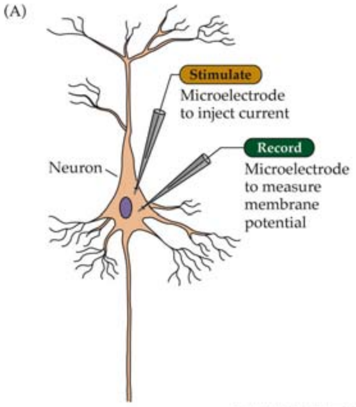
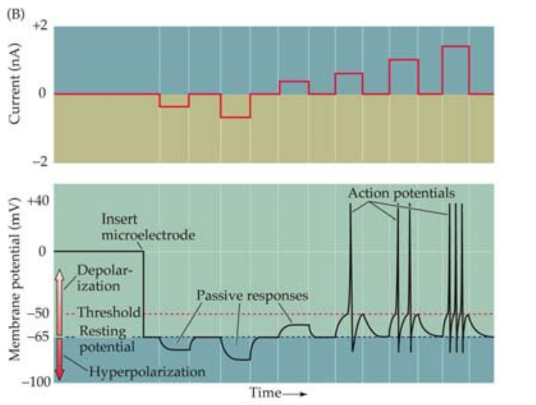
Innehåll - generellt

- Membranet som RC krets (Fosfolipider + proteiner)
- Vilomembranspänningen – hur, varför?
- Excitabilitetsegenskaper (AP)
- Jonkanaler - uppbyggnad

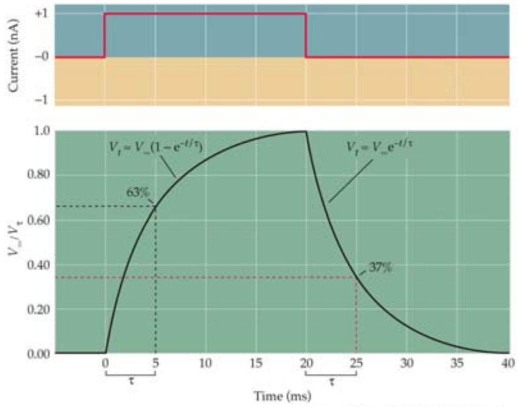
2.2 Recording passive and active electrical signals in a nerve cell



2.2 Current injection in the cell – measurement of voltage between in and outside



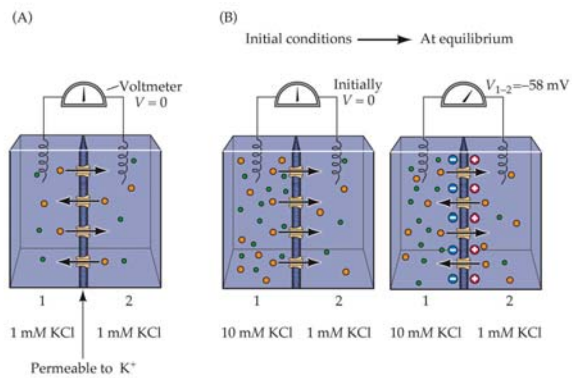
Box C Passive Membrane Properties (2)



RC – krets

Varför?

2.4 Electrochemical equilibrium.



Why resting potential and negative inside?

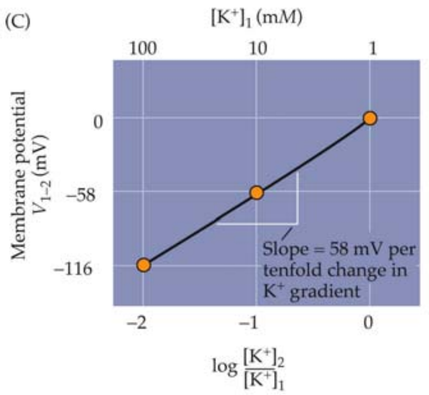
Nernst equation!

C=Q/U (kapacitans = ”laddning per volt”)

Hur många joner krävs för att ladda upp cellmembranet 100mV om cellen har r=20μm? (C = 0.01F)

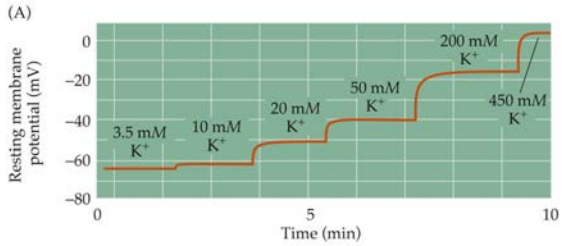
=> Väldigt liten andel jonomflyttningar behövs för att skapa membranspänning i vanlig cell

2.4 Electrochemical equilibrium.



2.7 Evidence that the resting potential is determined by K^+ concentration gradient.

Increase in extracellular K^+ concentration depolarizes the cell (but not exactly according to Nernst eq)



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

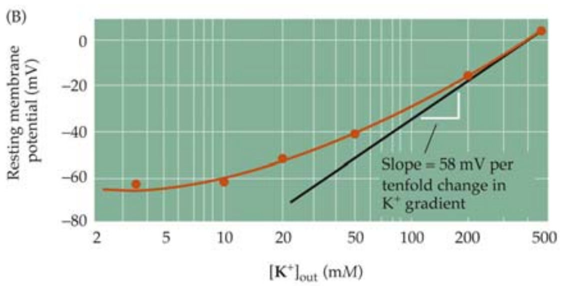


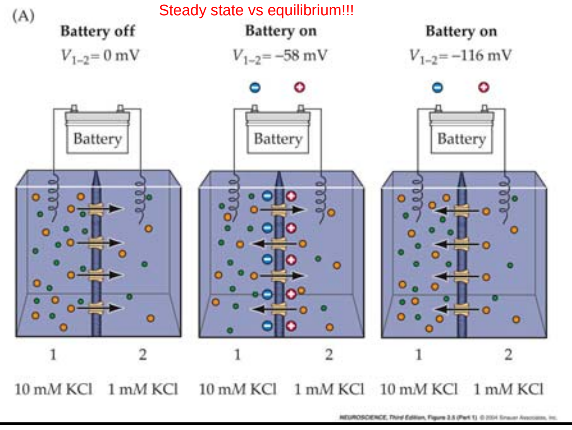
TABLE 2.1
Extracellular and Intracellular Ion Concentrations

	Concentration (mM)	
Ion	*Intracellular*	*Extracellular*
Squid neuron		
Potassium (K^+)	400	20
Sodium (Na^+)	50	440
Chloride (Cl^-)	40–150	560
Calcium (Ca^{2+})	0.0001	10
Mammalian neuron		
Potassium (K^+)	140	5
Sodium (Na^+)	5–15	145
Chloride (Cl^-)	4–30	110
Calcium (Ca^{2+})	0.0001	1–2

Tankeknep: NaCl ute (”havsvatten”), KCl inne i cell
(obs totalladdningen ute och inne är alltid noll om alla joner räknas med!)

