

Cells to Systems Lecture 9:

Transport of molecules across cell membranes

Video 1

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VETS30015 / VETS90121

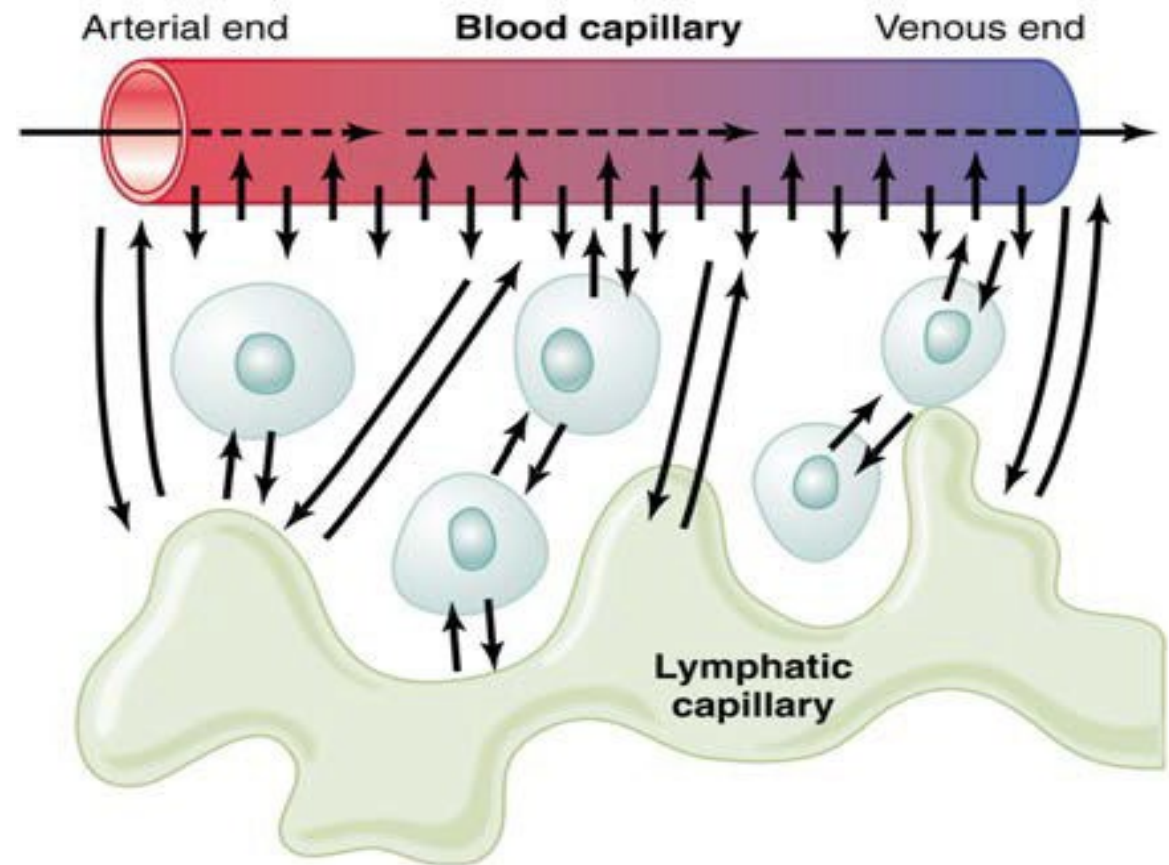


Lecture 9: ILOs

- Describe the composition of the cell membrane and explain how the distribution of phospholipids and proteins influences the membrane permeability to ions, hydrophilic and hydrophobic compounds, and cell-cell communication
- Describe how cells regulate the movement of substances across their membranes and the role of diffusion, facilitated diffusion, and primary and secondary active transport mechanisms
- Explain how energy from the Na^+ and K^+ electrochemical gradients across the plasma membrane are maintained

Transport of fluid and molecules across cell membranes

- Movement of fluid and solutes from blood to interstitial fluid (L8)
 - Diffusion, osmosis
 - Bulk flow and Starling' Forces
- Movement of fluid and solutes from interstitial fluid into cells (L9)
 - Diffusion
 - Facilitated Diffusion
 - Active Transport
 - Co-transport



Key functions of biological membranes

1. Selective Barrier

- Regulates flow of material into and out of the cell

2. Organization

- Form compartments (e.g. organelles)
- Help maintain separate and distinct molecular environments

3. Transport

- Contain specific molecular pumps and channels for transporting solutes

4. Controlling information flow

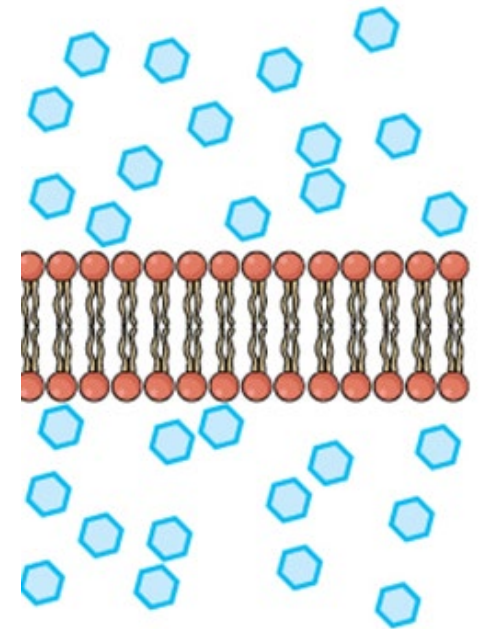
- Specific receptors for external signalling
- Generate chemical & electrical signals

