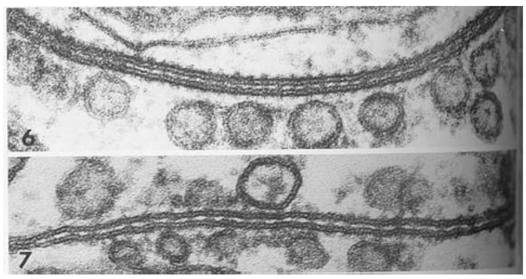
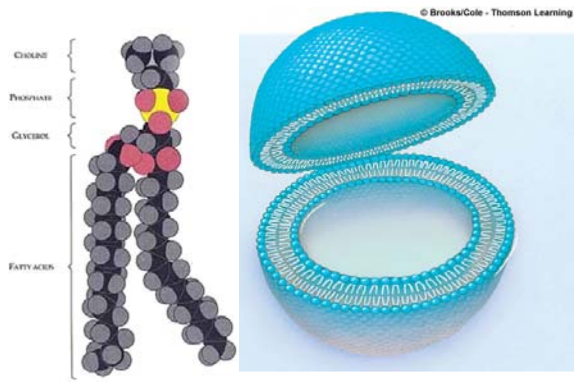
Νευροφυσιολογία και Αισθήσεις

Διάλεξη 3
Κυτταρική Μεμβράνη Σε Ηρεμία
(Membrane at Rest)

Membrane Structure

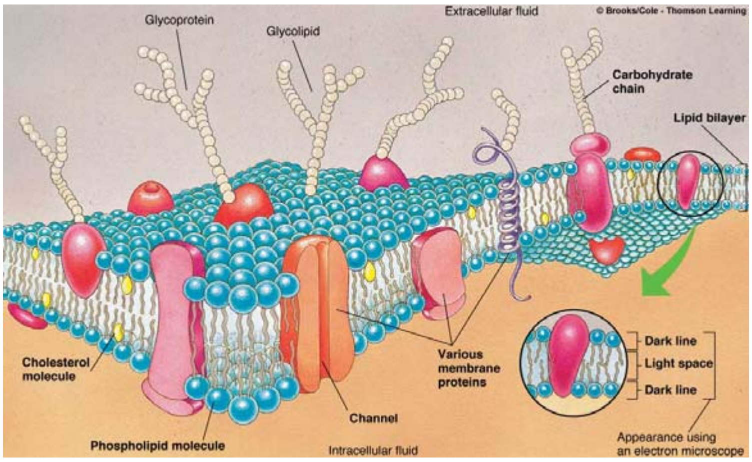
- **Plasma membrane**
  - Fluid lipid bilayer embedded with proteins and cholesterol
- **Phospolipid bilayer**
  - Phospholipids
    - Polar (charged) hydrophilic head
    - Two nonpolar hydrophobic fatty acid chains
  - Assemble in a bilayer which separates two water-based volumes, the ICF and ECF
  - Barrier to passage of water-soluble substances
  - Not solid! “Fluid mosaic surface” → fluidity of membrane





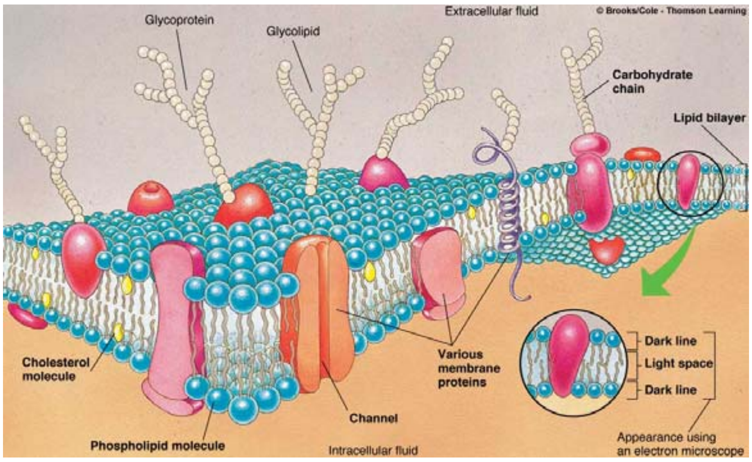
Membrane Structure

- **Other constituents**
  - Cholesterol stabilizes the membrane
  - Small amounts of carbohydrate "sugars" (glycoproteins or glycolipids)
  - Proteins are attached or inserted in the membrane
    - Channels
    - Carrier molecules
    - Receptors
    - Membrane bound enzymes
    - Cell adhesion molecules



