# Neuroscience 201A

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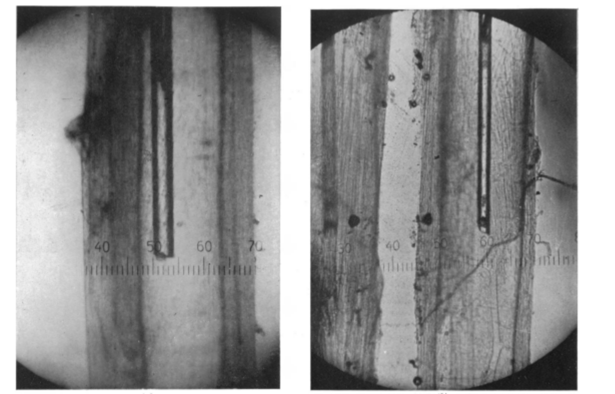
# Action Potentials – day 2

- Hodgkin and Huxley's analysis (briefly!)
  - Separation of currents
  - Activation and inactivation of sodium currents
  - modeling
- *Membrane* action potentials and *propagated* action potentials
- Gating current
- Threshold, why does it exist?
- Saltatory conduction

# From remarks made by Andrew Huxley on the occasion of his 90th birthday (2007)

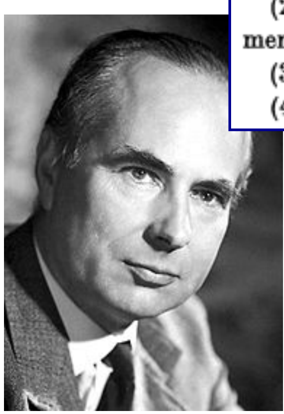
viscous liquid as we had supposed. Hodgkin saw that we could make use of this position of the fibre by pushing an electrode down from the top, so as to measure directly the potential difference between inside and outside. According to all the textbooks of the time, the interior of a fibre at rest was up to one-tenth of a volt negative relative to the external solution but rose to equality with the external potential at the peak of a nerve impulse. We confirmed this as regards the resting state, but the internal potential at the peak of the impulse was substantially positive. We published our result in a short letter to *Nature* with no discussion and no explanation. In 1945 we published a full-length paper in the *Journal of Physiology* with four possible explanations, all wrong. It was also in 1945 that we began discussing the correct explanation: the membrane becomes specifically permeable to sodium ions. These are about ten times more concentrated in the external solution than inside the fibre, so they diffuse inwards carrying their positive charge. This now

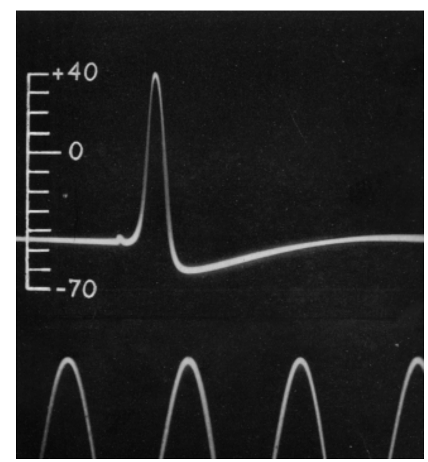



(a) (b)

Photomicrographs of electrodes inside giant axon. Adjacent tissues have not been completely removed from the giant fibre which shows as a clear space. One scale division equals 33 $\mu$. (*a*) Photomicrograph taken without double mirror device. (*b*) Photomicrograph taken with double mirror. The right-hand image is formed directly by the microscope, while the left-hand image is a side view seen in the small mirror.

(1) The active membrane becomes selectively permeable to anions which are present in the axoplasm, but are in low or zero concentration in sea water.
(2) Activity involves a change in the orientation of dipoles in the surface membrane.
(3) Explanation in terms of apparent membrane inductance.
(4) Series capacity hypothesis.






*500 Hz*

# HH – benefits from an internal axial wire and from voltage clamp

1. If internal axial resistance is ~0 (wire!), the inside is isopotential, and the action potential occurs everywhere at once (membrane action potential)
2. Voltage clamping allows one to study the effects of voltage upon conductance. Moreover, when
   $dV/dt=0$, there is no capacitative current (from $V=Q/C$ and $dV/dt=(1/C)\ dQ/dt$.

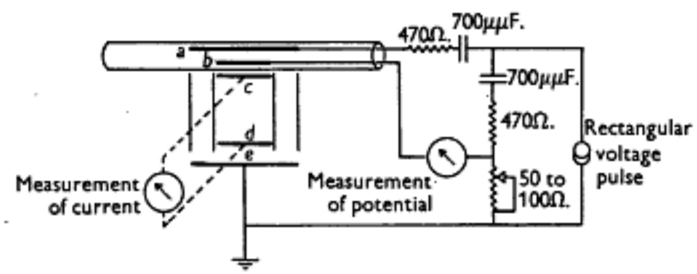
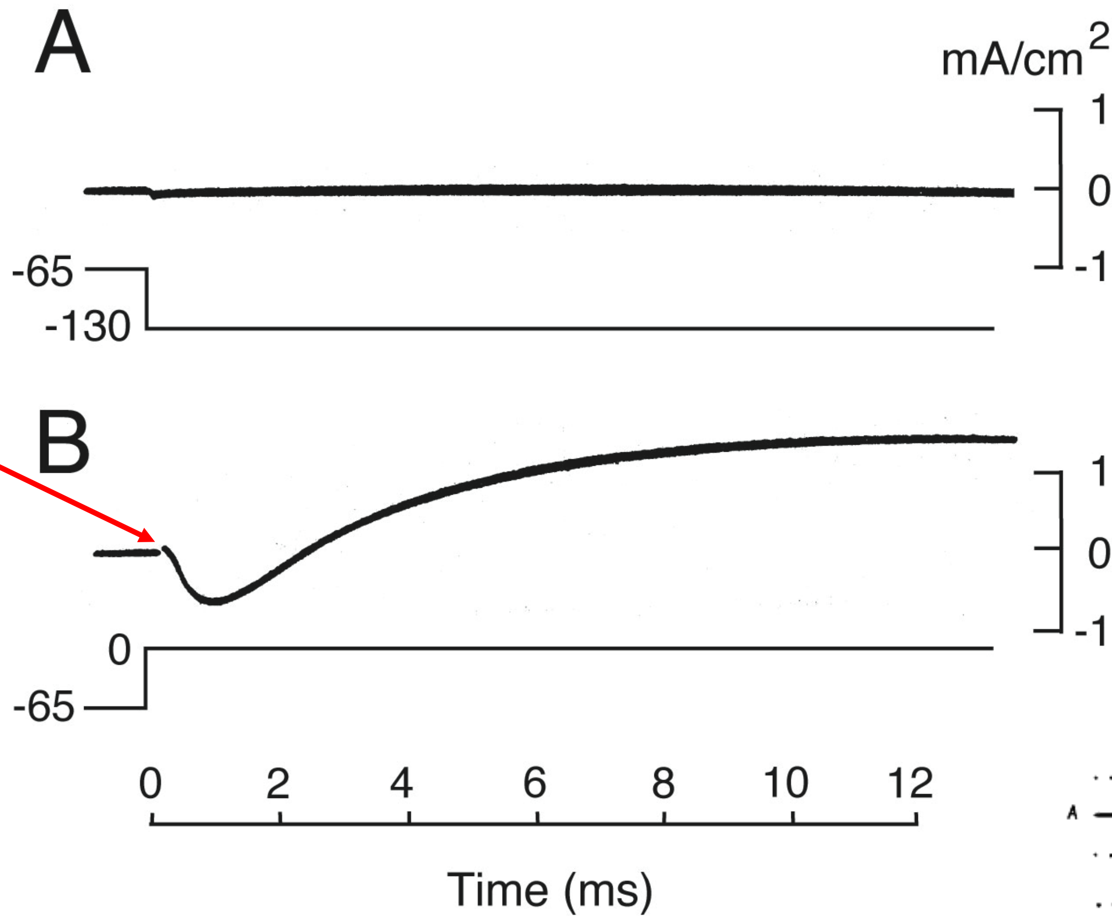


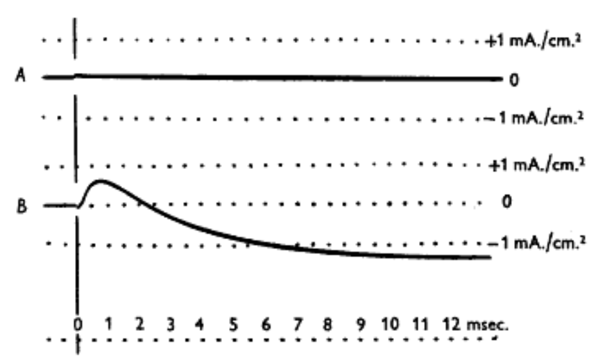

Fig. 7. Diagram of arrangement for recording response of membrane to short shock.

# HH - Strong depolarizations produce inward current followed by outward current

What is this small deflection in the current immediately after the step?