5. Cell-cell interactions

- Cell recognition
- Cell adhesion

6. Reactions

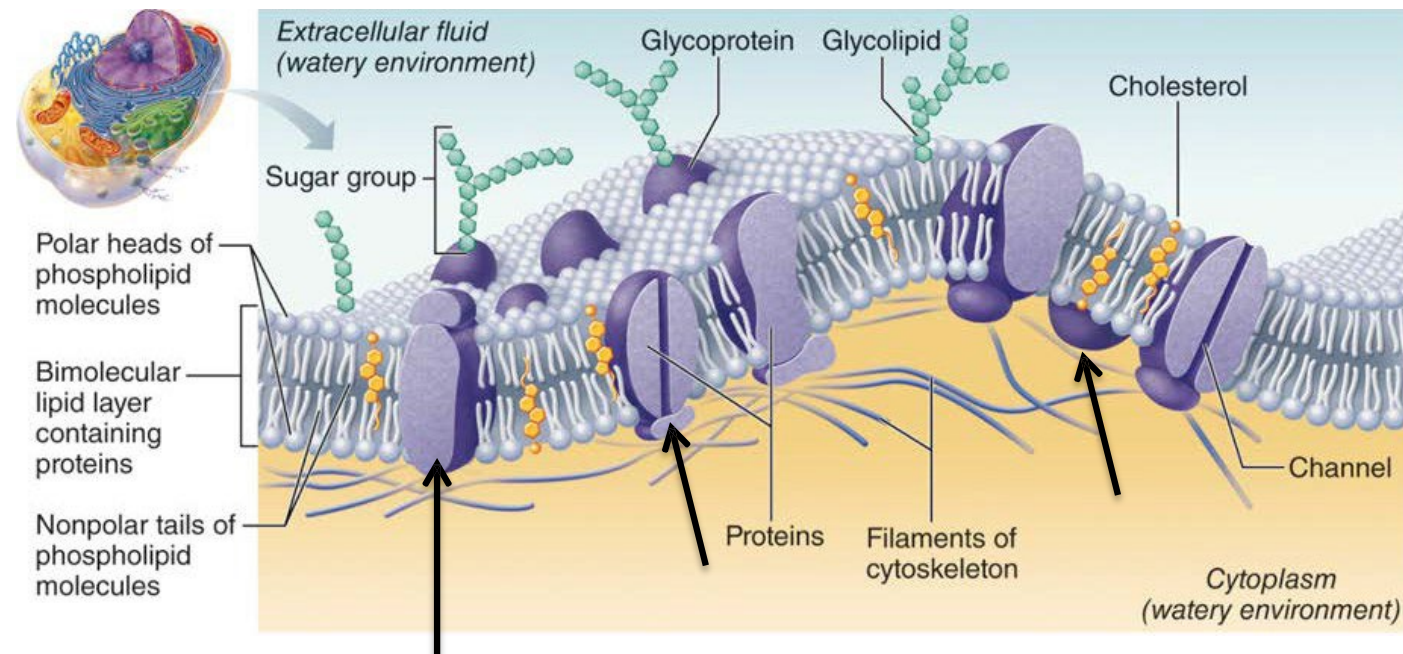
- Enzyme activity



Cell membrane structure and composition

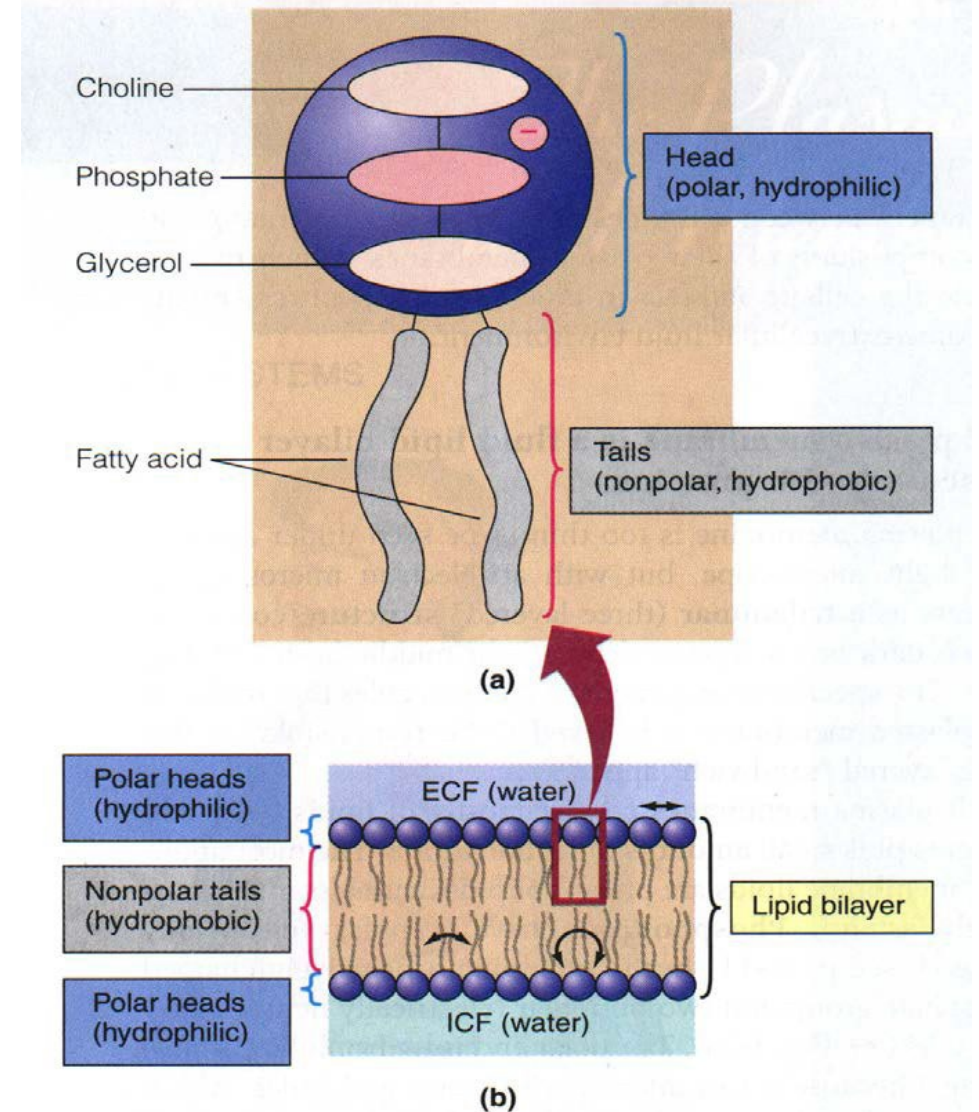
The cell membrane is composed of a phospholipid bilayer that regulates entry and exit of fluid and molecules

- Plasma membrane Structure:
 - Phospholipid bilayer
 - Proteins
 - Integral, surface
 - Cholesterol
 - Carbohydrates linked to proteins & lipids
- Fluid mosaic model:
 - Membrane proteins move freely in the lipid layer
 - Ever-changing pattern of proteins
 - Cytoskeleton can restrict proteins to specific areas of cell membrane



Phospholipid bilayer

- Lipid bilayer
- Phospholipids
 - ❖ Have a hydrophilic
 - Polar 'head group'
 - Attracted to water
 - ❖ Hydrophobic
 - Non polar 'tail' region
 - Fatty acids
- Cholesterol molecules are tucked between phospholipid molecules – support membrane fluidity



Lipid bilayer permeability: determined by size & solubility in lipid

Hydrophobic (lipid soluble)

Diffuses quickly

Hydrophilic (lipid insoluble)

Hydrophilic (polar) substances in membrane are sparingly soluble

1. Nonpolar molecules

Pass freely e.g., fatty acids, steroid hormones, CO_2 , & O_2 (act as nonpolar – because they are linear)

2. Small uncharged polar molecules

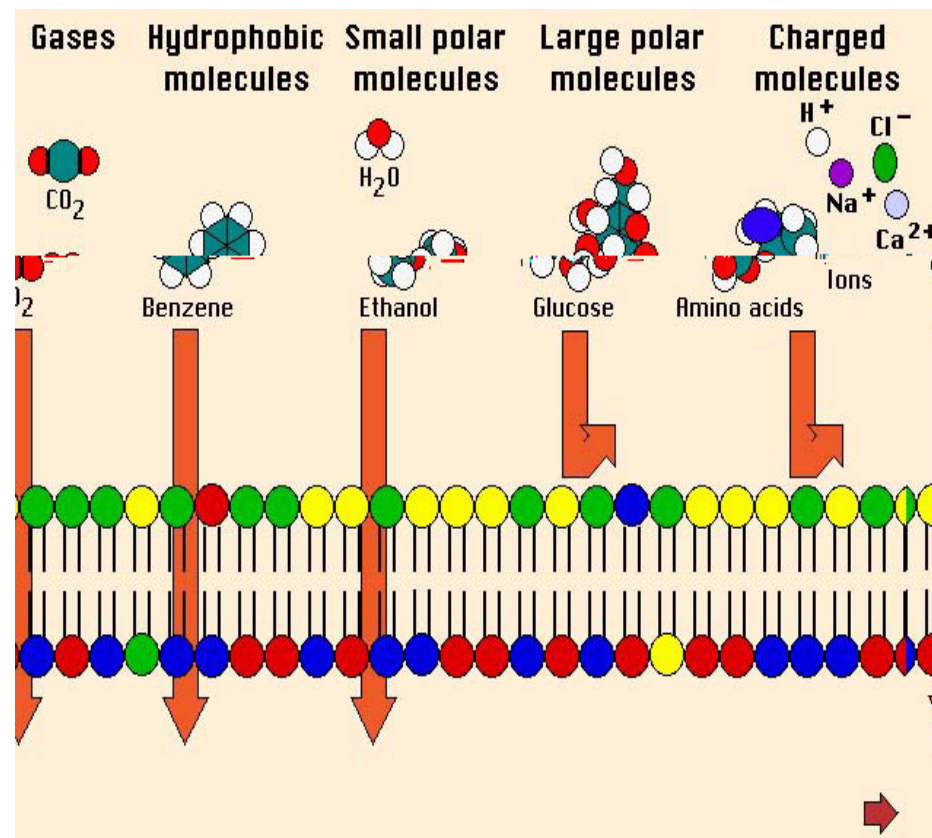
Pass freely but more slowly than nonpolar molecules e.g., H_2O