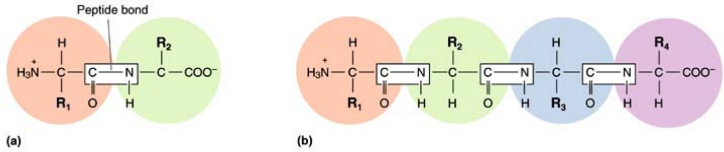
Membrane Structure

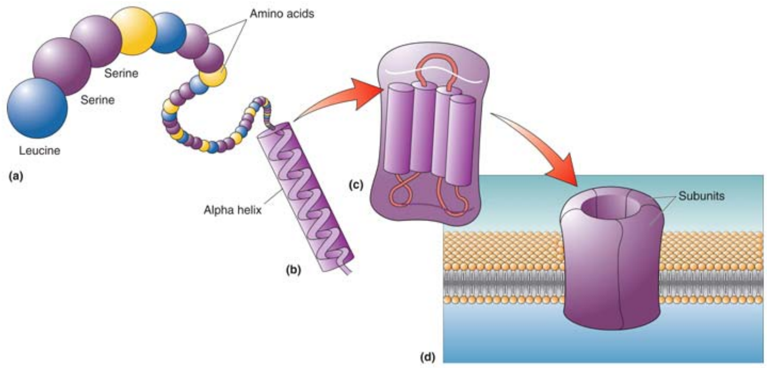
- **Other constituents**
  - Proteins are attached or inserted in the membrane
    - Highly selective, water-filled, channels
    - Carrier molecules which transfer specific large molecules across the membrane
    - Docking marker acceptors for binding with secretory vesicles
    - Receptors for recognizing specific molecules
    - Membrane bound enzymes for catalyzing reactions
    - Cell adhesion molecules for adhesion and signaling



Proteins

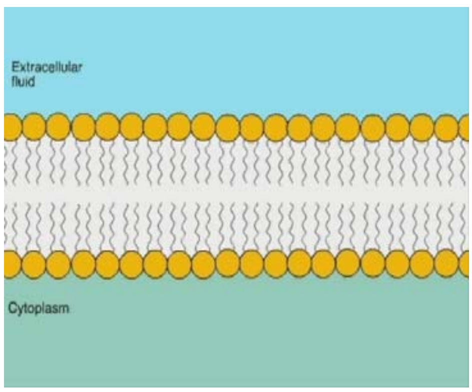
- **Synthesized by ribosomes**
- **Stucture**
  - Primary structure
    - Chain with peptide bonds
    - Amino acids (20 types)
    - Polypeptides
  - Secondary structure
    - Foldings, helices, etc
  - Tertiary structure
    - 3-d foldings
    - Final form
  - Quaternary structure
    - Combination of two or more proteins





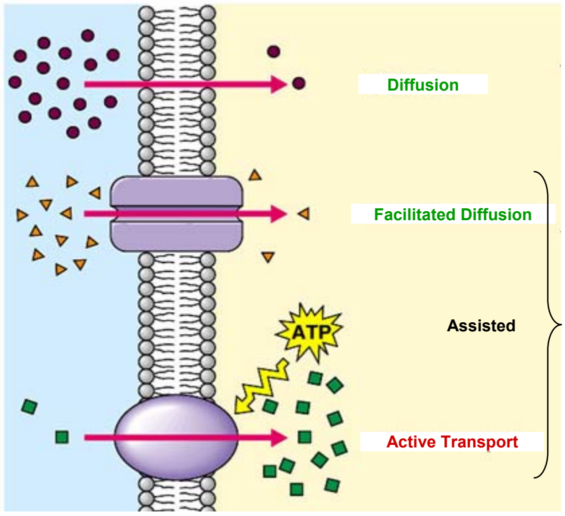
Membrane Transport

- **Selective membrane permeability**
  - Lipid soluble substances (e.g. some vitamins) → high
  - Small substances (O_2, CO_2, etc) → high
  - Charged, ionic substances → none
  - Particles can also cross through substance-specific channels and carriers



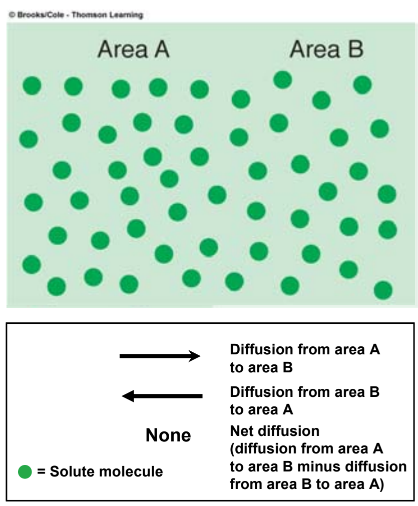
Membrane Transport

- **Unassisted vs. assisted transport**
  - Unassisted → permeable molecules can cross the membrane
  - Assisted →impermeable molecules must be assisted by other proteins in order to cross the membrane
- **Energy expenditure**
  - Passive membrane transport
    - Due to forces that require no energy expenditure
    - Can be unassisted or assisted
  - Active membrane transport
    - Require energy expenditure from the cell
    - Always assisted



