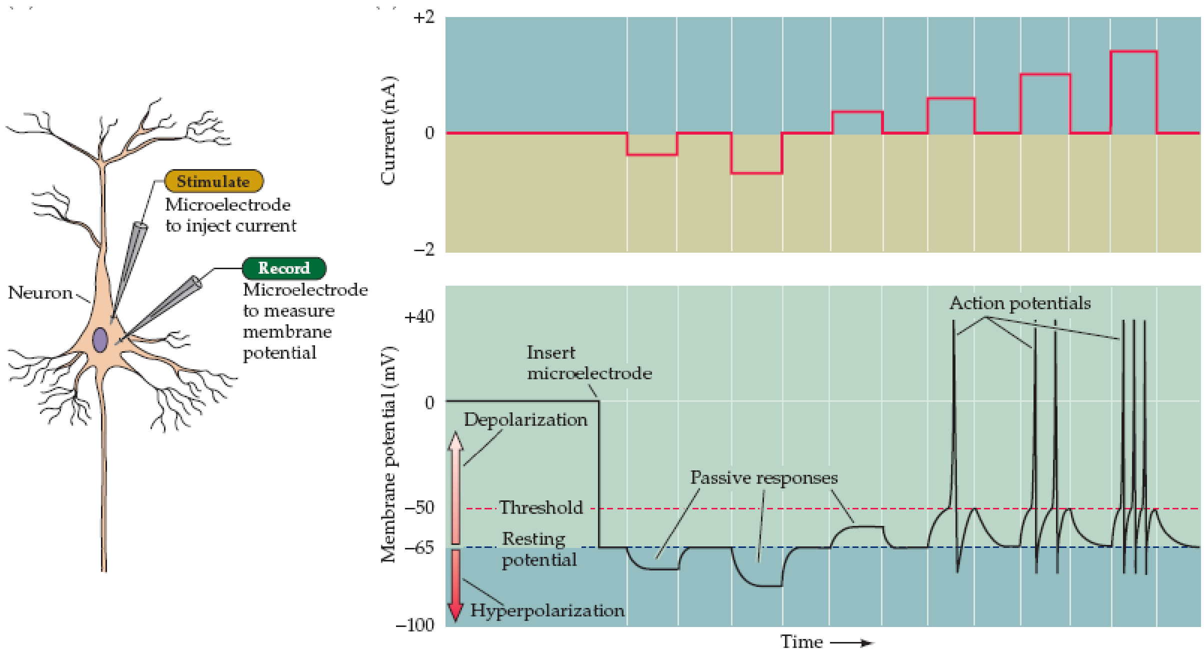
Νευροφυσιολογία και Αισθήσεις

Διάλεξη 5

Μοντέλο Hodgkin-Huxley (Hodgkin-Huxley Model)

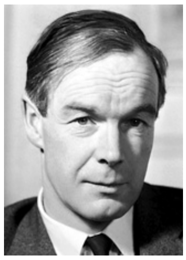
Response to Current Injection



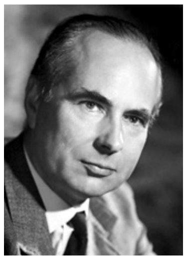
Hodgin & Huxley

- **Sir Alan Lloyd Hodgkin and Sir Andrew Huxley described the model in 1952 to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the giant axon of squid.**
- **The model was proposed long before the channel mechanisms were known clearly. Amazing!**
- **This work was recognized by the Nobel prize.**

Hodgkin



Huxley



Nobel Prize in Physiology and Medicine 1963

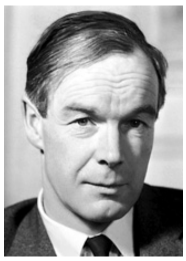
"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane“

Sir John Carew Eccles – Australia 1/3 (Canberra)

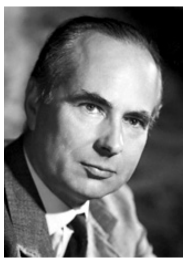
Alan Lloyd Hodgkin – UK 1/3 (Cambridge)

Andrew Fielding Huxley – UK 1/3 (London)

