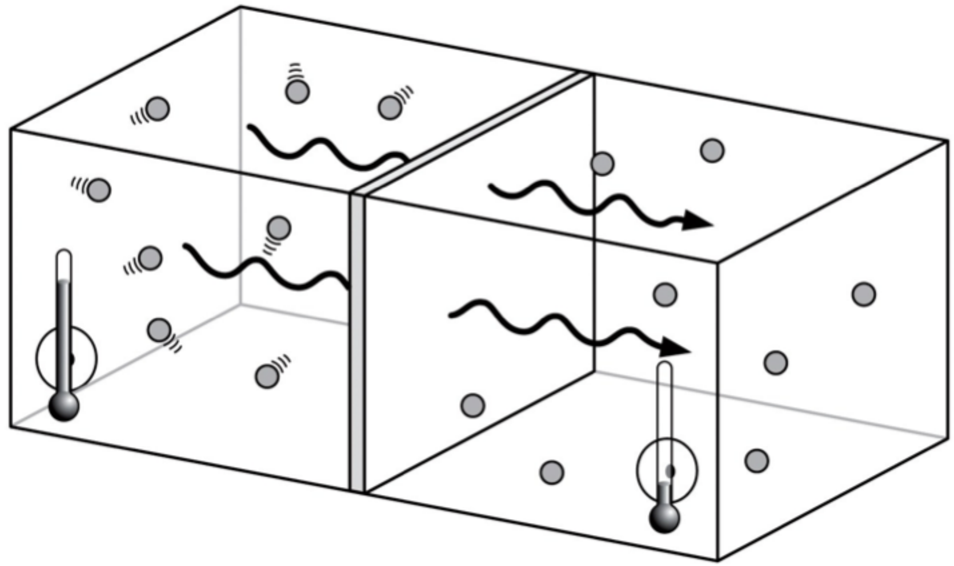
Transport across the biological membrane

Energy flow



Maximal entropy principle:

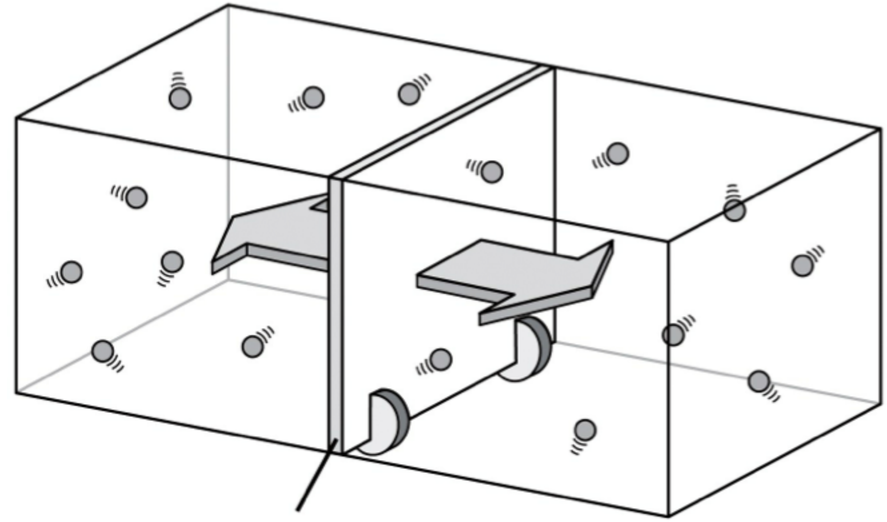
$$dS = (\partial S/\partial E_1)dE_1 + (\partial S/\partial E_2)dE_2 = [(\partial S/\partial E_1) - (\partial S/\partial E_2)]dE_1 = 0$$

where we considered: $dE_2 = - dE_1$

$(dS/dE_{1,2}) = 1/T_{1,2}$ ... thermodynamic definition of temperature

$$T_1 = T_2$$

Volume change



Maximal entropy principle:

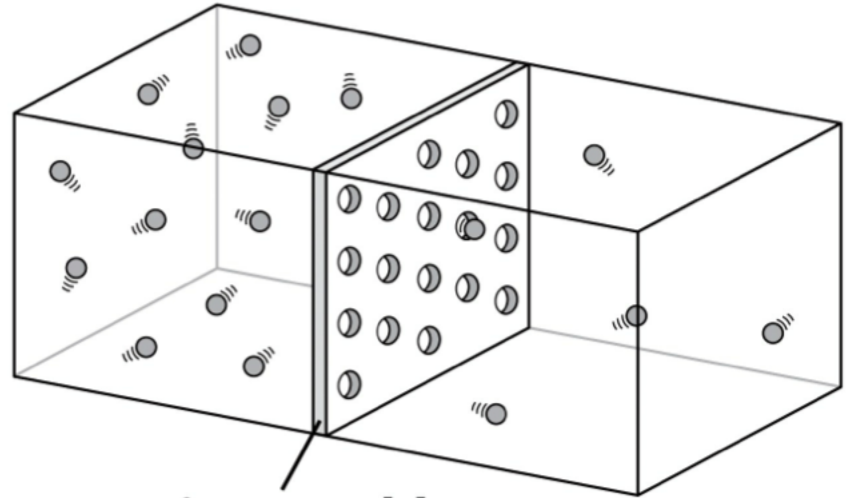
$$dS = (\partial S/\partial V_1)dV_1 + (\partial S/\partial V_2)dV_2 = [(\partial S/\partial V_1) - (\partial S/\partial V_2)]dV_1 = 0$$

where we considered: $dV_2 = - dV_1$

$(\partial S/\partial V_{1,2})E,N = p_{1,2} /T$ ... Thermodynamic identity

$$p_1 = p_2$$

Particle flow



Maximal entropy principle:

$$dS = (\partial S/\partial N_1)dN_1 + (\partial S/\partial N_2)dN_2 = [(\partial S/\partial N_1) - (\partial S/\partial N_2)]dN_1 = 0$$

where we considered: $dN_2 = - dN_1$

$(\partial S/\partial N_{1,2})E,V = \mu_{1,2} /T$ ... Thermodynamic definition of a chemical potential μ:

$$\mu_1 = \mu_2$$

Membrane Transport and Human Disease

- ***Cystic Fibrosis and CFTR*** (the most common fatal childhood disease in Caucasian populations). Inadequate secretion of pancreatic enzymes leading to nutritional deficiencies, bacterial infections of the lung and respiratory failure, male infertility.

- ***Bile Salt Transport Disorders*** Several ABC transporters, specifically expressed in the liver, have a role in the secretion of components of the bile, and are responsible for several forms of progressive familial intrahepatic cholestasis, that leads to liver cirrhosis and failure.

- ***Retinal Degeneration*** The ABCA4 gene products transports retinol (vitamin A) derivatives from the photoreceptor outer segment disks into the cytoplasm. A loss of ABCA4 function leads to retinitis pigmentosa and to macular dystrophy with the loss of central vision.

- ***Mitochondrial Iron Homeostasis*** ABCB7 has been implicated in mitochondrial iron homeostasis. Two distinct missense mutations in ABCB7 are associated with the X-linked sideroblastic anemia and ataxia.

- ***Multidrug Resistance*** ABC genes have an important role in MDR and at least six different ABC transporters are associated with drug transport.