3. Large polar molecules & ions

Don't pass freely (e.g. glucose, Na^+)

4. Macromolecules

Don't pass (e.g. proteins, polysaccharides, nucleic acids)



Plasma Membrane Proteins: integral and peripheral

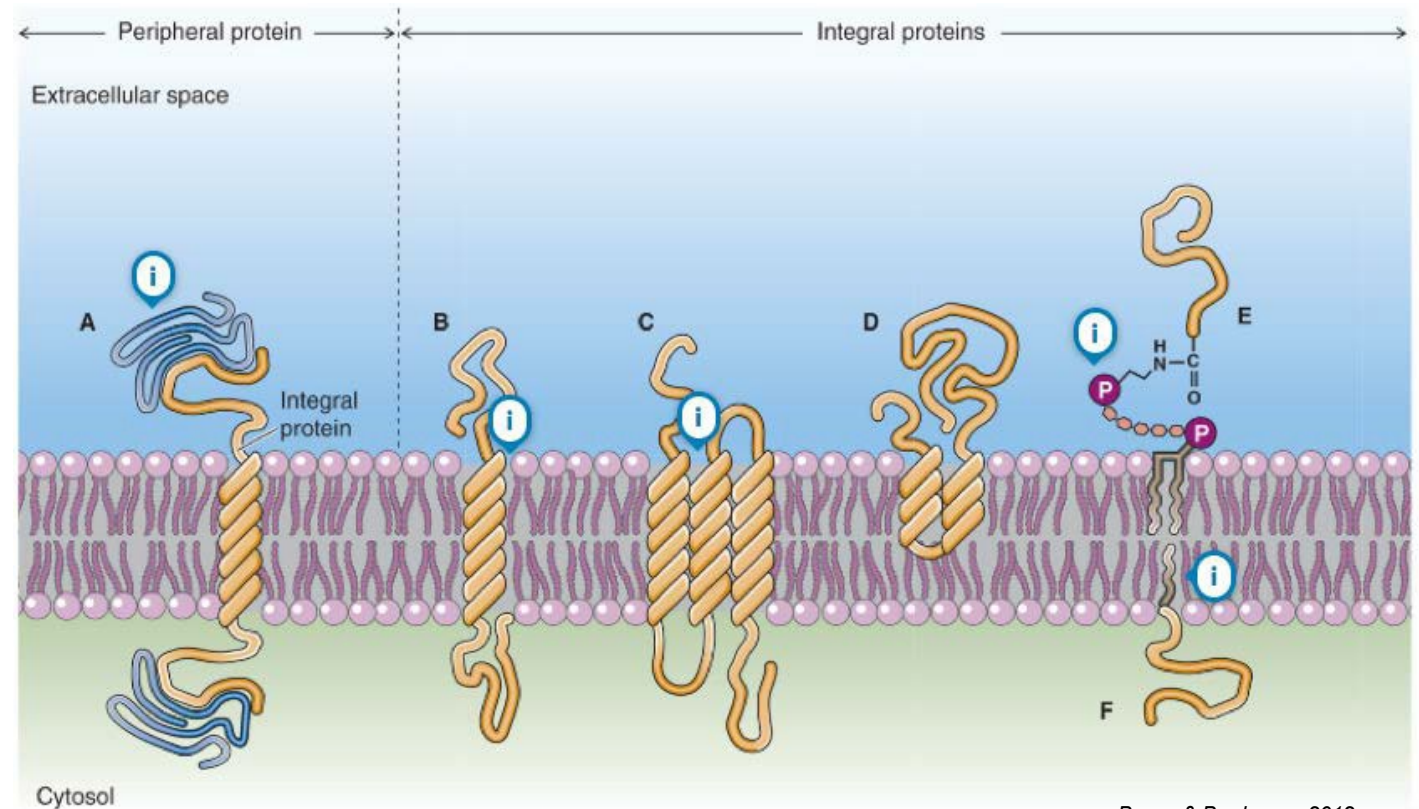
Integral membrane protein:

permanently attached to the cell membrane lipid bilayer

- Some span the entire membrane (e.g. ion channels, hormone receptors)
- Others are embedded (e.g. enzymes)

Peripherally associated membrane proteins: not permanently attached to the cell membrane lipid bilayer

- Non-covalently bound, often attached to integral proteins (e.g. regulatory proteins, transporter proteins, enzymes)



Boron & Boulpaep, 2012

A: peripheral protein, B: α helix, single span C: α helix, triple span, D: embedded, but not spanning membrane, E: Linked to phospholipid by an oligosaccharide, F: Direct link to a fatty acid

Functions of the membrane proteins

Transport:

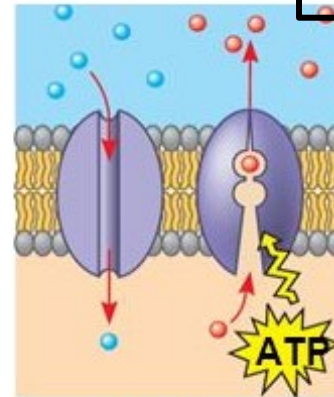
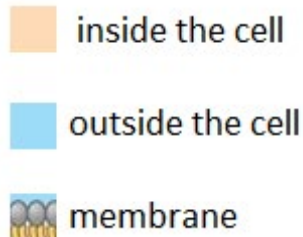
- Form hydrophilic channels across lipid bilayer
- Highly selective channels

Enzymatic activity:

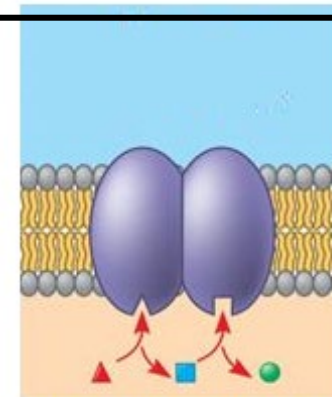
- Control chemical reactions inside or outside cell

Signal transduction

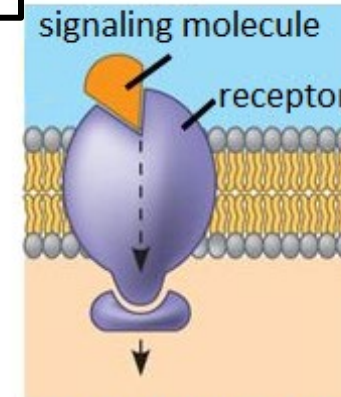
- Receptor proteins that receive external signals



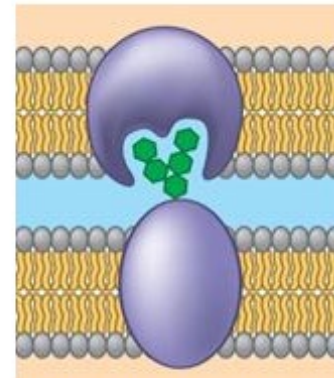
Transport



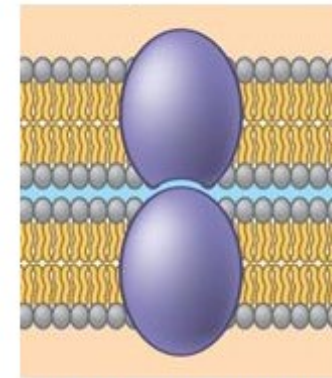
Enzymatic activity



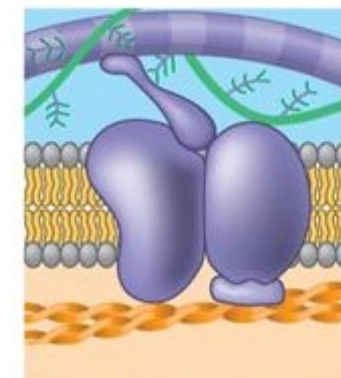
Signal transduction



Cell-cell recognition



Intercellular joining



Attachment

Cell recognition:

- Facilitate cell-to-cell interactions
- Cell's ability to recognise 'self'

Intercellular joining

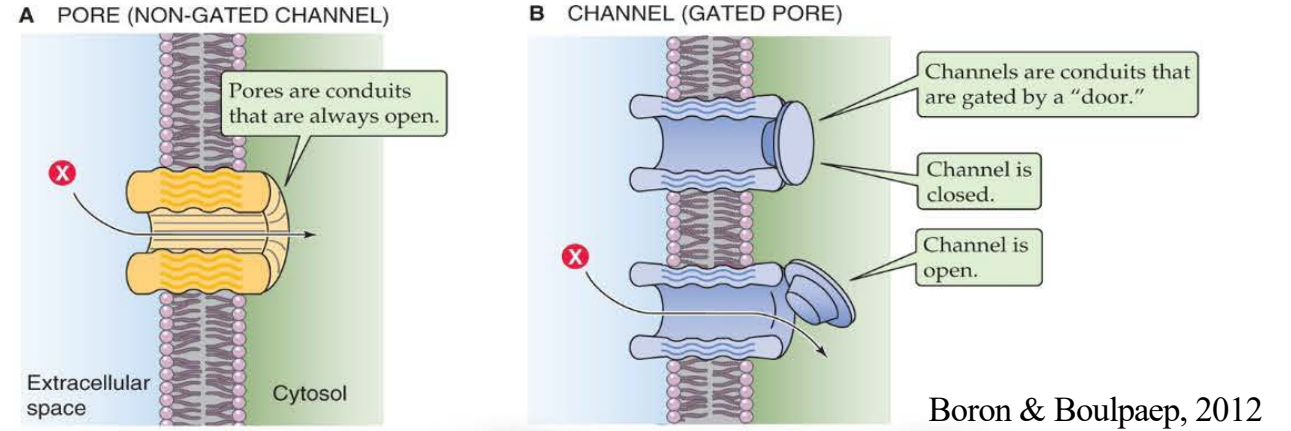
- Cell adhesion molecules
- Form loops or hooks to grip other cells

Attachment

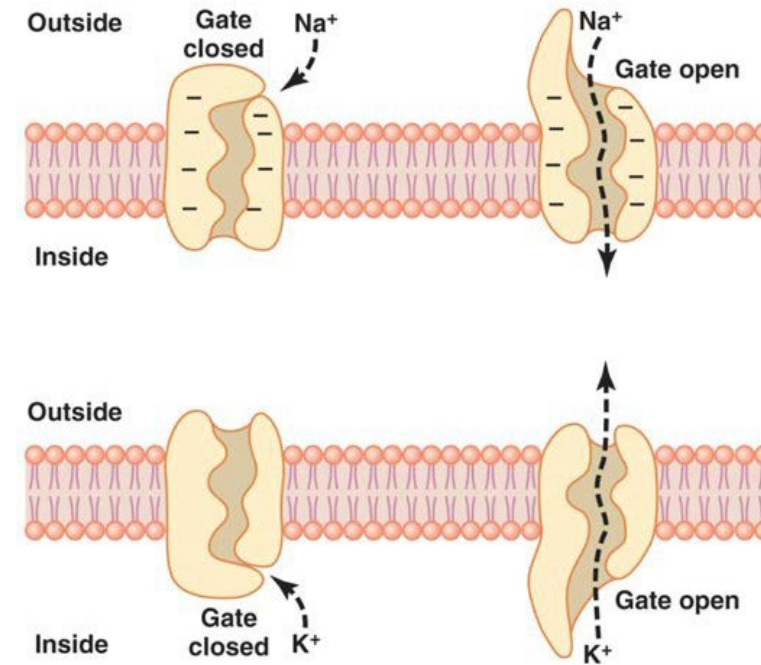
- Proteins that connect the cell to extracellular matrix

Membrane channels

- The protein transmembrane channels that permit simple diffusion:
 - pores and channels (gated)



- Types of gated ion channels
 - voltage-gated, e.g. Na^+ or K^+ (specific channel for each)
 - Chemical or ligand-gated, e.g. acetylcholine
 - mechanically-gated, e.g. sound waves in inner ear open ion channels



Guyton and Hall, 2011

Transport across biological membranes

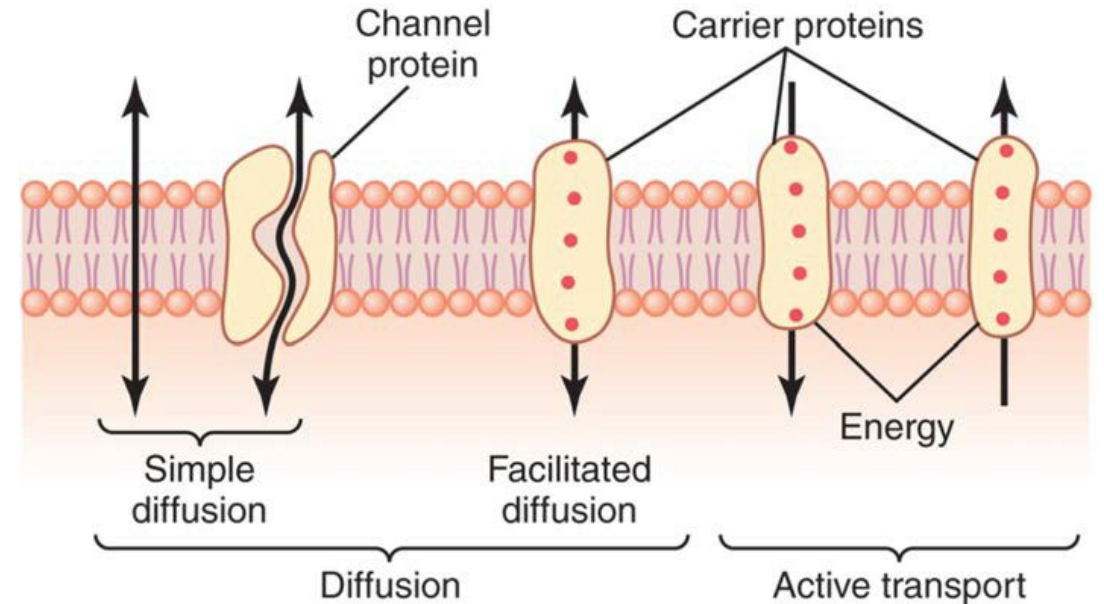
1. Simple diffusion

Down a concentration or electrical gradient

- ❖ Through membrane (lipid-soluble molecules)
- ❖ Through pores – integral cell membrane protein, e.g. aquaporin for water
- ❖ Through protein channels – selectively permeable, may be gated, eg ion channels

2. Facilitated Diffusion

- Down a concentration or electrical gradient
 - ❖ Carrier mediated - need integral membrane protein
 - ❖ Transporter is specific for the molecule
 - ❖ Rate limited by binding and conformational change in carrier protein; eg glucose, amino acids