Hodgkin

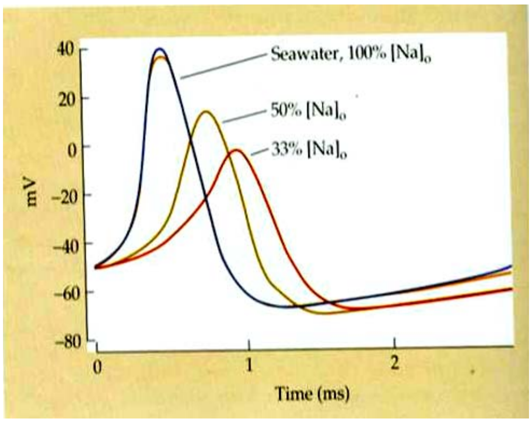


Huxley



Explain Action Potentials?

- **The problem:**
  - Explain action potentials
- **Early clues:**
  - Total conductance is increased during action potential (Cole and Curtis, 1938)
  - Voltage overshoot at the peak of the action potential (Hodgkin and Huxley, 1939)
  - Rapid repolarization of the membrane
  - Multiple batteries in play
  - Action potential amplitude depends on extracellular Na+ concentration (Hodgkin and Katz, 1949)

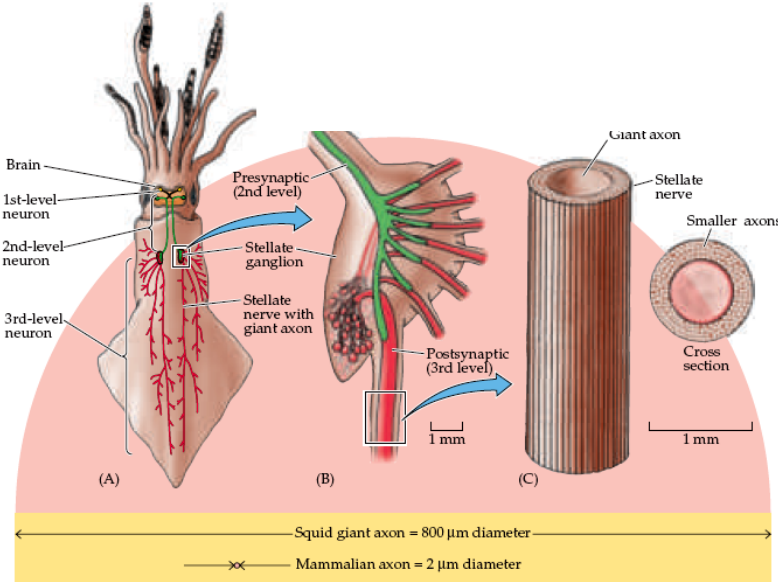


The Preparation

- **Loligo giant axons**

The Preparation

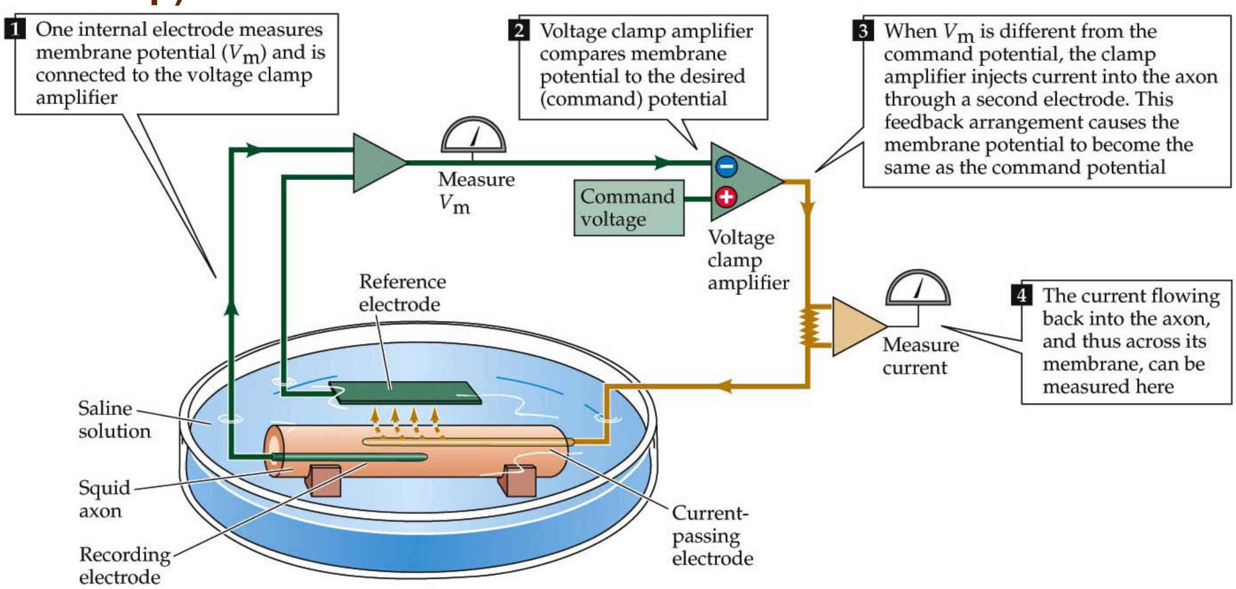
- **Giant neurons evidently evolved in squid because they enhanced survival**
  - A simple neural circuit
  - Activate the contraction of the mantle muscle → produce jet propulsion → escape predators at a remarkably fast speed.