2.5 Ion fluxes decides membrane potential and membrane potential influences ion fluxes.

Steady state vs equilibrium!!!



Resting membrane potential

- Vm over the membrane depends on the movement of ions into or out of the cell (Na^+, K^+, Cl^-, Ca^{2+}). K^+ dominates.
- Passive ion fluxes determined by electro-chemical driving force (Nernst and GHK eq).
- Steady-state currents during rest in real cell (not equilibrium)

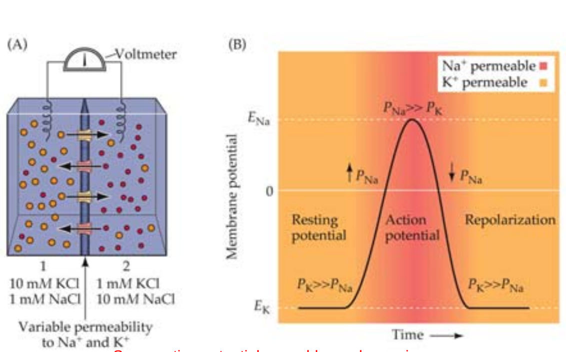
Review Questions for Chapter 2:
Electrical Signals of Nerve Cells

1. Draw the basic experimental setup for recording membrane potentials.
2. Draw a recording of a typical action potential. Label the axes and the key features of the action potential. Identify the underlying events for each of the following:
   - rising phase
   - overshoot
   - peak
   - falling phase
   - undershoot
3. Suppose a water-filled aquarium is divided into two compartments by a membrane that is not permeable to any ions. Add KCl to one side. What happens? Is there a potential difference between the two sides? What will happen to the membrane potential if the membrane suddenly becomes selectively permeable to K^+ (but not Cl^-)? What happens if you then add NaCl to one side only?
4. What is the magnitude of a typical neuron's resting membrane potential? Why do neurons and other cells have a negative resting membrane potential?
5. What is meant by the statement that ion channels and ion pumps have complementary functions?
6. Explain the difference between action potentials (all-or-none) and synaptic potentials (graded).
7. Distinguish between hyperpolarization and depolarization.
8. What is meant by electrochemical equilibrium?
9. Write the Nernst equation. Explain how it could be used to determine the equilibrium potential for K^+. What good is it to know the K^+ equilibrium potential?
10. What situation calls for the Goldman equation instead of the Nernst equation?
11. Suppose you are recording a neuron's resting membrane potential. You add KCl to the external medium. What do you think would happen to the resting potential? Compare this to what would happen if you had added the same amount of NaCl. What could you conclude from this comparison?

Active membrane properties

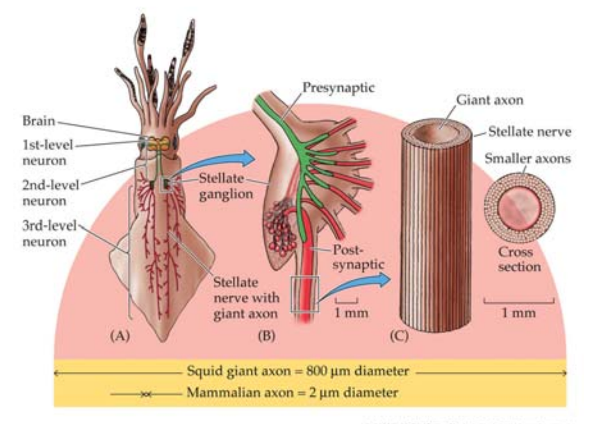
- If suddenly the permeability of e.g. Na is increased the cell membrane depolarizes.
- Why does the permeability change?
- How was this found out? (Hodgkin, Huxley)

2.6 What if permeabilities to different ions are changed over time?

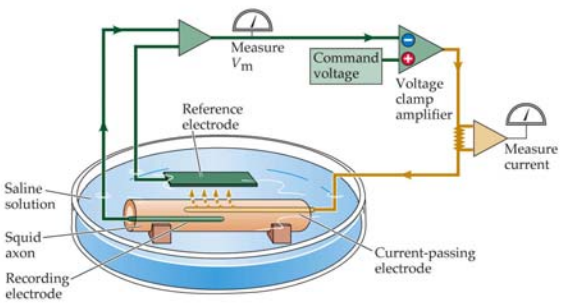


So an action potential resembles a change in Na^+ permeability/conductance. What is triggering this conductance change?

Box A The Remarkable Giant Nerve Cells of a Squid

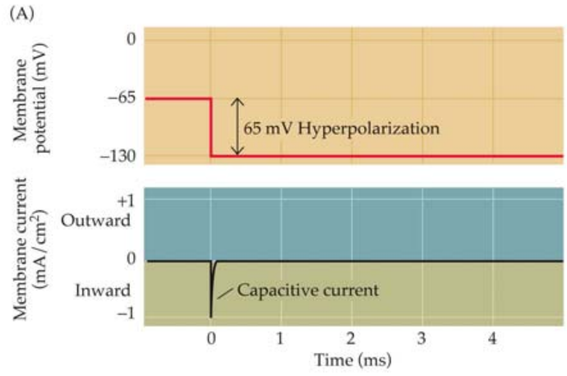


Box A Voltage Clamp Method



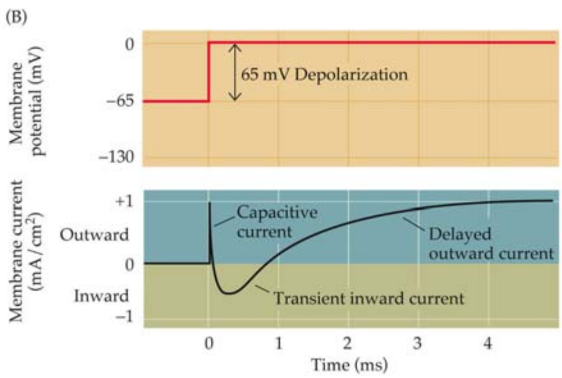
Note – compensate for "leak currents"
(i.e. passive membrane resistance)