Nobel Prizes in Membrane Transport

1978	Peter Mitchell (UK)	Concept of chemiosmotic coupling
1988	Johan Deisenhofer (D) Robert Huber (D) Hartmut Michel (D)	Structure of electron-translocating photosynthetic reaction centre
1991	Erwin Neher (D) Bert Sakmann (D)	Patch clamp technique for single channel recording
1997	Jens-Christian Skou (DK) Paul Boyer (USA) John Walker (UK)	Mechanisms of ATP-driven ion translocation
2004	Peter Agre (USA) Rod MacKinnon (USA)	Structure of water- and ion-channels

General comment on transport process

Transport is the flux of an entity in response to a driving force:

Flux $$j_i = \rho_i \omega_i F$$

where ρ_i is the density of the material or species i (or concentration, c_i), and ω_i is its equivalent mobility under the influence of a force.

The flux of i (j_i) is the net movement of i per unit area per unit time; the units are i cm^{-2} s^{-1}.

Force can be expressed as a potential gradient: $$F = -\frac{\partial U}{\partial x}$$

In one dimension:

$$j_i = -v_i \frac{\partial U}{\partial x}$$ in 3D $$j_i = -v_i \nabla U$$

Examples of Transport

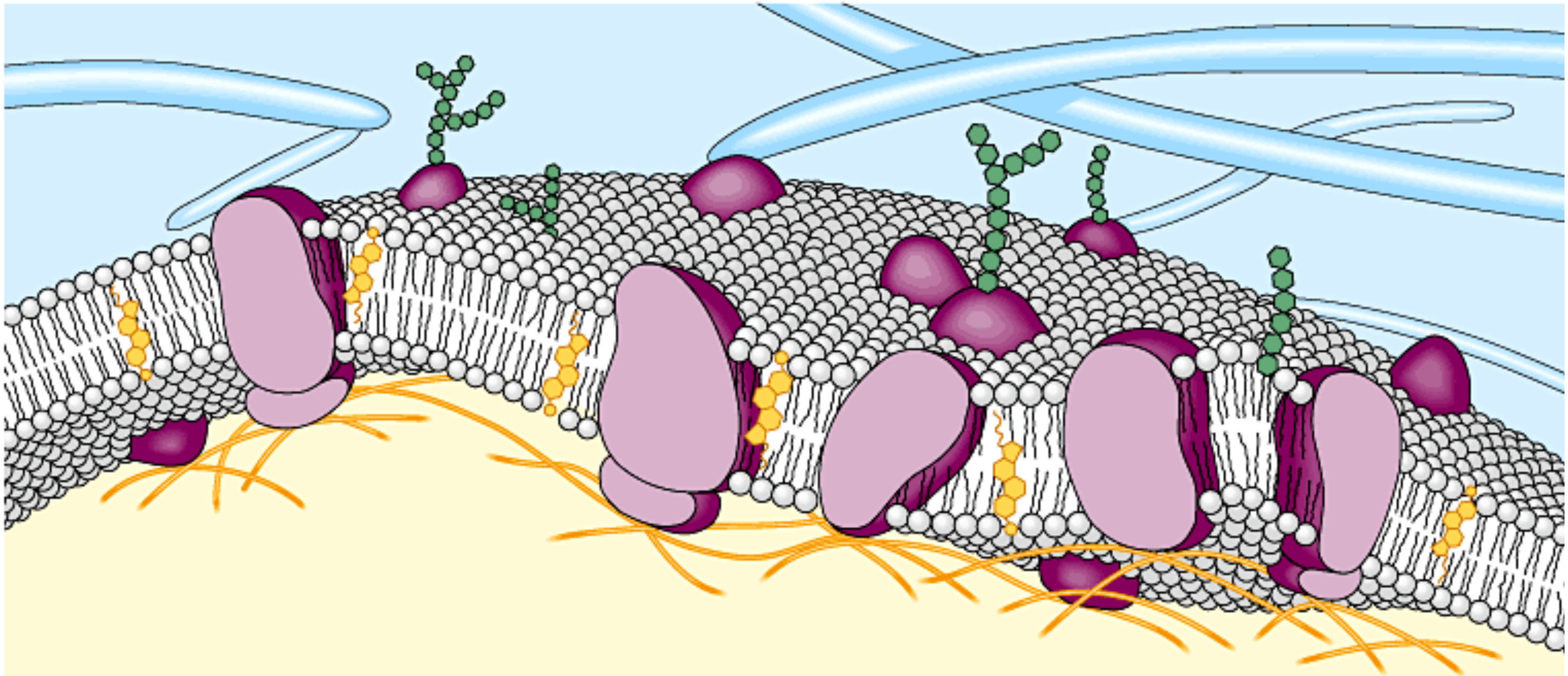
Heat $$j_H = -\kappa \frac{\partial T}{\partial x}$$ Fourier's Law

Charge $$j_e = -\sigma \frac{\partial V}{\partial x}$$ Ohm's Law

Volume/mass $$j_v = -\Re \frac{\partial P}{\partial x}$$ Poiseuille's Law

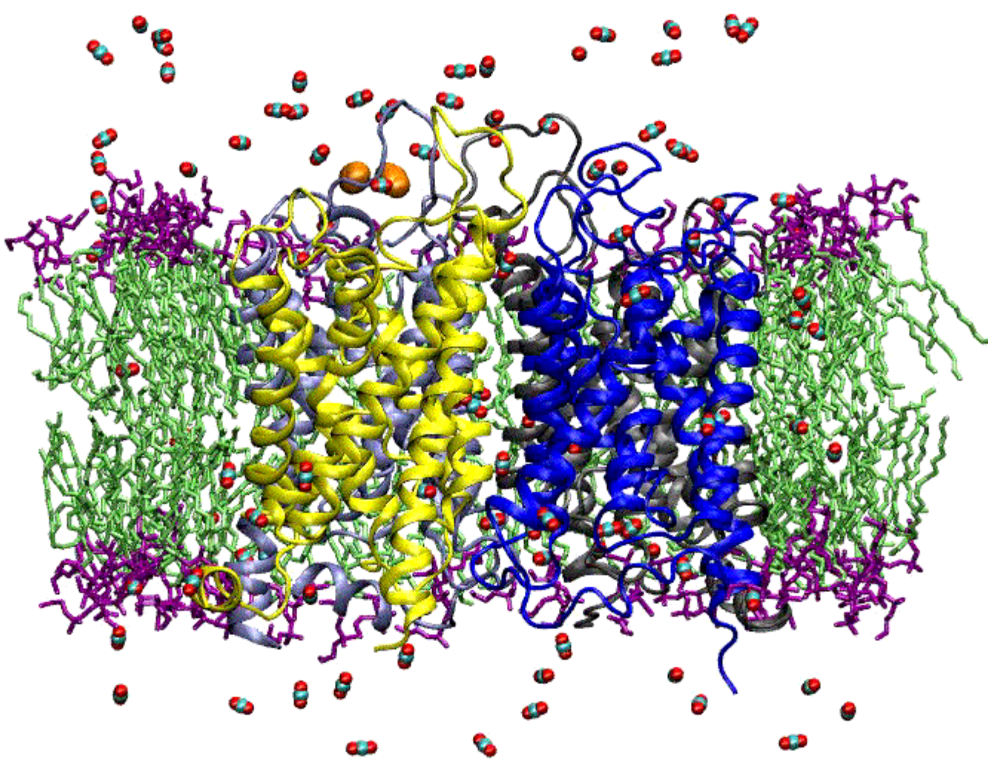
Particles/Solute: $$j_s = -D \frac{\partial \rho}{\partial x} = -D \frac{\partial c}{\partial x}$$ Fick's Law