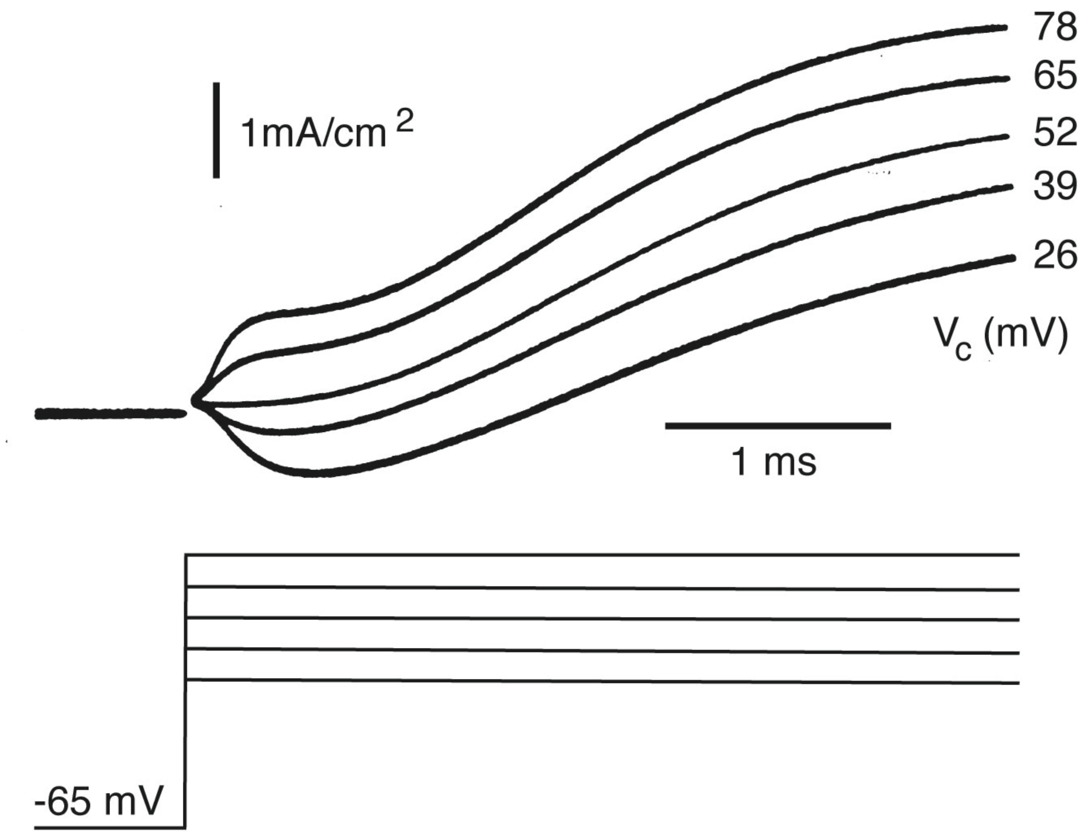



Original figure!!!




*Fain G (2014) Molecular and Cellular Physiology of Neurons. 2nd ed., Harvard Univ. Press.*

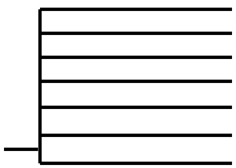
# The inward current reverses at about +50 mV



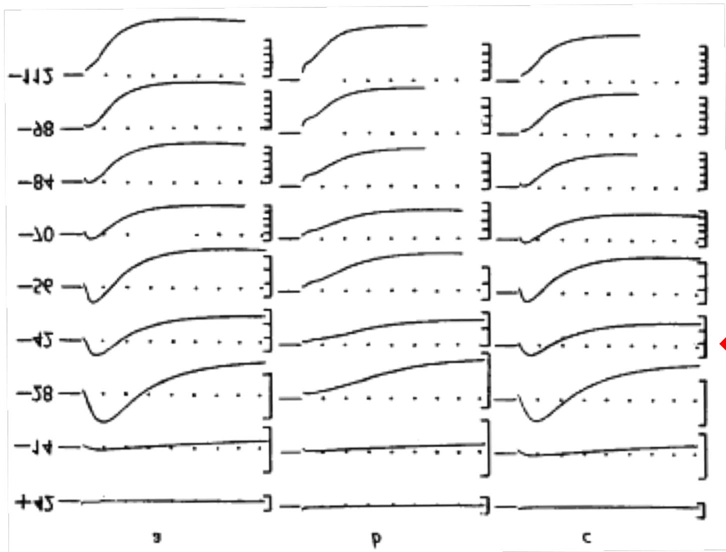

*Fain G (2014) Molecular and Cellular Physiology of Neurons. 2nd ed., Harvard Univ. Press.*

# HH - The inward current is carried by sodium

voltage

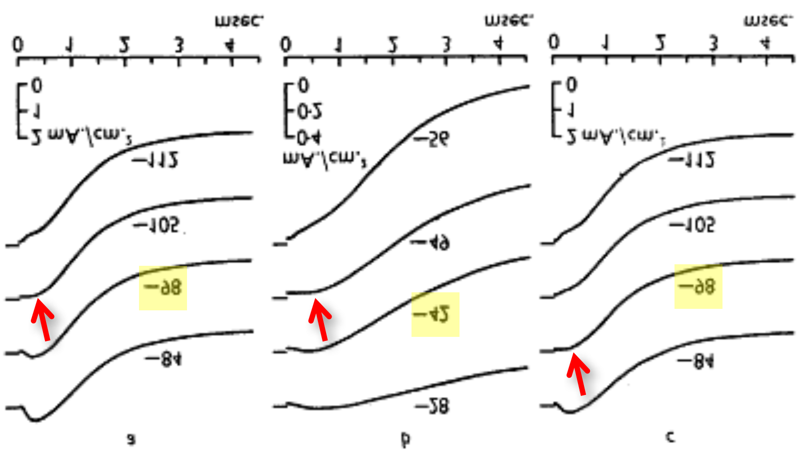


current



a. Sodium sea water
b. Choline sea water
c. Sodium sea water

Flipped from the original figures! The numbers refer to the mV of depolarization, not to the final value of V.

