinated axons. (Part 3)

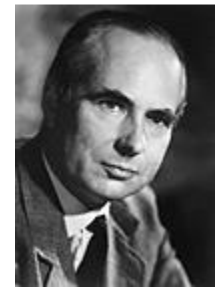


Box B Action Potential Form and Nomenclature



"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

The Nobel Prize in Physiology or Medicine 1963



Sir John Carew Eccles

1/3 of the prize

Australia

Australian National University
Canberra, Australia

b. 1903
d. 1997

Alan Lloyd Hodgkin

1/3 of the prize

United Kingdom

University of Cambridge
Cambridge, United Kingdom

b. 1914
d. 1998

Andrew Fielding Huxley

1/3 of the prize

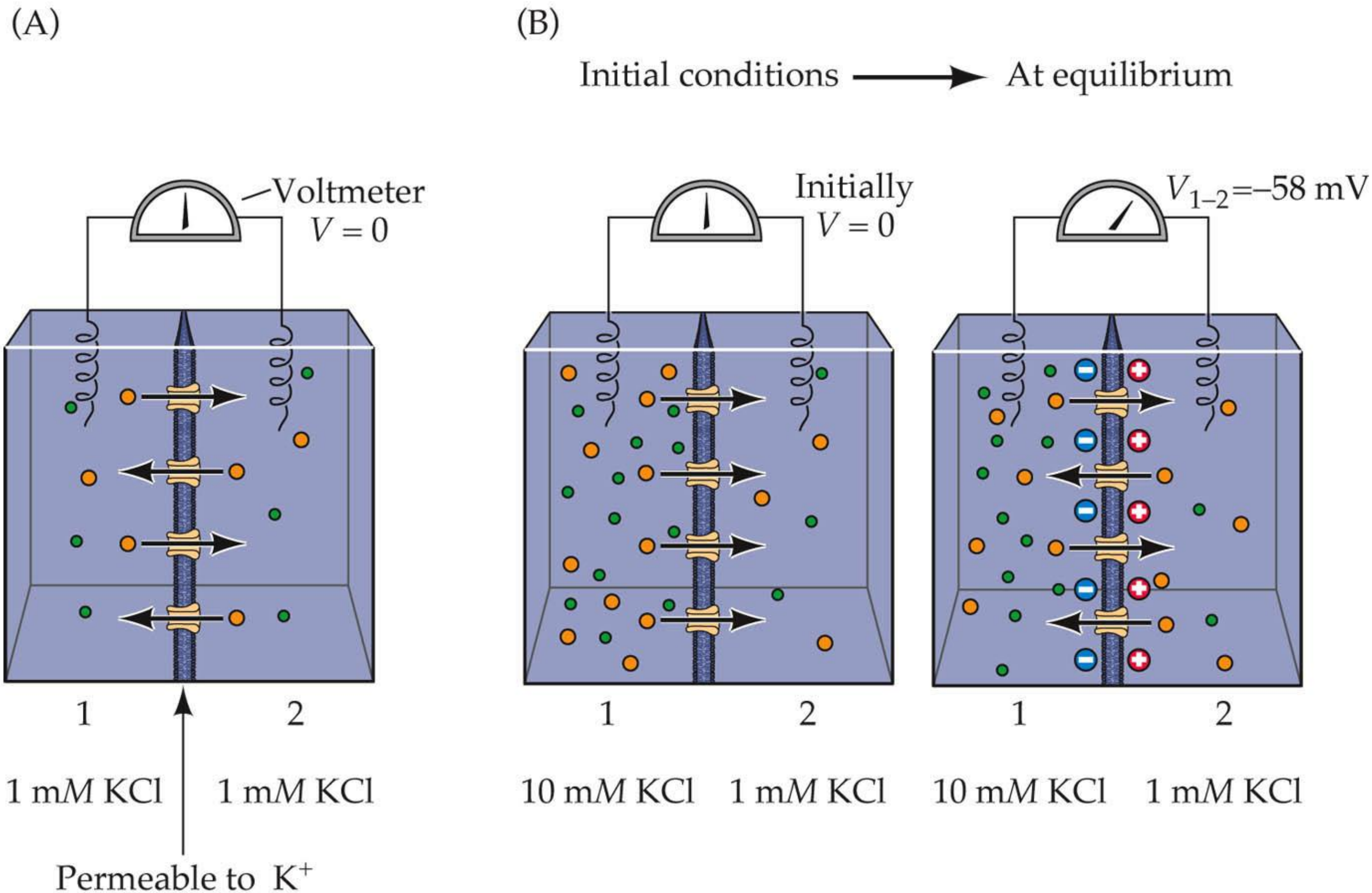
United Kingdom

London University
London, United Kingdom

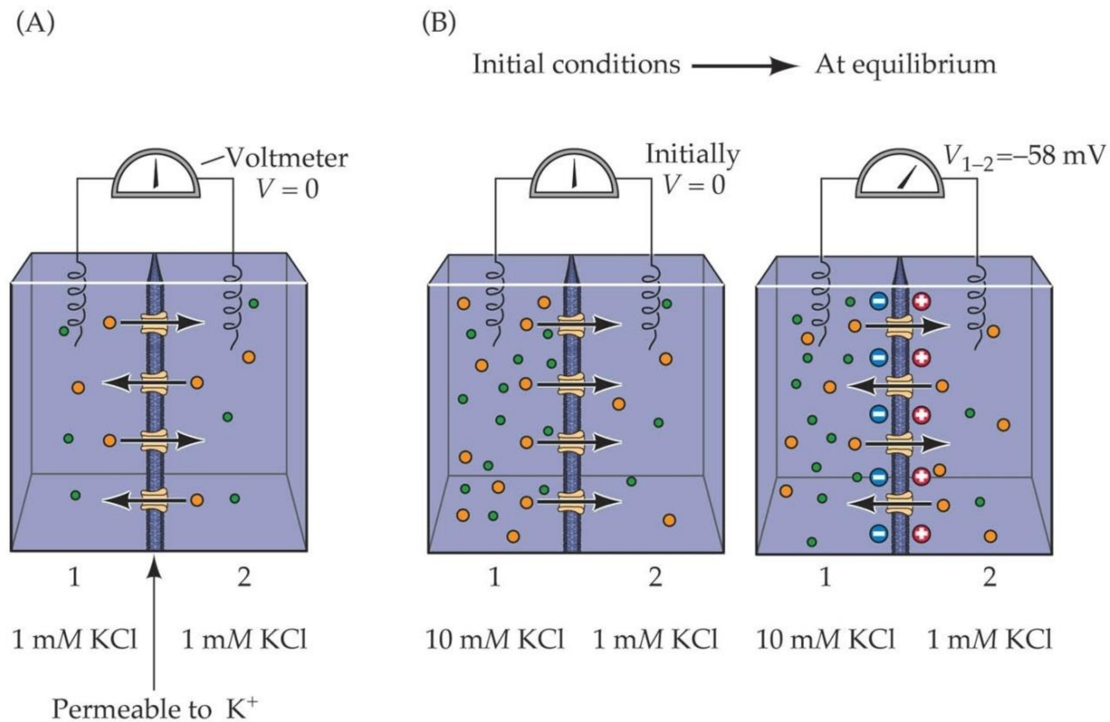
b. 1917

Supplementary slides

Electrochemical equilibrium. (Part 1)