Homeostasis

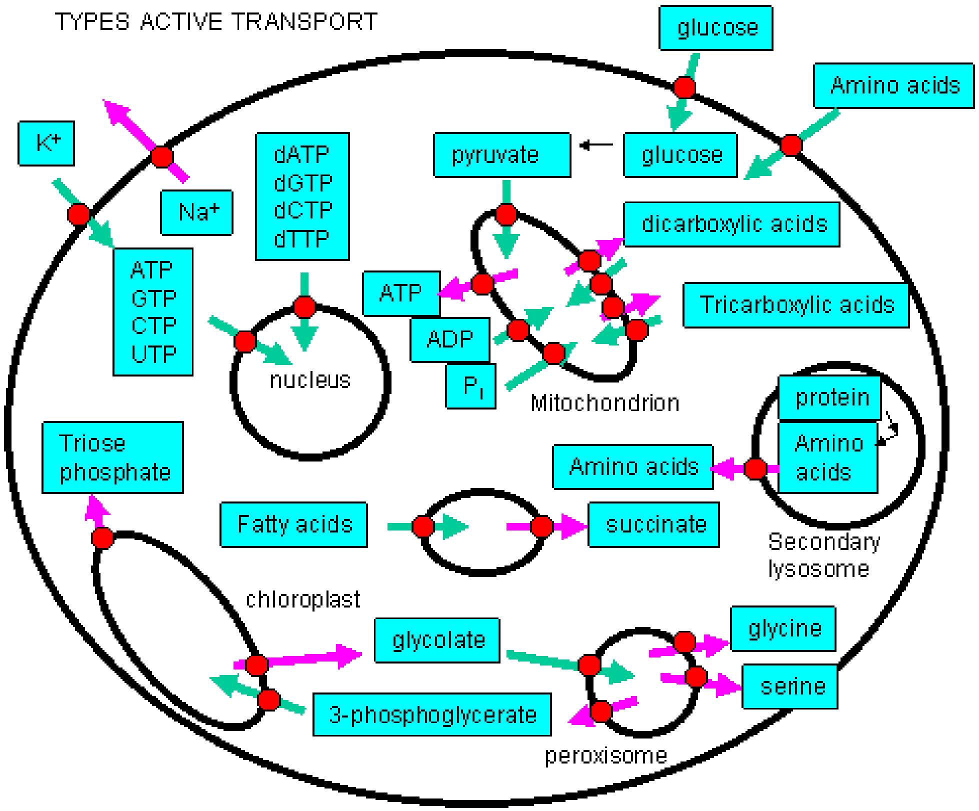


It is maintained by a combinations of fluxes

Membranes are flexible, non-extendible, self-sealing, differentially permeable barriers that separate "IN" from "OUT"



Function of transport



- *Cell volume - osmolarity*
- *Intracellular pH*
- *Membrane potential*
- *Ions gradients*
- *Exchange of molecules*

Ion	*In*	*Out*
Potassium	*140 mM*	*1 – 4.5 mM*
Sodium	*5 – 15 mM*	*145 mM*
Magnesium	*5 mM*	*1 – 2 mM*
Calcium >	*0.5 µM*	*2.5 – 5 mM*
Chloride	*4 mM*	*110 mM*

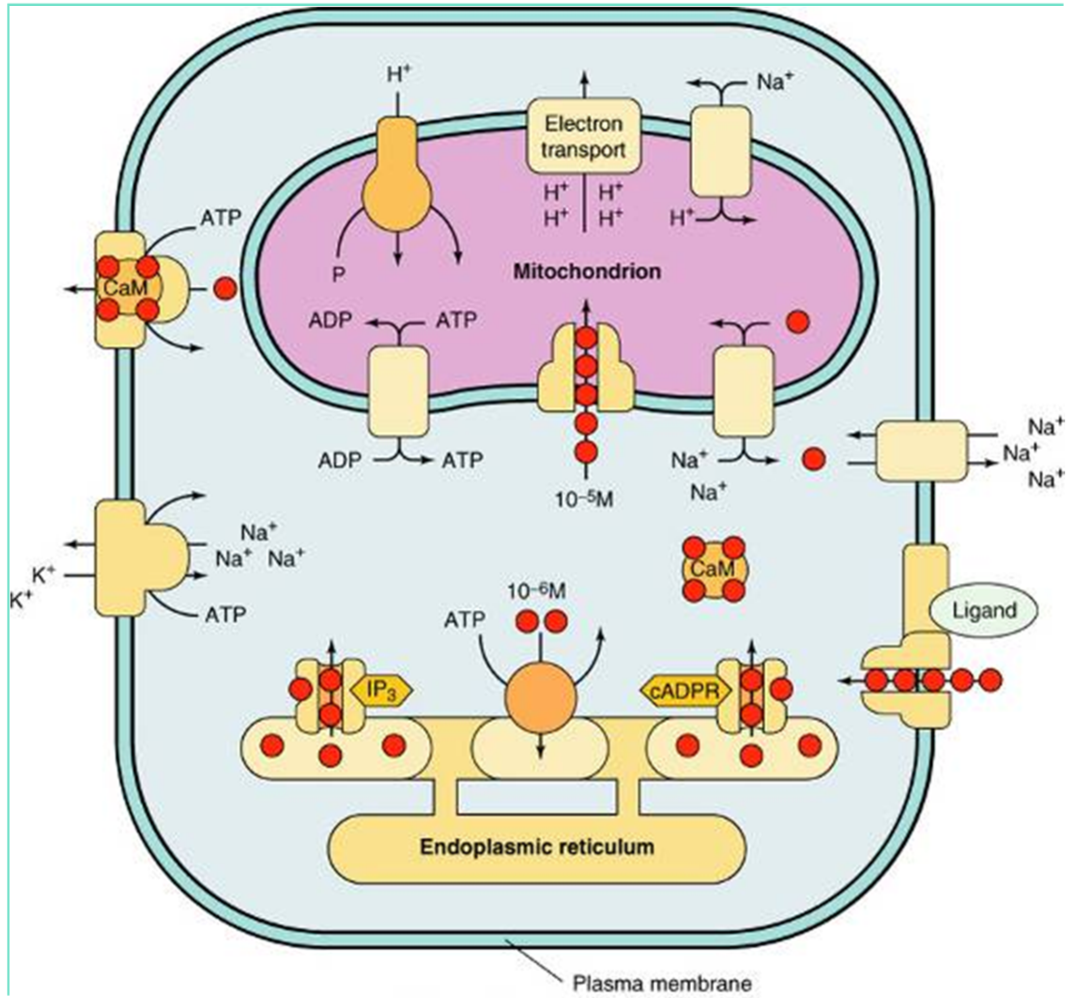
Analysis of various genomes revealed that about 10% of **all** proteins function in **transport** (in E.coli – 427 transporters)

In eucaryotic cells, 2/3 of cellular energy at rest is used to transport ions (H^+, K^+, Na^+, Ca^{++})