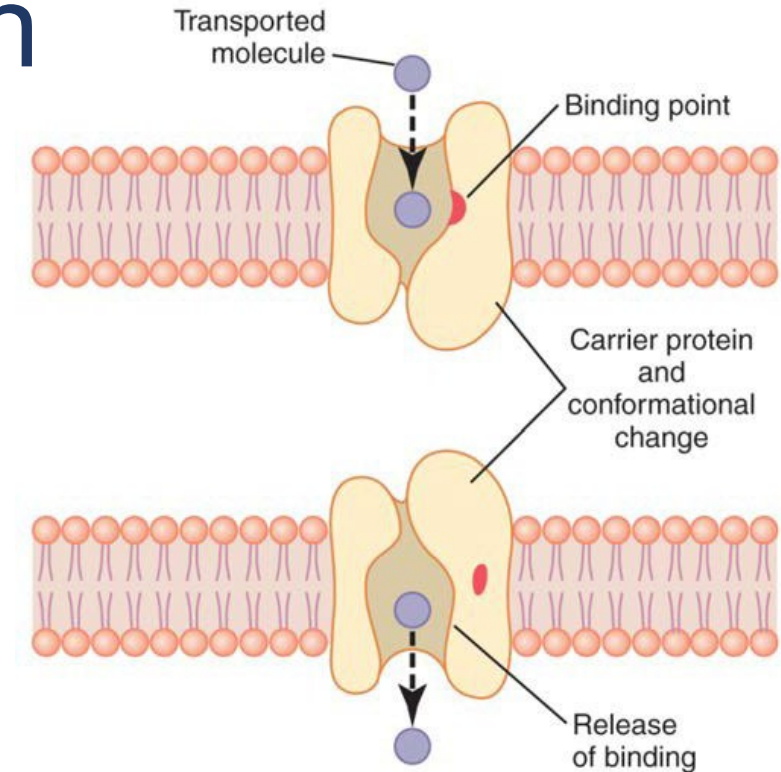
Guyton and Hall, 2011

3. Active transport

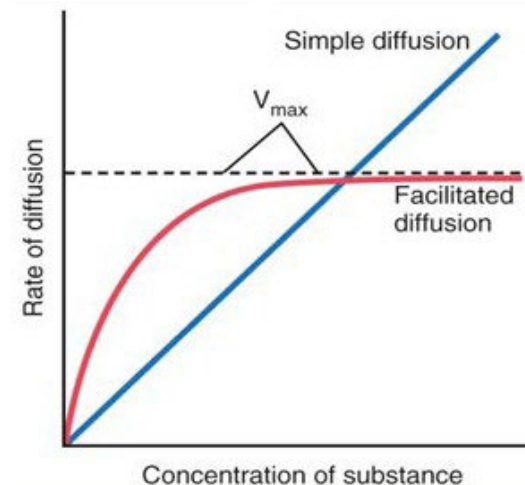
- Up a concentration or electrical gradient
 - ❖ Carrier mediated and energy dependent

Facilitated diffusion

- Use of a carrier protein to facilitate transfer across membrane, down a concentration gradient
- Molecule binds to a receptor within the carrier protein
- Binding triggers a shape (conformation) change of carrier protein allowing entry to the opposite side of the membrane
- Release returns carrier protein's shape to the original or unoccupied state.
- Carrier proteins demonstrate specificity
- Transport rate is limited by concentration of molecule and number of channels (receptors become saturated)
- Examples: glucose (*in most cells*) and amino acids



Guyton and Hall, 2011



Comparison of simple and facilitated diffusion Hall, 2016

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Video 2

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Transport across biological membranes

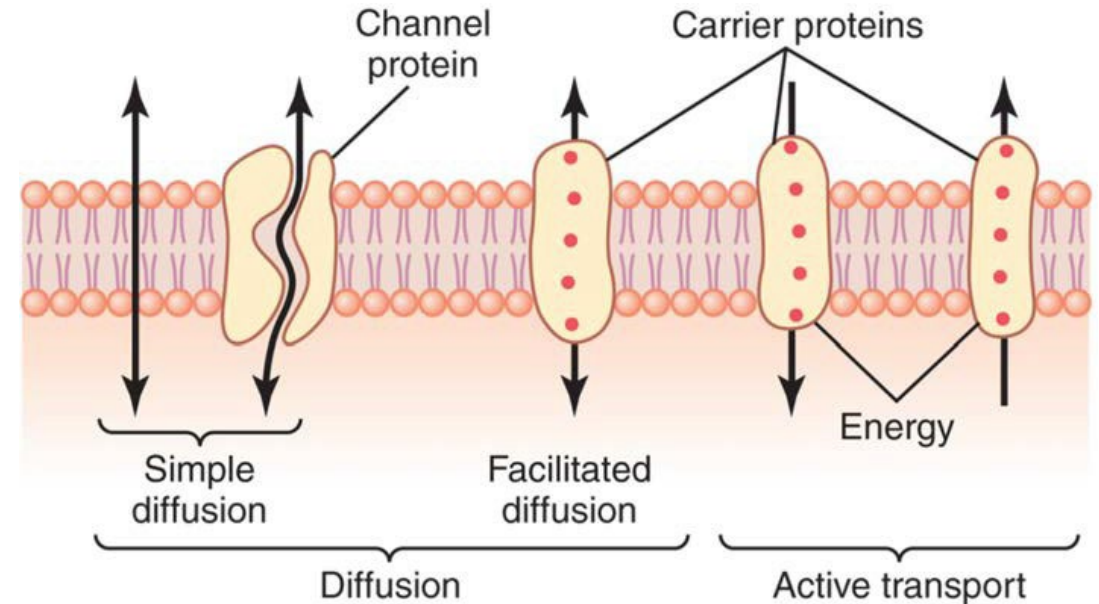
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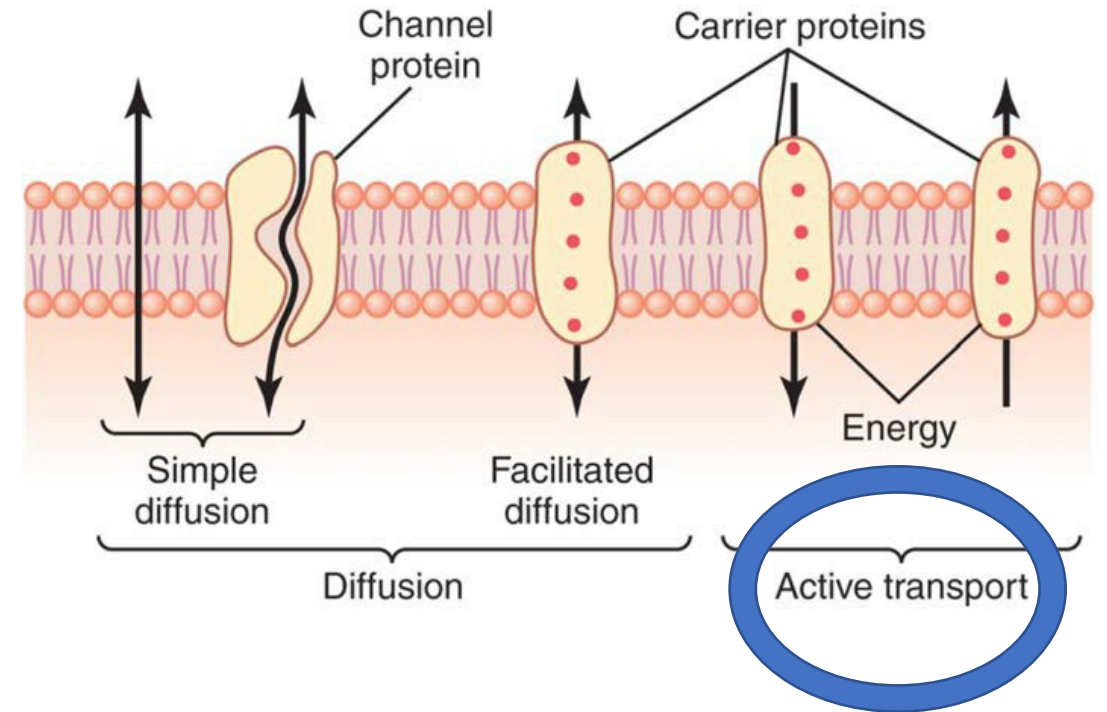
Guyton and Hall, 2011

3. Active transport

- Up a concentration or electrical gradient
 - ❖ Carrier mediated and energy dependent