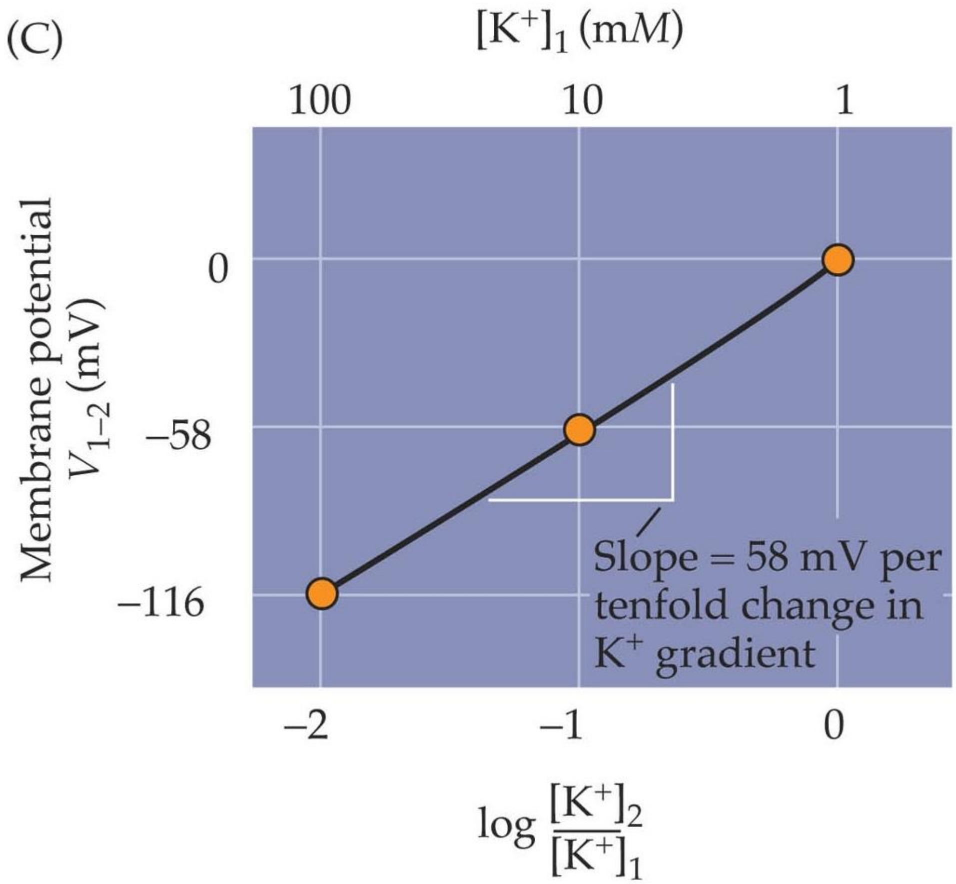
Electrochemical equilibrium potential: Why do cells have negative resting membrane potentials?



- In (A), the membrane separating compartments 1 and 2 is permeable only to K^+ (yellow spheres). Note equal concentrations of K^+. No net flux occurs, and potential difference between the two compartments is 0.