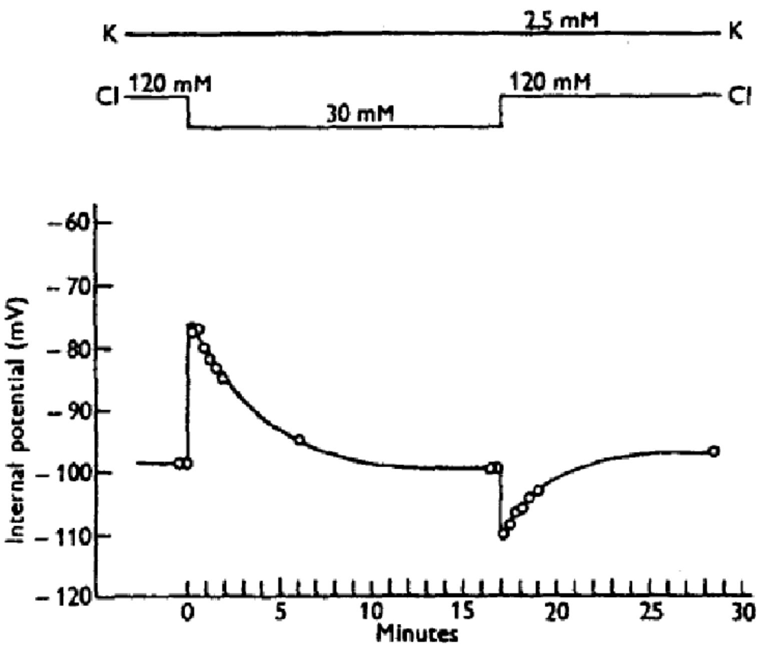
About 200 families of transporters are recognized

The largest family: ABC-transporters

Transport Processes in an Idealized Eukaryotic Cell

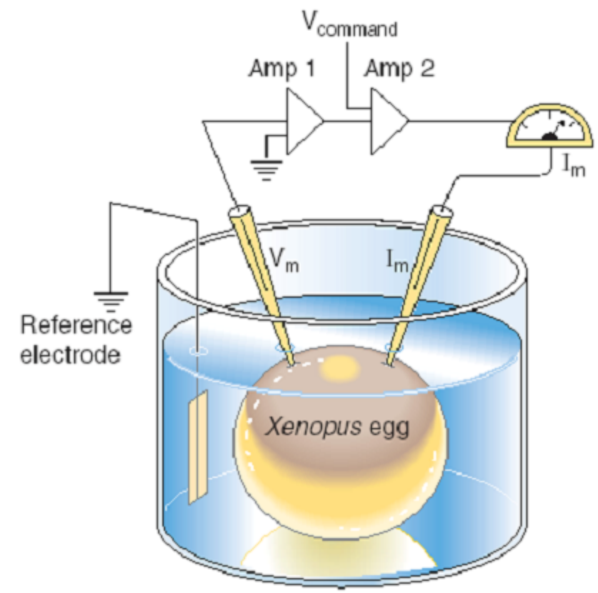


The membrane potential control



The effect of changes in external chloride ion concentration on the membrane potential of an isolated frog muscle fibre (*Hodgkin & Horowicz, 1959*)

One electrode monitors membrane potential (V_m) and the other passes enough current (I_m) through the membrane to clamp V_m to a predetermined command voltage ($V_{command}$).



Four major contributors to the work required to transfer ion from the aqueous environment into the membrane:

$$W_{total} = W_{Born} + W_{image} + W_{dipole} + W_{neutral}$$

Born (self) energy of an ion (W_{Born})

Image charge energy (W_{image})

Membrane dipole energy (W_{dipole})

All other contributions ($W_{neutral}$)

Born Energy

$$W_{total} = W_{Born} + W_{image} + W_{dipole} + W_{neutral}$$

$$G = u_{(self)} = W_{Born} = \frac{q^2}{8\pi\varepsilon_0 \varepsilon a}$$

Born (self) energy of an ion in the medium with dielectric coefficient ε (i.e. the work required to charge the ion from 0)

If the ion is transferred between media with different dielectric constants:

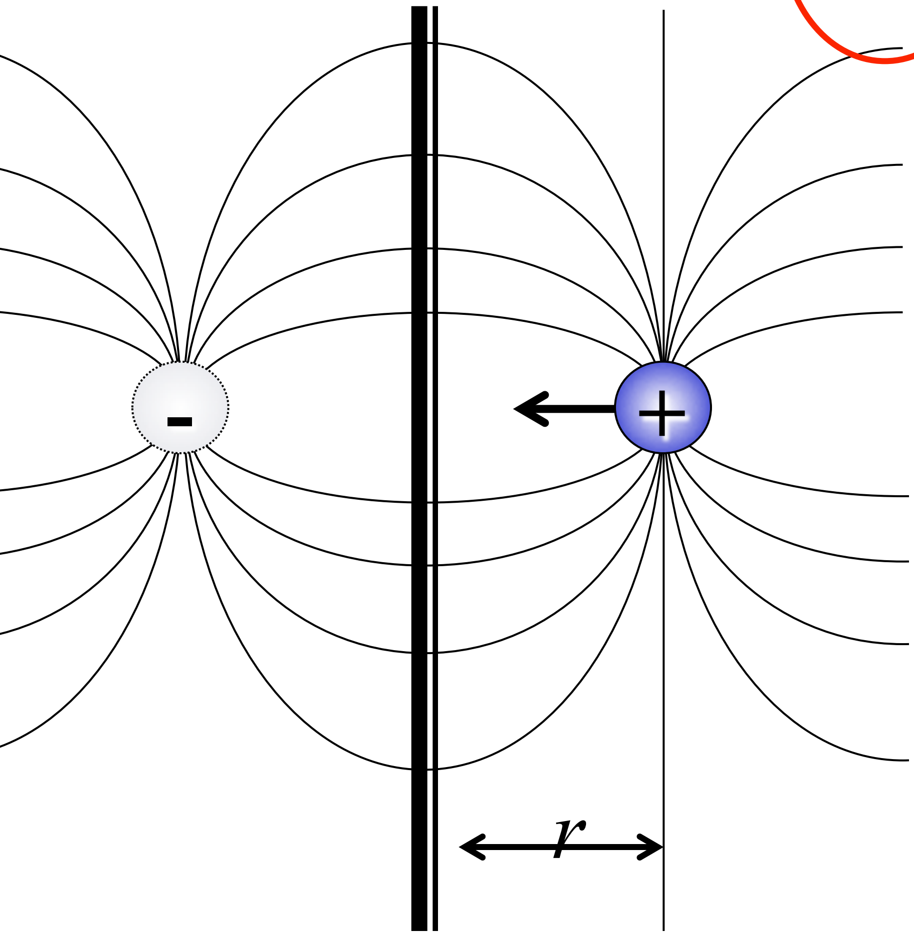
$$\Delta U = \Delta W_{Born} = \frac{q^2}{4\pi\varepsilon_0} * \frac{1}{2a}\left(\frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1}\right) = \frac{cz^2}{2a}\left(\frac{1}{\varepsilon_2} - \frac{1}{\varepsilon_1}\right)$$

$c = e^2/4\pi\varepsilon_0$ = **14.4 eV*Å**

For $\varepsilon_1 = 80$ (water) and $\varepsilon_2 = 2$ (membrane), the Born energy is very large for most ions, i.e., 30-60 kcal/mol for a = 4-2 Å.