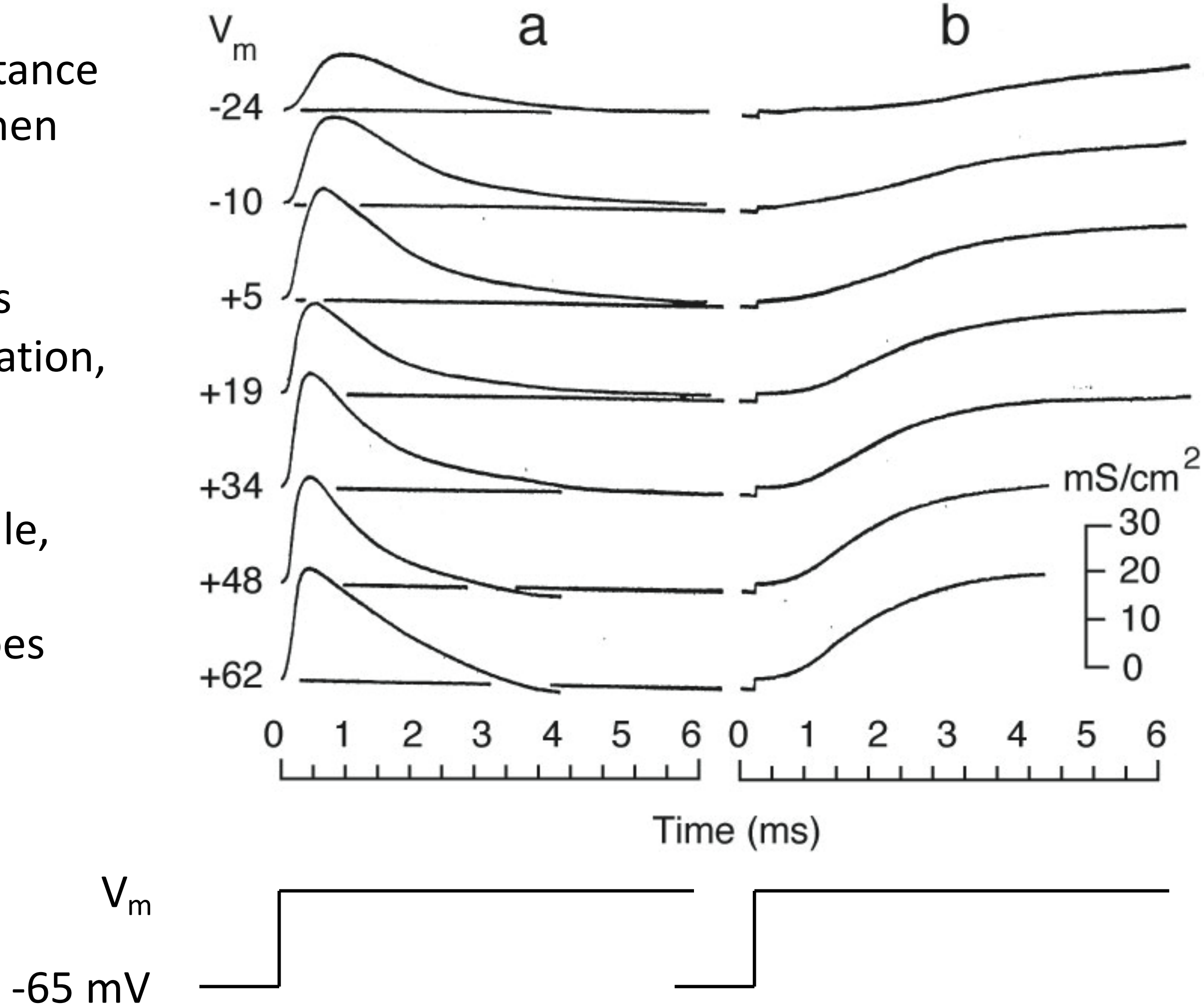


a. Sodium sea water
b. 10% Sodium sea water
c. Sodium sea water

# HH - Separation into sodium and potassium conductances

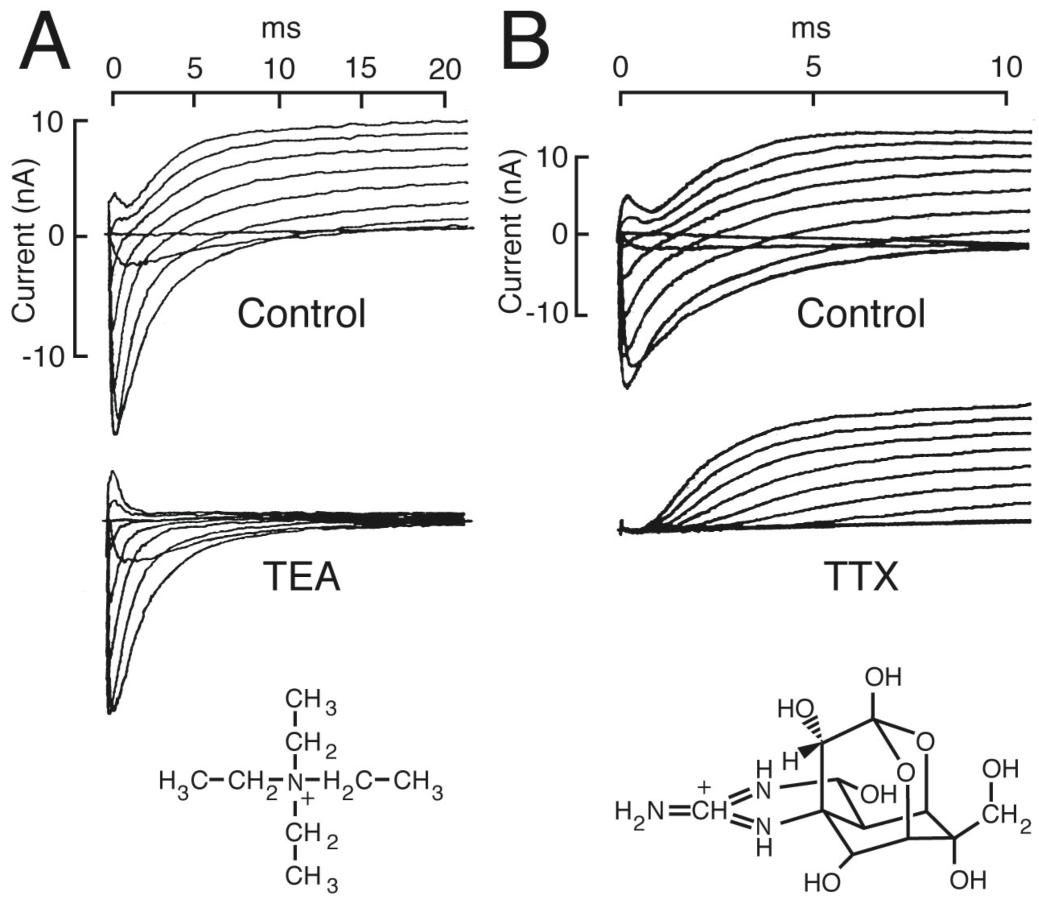
Sodium conductance increases and then increases, even though the depolarization is sustained (activation, inactivation)

On this time scale, potassium conductance does not inactivate

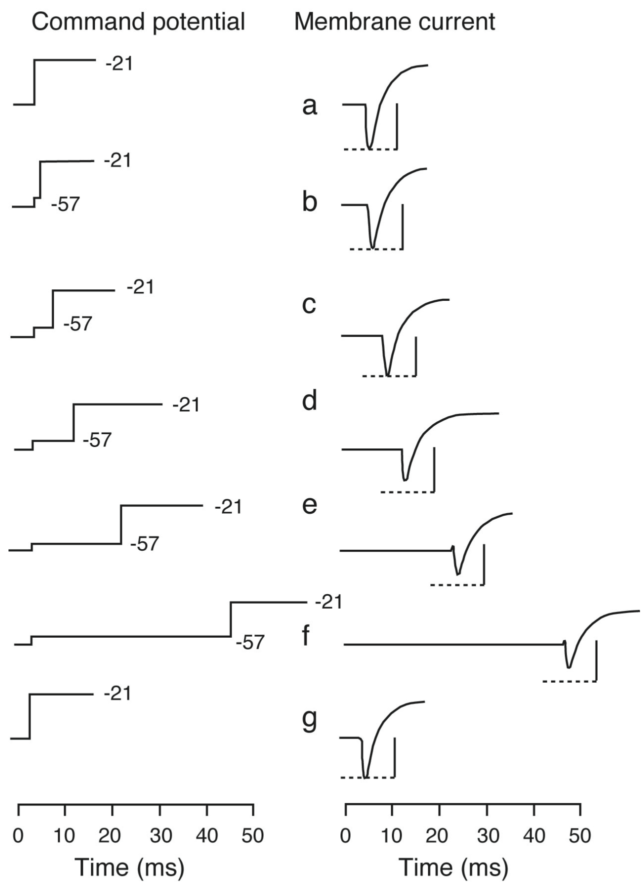


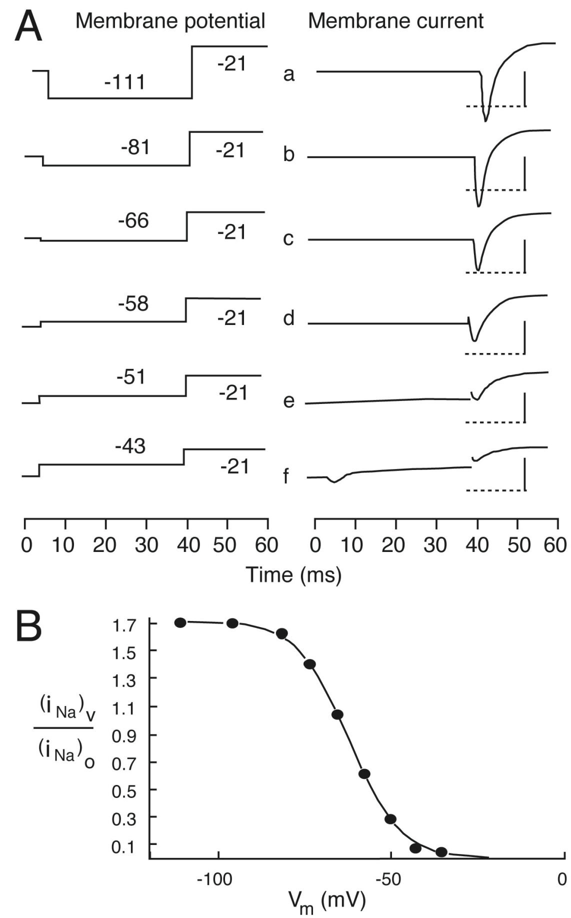

How do one get from current (measured) to conductance (calculated)?

# Modern day separation is cleaner!



# Depolarization has two effects on inward current!



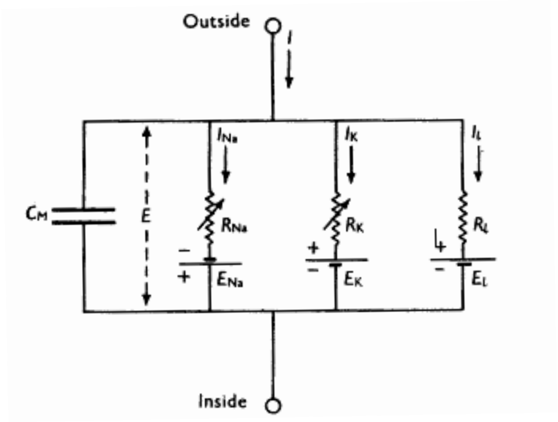




*Fain G (2014) Molecular and Cellular Physiology of Neurons. 2nd ed., Harvard Univ. Press.*