3.1 Current flow across an axon membrane during a voltage clamp experiment. (Part 1)



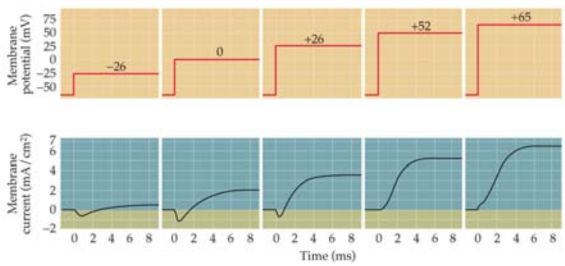
(compensated for passive membrane resistance)

3.1 Current flow across an axon membrane during a voltage clamp experiment. (Part 2)

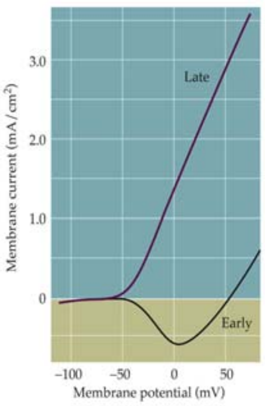


(definition of positive/negative current can vary!)

3.2 Current produced by membrane depolarizations to several different potentials.

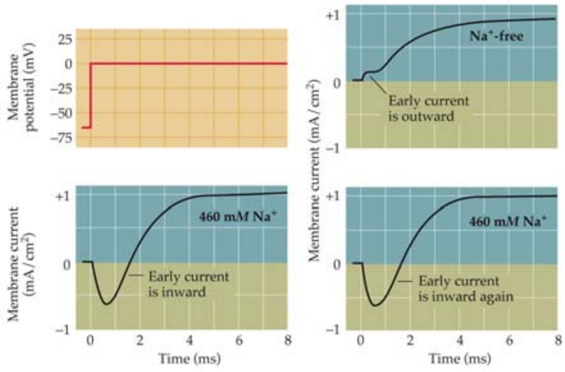


3.3 Relationship between current amplitude and membrane potential.



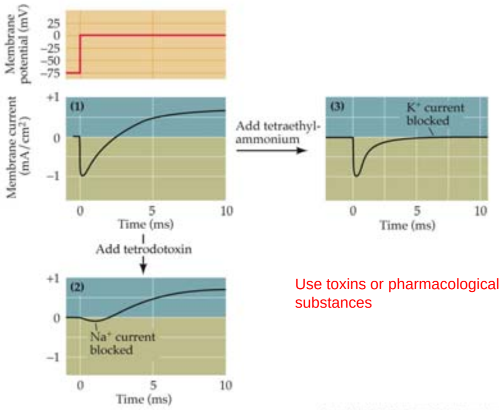
- Early current has $E_{reversal}$ (E_{nernst}) at around +50mV
- Late current has $E_{reversal}$ at around –70mV
- One can separate currents by using: $I=g(V-E_{reversal})$

3.4 Dependence of the early inward current on sodium.



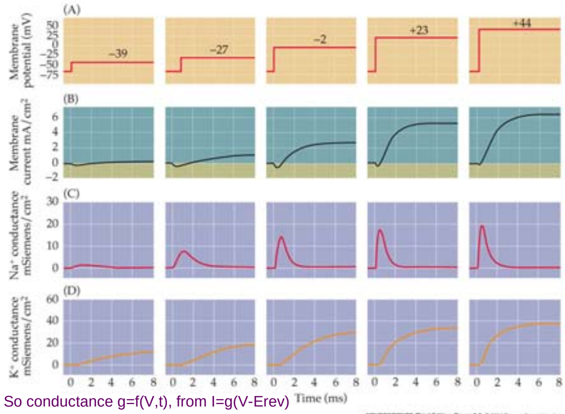
Vary extracellular ion concentrations

3.5 Pharmacological separation of Na^+ and K^+ currents into components.



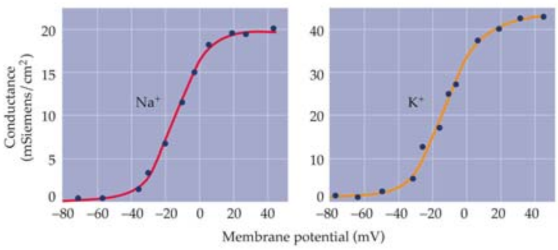
Use toxins or pharmacological substances

3.6 Membrane conductance changes are time- and voltage-dependent (HH used I=g*(Vm-Erev)



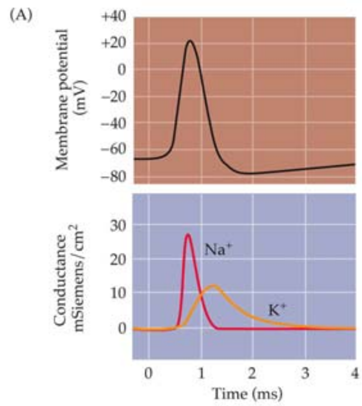
So conductance g=f(V,t), from I=g(V-Erev)