Image Forces and Image Charges:

$$W_{total} = W_{Born} + W_{image} + W_{dipole} + W_{neutral}$$



Infinite plane conductor

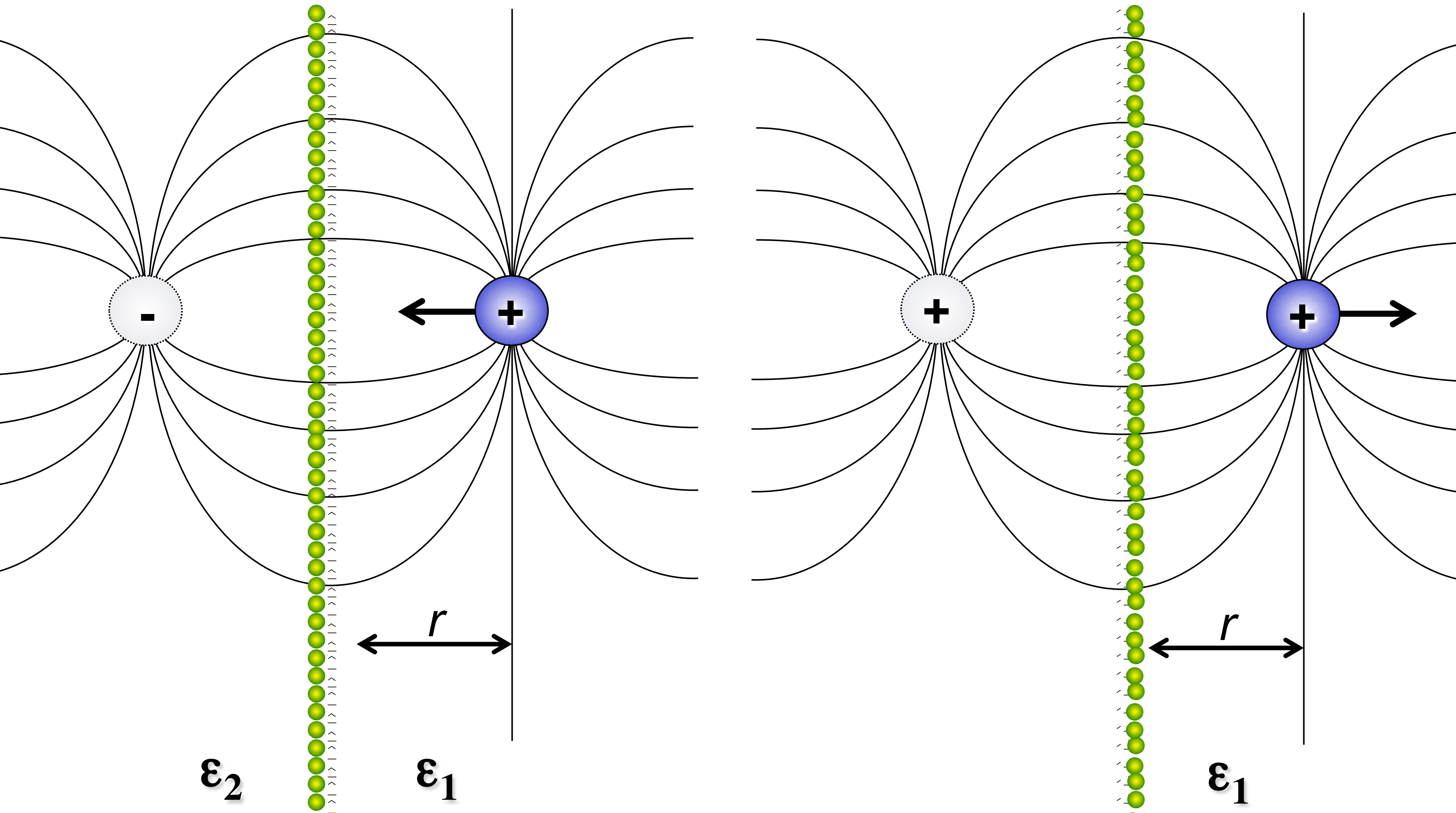
$\varepsilon_2 = \infty$ ε_1

When a charge approaches a dielectric discontinuity:

$$q_{image} = -\left(\frac{\varepsilon_2 - \varepsilon_1}{\varepsilon_2 + \varepsilon_1}\right)Q = tQ$$

$$Force = \frac{tQ^2}{4\pi\varepsilon_0\varepsilon_1(2r)^2}$$

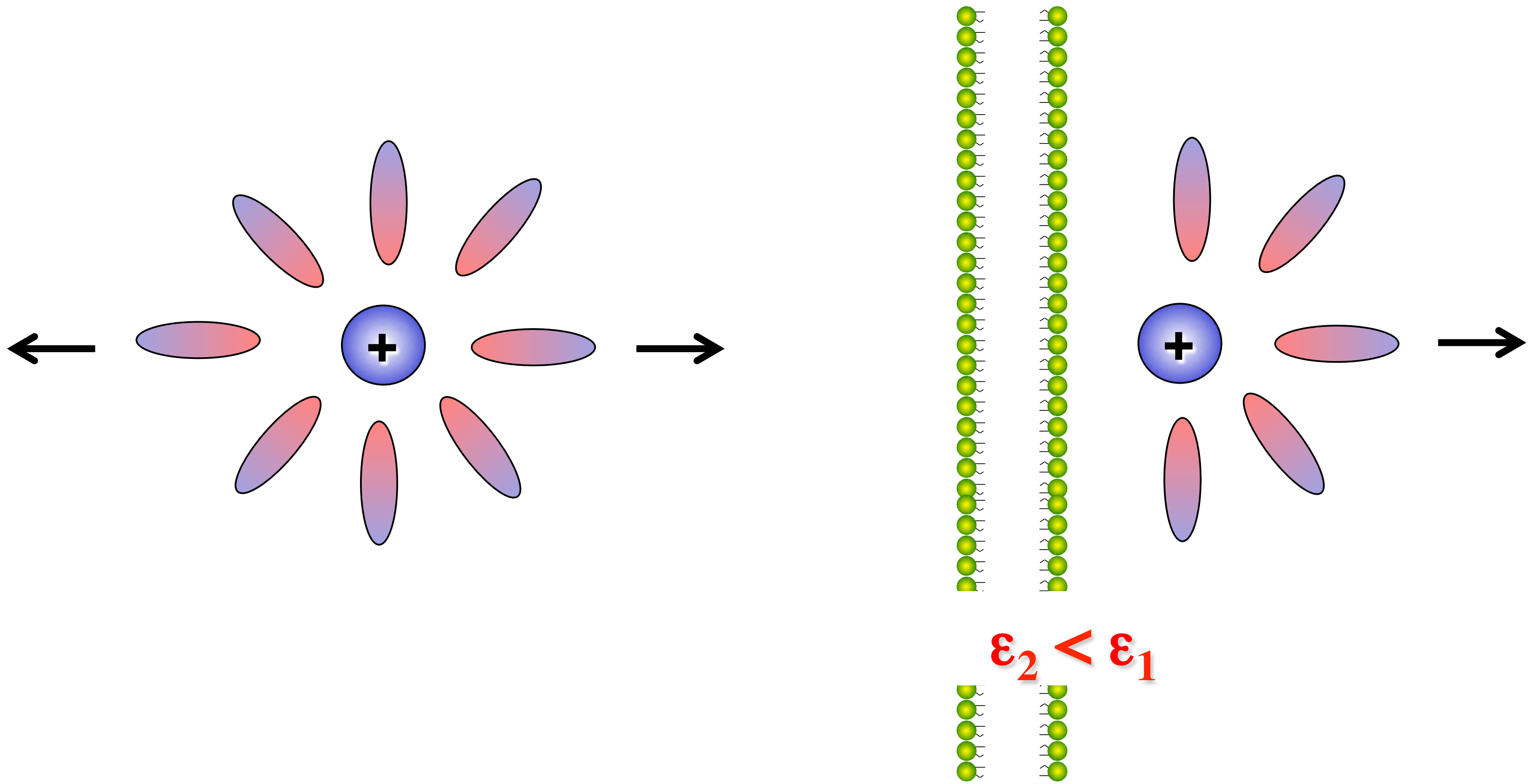
Image Forces and Image Charges:



$\varepsilon_2 > \varepsilon_1$

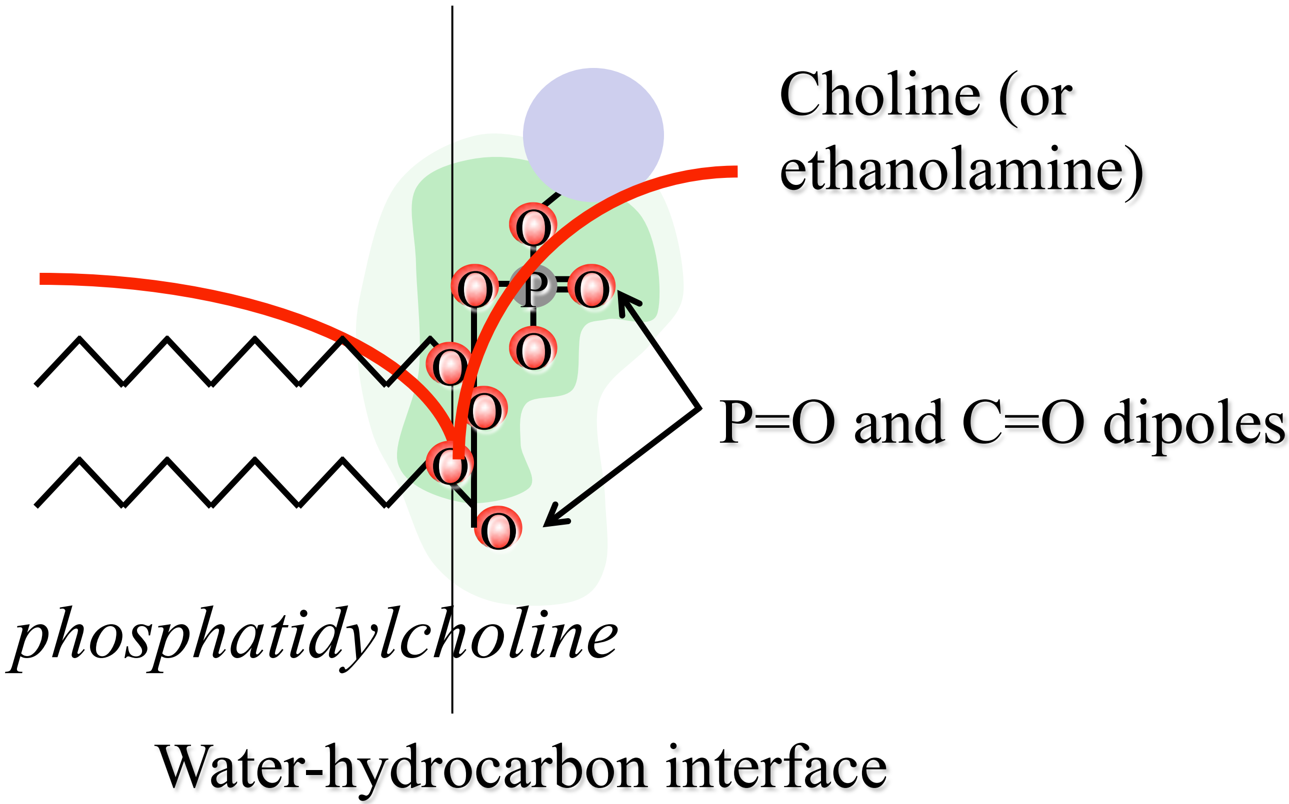
$\varepsilon_2 < \varepsilon_1$

Image Forces and Image Charges:



Membrane dipole potential

$$W_{total} = W_{Born} + W_{image} + W_{dipole} + W_{neutral}$$



Crossing the Barrier - Membrane Transport Mechanisms

1. **Diffusive carriers - ionophorous antibiotics, *but not proteins***

2. **Transporters/permeases, etc:**
   1. **Uniporters - liver cell glucose transport**
   2. **Symporters - epithelial glucose/Na^+ transport**
   3. **Antiporters - red blood cell HCO_3^-/Cl^- transport**