Unassisted Membrane Transport

- **Unassisted transport due to**
  - Concentration gradient
  - Electrical gradient
- **Diffusion down a concentration gradient**
  - Random motion of molecules
  - Net diffusion = net motion in direction of low concentration
  - Concentrations tends to equalize → steady state
  - E.g. O_2 transferred by diffusion
    - Lungs → Low concentration in blood, high in air
    - Tissue → Low concentration in tissue, high in blood



Unassisted Membrane Transport

- **Fick's Law of Diffusion**
  - Net diffusion rate (Q) depends on

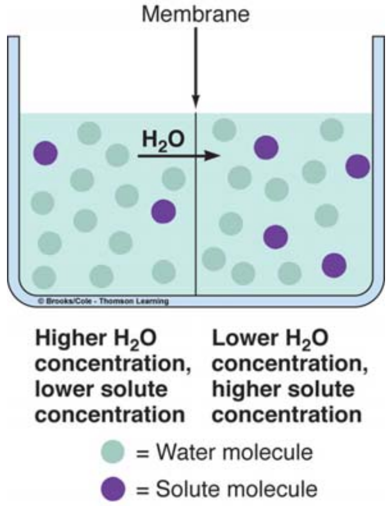
  - Concentration gradient (ΔC)
  - Permeability of membrane to substance (P)
  - Surface area of membrane (A)
  - Molecular weight of substance (MW)
  - Distance or thickness (ΔX)

$$Q = \frac{\Delta C \cdot P \cdot A}{MW \cdot \Delta X}$$

Unassisted Membrane Transport

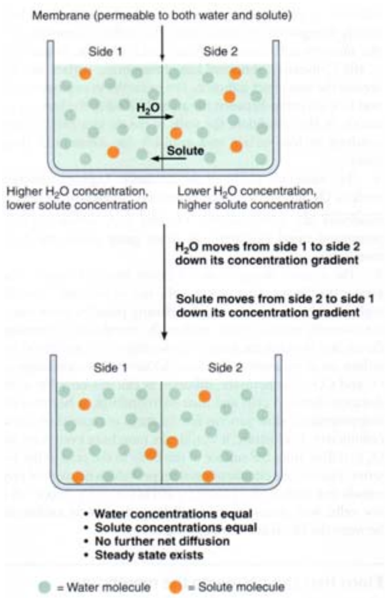
- **Osmosis**
  - Net diffusion of water (either through membrane or through porins)
  - Water flows to regions of lower water (i.e. higher solute) concentration → osmotic pressure
  - Tends to equalize the concentrations

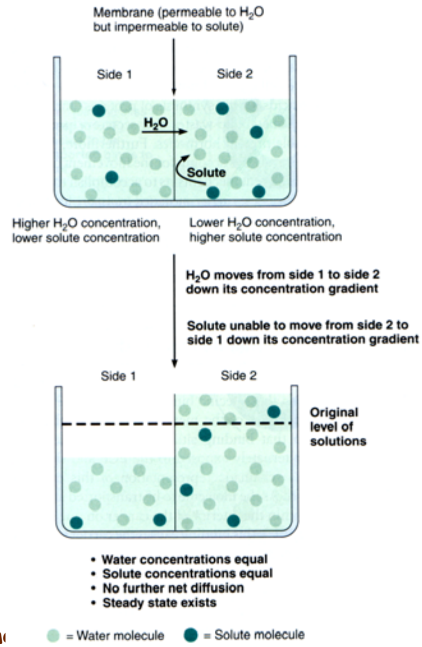
  - Osmosis when a membrane separates
    - Unequal volumes of a penetrating solute
    - Unequal volumes of non-penetrating solute
    - Pure water from a non-penetrating solute



Unassisted Membrane Transport

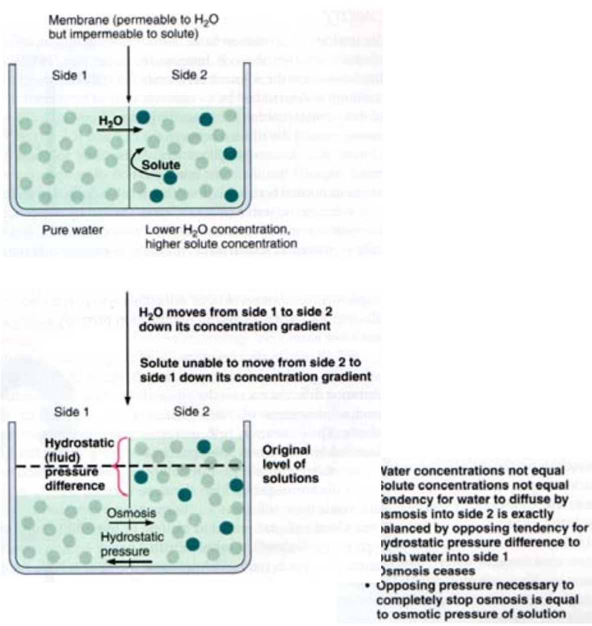
- Unequal volumes of a penetrating solute
- Unequal volumes of non-penetrating solute