- **The axons can be up to 1 mm in diameter—100 to 1000 times larger than mammalian axons.**
  - Not difficult to insert simple wire electrodes inside and make reliable electrical measurements.
  - Practical to extrude the cytoplasm and measure its ionic composition
  - They produce very large synapses

The Voltage Clamp Method

- **Electronic feedback circuitry to fix membrane potential & measure the required current (or vice versa for current clamp)**

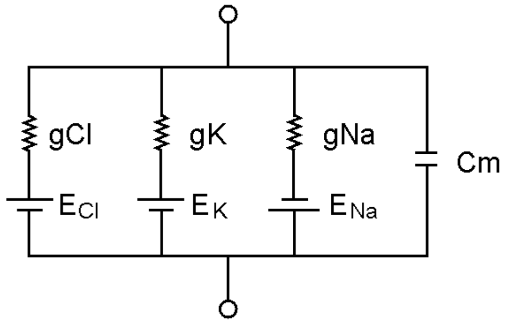


Equivalent electrical circuit model

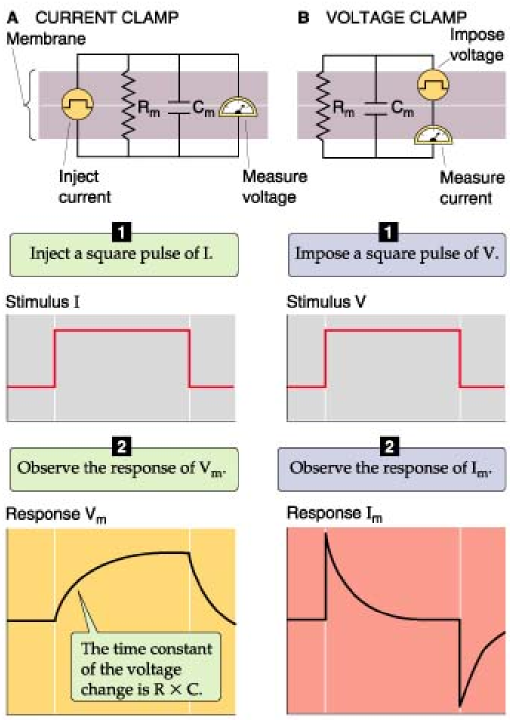
- With unequal distribution of ions and differential resting conductances to those ions, we can use the Nernst equation and Ohm's law in an equivalent circuit model to predict a stable resting membrane potential of -75 mV, as is seen in many cells
- This is a steady state and not an equilibrium, since K+ and Na+ are not at their equilibrium potentials; there is a continuous flux of those ions at the resting membrane potential

Resting Membrane Potential

$$E_m = \frac{(g_k E_k) + (g_{Na} E_{Na}) + (g_{Cl} E_{Cl})}{g_K + g_{Na} + g_{Cl}}$$