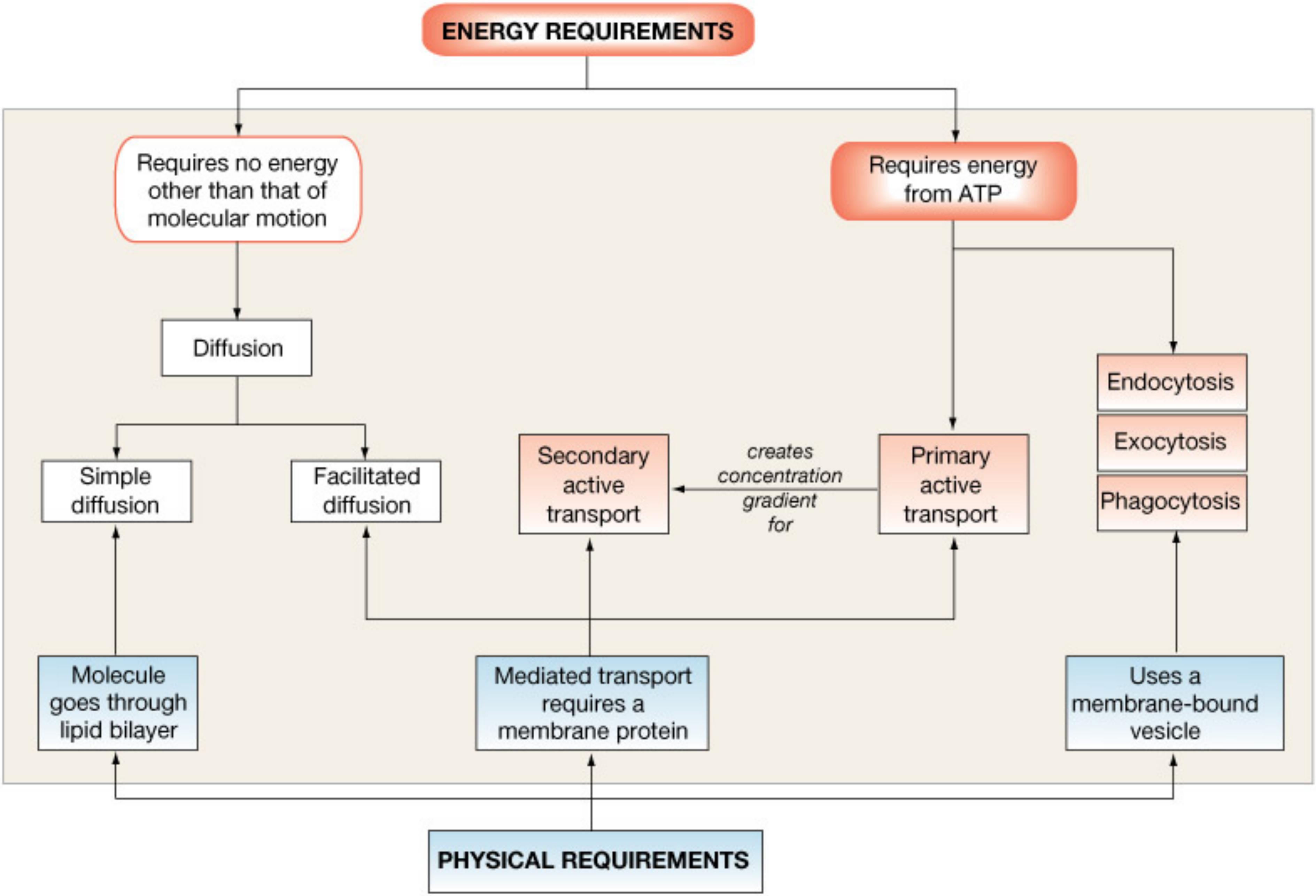
Secondary active transport

3. **Channels:**
   1. **Unregulated - porins; gramicidin A (a channel-type ionophore for monovalent cations)**
   2. **Voltage regulated, e.g., Na^+ channel Ligand-gated, e.g., nicotinic acetylcholine receptor**

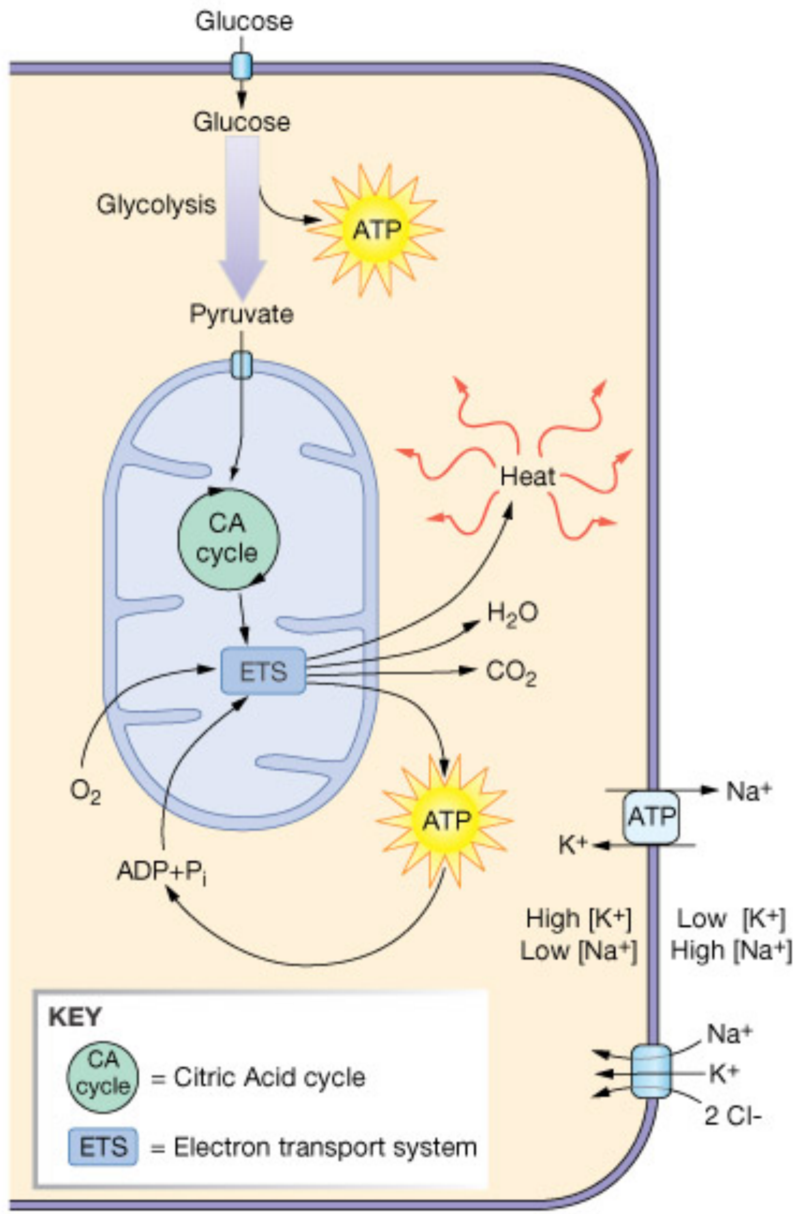
4. **Pumps - chemically and conformationally driven**

Primary active transport

Movement Across Membranes



Active transport



Energy is imported into the cell as energy stored in chemical bonds of nutrients such as glucose.

Metabolism

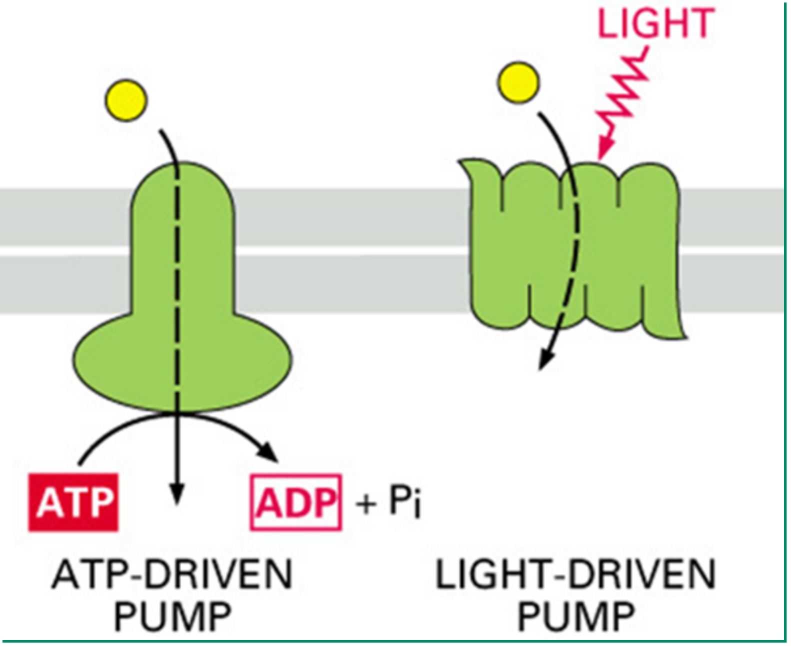
The chemical bond energy is converted into high-energy bonds of ATP through the process of metabolism.

Primary active transport

The energy in the high-energy phosphate bond of ATP is used to move K^+ and Na^+ against their concentration gradients. This creates potential energy stored in the ion concentration gradients.