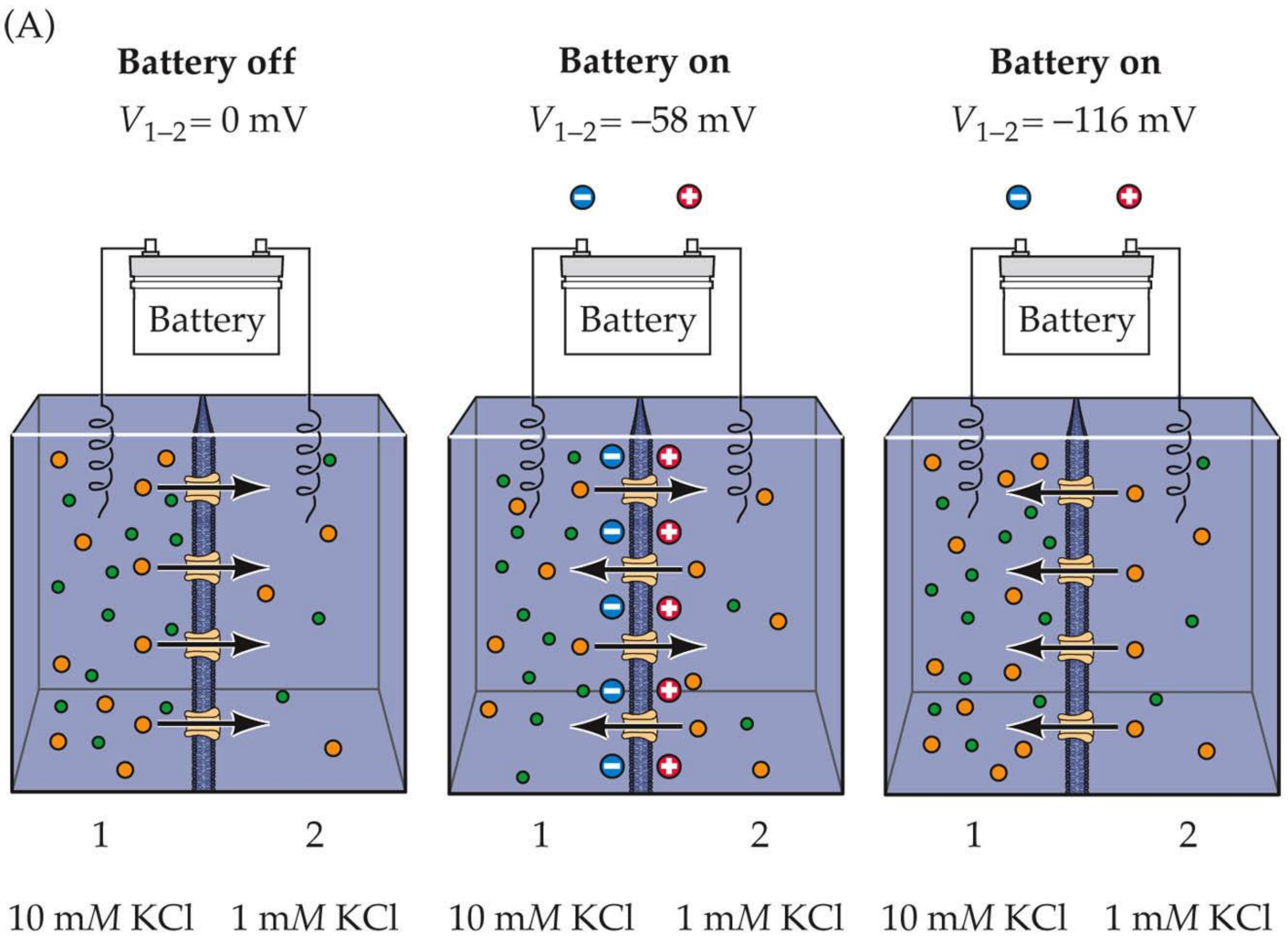
- In (B), with a higher concentration of K^+ in compartment 1, K^+ flows down its concentration gradient, leaving behind unpaired Cl^- anions. A potential difference between compartments 1 and 2 arises. K^+ flux continues until the electrochemical force balances the concentration gradient. Net flux eventually becomes 0, though individual K^+ ions will continue to drift across.

The Nernst equation predicts the relationship between the transmembrane concentration gradient ($[K^+]_2/[K^+]_1$) and the membrane potential