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

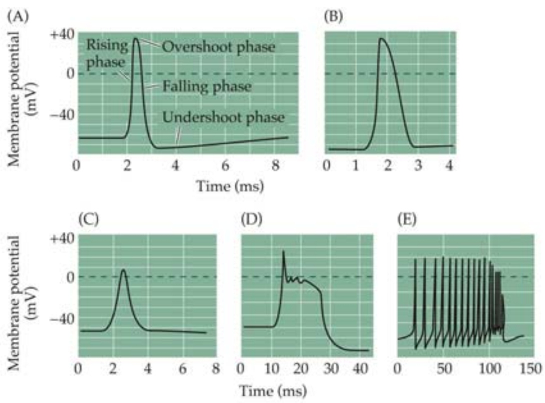


... but Na^+ conductance decreases over time again

3.8 Mathematical reconstruction of the action potential – assumption of gating particles



Box B Action Potential Form and Nomenclature

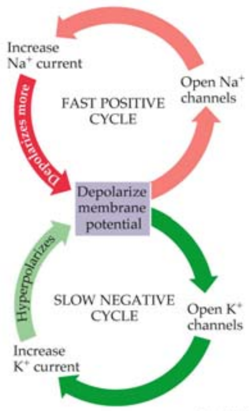


3.9 Feedback cycles responsible for membrane potential changes.

$I_{leak}=g_{leak}*(Vm-E_K)$

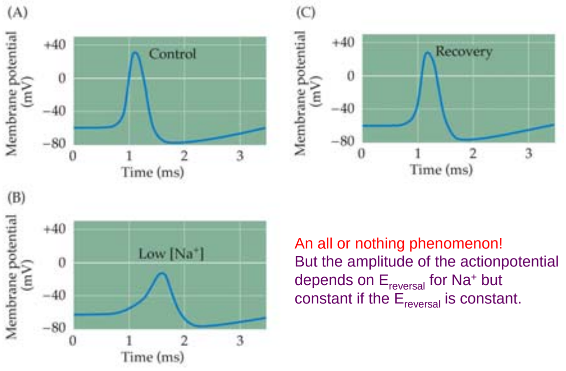
$I_{Na}=g_{Na}*(Vm-E_{Na})$

If $I_{leak}>I_{Na}$ then the depolarization is counteracted. Otherwise the depolarization is further enhanced.



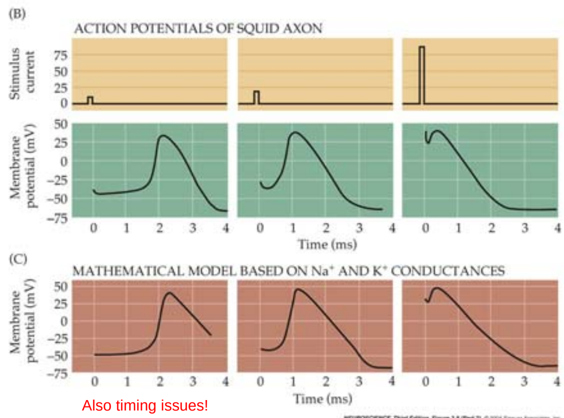
- Action potential is a threshold phenomenon
- Note that height of the action potential can vary depending on extracellular environment

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



An all or nothing phenomenon!
But the amplitude of the actionpotential depends on $E_{reversal}$ for Na^{+} but constant if the $E_{reversal}$ is constant.

3.8 Mathematical reconstruction of the action potential – exp vs simulations

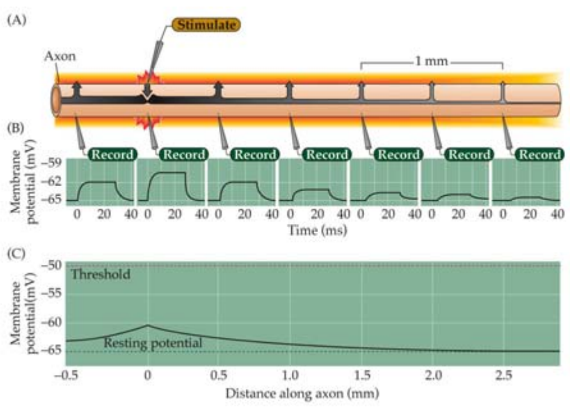


Also timing issues!

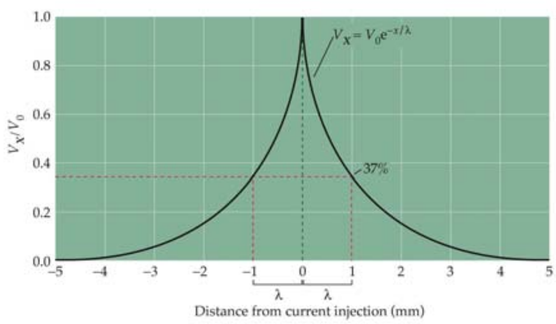
Hodgkin-Huxley models!

Hur fortleds aktionpotentialerna till nästa cell?

3.10 Passive current flow in an axon. (Part 1)

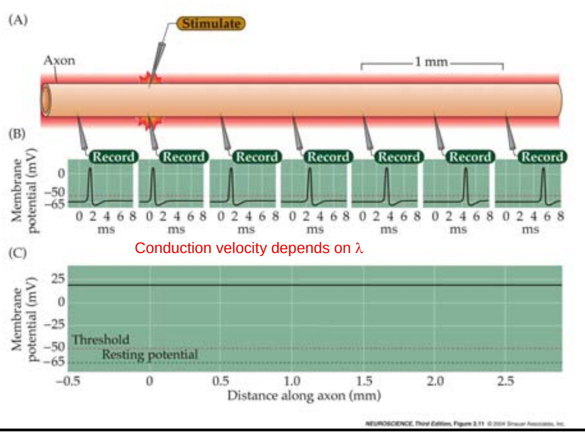


Box C Passive Membrane Properties (Part 1)



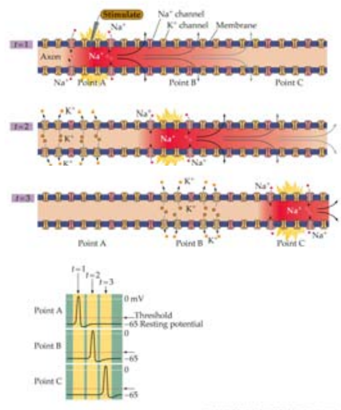
$\lambda = \mathrm{sqrt}(R_{membrane}/(R_{internal}+R_{extracellular}))$