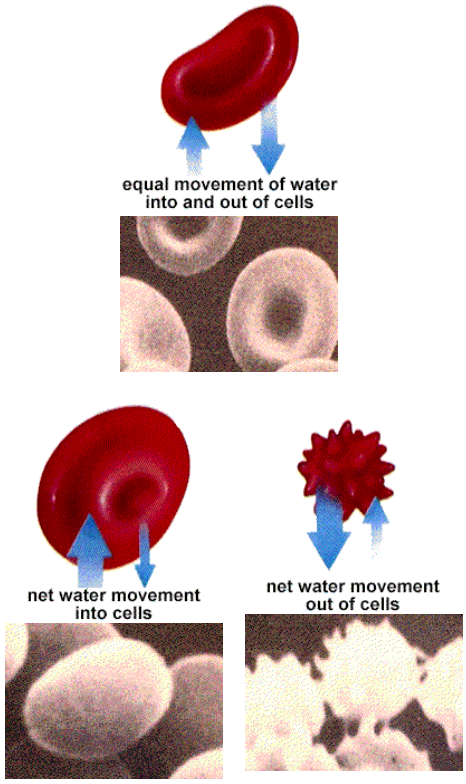
Unassisted Membrane Transport

- Pure water from a non-penetrating solute



Unassisted Membrane Transport

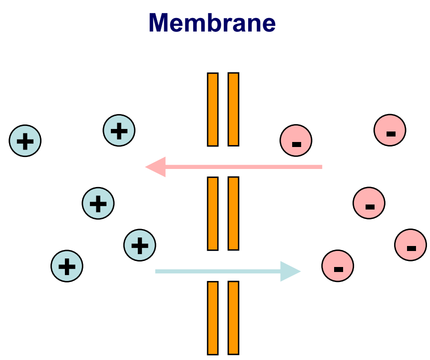
- **Tonicity of a solution**
  - Isotonic
    - Same concentration of non-penetrating solutes as the cell
    - No water movement by osmosis
    - Cell volume ~
  - Hypotonic
    - Lower concentration of non-penetrating solutes
    - Water moves in the cell
    - Cell volume ↑
  - Hypertonic
    - Higher concentration of non-penetrating solutes
    - Water moves out of the cell
    - Cell volume ↓



Unassisted Membrane Transport

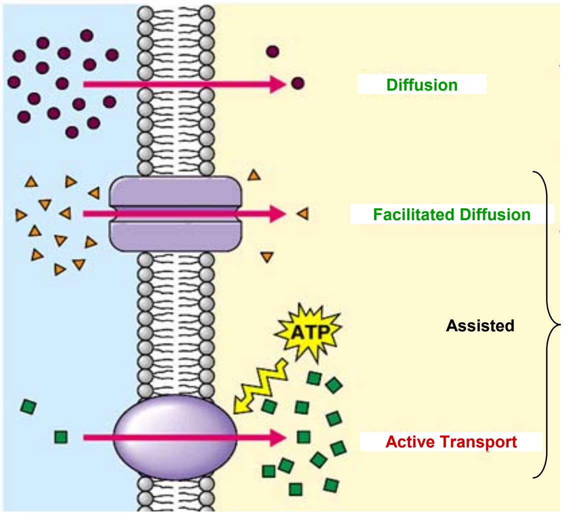
- **Diffusion down an electrical gradient**
  - Ions diffuse down electrical gradients → to opposite charge
  - If electrical gradient exists across a membrane, permeable ions will diffuse passively

- **Combination of concentration and charge**
  - Electrochemical gradient
  - Tend to balance out (we will see this in action later)



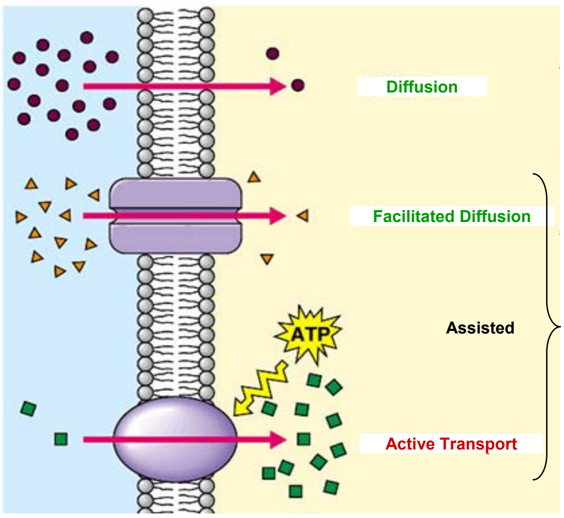
Assisted Membrane Transport

- **Cells must be able to exchange larger molecules**
  - Glucose, aminoacids, waste, etc.
- **Two types of assisted transport**
  - Carrier mediated transport
    - May be passive or active
    - Small molecules
  - Vesicular transport
    - Always active
    - Very large molecules, particles