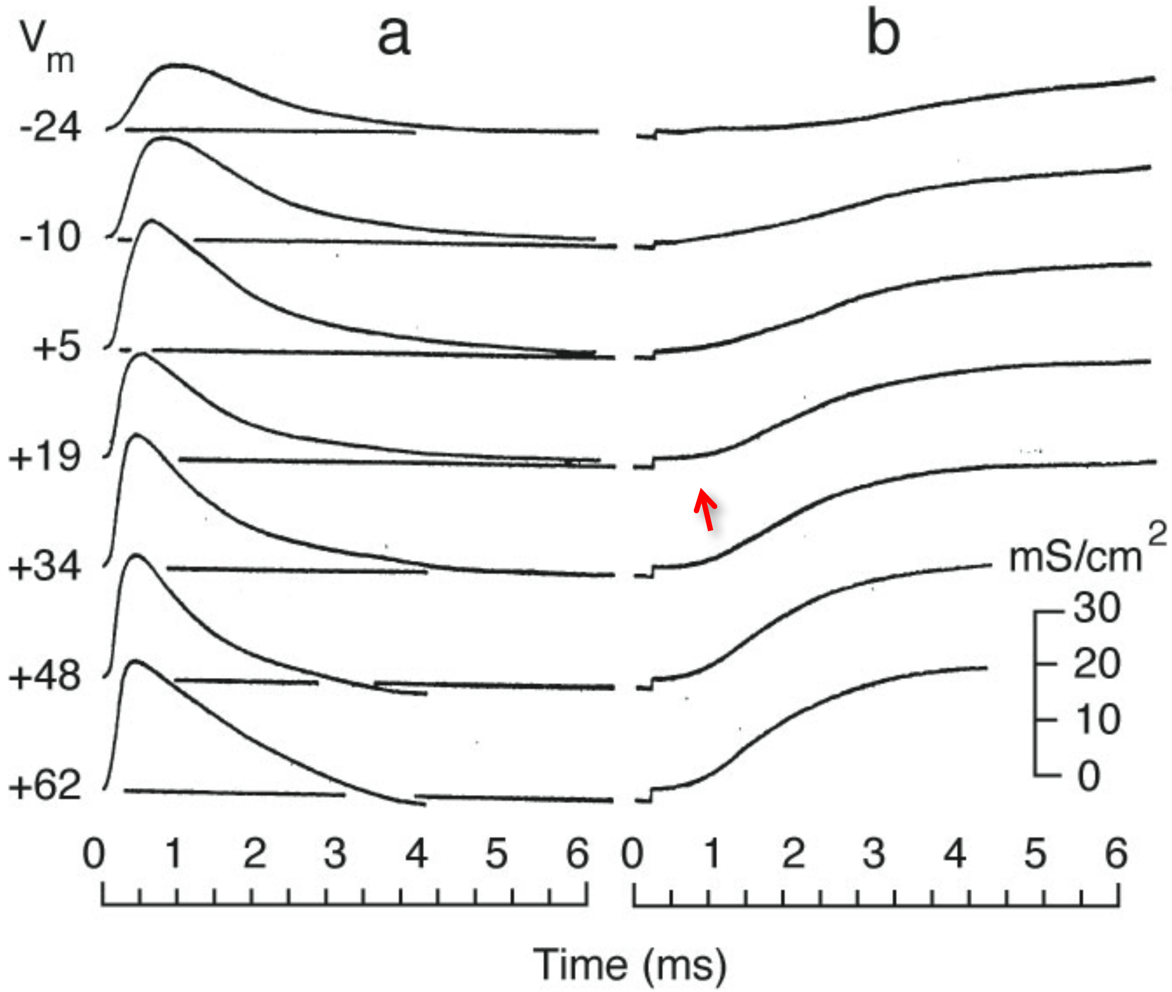
# Modeling

- HH assumed that voltage changes led to the movement of charged particles in the membrane (*what is the voltage gradient in the membrane?*)
- The particles were supposed to occupy one of two locations, one of which would promote channel opening
- To best account for the data, HH proposed four independent particles for the potassium conductance (n), three for activation of the sodium conductance (m), and one for inactivation of the sodium channel conductance (h). They assumed that activation and inactivation of sodium channel conductance were independent of one another.

$$I = C_M \frac{dV}{dt} + \overline{g_K} n^4 (V - V_K) + \overline{g_{Na}} m^3 h (V - V_{Na}) + g_L (V - V_L)$$



# Why *multiple* particles? Why not "first order?"



# Modeling (cont.)

- Each of the particles (n, m, and h) was assumed to exist in one of two states, with the rate constants of interconversion regulated by voltage. *e.g.*, for n,

$$I_K = \overline{g_K} n^4 (V - V_K)$$

$$(1\text{-}n) \underset{\beta_n}{\overset{\alpha_n}{\rightleftarrows}} n$$

$$\frac{dn}{dt} = \alpha_n (1-n) - \beta_n n$$

$$n = n_\infty - (n_\infty - n_0)\exp(-t/\tau_n)$$

$$n_\infty = \alpha_n/(\alpha_n + \beta_n)$$

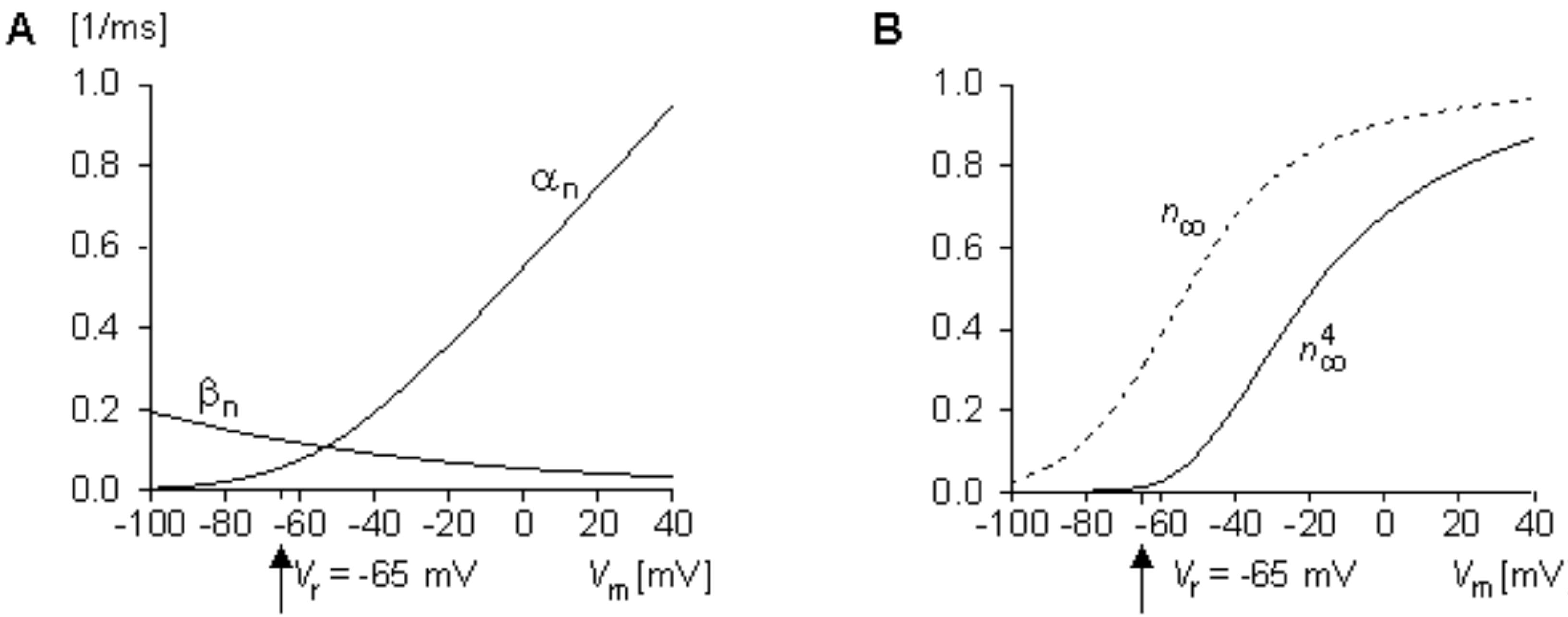
$$\tau_n = 1/(\alpha_n + \beta_n)$$

$$(1-n) \underset{\beta_n}{\overset{\alpha_n}{\rightleftarrows}} n$$

"HH1952e"

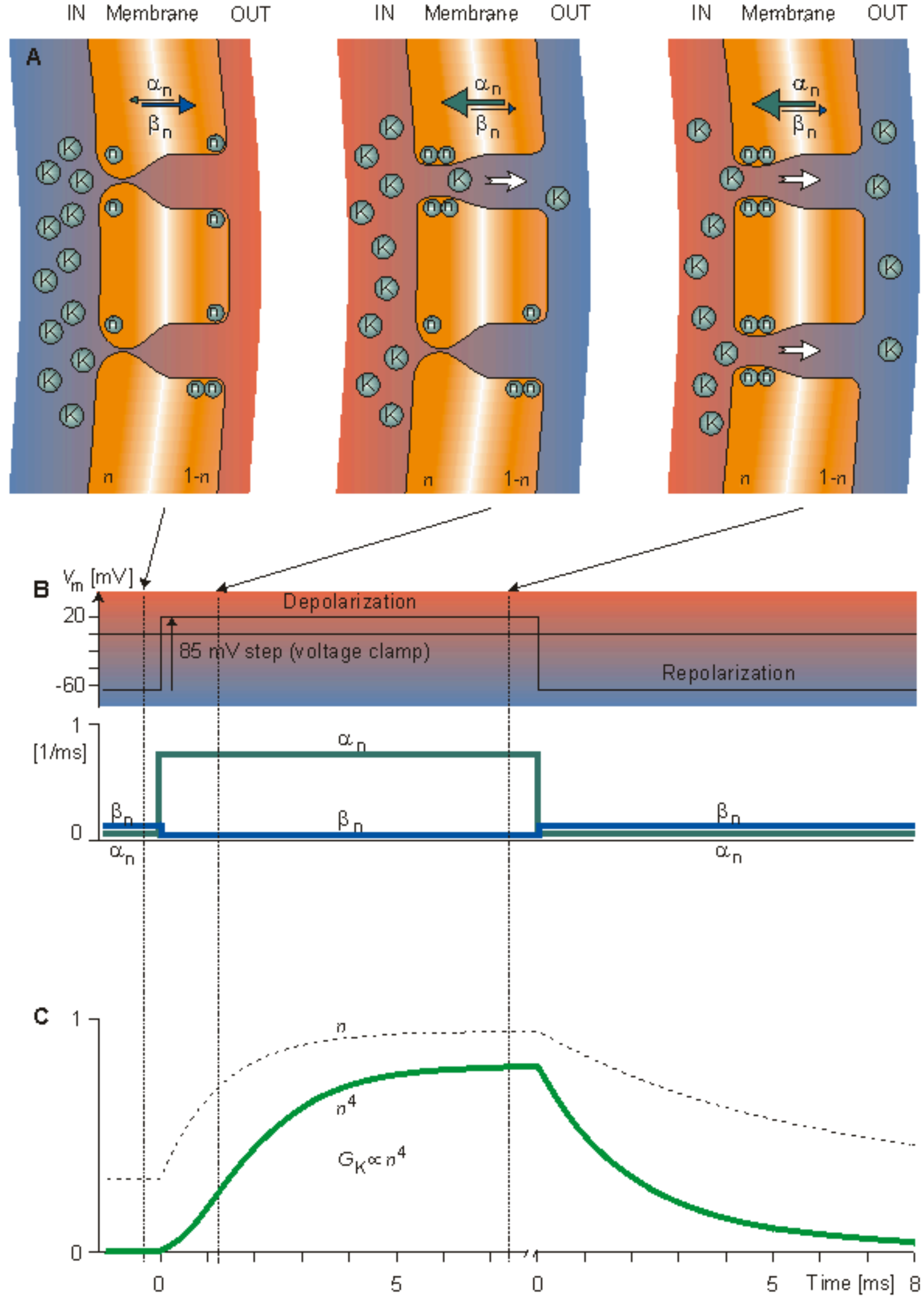
$$\alpha_n = \frac{0.01(V+10)}{\exp\frac{V+10}{10} - 1}$$