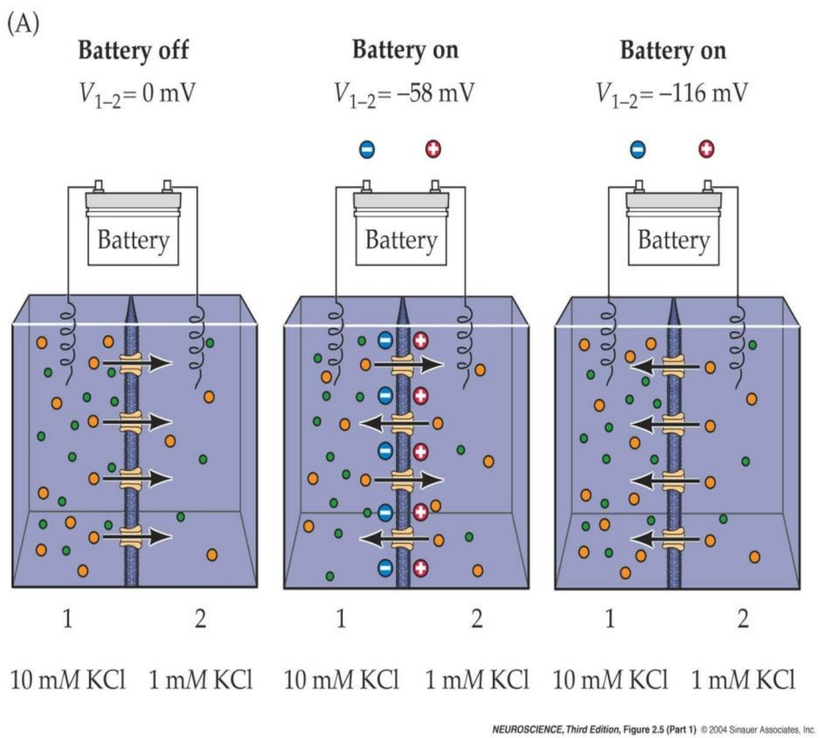


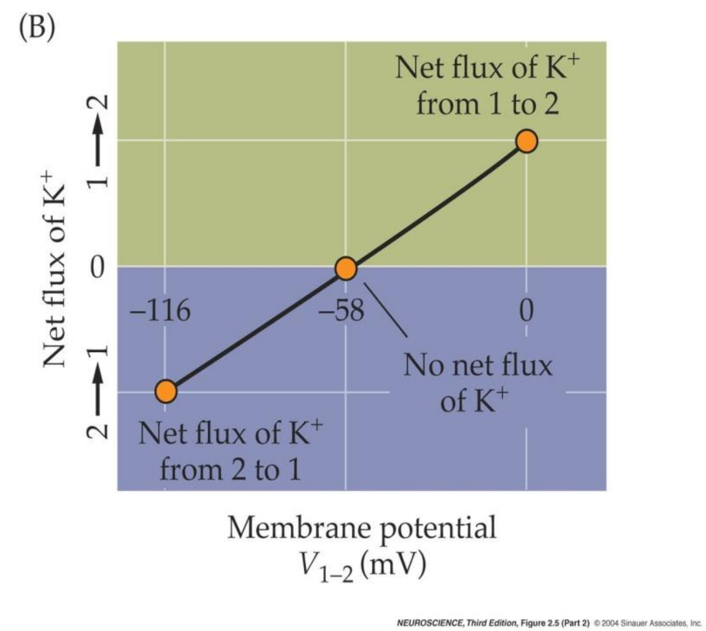
- As predicted by the Nernst equation, this relationship is linear when plotted on semi-logarithmic coordinates, with a slope of 58 mV (at 20 C) per tenfold difference in the concentration gradient.

Membrane potential influences ion fluxes. (Part 1)