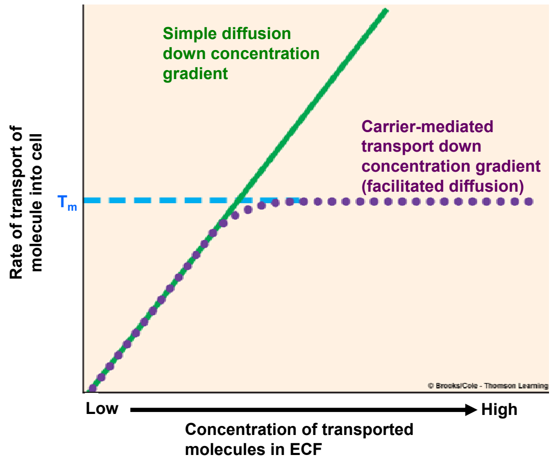
Assisted Membrane Transport

- **Carrier mediated transport**
  - Carriers are proteins that span the membrane
  - They change their shape to help molecules cross from one side to the other
  - Three categories
    - Facilitated diffusion
    - Active transport
    - Secondary active transport



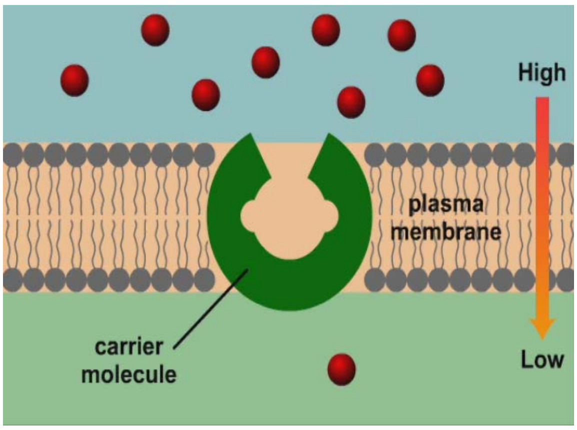
Assisted Membrane Transport

- **Important characteristics of carrier mediated transport**
  - Specificity
    - One or a few similar molecules
    - No crossing over
  - Saturation
    - There is a maximum amount of substance a set of carriers can transport in a given time → Transport maximum (Tm)
    - Number of carriers can be upregulated (e.g. insuline → ↑ glucose carriers)
  - Competition
    - If the carrier can transport more that one substance → competition between substances



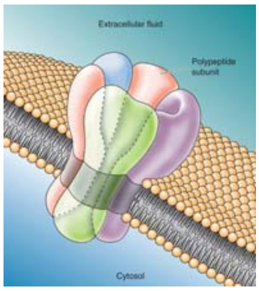
Assisted Membrane Transport

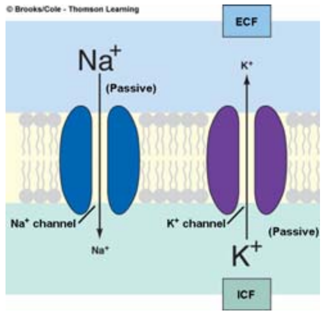
- **Facilitated Diffusion**
  - No energy expenditure
  - Transport molecules, which can not cross the cell membrane, down their concentration gradient
  - Binding triggers conformation change → unloading on the other side
  - Carrier can bind on either side of membrane
  - High concentration side binding is more likely
  - Net movement in the direction of the concentration gradient
  - E.g. glucose

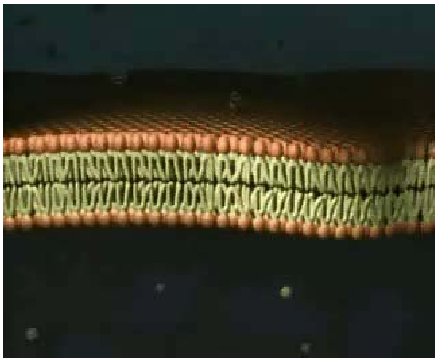


Assisted Membrane Transport

- **Diffusion through channels**
  - Membrane proteins form channels → water filled pores through the membrane
  - Diffusion of specific molecules through specific channels
    - E.g. Na^+ or K^+ channels
  - Diffusion down their electrochemical gradients (passive)
  - Can be gated (i.e. opened or closed) from external stimuli
    - Electrically gated
    - Chemically gated