3.11 Propagation of an action potential.

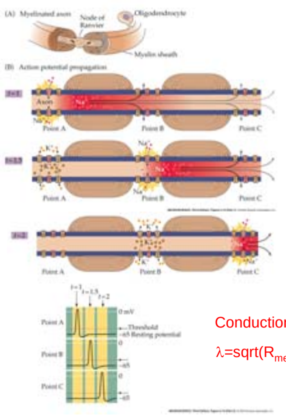


Conduction velocity depends on λ

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



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



Conduction velocity depends on λ

$\lambda = \mathrm{sqrt}(R_{membrane}/(R_{internal}+R_{extracellular}))$

Review Questions for Chapter 2:
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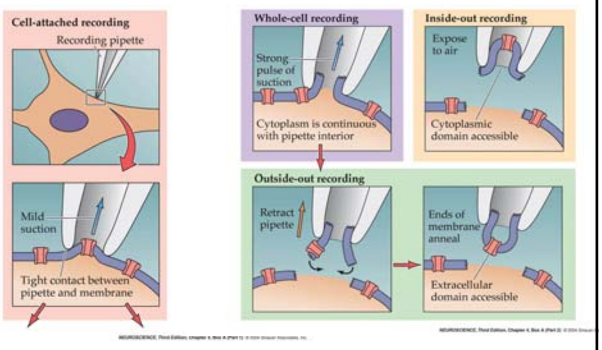
Review Questions for Chapter 3:
Voltage-Dependent Membrane Permeability

1. What is the voltage clamp method? Explain how it allowed Hodgkin and Huxley to determine the contribution of Na^+ and K^+ conductances to the action potential.
2. Does current flow from positive to negative, or negative to positive? Which way does current flow across the membrane during the rising phase of the action potential? During the falling phase?
3. Suppose you are recording action potentials from a neuron. How would the action potential be affected if you remove Na^+ from the external medium? What if you remove external K^+ instead?
4. How does the voltage sensitivity of K^+ conductance contribute to the action potential?
5. Do unmyelinated axons carry action potentials? Draw a diagram to help explain the regenerative property of the action potential, using the concepts of active and passive current flow.
6. What is the purpose of myelin? Explain how myelin speeds the conduction of the action potential.
7. Why don't action potentials turn around and go back up the axon?
8. Other terms to know:
   - tetrodotoxin
   - saltatory conduction
   - nodes of Ranvier
   - membrane conductance, permeability, resistance
   - multiple sclerosis

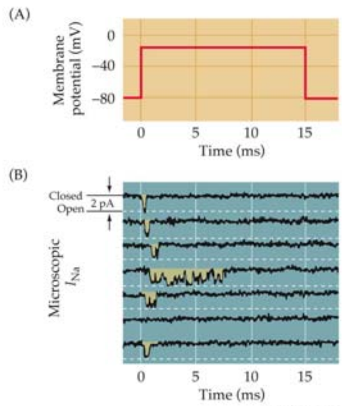
Hur vet man så mycket om olika jonkanaler?

- Patch clamp
- Farmaka som blockar/stim

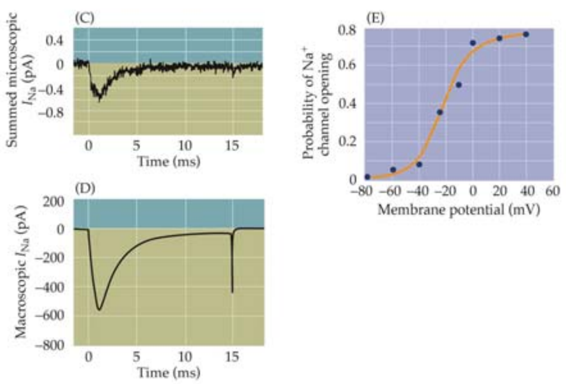
Box A The Patch Clamp Method (Part 1)



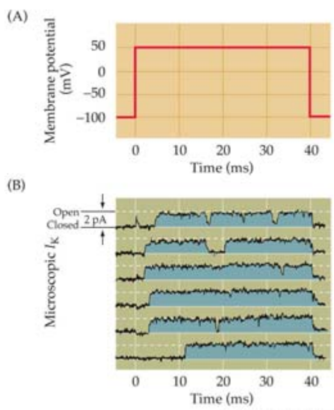
4.1 Measurements of ionic currents flowing through single Na^+ channels. (Part 1)



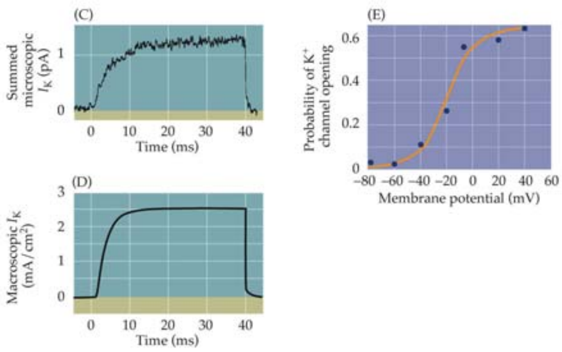
4.1 Measurements of ionic currents flowing through single Na^+ channels. (Part 2)



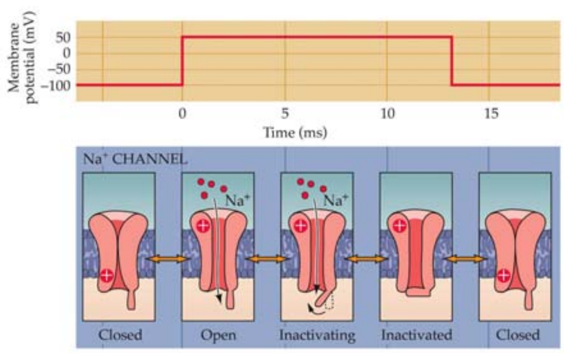
4.2 Measurements of ionic currents flowing through single K^+ channels. (Part 1)



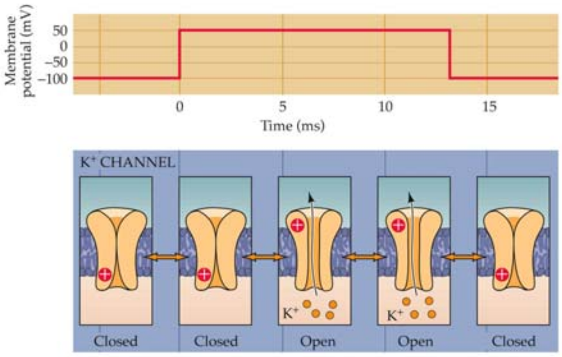
4.2 Measurements of ionic currents flowing through single K^+ channels. (Part 2)