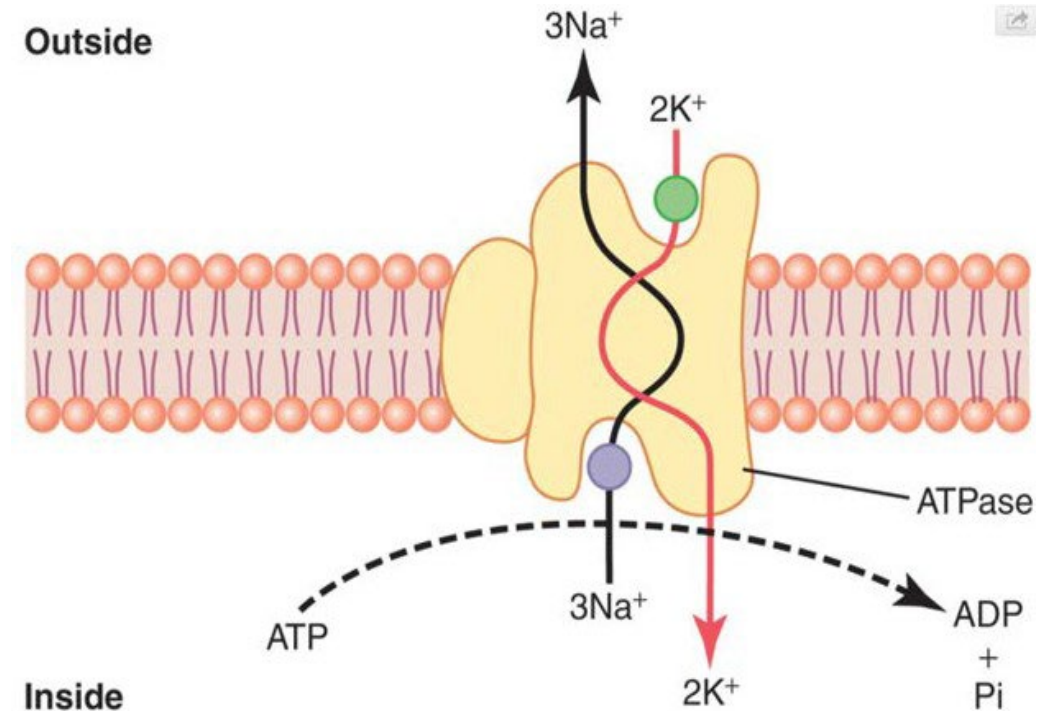
Active transport

- Use of protein carrier to carry a specific substance
- Transported against concentration or electrochemical gradient
- Requires expenditure of energy (in the form of ATP) to drive carrier
- Active transport mechanisms are often called 'pumps'
- **Primary active transport** directly uses chemical energy (primarily ATP) to move molecules
- **Secondary active transport** uses an electrochemical gradient – generated by active transport – as an energy source to move molecules against their gradient. It does not directly require a chemical source of energy such as ATP.



Primary active transport example: $\text{Na}^+\text{-K}^+$ ATPase pump

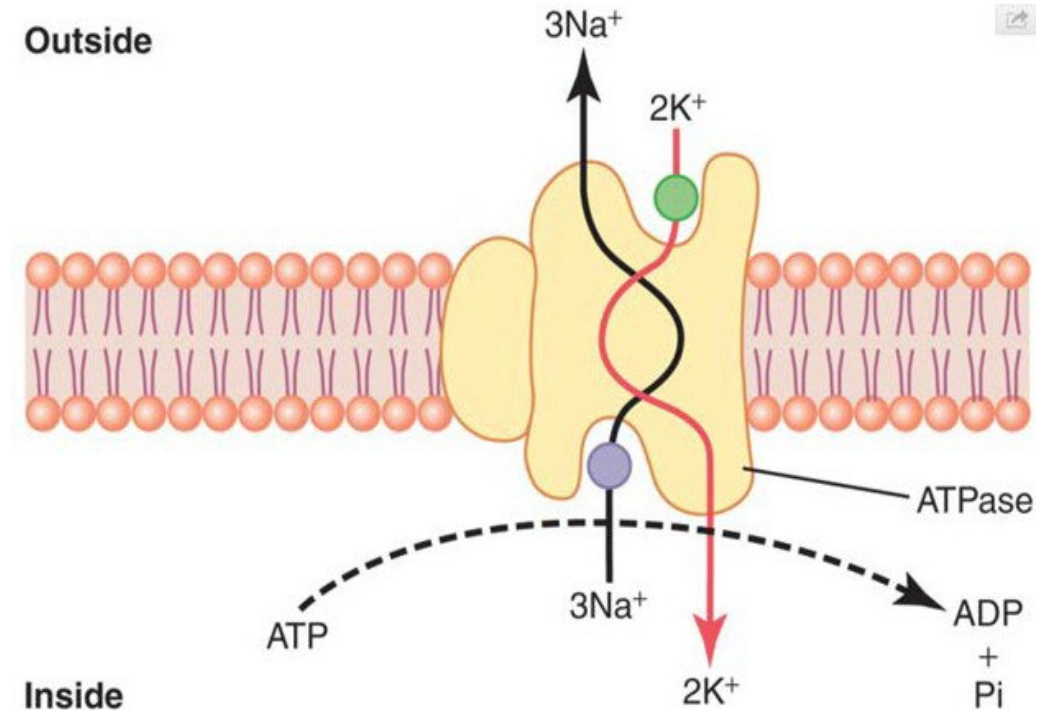
- Membrane of all cells contains an active $\text{Na}^+\text{-K}^+$ ATPase pump
- Functions to concentrate Na^+ in the ECF and K^+ in the ICF
- 3 receptors for Na^+ inside cell & 2 receptors for K^+ outside cell
- ATPase activated when ions bind → cleaves 1 molecule of ATP
- Liberated energy causes conformational change in carrier which flips the ions across the membrane



Primary active transport example: Na^+ - K^+ ATPase pump

Functions:

1. Establishes Na^+ and K^+ concentration gradients across the cell membrane → interior of cell negative with respect to exterior → critical for propagation of action potentials in nerves and for muscle contraction
 2. Regulates cell volume by controlling solute concentrations– minimise osmotic effects that would induce swelling/shrinking of cell
 3. Energy used also indirectly serves as energy source for cotransport of glucose and amino acids through *secondary active transport*
- Similar primary active transport pumps for Ca^{2+} and H^+