$$\beta_n = 0.125 \exp(V/80)$$




The rate constants $\alpha_n$ and $\beta_n$ are instantaneously regulated by voltage, but n is not. Once the voltage changes, n (and $n^4$) will move to a new value as a function of the new values of $\alpha_n$ and $\beta_n$.

# “HH1952e”



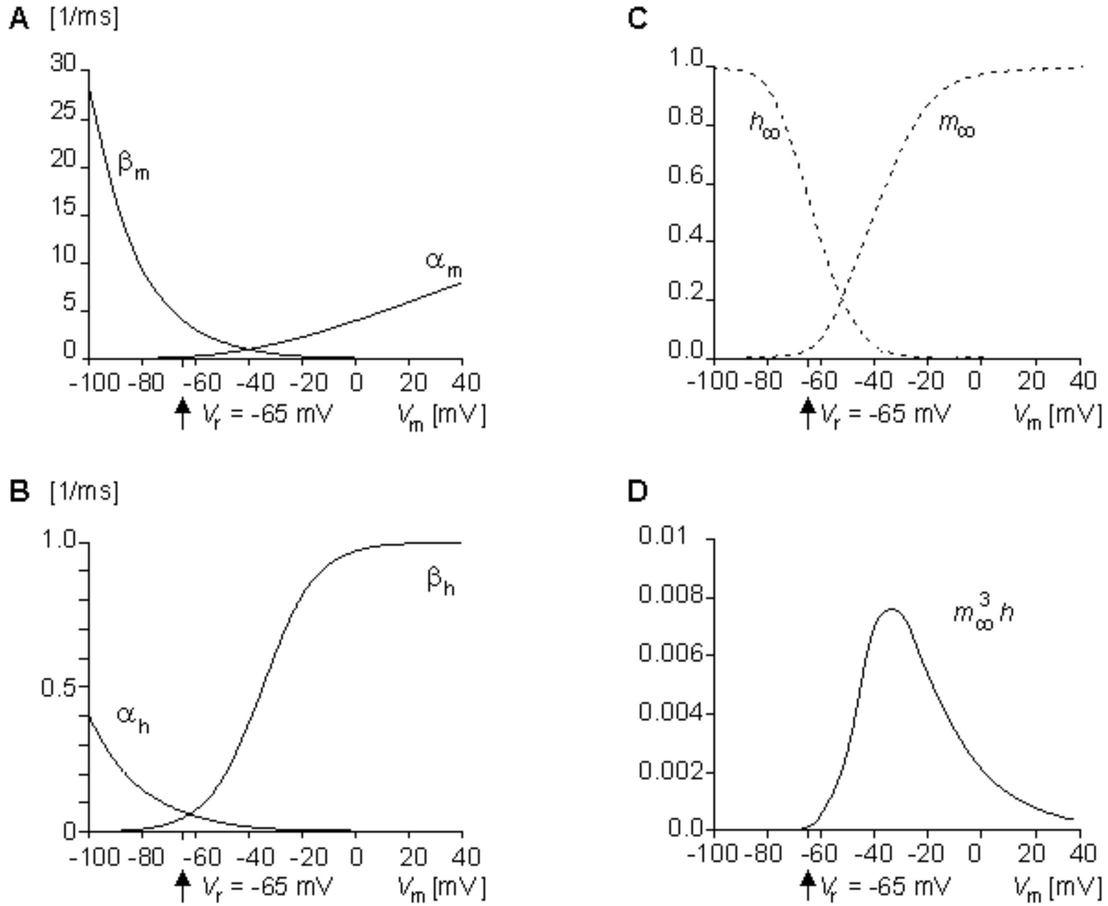

http://www.bem.fi/book/04/04.htm

# “HH1952e”

$$I_{Na} = \overline{g_{Na}} m^3 h (V - V_{Na})$$

$$(1\text{-}m) \underset{\beta_m}{\overset{\alpha_m}{\rightleftarrows}} m$$

$$(1\text{-}h) \underset{\beta_h}{\overset{\alpha_h}{\rightleftarrows}} h$$



# Current-Voltage (IV) curve

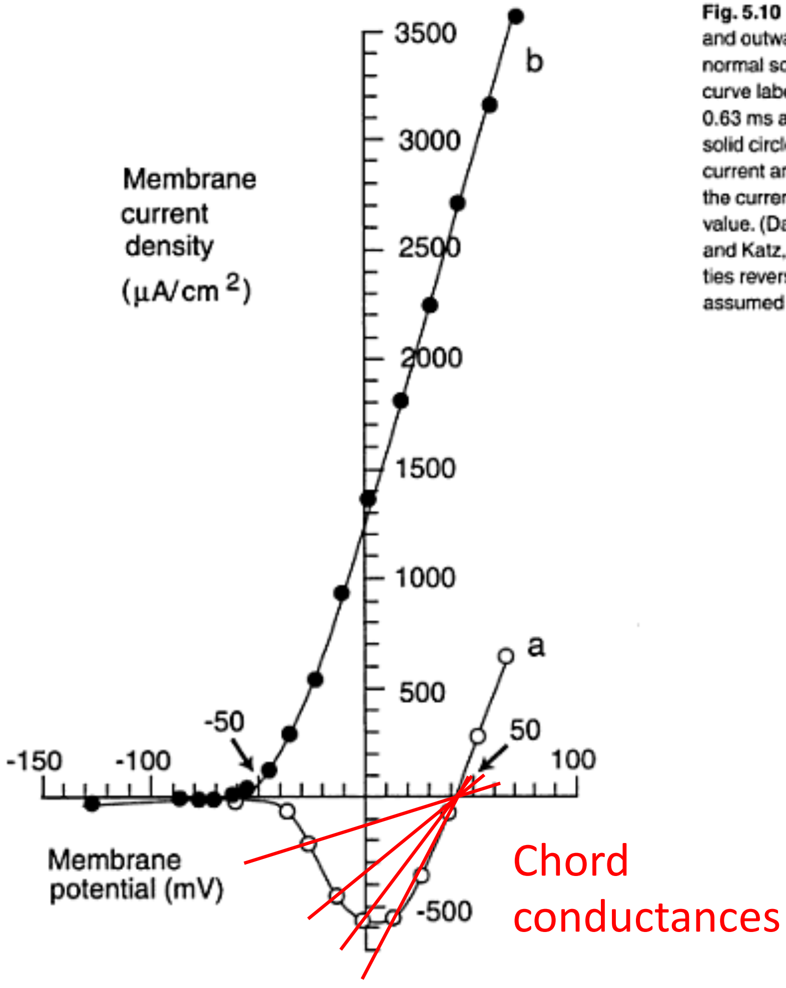
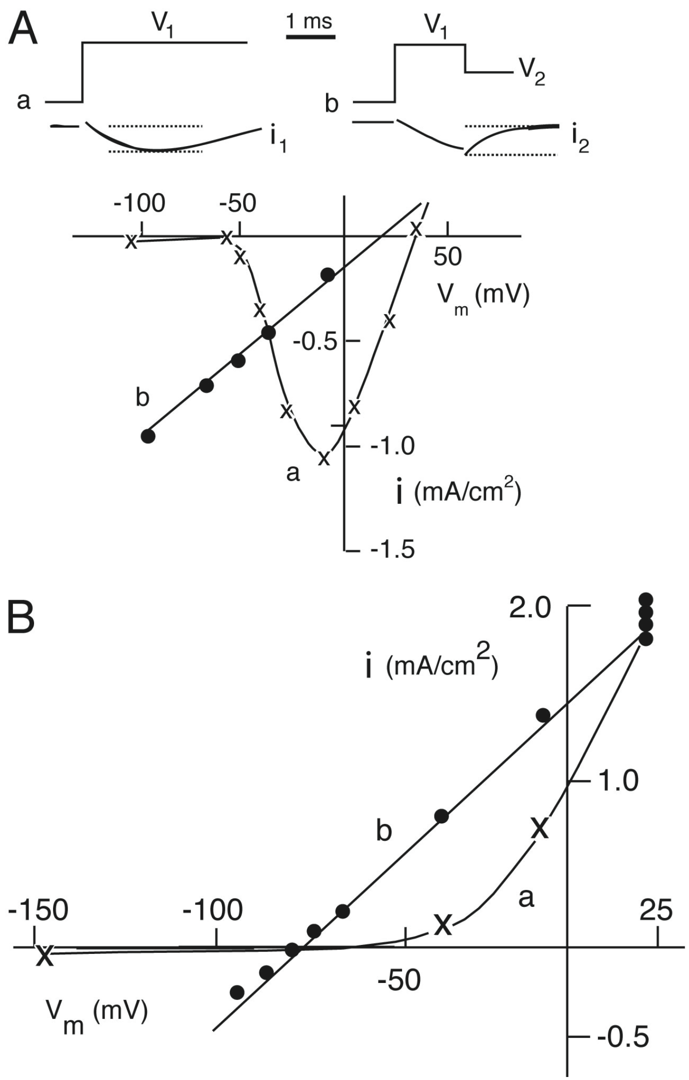