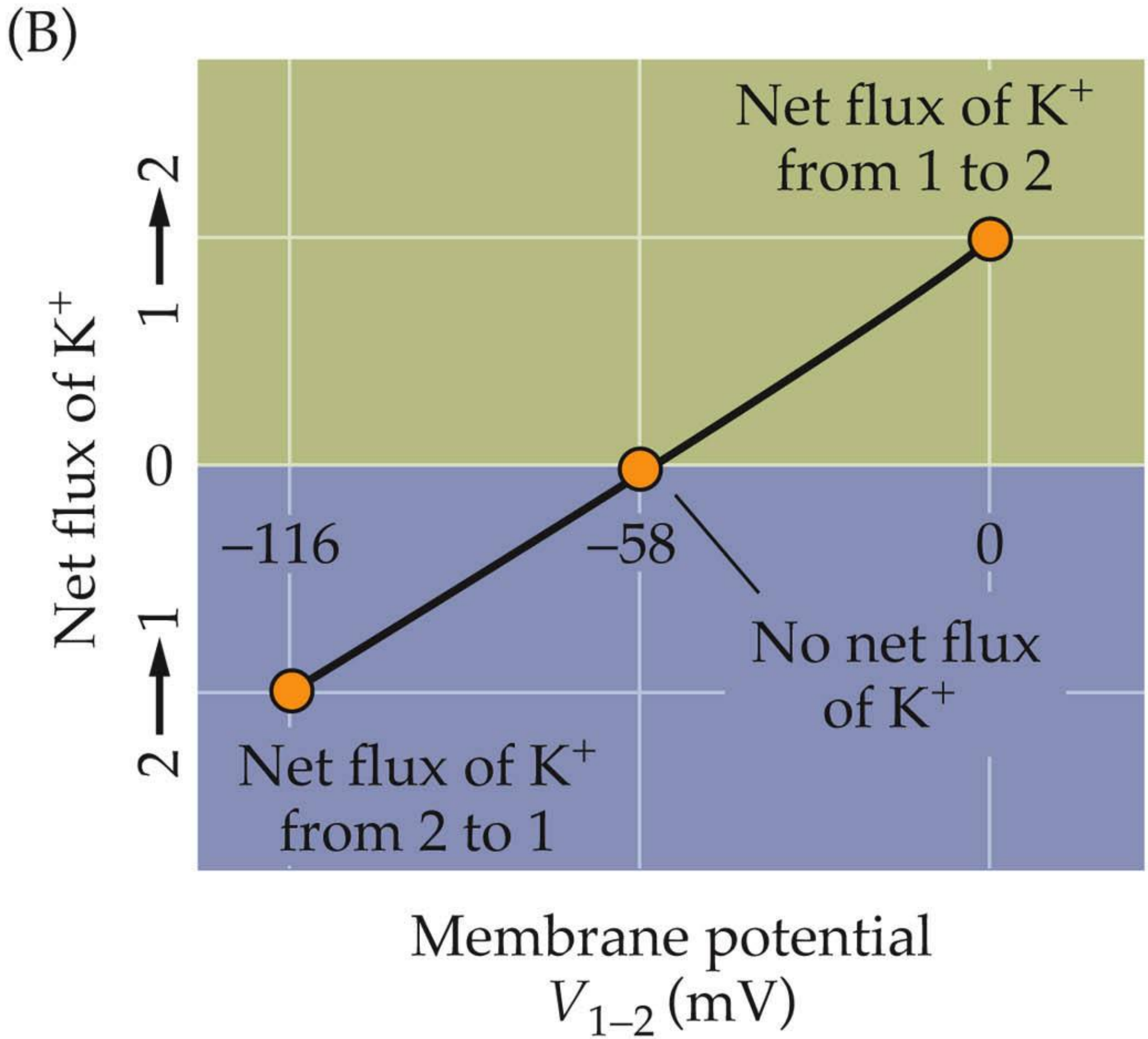
Membrane potential influences ion fluxes