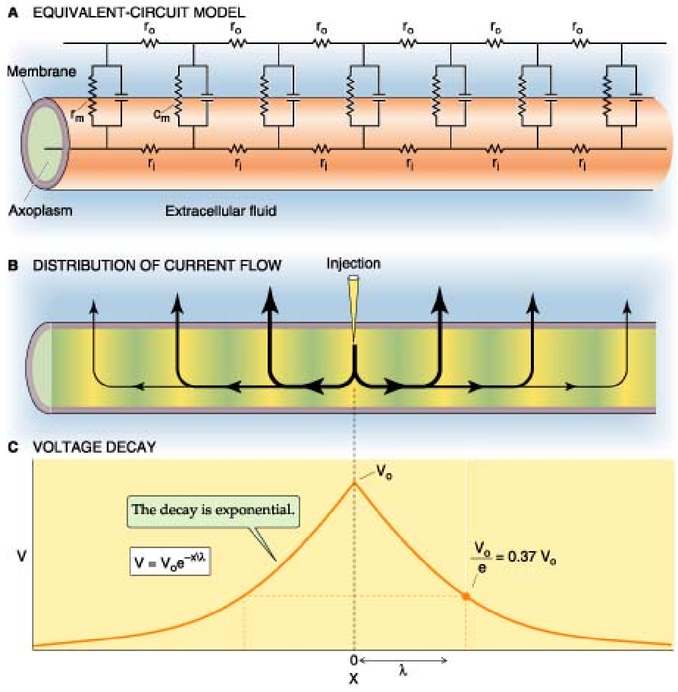


Passive membrane properties



- **Under voltage clamp, the passive response includes:**
  - capacitive current, which flows only at the step onset and offset
  - resistive current (through leak channels), also given by Ohm's law (I = V/R)
- **Under current clamp, the passive response to current injection is a function of the RC characteristics of the membrane**
  - V = IR (Ohm's law) gives the steady state voltage
  - t = RC (gives the kinetics)

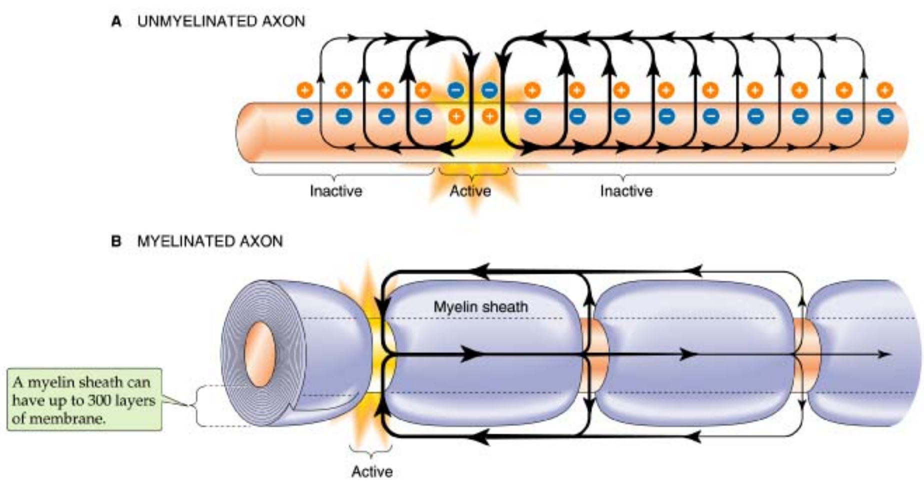
Passive cable properties: length constant



$\lambda = \sqrt{(r_m/r_i)}$

- r_i is inversely proportional to cross sectional area
  - bigger cables have lower r_i, and therefore pass more axial current – this strategy for increasing λ is used to an extreme in the squid giant axon
- Increased r_m promotes more effective axial current flow by discouraging transmembrane current