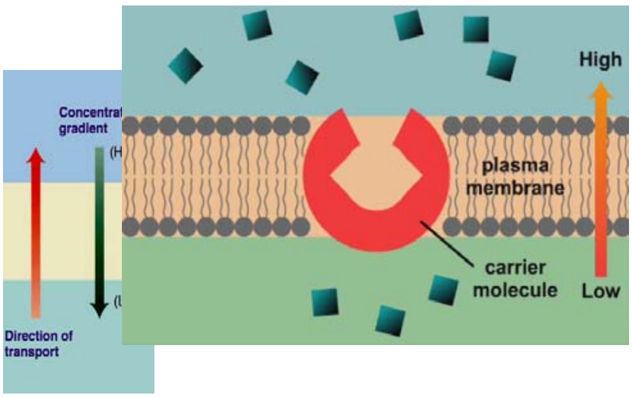






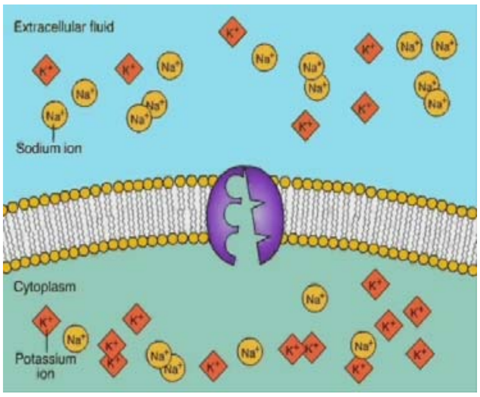
Assisted Membrane Transport

- **Active Transport**
  - Transport molecules against their concentration gradient
  - Energy expenditure
  - A.k.a. “ATPase pumps” or “pumps”
  - On the low concentration side
    - Phosphorylation by ATPase (ATP→ADP)
    - High affinity sites bind solute
    - Conformation change → flip to the other side
  - On high concentration side
    - Dephosphorylation
    - Reduced affinity to the solute
    - Unload the solute
    - Return to previous conformation



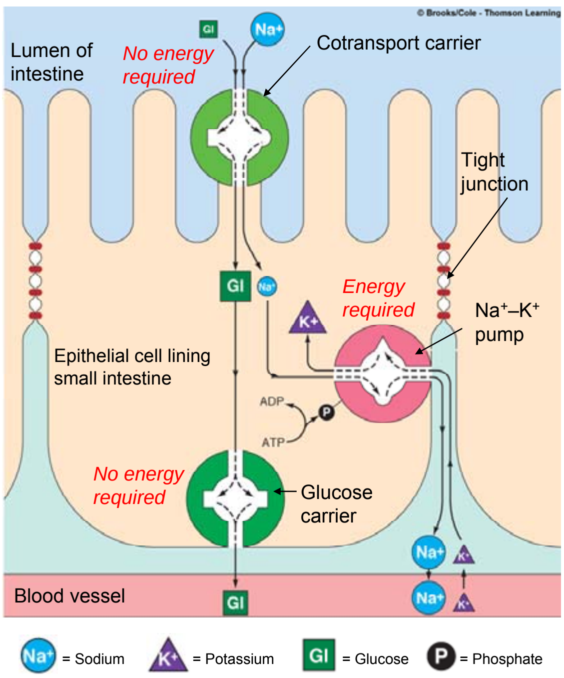
Assisted Membrane Transport

- **Examples of active pumps**
- **H^+-pump**
  - Transports H^+ into stomach
  - Against gradients of x 3-4.10^6
- **Na^+-K^+-pump**
  - All cells
  - 3xNa^+ out, 2xK^+ in
  - Phosphorylation increases affinity to Na^+
  - Dephosphorylation increases affinity to K^+
  - Very important role
    - Establish Na^+ and K^+ concentration gradients important for nerve and muscle function
    - Maintain cell volume by controlling solute regulation
    - Co-transport of glucose (see next)



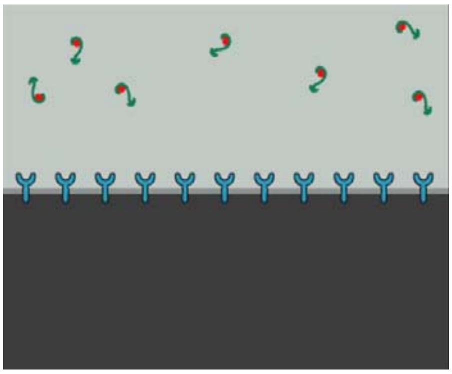
Assisted Membrane Transport

- **Secondary Active Transport**
  - Intestine and kidneys must transport glucose <u>against</u> its concentration gradient
  - Cotransport carrier = Glucose + Na^+
    - Cotransport uses Na^+ gradient to push along glucose against its concentration gradient
  - Na^+-K^+-pump maintains Na^+ concentration gradient (ATP required)
  - Energy required for the overall process → secondary active transport