**Fig. 5.10** Current-voltage curves of inward and outward currents from squid giant axon in normal solution (sea water). Open circles and curve labeled *a* give amplitude of inward current 0.63 ms after the beginning of the voltage step; solid circles and curve labeled *b* give outward current amplitude at "steady state," that is when the current appeared to have reached a steady value. (Data from fig. 13 of Hodgkin, Huxley, and Katz, 1952, with current and voltage polarities reversed and resting membrane potential assumed to be −65 mV.)

*Fain G (1999) Molecular and Cellular Physiology of Neurons.*

# What's voltage-dependent: opening or open channel conductance?




- "instantaneous" current-voltage relationship of channels is ohmic
- HH reasoned that the channels do not rectify (display voltage senstive conductance), suggesting that it's their the opening that is voltage-sensitive

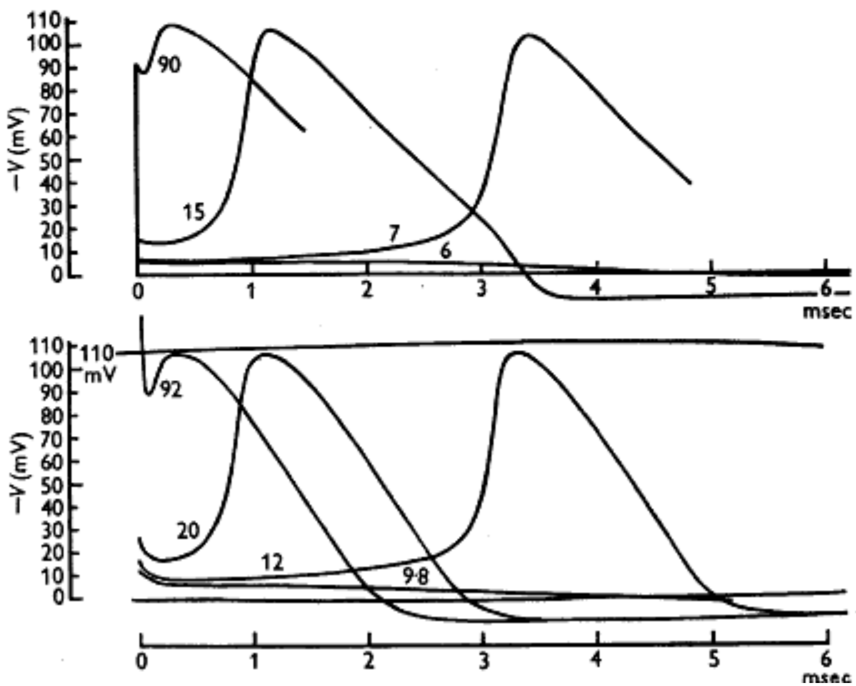
# Predictions Verified

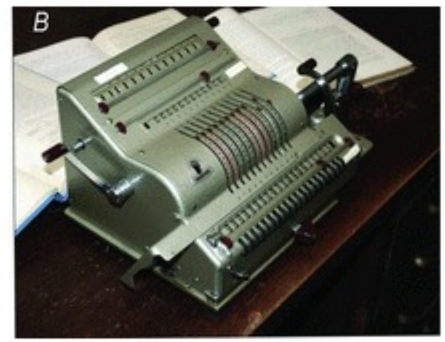
- Existence of independent mechanisms for permeation of sodium and potassium
- Gating current (added)
- Accommodation (sodium channel inactivation)
- Anode break excitation
- Refractory period
- Propagating action potentials

# What did they miss?

- Is inactivation independent of activation?
- Is inactivation strongly voltage-dependent?

# Propagating Action Potential




*Schwiening CJ (2012) J. Physiol. 590: 2571-2575. (60th anniversary of the publication of the 1952 papers)*

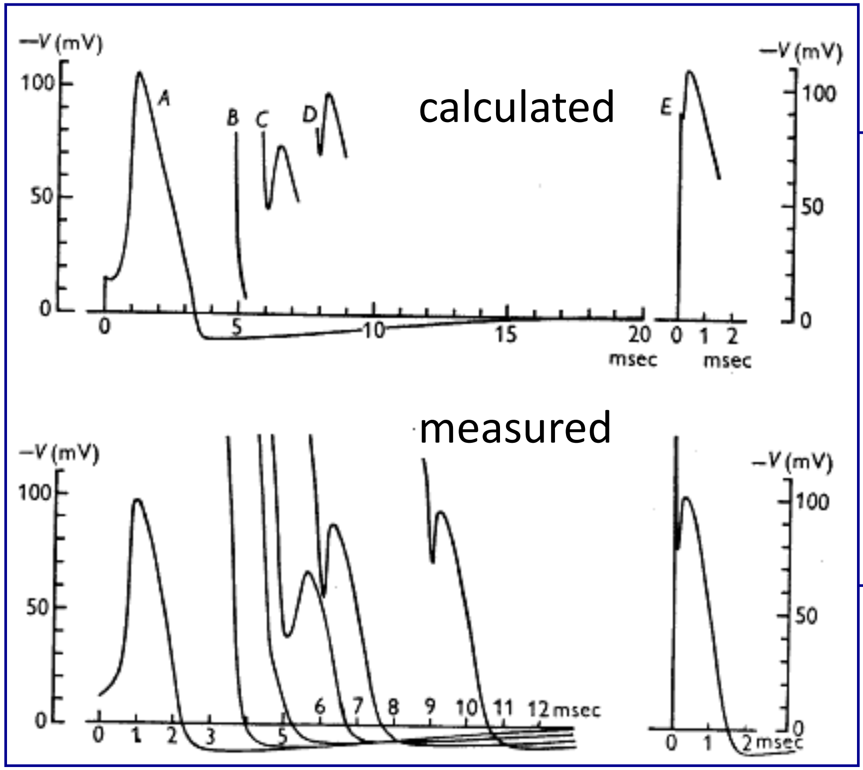
*The Brunsviga 20 (produced in Braunschweig by Brunsviga Maschinenwerke, Grimme, Natalis & Co.), one of the most popular mechanical calculators. It was produced up to the early 1970s and marketed with the slogan 'Brains of Steel'.*

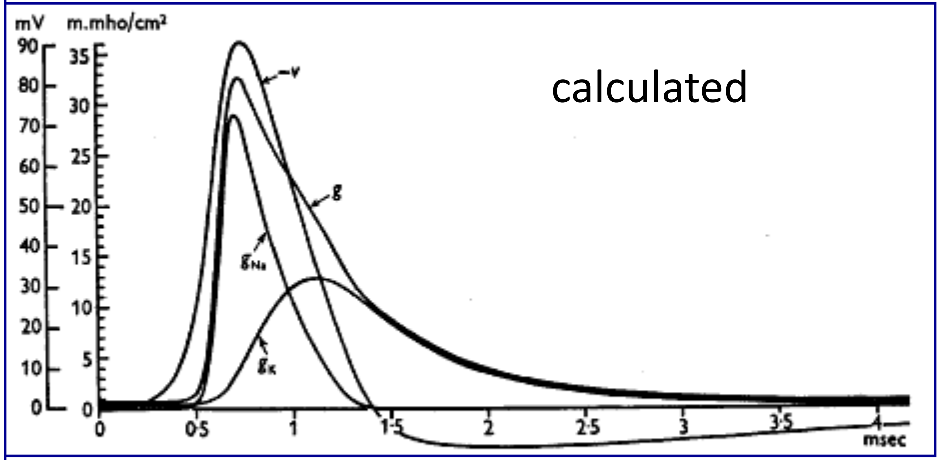
Using the cable equation, HH were successful in predicting the <u>propagating action potential</u>, including a fairly accurate prediction of its conduction velocity.