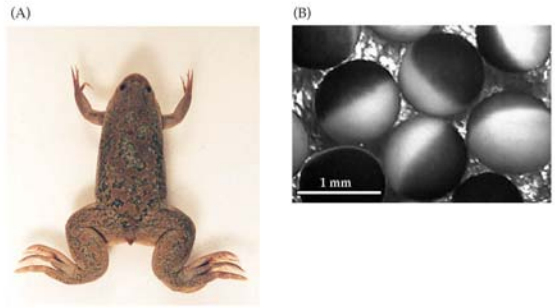
4.3 Functional states of voltage-gated Na^+ and K^+ channels. (Part 1)



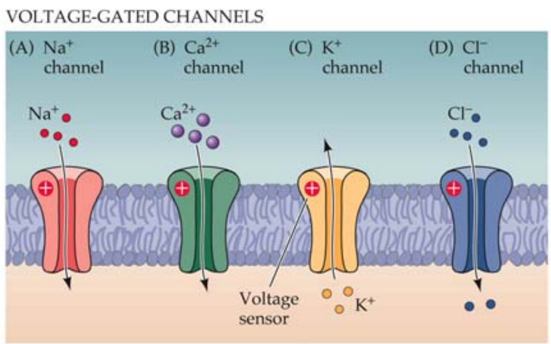
4.3 Functional states of voltage-gated Na^+ and K^+ channels. (Part 2)



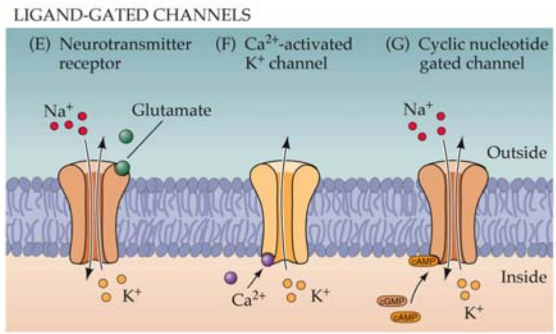
Box B Expression of Ion Channels in *Xenopus* Oocytes (Part 1)



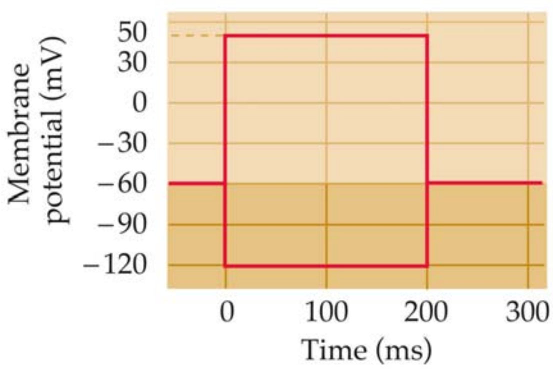
4.4 Types of voltage-gated ion channels. (Part 1)



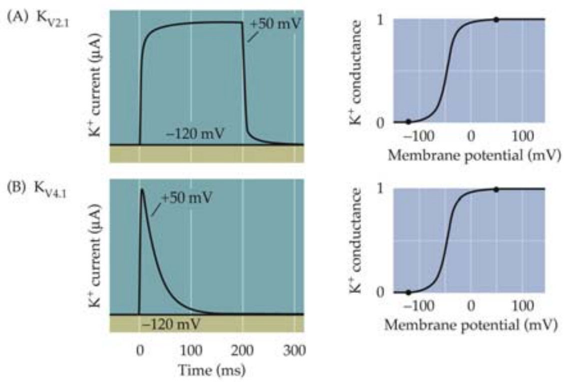
4.4 Types of voltage-gated ion channels. (Part 2)



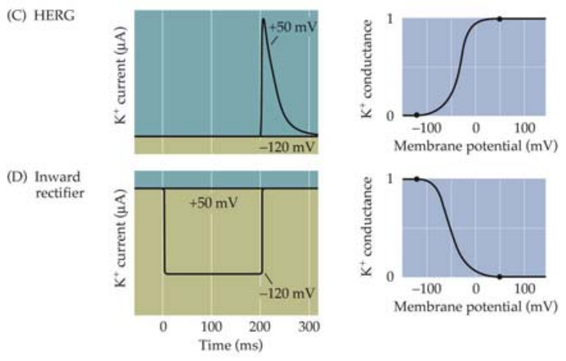
4.5 Diverse properties of K^+ channels. (Part 1)



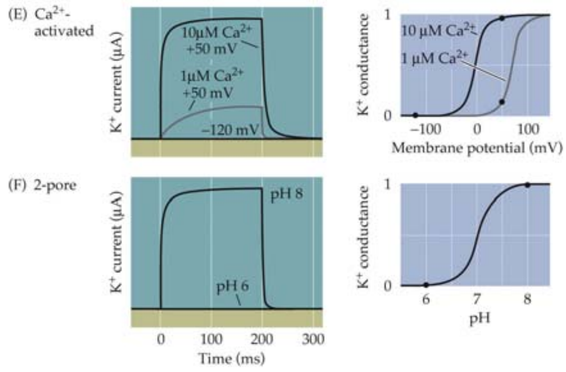
4.5 Diverse properties of K^+ channels. (Part 2)



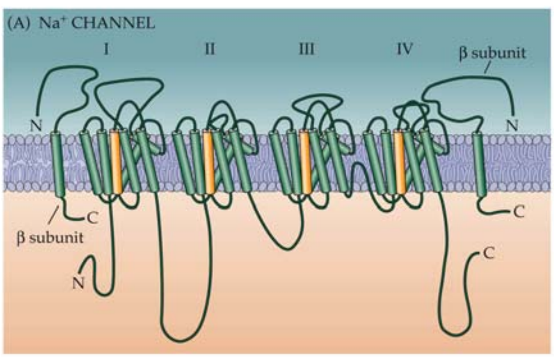
4.5 Diverse properties of K^+ channels. (Part 3)