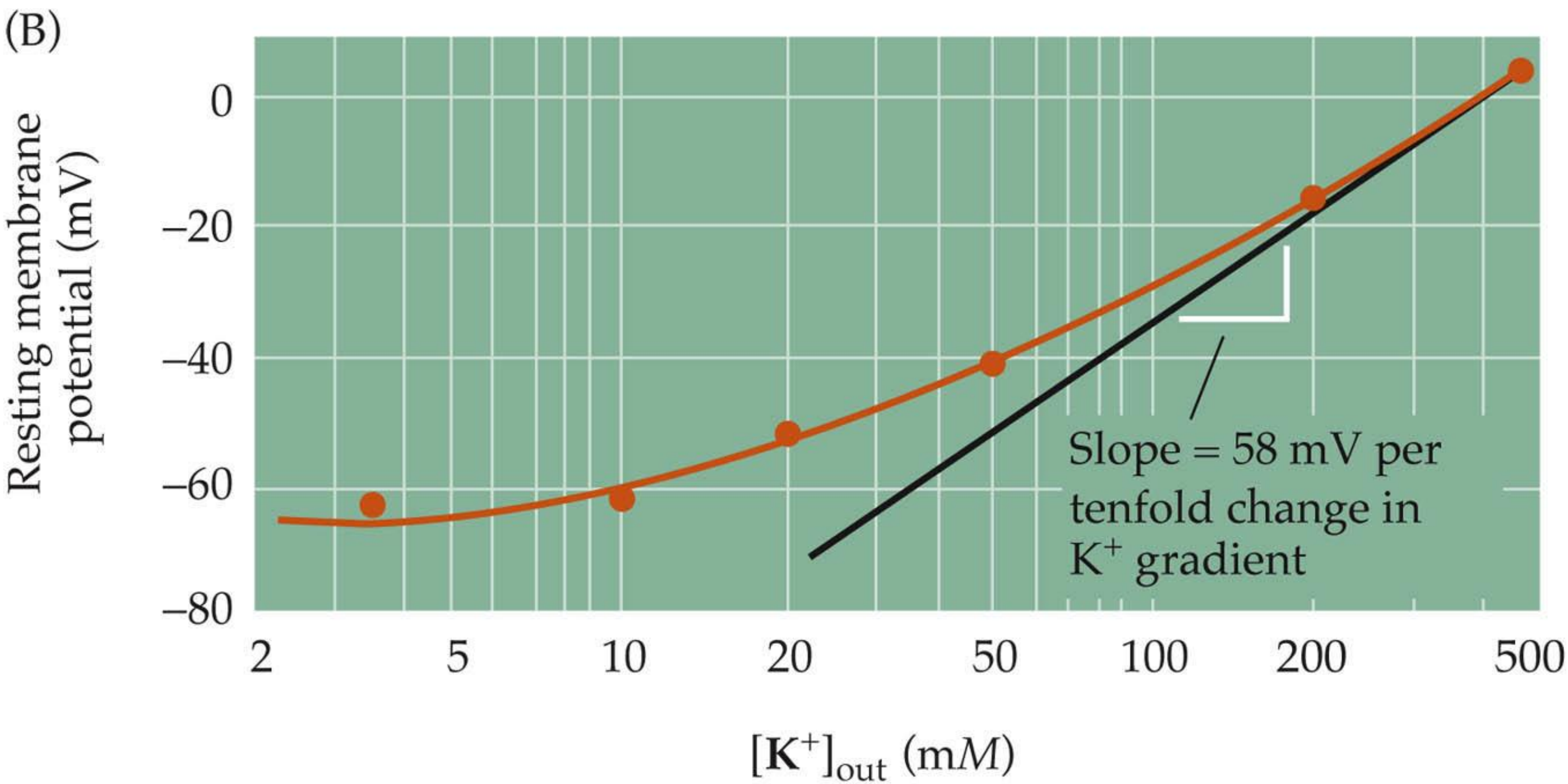


- (A). Connecting a battery across the K^+-permeable barrier membrane allows direct control of membrane potential. When battery is off (left), K^+ ions (yellow) flow according to their concentration gradient.
- Turning the battery on so that the initial membrane potential (V_1-V_2) equals the membrane potential (center), yields no net flux of K^+.
- Making the membrane potential more negative than the K^+equilibrium potential (right) causes K^+ to flow against its concentration gradient.
- (B) Relationship between membrane potential and direction of K^+ flux.