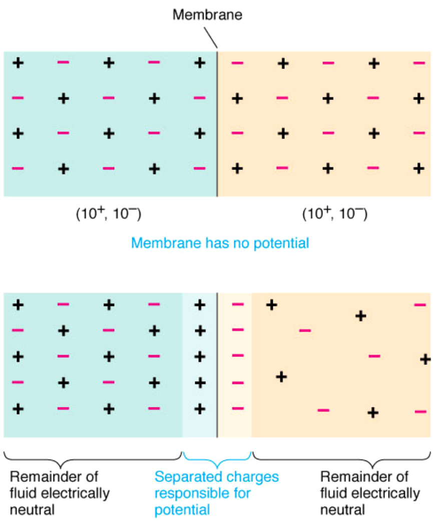
Assisted Membrane Transport

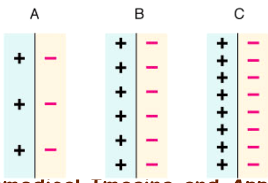
- **Vesicular Transport**
  - Endocytosis
    - Membrane surrounds the molecules or particle creating a vescicle
    - Transport inside the cell and
      - Fusion with lysosome
      - Transport directly to the opposite site
  - Exocytosis
    - Opposite of endocytosis
    - Fusion of vesicle with membrane and release of contents to the other side
  - Slow process for larger particles (bacteria) or larger quantities (stored hormones)
  - Membrane size must be maintained (added or retrieved)
  - See table 3-2, p.74



Membrane Potential

- **Opposite charges attract and similar repel**
  - Energy must be expended to separate opposite charges
  - Energy can be harnessed from the field created by opposite charges
- **Membrane potential → opposite charges across the membrane**
  - Equal number of + and – on each side → electrically neutral
  - Charges separated (more + on one side, more – on other) → electrical potential
  - Measured in V
- **Note:**
  - Only a very small number of charges is involved → majority of ECF and ICF are still neutral
  - More charge → ↑ V





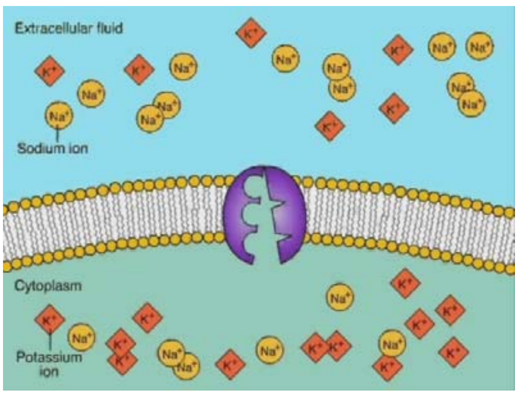
Membrane Potential

- **All cells are electrically polarized**
- **Changes in membrane potential serve as signals (nerve & muscle)**
- **Resting membrane potential**
  - Potential at steady state
  - Primarily by Na^+, K^+, and A^- (negatively charges intracellular proteins)
  - Note table 3-3
    - A^- found only in cells
    - Na^+ and K^+ can diffuse through channels ($K^+ > Na^+$)
    - Concentration of Na^+ and K^+ maintained by Na^+-K^+-pump

ION	Concentration (millmoles/liter)		Relative Permeability
	Extracellular	Intracellular	
Na^+	150	15	1
K^+	5	150	50-75
A^-	0	65	0

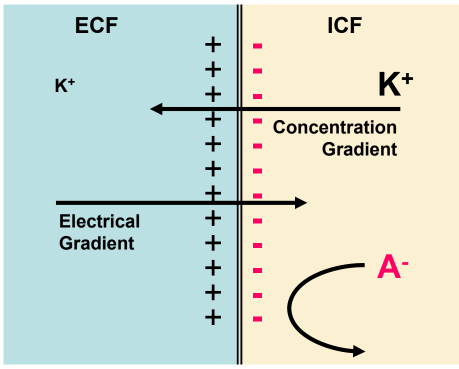
Membrane Potential

- **Resting membrane potential**
  - Effect of Na^+-K^+-pump
    - Pumps 3 Na^+ out for every 2 K^+ in
    - Net + charge in ECF
    - About 20% of membrane potential
    - Most critical role → maintenance of concentrations



Membrane Potential

- **Resting membrane potential**
  - Effect of K^+ alone
    - Assume no potential and only K^+ and A^- present
    - K^+ will tend to flow out
    - Net + charge in the ECF, net – charge in ICF
    - Potential opposes flow of K^+
    - Forces balance → no net flow
    - Equilibrium → K^+ equilibrium potential (calculated from Nerst equation)