4.5 Diverse properties of K^+ channels. (Part 4)



4.6 Topology of principal subunits of voltage-gated Na^+, Ca^{2+}, K^+, and Cl^- channels. (Part 1)



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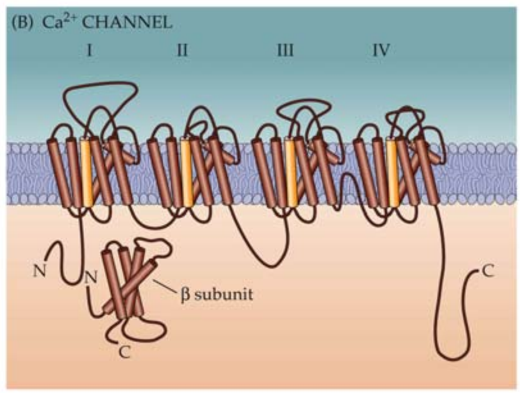

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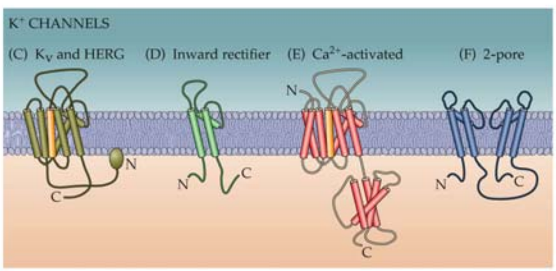
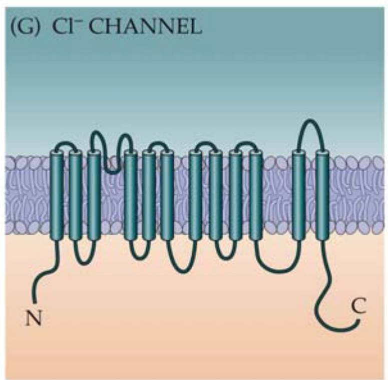
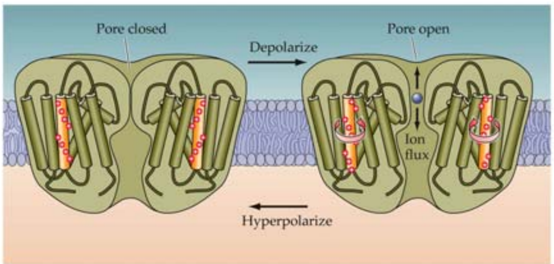


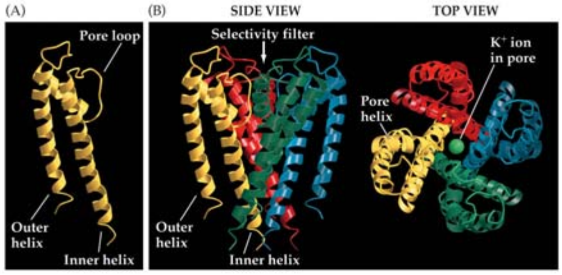
4.6 Topology of principal subunits of voltage-gated Na^+, Ca^{2+}, K^+, and Cl^- channels. (Part 4)



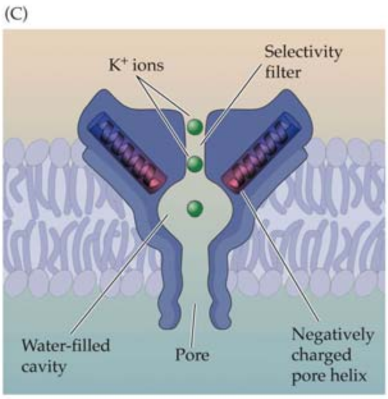
4.7 A charged voltage sensor permits voltage-dependent gating of ion channels.



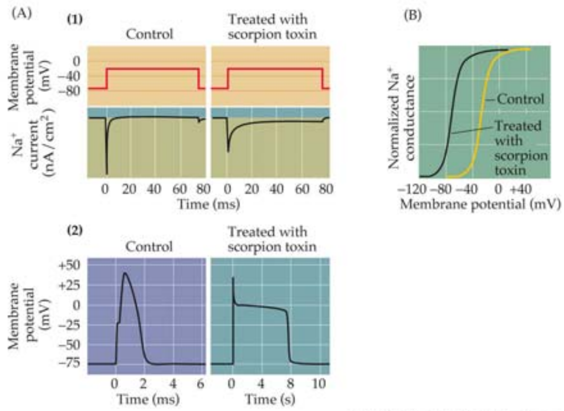
4.8 Structure of a simple bacterial K^+ channel determined by crystallography. (Part 1)



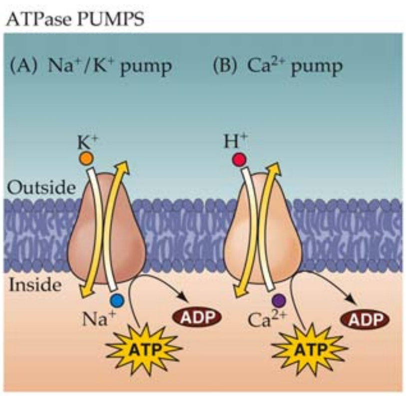
4.8 Structure of a simple bacterial K^+ channel determined by crystallography. (Part 2)



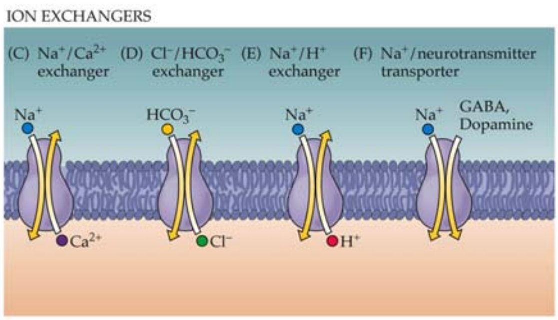
Box C Toxins that Poison Ion Channels



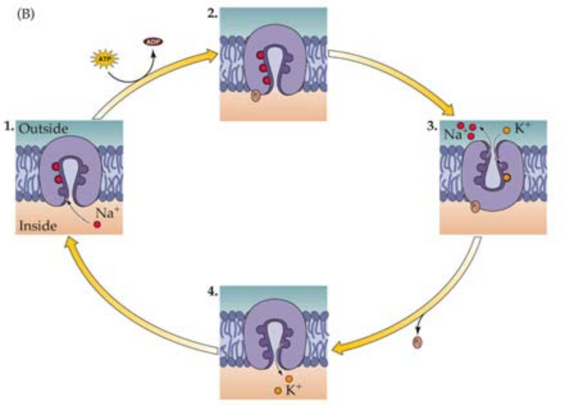
4.10 Examples of ion transporters found in cell membranes. (Part 1)