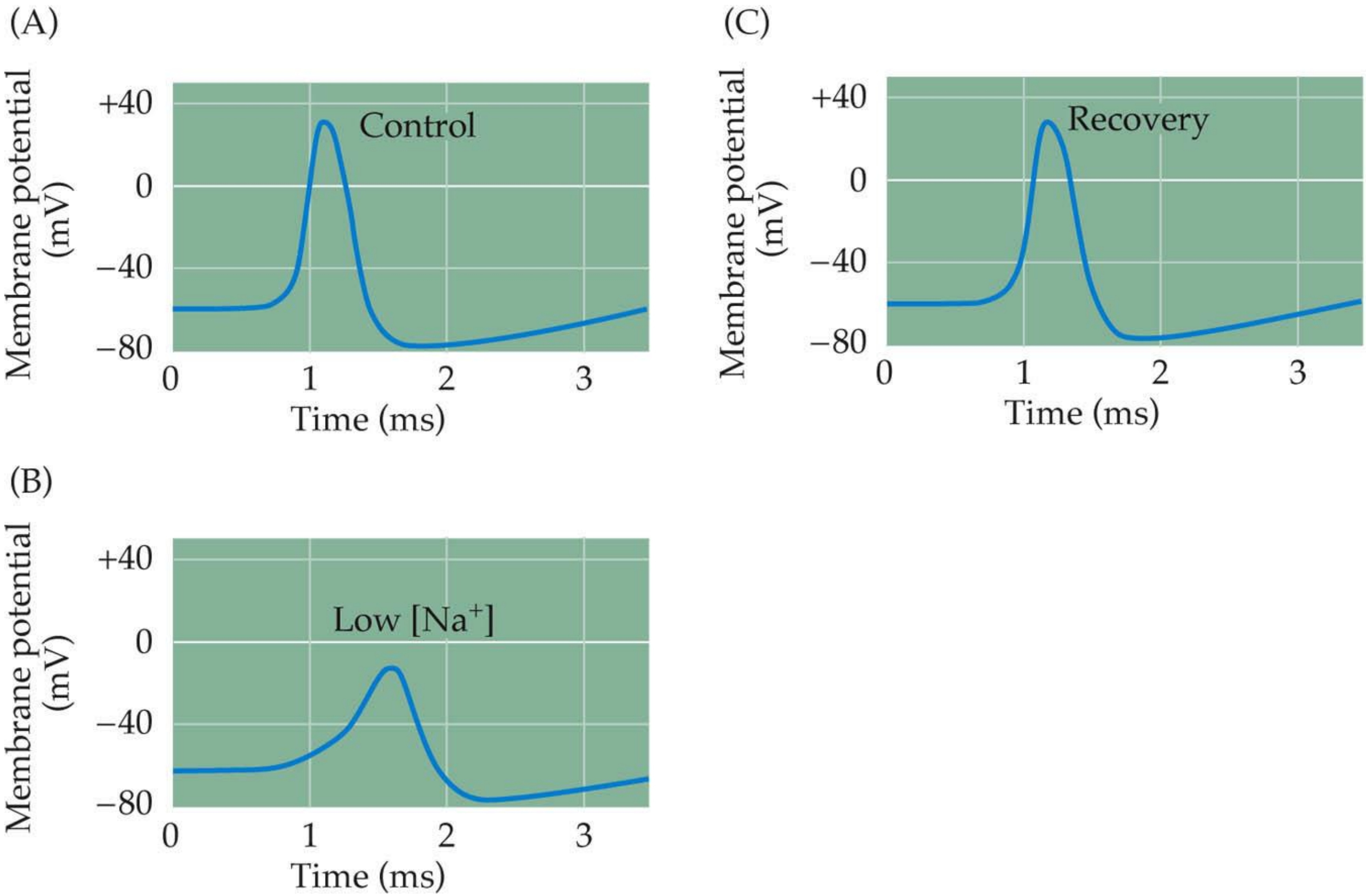
Membrane potential influences ion fluxes. (Part 2)



Evidence that the resting potential is determined by K^+ concentration gradient. (Part 2)



The role of sodium in the generation of an action potential. (Part 1)



NEUROSCIENCE, Third Edition, **Figure 2.8 (Part 1)**

The role of sodium in the generation of an action potential. (Part 2)