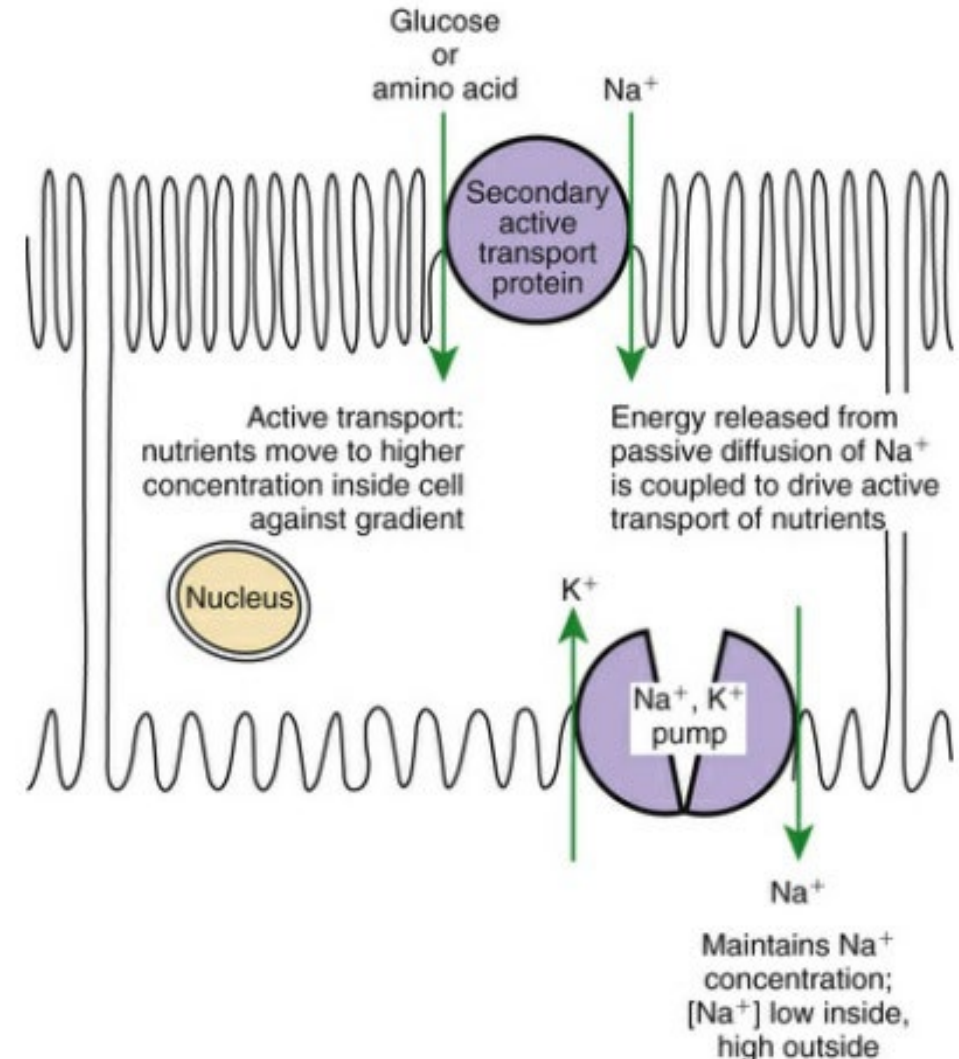


Secondary active transport

Secondary active transport uses an electrochemical gradient – generated by active transport – as an energy source to move molecules against their gradient.

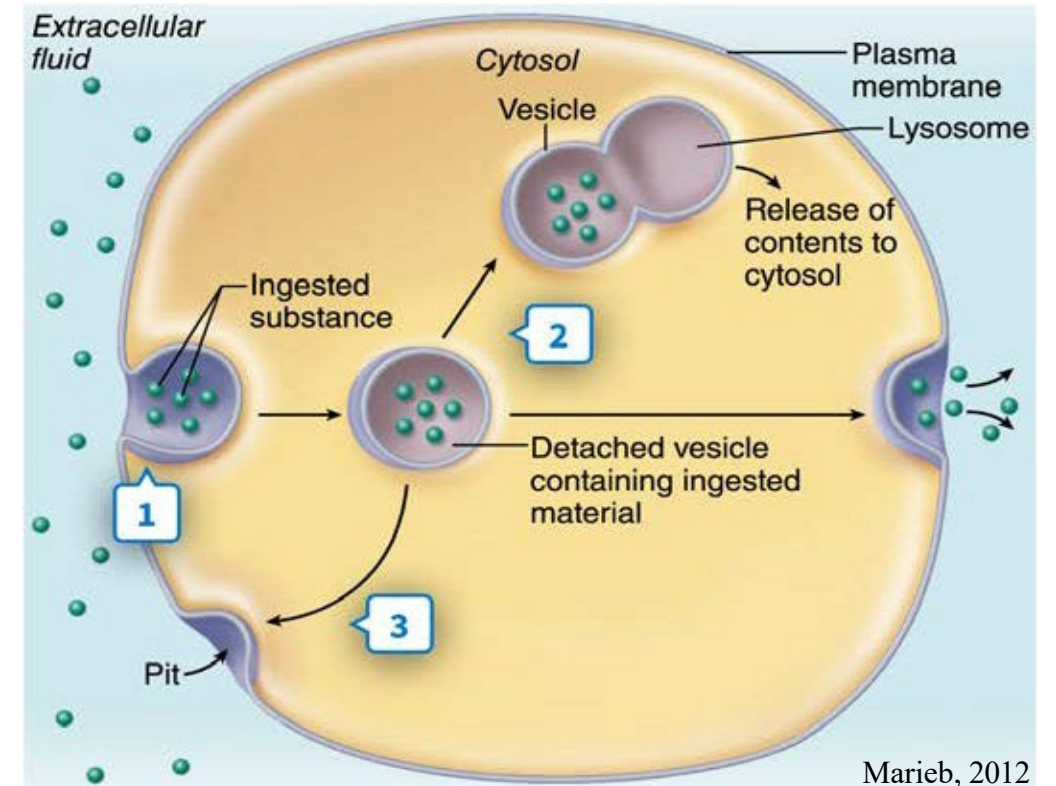
For example:

- Intestinal and kidney cells actively transport glucose and amino acids up their concentration gradients
- Co-transport carriers have two binding sites – one for Na^+ and the other for the nutrient molecule (e.g. glucose)
- When both glucose and Na^+ are bound to the carrier, it changes shape and opens to the inside of the cell – both Na^+ and glucose are released into the ICF
- Released Na^+ is quickly pumped out again by the Na^+ - K^+ ATPase pump, to keep the intracellular Na^+ low (maintaining Na^+ concentration gradient across membrane)



Vesicular transport

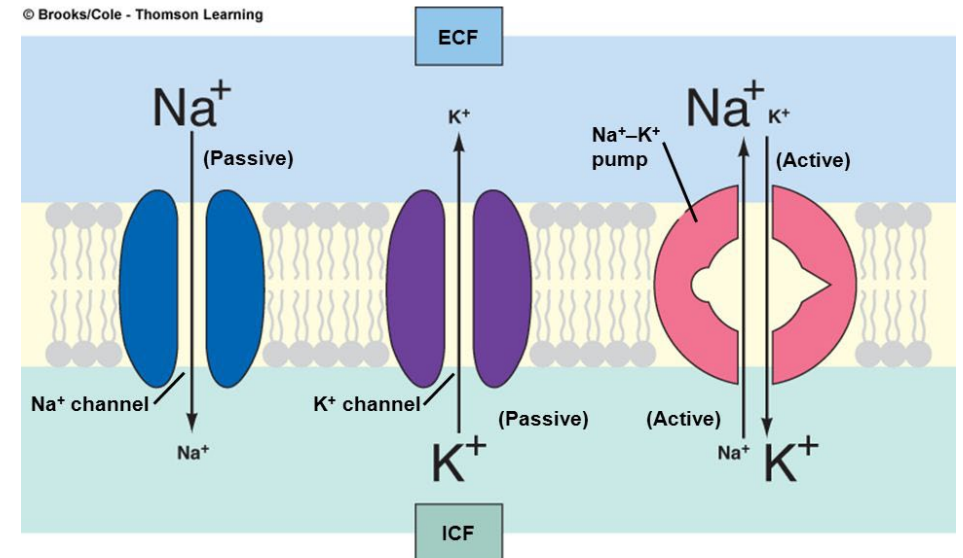
- Some large molecules/multimolecular materials are too large for channels and carriers
- They are transferred in a membrane-enclosed vesicle → vesicular transport
- Vesicular transport requires energy → active transport mechanism
- Transport into the cell = endocytosis; Transport out of cell = exocytosis
- Three forms of endocytosis:
 1. pinocytosis – non-selective uptake of ECF
 2. receptor-mediated endocytosis (large molecule)
 3. phagocytosis (multimolecular particles)



1. Vesicle buds off from plasma membrane
2. Vesicle transported intact, releasing contents to exterior by exocytosis or fuses with a lysosome
3. Membrane components recycled to the plasma membrane