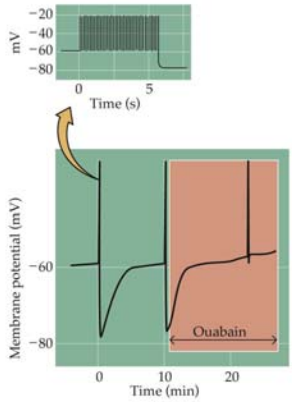
4.10 Examples of ion transporters found in cell membranes. (Part 2)



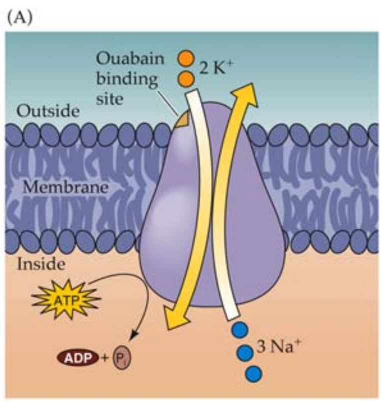
4.11 Ionic movements due to the Na⁺/K⁺ pump. (Part 2)



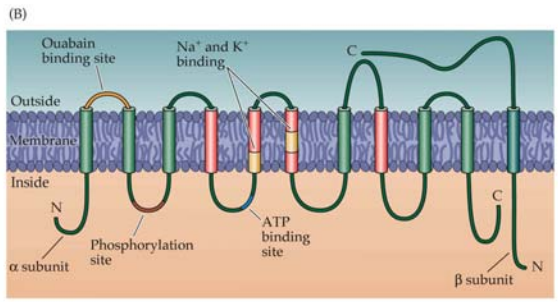
4.12 Electrogenic transport of ions by the Na⁺/K⁺ pump can influence membrane potential.



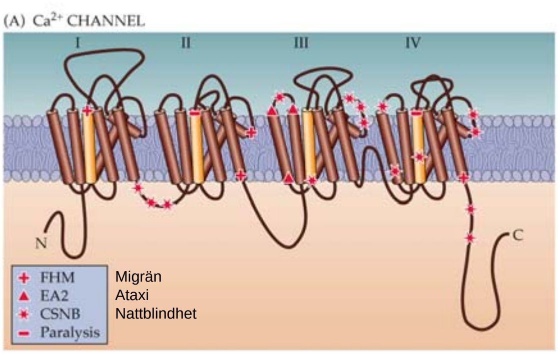
4.13 Molecular structure of the Na⁺/K⁺ pump. (Part 1)



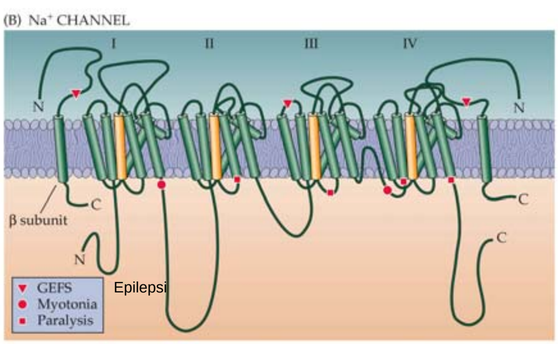
4.13 Molecular structure of the Na⁺/K⁺ pump. (Part 2)



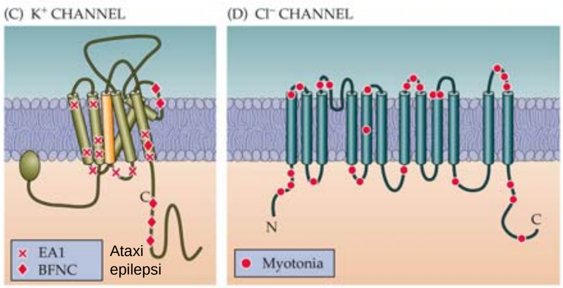
Box D Diseases Caused by Altered Ion Channels (Part 1)



Box D Diseases Caused by Altered Ion Channels (Part 2)



Box D Diseases Caused by Altered Ion Channels (Part 3)



Review Questions for Chapter 4:
Channels and Transporters

1. Why did Hodgkin and Huxley surmise that neuronal membranes must have ion channels? What properties did they think ion channels would have? What properties did they not anticipate?

2. What is patch clamping useful for?

3. What makes the frog oocyte a useful expression system for studying proteins such as ion channels?

4. Compare the responses of voltage-gated Na^+ and K^+ channels to depolarization. How would you expect these channel properties to affect the shape, duration and frequency of action potentials?

5. Compare ion channels and active transporters with regard to structure and function.

6. What must all active transporters be able to do? Distinguish between the two classes of active transporters: ATPase pumps and ion exchangers. Give an example of each.

7. What experimental approaches can be used to determine which ions can pass through a particular ion channel?

8. There are nearly 100 genes for K^+ channels. Why so many? Wouldn't one or two be enough?

9. List major stimulus types that can gate (open or close) various kinds of ion channels.

10. Describe briefly how each of the following can be used to learn about ion channels:
    - X-ray crystallography
    - expression of mRNA in *Xenopus* oocyte
    - patch clamping
    - mutagenesis
    - toxins

11. What do Cl^-, Ca^{2+}, N^+ and K^+ channels have in common structurally? How are they different?

12. Does the Na^+/K^+ pump make a major contribution to a neuron's resting potential? Explain.

13. Other terms to know:
    - microscopic and macroscopic currents
    - cyclic nucleotide gated channels
    - channelopathies
    - electrogenic pumps
    - ouabain