# In retrospect …

- Nobel Prize, 1963, shared with John Eccles
- "The modern history of ion channels began in 1952 when Hodgkin and Huxley published their seminal papers on the theory of the action potential in the squid giant axon …" (Rod McKinnon, Nobel lecture, 2003)
- It took nearly 15 years (after 1952) for any additional advances of significance to be made in the field. Much of the exciting work of the 1970s and even 1980s was focused on areas where the HH might have been wrong.
- Is it all correct? No. It's a model. It works well, but improvements have been made.

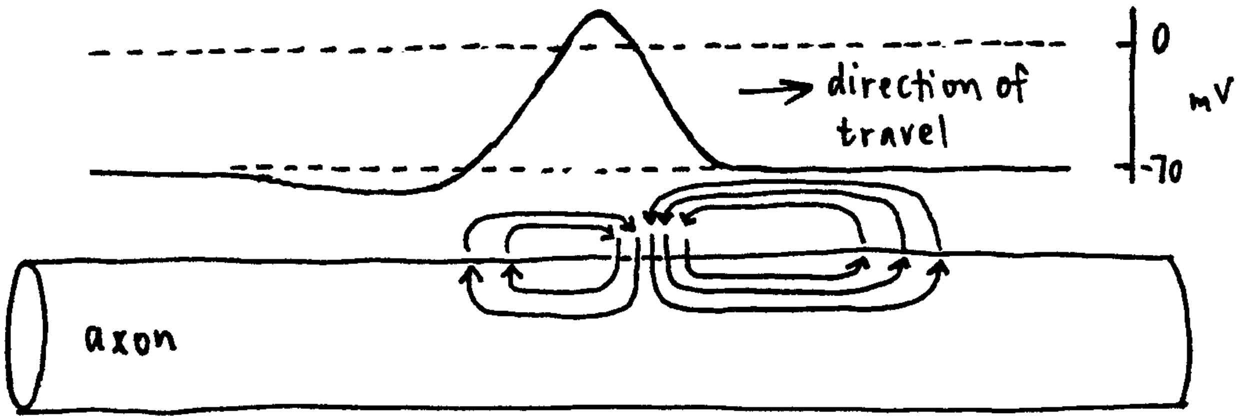
# Refractory Period (relative and absolute)



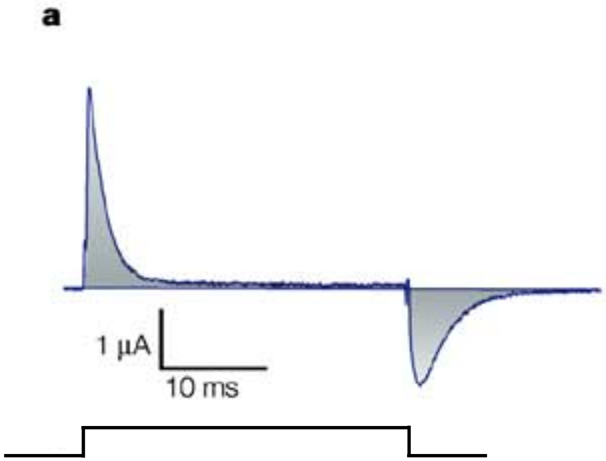

- What is the cause of the refractory period? The absolute part? The relative part?

# Refractory Area
# (propagating action potential)



# Gating current

- "…it seems difficult to escape the conclusion that the changes in ionic permeability depend on the movement of some component of the membrane which behaves as though it had a large charge or dipole moment" *(Hodgkin and Huxley, 1952)*
- Remove ionic currents, subtract out capacitative currents arising from the charging of the membrane at the beginning and end of the voltage step.
- How large? On the order of 300 charged particles/$\mu m^2$ moving across the entire voltage field, or ~6 per channel.

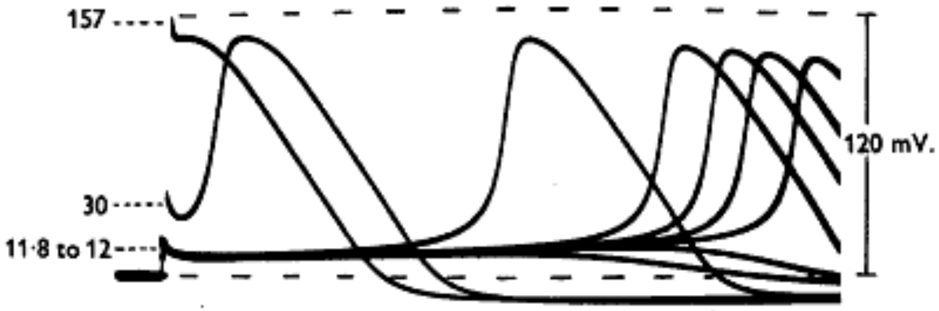


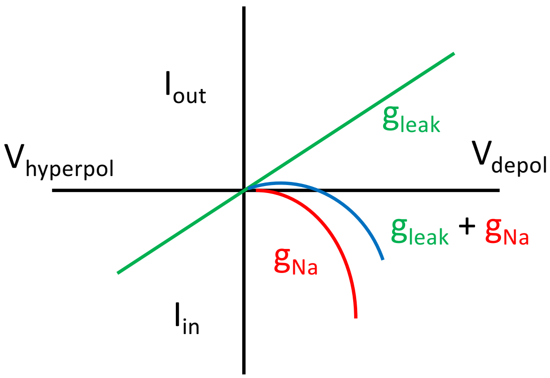

*Why is the current outward upon depolarization?*

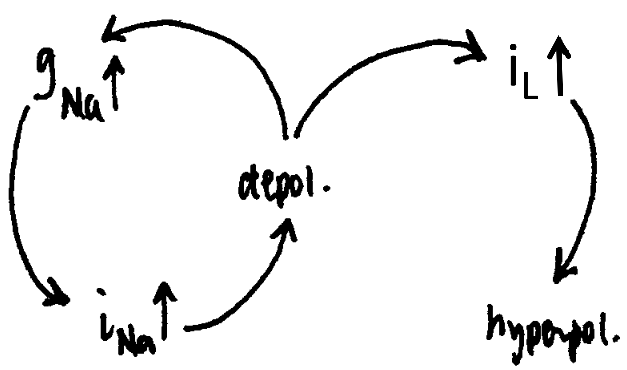
*Is this an ionic current?*

# Threshold

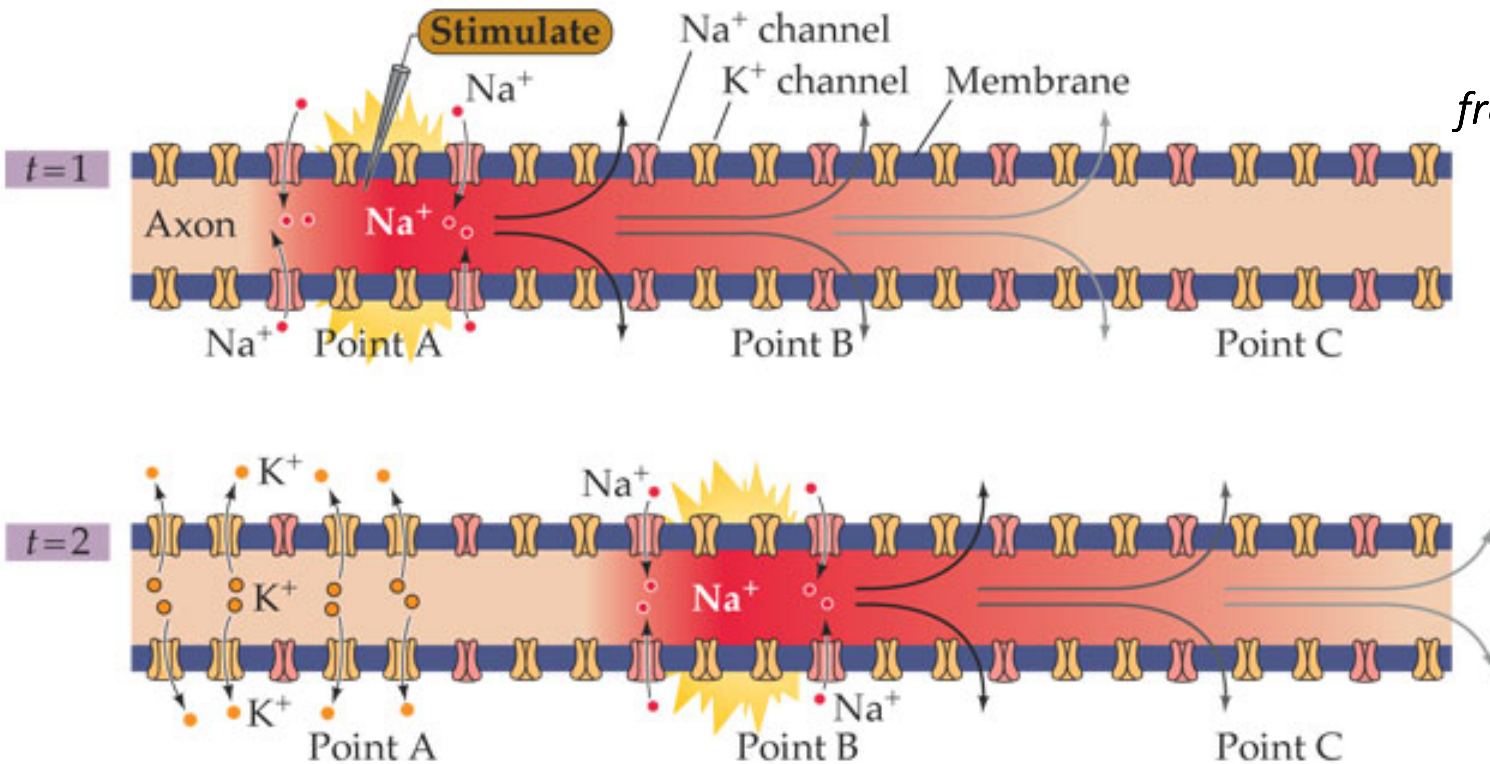
- Why is there a threshold?