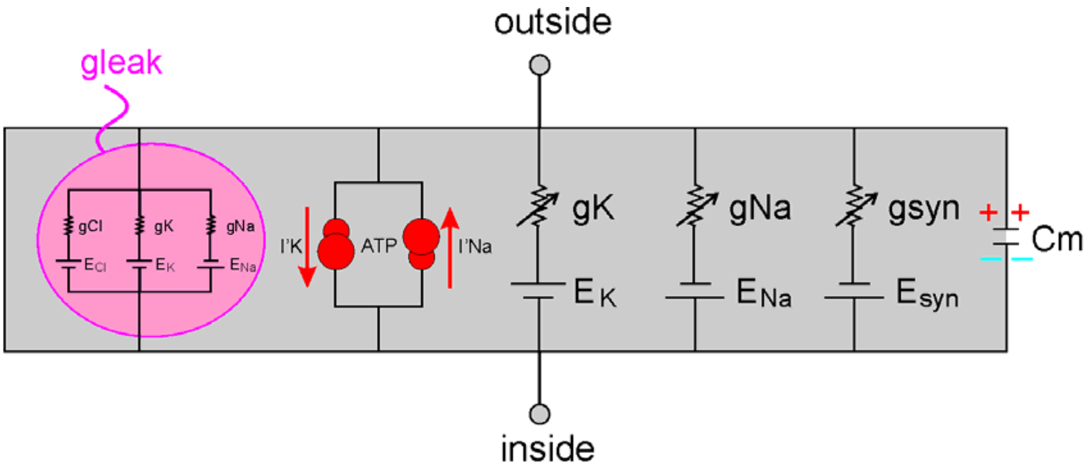
Myelination increases conduction velocity



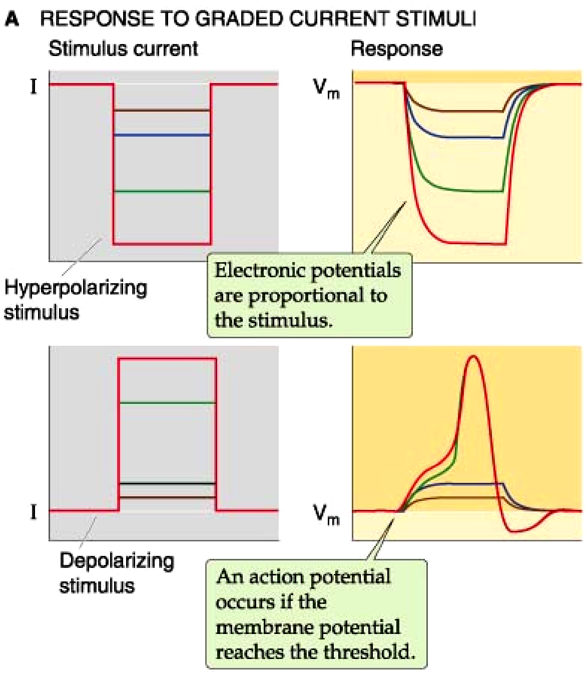
- Myelination increases conduction velocity by:
  - increasing r_m and thereby increasing λ
  - decreasing capacitance and lowering Q (V=Q/C)
    - the net result is that less current will escape through the membrane resistance; less current needed to charge the smaller capacitance

Equivalent electrical circuit model

- **More complete model**
  - Provide energy-dependent pump to counter the steady flux of ions
  - Add voltage-gated K+ and Na+ channels for electrical signaling
  - Add ligand-gated (e.g. synaptic conductances)
  - Obviously, much greater complexity could be imagined