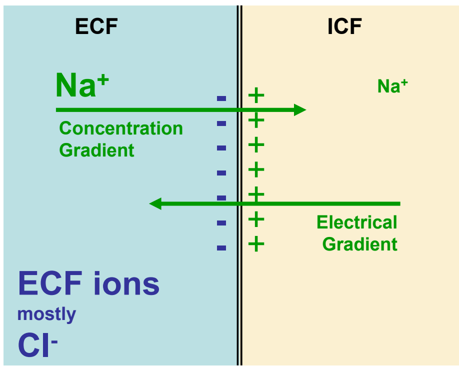


$$E=\frac{61}{z}\log\frac{C_o}{C_i} \Rightarrow E_k=\frac{61}{1}\log\frac{5mM}{150mM}=-90mV$$

- Concentration does not significantly change since infinitesimal changes of K^+ are enough to set up the potential

Membrane Potential

- **Resting membrane potential**
  - Effect of Na^+ alone
    - Assume no potential and only Na^+ and Cl^- present
    - Na^+ will tend to flow in
    - Net + charge in the ICF, net – charge in ECF
    - Potential opposes flow of Na^+
    - Forces balance → no net flow
    - Equilibrium → Na^+ equilibrium potential (calculated from Nerst equation)

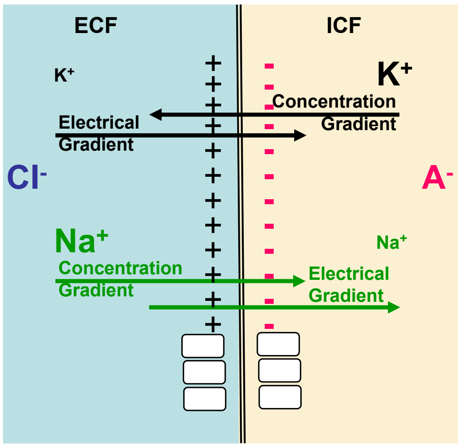


$$E=\frac{61}{z}\log\frac{C_o}{C_i} \Rightarrow E_k=\frac{61}{1}\log\frac{150mM}{15mM}=+60mV$$

- Concentration does not significantly change since infinitesimal changes of Na^+ are enough to set up the potential

Membrane Potential

- **Resting membrane potential**
  - Concurrent effects
  - Both K^+ and Na^+ present
  - The higher the permeability the greater the tendency to drive the membrane potential to its equilibrium value
  - Na^+ neutralizes some of the K^+ potential but not entirely
    - K^+ permeability is much higher
  - Resting membrane potential = -70mV



Δυναμικό Μεμβράνης

- **Nerst Equation**

$$E = \frac{RT}{zF}\ln\frac{C_o}{C_i} = 2.303\frac{RT}{zF}\log\frac{C_o}{C_i} = \frac{61.54mV}{z}\log\frac{C_o}{C_i} \quad \text{(T=37}^o\text{C)}$$

- **GHK Equation (Goldman-Hodgkin-Katz)**

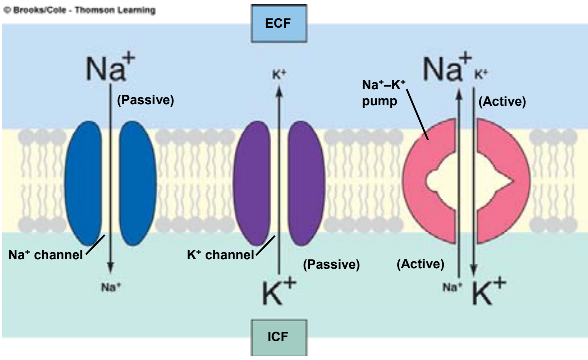
$$E = \frac{RT}{F}\ln\frac{\sum P_{C^+}[C^+]_o + \sum P_{A^-}[A^-]_i}{\sum P_{C^+}[C^+]_i + \sum P_{A^-}[A^-]_o} = 2.303\frac{RT}{F}\log\frac{\sum P_{C^+}[C^+]_o + \sum P_{A^-}[A^-]_i}{\sum P_{C^+}[C^+]_i + \sum P_{A^-}[A^-]_o}$$

$$E = 61.54mV\log\frac{P_K[K]_o + P_{Na}[Na]_o}{P_K[K]_i + P_{Na}[Na]_i} \quad \text{(T=37}^o\text{C)}$$

- R: Gas constant = 8.314472 (Volts Coulomb)/(Kelvin mol)
- F: Faraday constant = 96 485.3383 (Coulomb)/(mol)
- z: Valance
- T: Absolute temperature = 273.16 + ^{o}C (Kelvin)

Membrane Potential

- **Balance of passive leaks and active pumping**
  - At -70 nm both K^+ and Na^+ continue to flow
  - Na^+-K^+-pump maintains the concentrations
  - Implication: cells need energy continuously just to maintain their membrane potential
- **Chloride movement at resting membrane potential**
  - Cl^- is the major anion of the ECF
  - Flow into the cell is counterbalanced by the membrane potential
  - Cl^- Resting potential = -70 mV
  - Cl^- distribution is passively established by the membrane potential



Next Lecture …

Διάλεξη 4

Δυναμικά Ενεργείας (Action Potentials)