Membrane potential

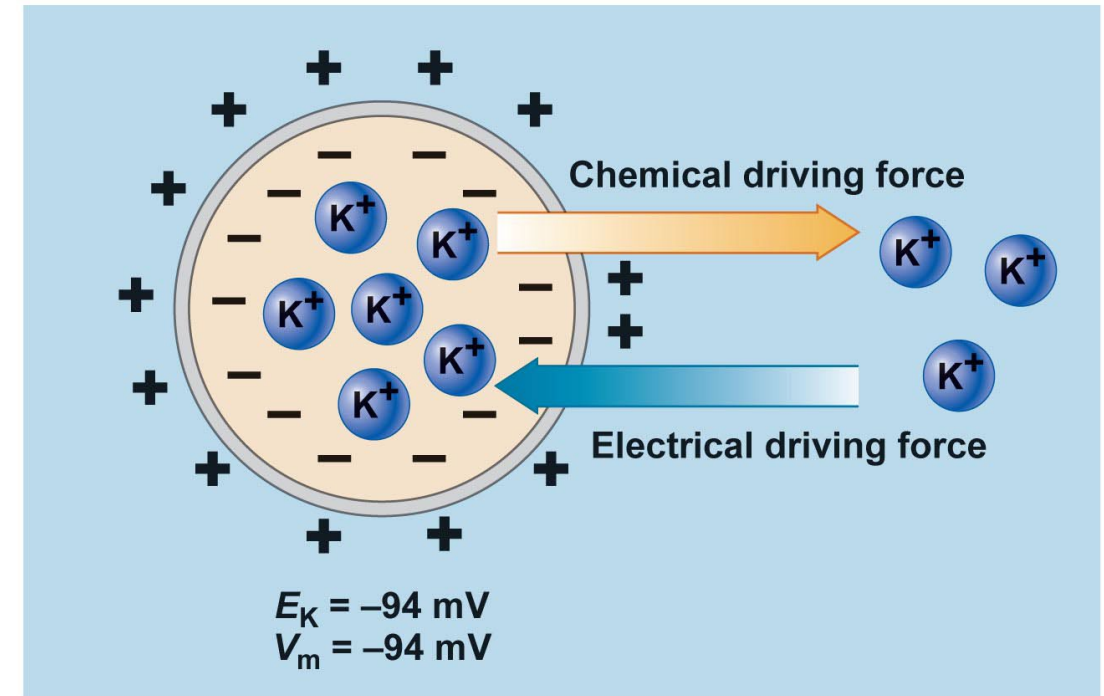
- All cell membranes have a membrane potential due to difference in the relative number of cations and anions in the ICF and ECF
 - The ions primarily responsible are Na^+ , K^+ , and negatively charged intracellular proteins
 - Negatively charged intracellular proteins cannot permeate the membrane → unbalanced distribution → ICF is more negative than ECF
-
- 20% of membrane potential is generated by the Na^+-K^+ ATPase pump (active transport mechanism)
 - The rest is generated through the passive diffusion of Na^+ and K^+ down concentration gradients



Ion concentrations and electrochemical gradients

Extracellular fluid		Intracellular fluid
Blood plasma	Interstitial fluid	Intracellular fluid
1.0 litre*	3 litre*	8 litres*
[Na ⁺] = 153 mM	[Na ⁺] = 145 mM	[Na ⁺] = 10-15 mM
[K ⁺] = 4.7 mM	[K ⁺] = 4.5 mM	[K ⁺] = 120-140 mM
[Cl ⁻] = 110 mM	[Cl ⁻] = 116 mM	[Cl ⁻] = 20 mM Range 3-30mM

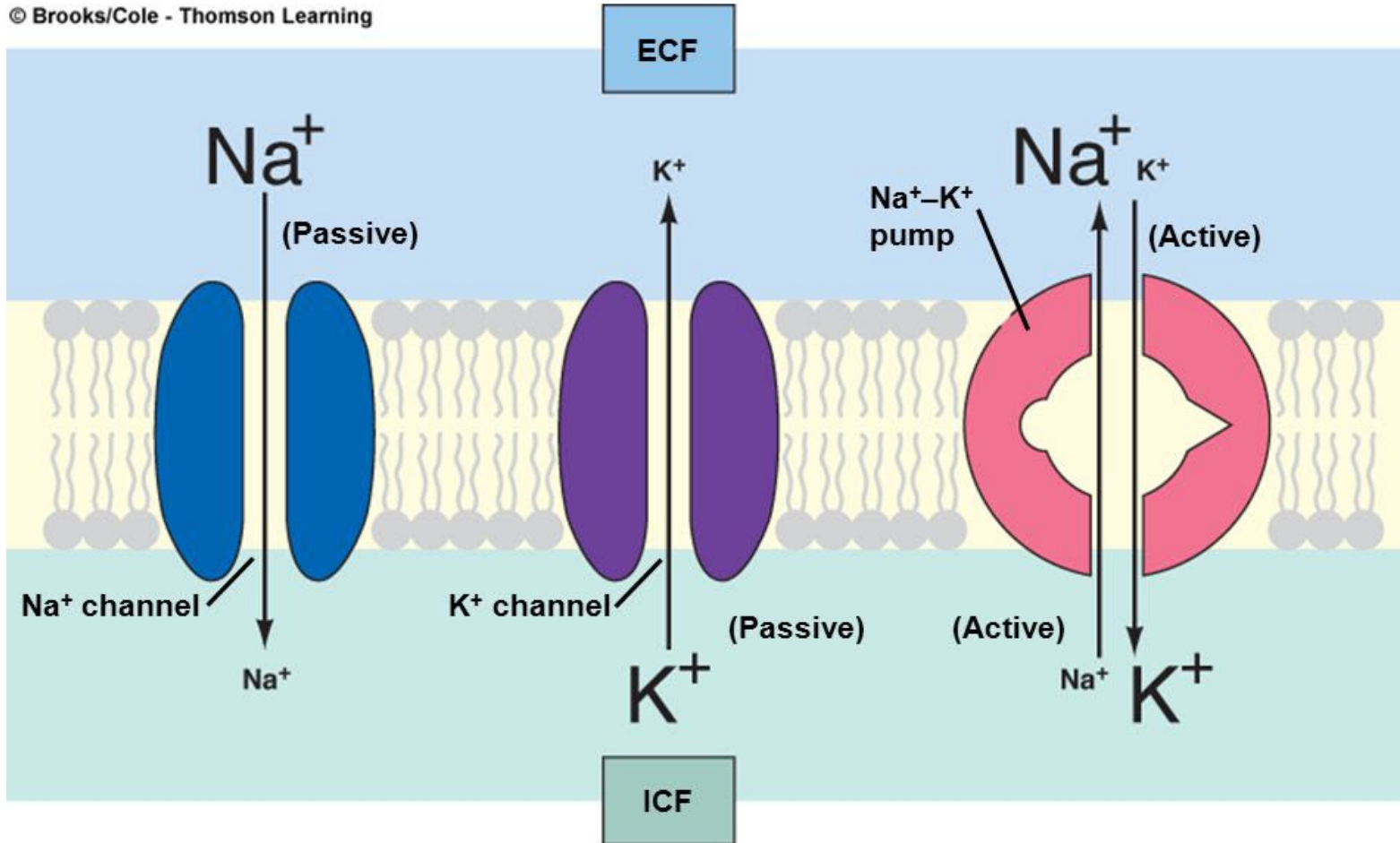
- For K⁺, the concentration gradient would tend to move the ion out of the cell, but the electrical gradient would tend to move K⁺ into the cell
→ K⁺ diffuses out of the cell down its concentration gradient until electrical forces prevent further net diffusion
- More diffusion (leak) channels for K⁺ than Na⁺ → so more K⁺ leaves than Na⁺ enters
- Negative ions that can't easily diffuse remain in ICF
→ Results in a net **negative** charge within the cell



(a)

Membrane potential

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At resting membrane potential:

- Passive leaks of Na⁺ and K⁺ down their electrochemical gradients
- This is counterbalanced by the Na⁺-K⁺ ATPase pump
- No net movement of Na⁺ and K⁺ → membrane potential remains constant

Transport of fluid and molecules across cell membranes

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