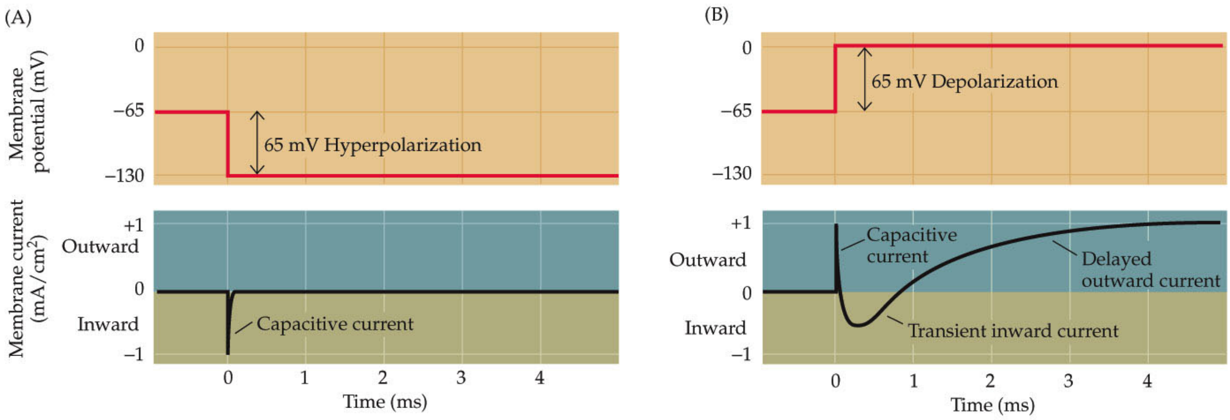


Action potential: all-or-none properties

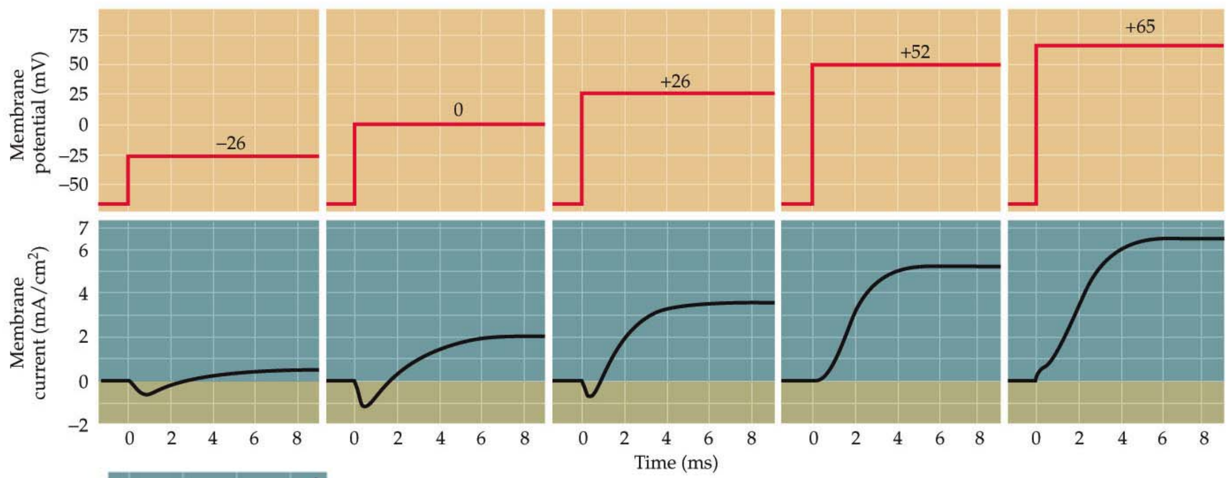


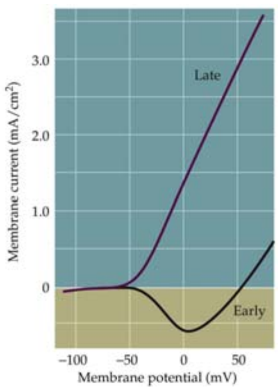
- **Hyperpolarizing stimuli**
  - Passive membrane responses are determined by membrane resistance and capacitance
    - $V=I*R$ & $\tau=R*C$
- **Depolarizing stimuli**
  - Passive responses are determined by the resistive and capacitive components up to 'threshold'
  - When membrane depolarization exceeds threshold, a stereotyped active response is observed