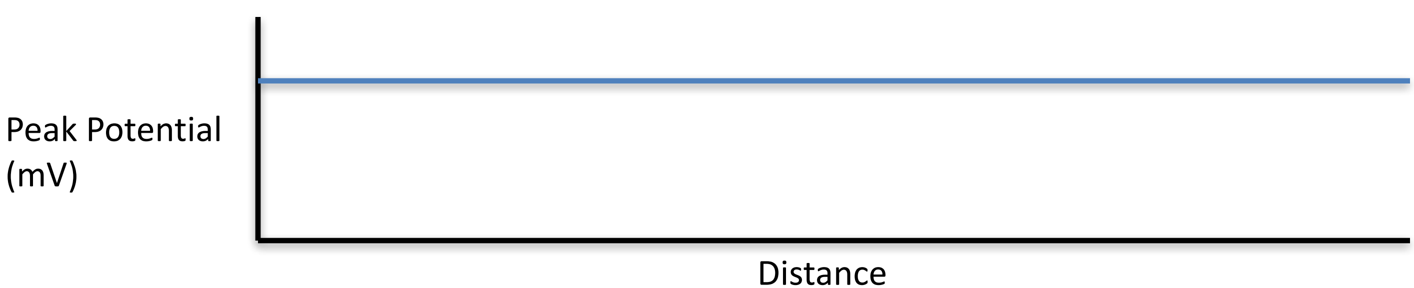



# Conduction is continuous in unmyelinated nerve

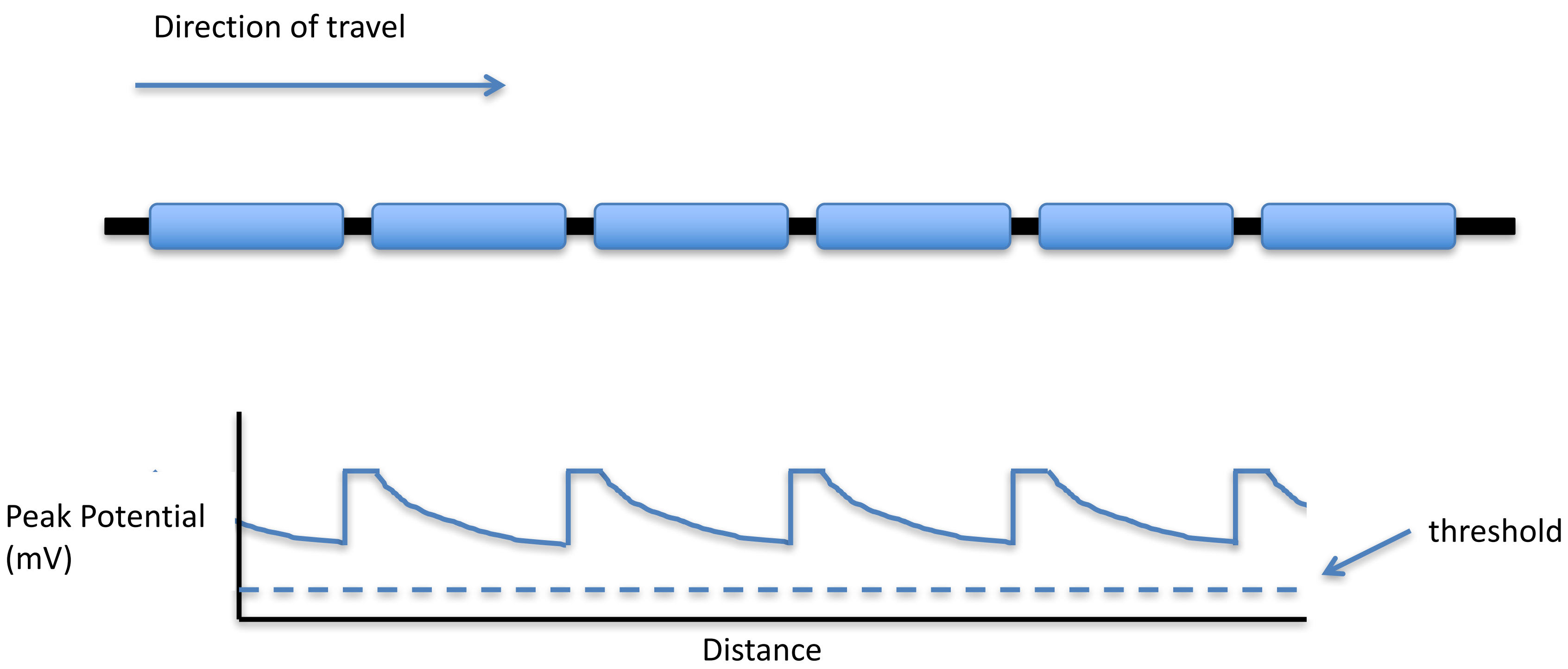



*from Purves*

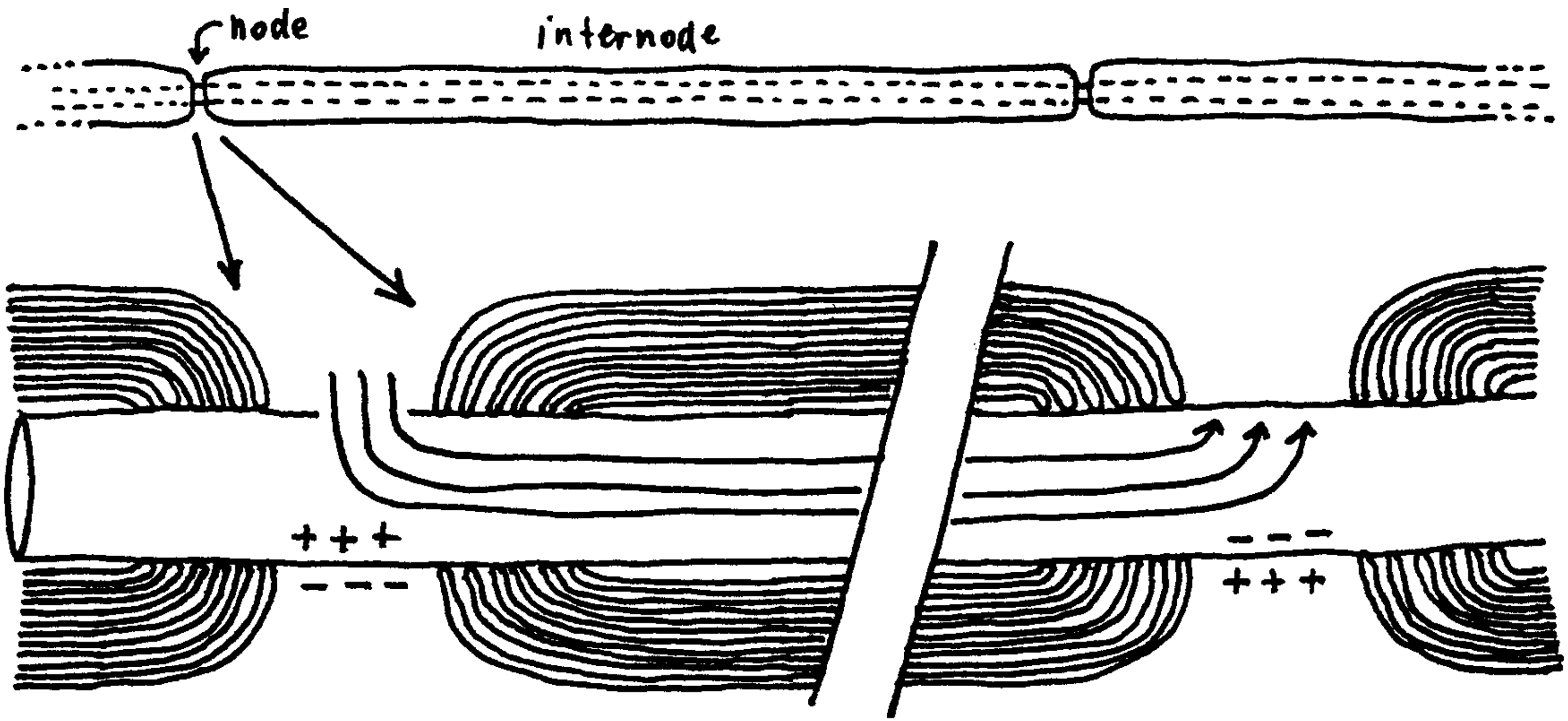
What molecule(s) move down the axon at the same rate as the action potential?



# Conduction is discontinuous in myelinated nerve (saltatory conduction)



# Myelin speeds conduction




<u>saltatory conduction</u>, from *saltare*, to jump or dance (Latin)

1. resistance
2. capacitance