Voltage clamp: analysis of action potential



Voltage clamp: analysis of action potential





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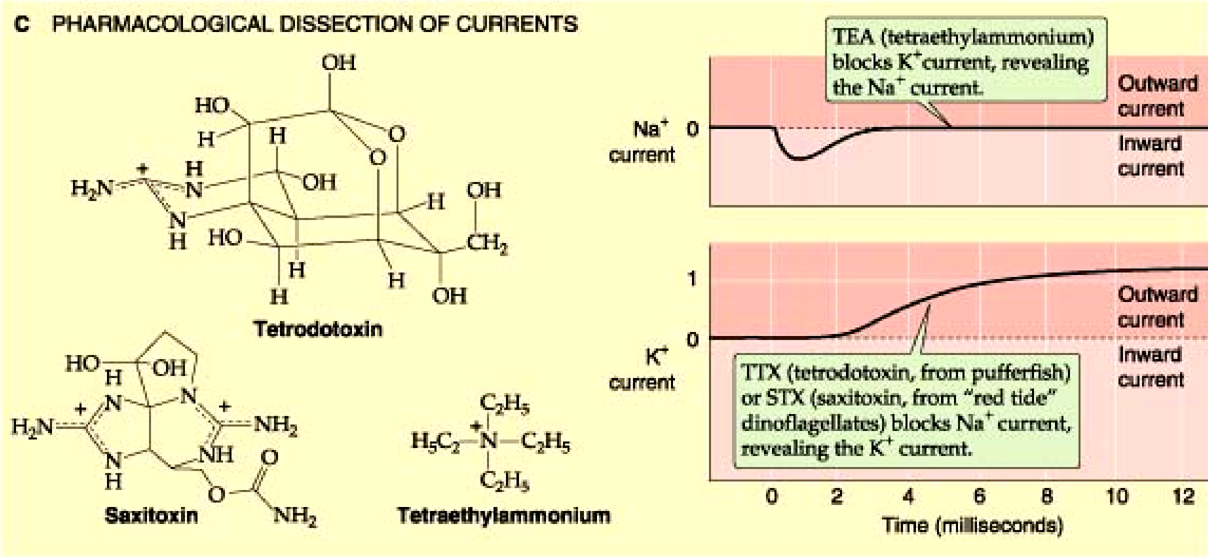
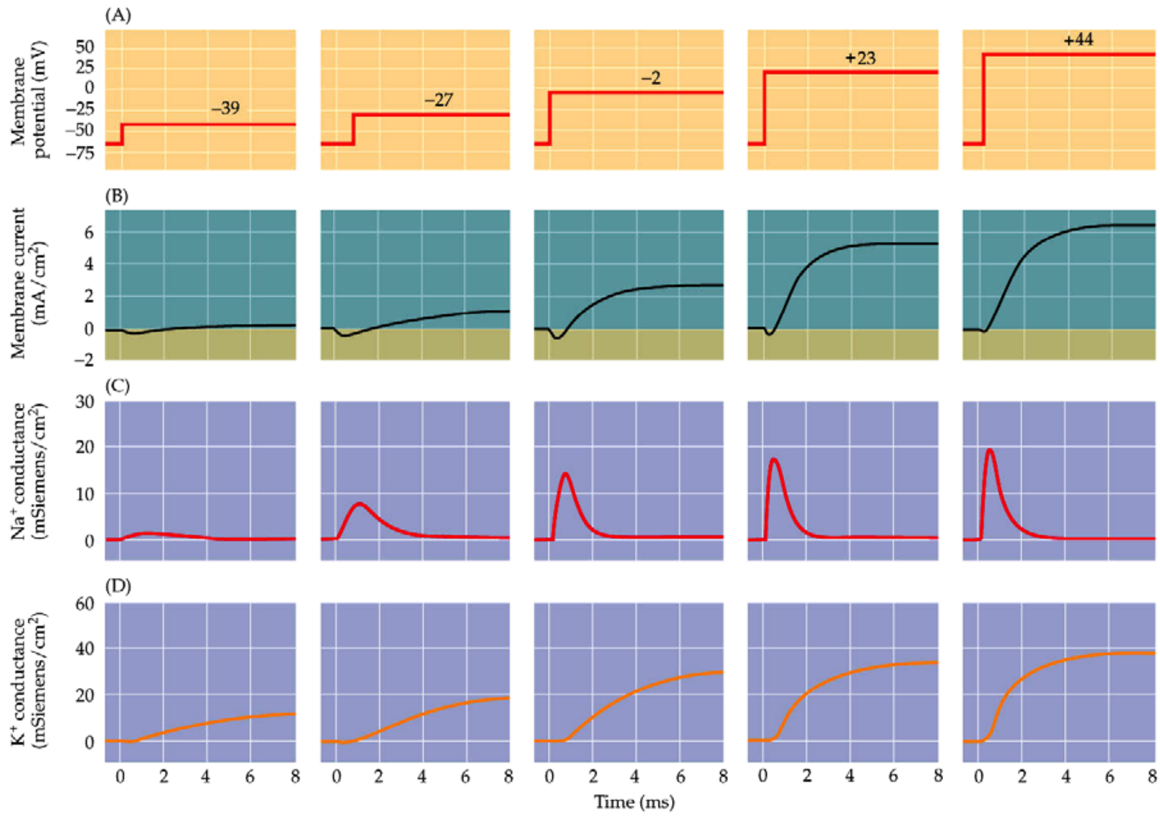


Voltage clamp: analysis of action potential



Na^+ and K^+ conductance in the AP

- **Hodgkin & Huxley used their empirical measures to model Na^+ and K^+ currents:**

$$I_{Na} = m^3\, h\, \bar{G}_{Na}\, (V_m - E_{Na}) \qquad I_K = n^4\, \bar{G}_K\, (V_m - E_K)$$

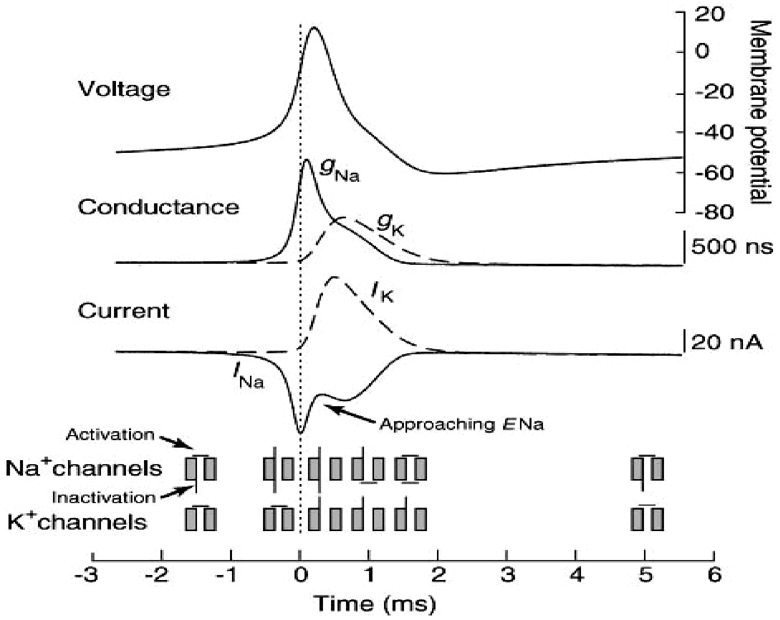
- **they developed an equation that predicts membrane potential based on the sum of capacitive and ionic currents:**

$$I_m = C_m\,(dV_m/dt) + \bar{G}_K\, n^4\,(V_m - E_K) + \bar{G}_{Na}\, m^3 h\,(V_m - E_{Na}) + \bar{G}_L\,(V_m - E_L)$$

  - The n^4 term provides the pronounced delay in K^+ current activation
  - The m3 term is the Na+ current activation
    - The smaller exponent on the m term allows for faster Na^+ current activation
  - The h term is the Na^+ current inactivation

Na^+ and K^+ conductance in the AP

$$I_m = C_m\,(dV_m/dt) + \bar{G}_K\, n^4\,(V_m - E_K) + \bar{G}_{Na}\, m^3 h\,(V_m - E_{Na}) + \bar{G}_L\,(V_m - E_L)$$



Very Little K^+ Flux Needed to Reach Equilibrium

- Question: How much K^+ flows for the potential to reach equilibrium?
- Answer: $q = CV = (C/A) \times A \times V$

$$\# K^+ \text{ ions} = q/q_e = (1\ \mu F/cm^2) \times 4\pi(10\ \mu m)^2 \times 58\ mV / 1.6 \times 10^{-19}\ C = 4.6 \times 10^6 \text{ ions}$$

$$\text{Tot. } K^+ \text{ ions} = [K^+] \times N \times 4/3\pi(10\ \mu m)^3 = 3 \times 10^{11} \text{ ions}$$

- Implication:
  1. Need to move only a minute fraction of the ions to change V
  2. Huge amount of energy stored in the ionic gradient (like a battery)

Επόμενη Διάλεξη …

Διάλεξη 6

Συναπτική Διαβίβαση (Synaptic Transmition)