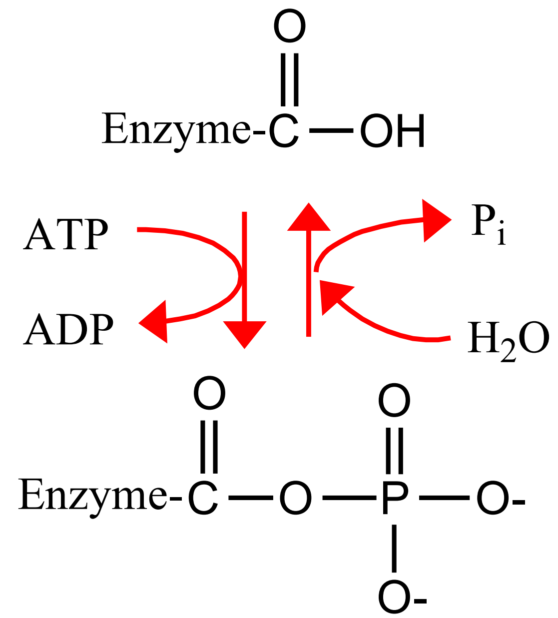
Secondary active transport

The energy of the Na^+ gradient can be used to move other molecules across the cell membrane against their concentration gradients.



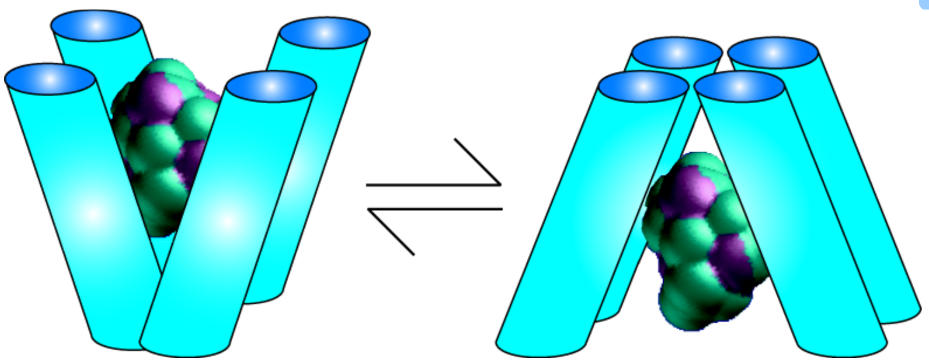
Primery active transport

(utilizes energy of ATP hydrolysis)



P-Class Pumps

❑ Phosphorilation changes protein shape and affinity for solute



Active transporters

Classified according to their protein sequence homology and structures.

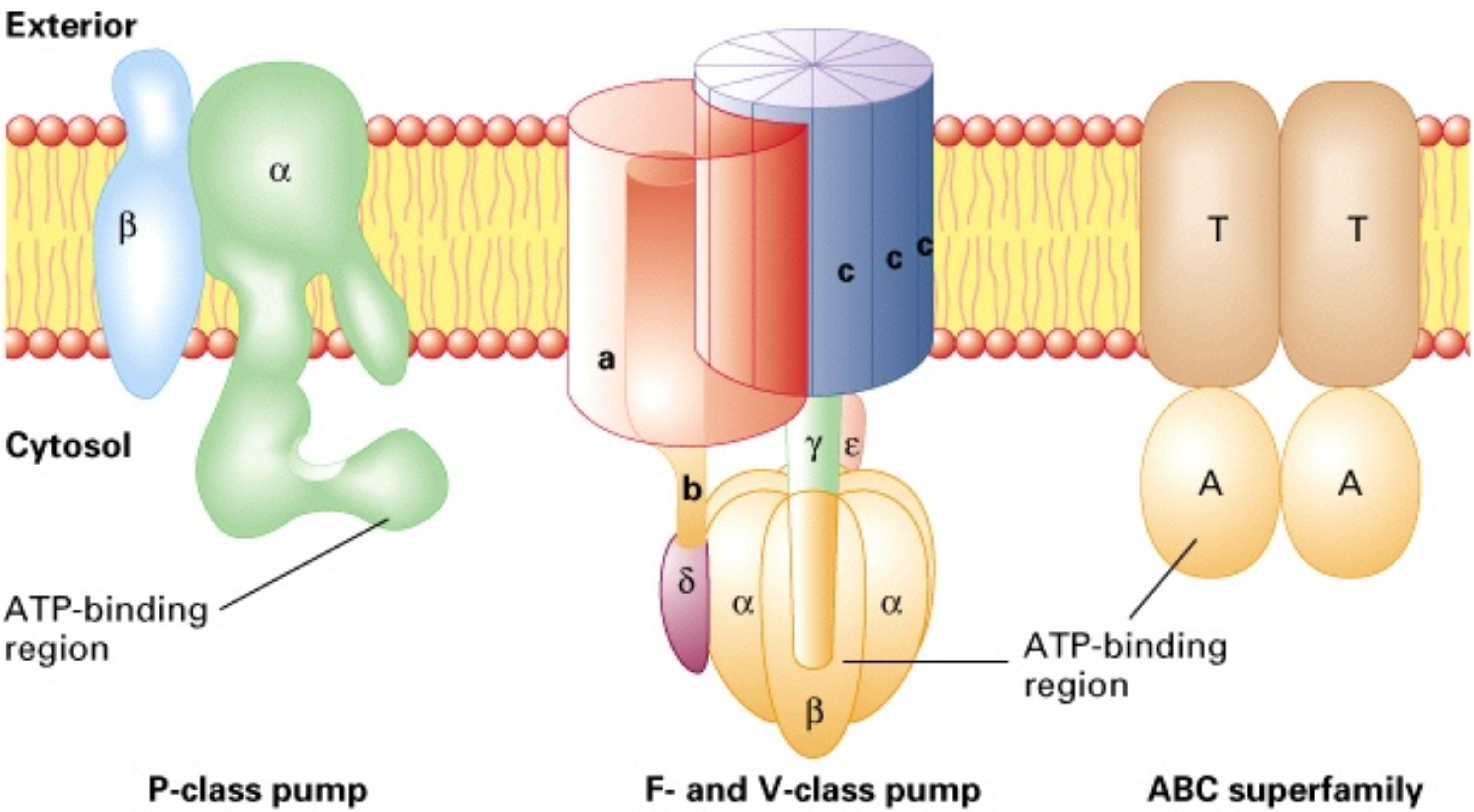
- ***P-type***: Na^+-K^+-ATPase, Ca^{2+} and H^+ pump, P means they have ***p***hosphorylation and they all sensitive to vanadate inhibition.

- ***V-type***: inner membrane ATPase to regulate H^+ and adjust proton gradients, v means ***v***acuole type for acidification of lysosomes, endosomes, golgi, and secretory vesicles.

- ***F-type***: ATP synthase to generate ATP energy from moving the proton across; F means energy coupling ***f***actor. There are F_1 and F_0 subcomplexes: F_1 generates ATP, F_0 lets H^+ go through the membrane.

- ***ABC transporters***: ***A***TP-***b***inding ***c***assette protein for active transport of hydrophobic chemicals and Cl^-.

Active transport by ATP-powered pumps



ATPase-pump classes

Class	P	F	V	ABC
Ion	H^+, Na^+, K^+, Ca^{2+}	H^+	H^+	various
Location Example	Na^+/K^+ pump	Mitochondrial F_1F_0	Endosomes	Bacteria
Function	Maintain Na/K gradients	Generate ATP	Acidify endosomes	Drug resistance

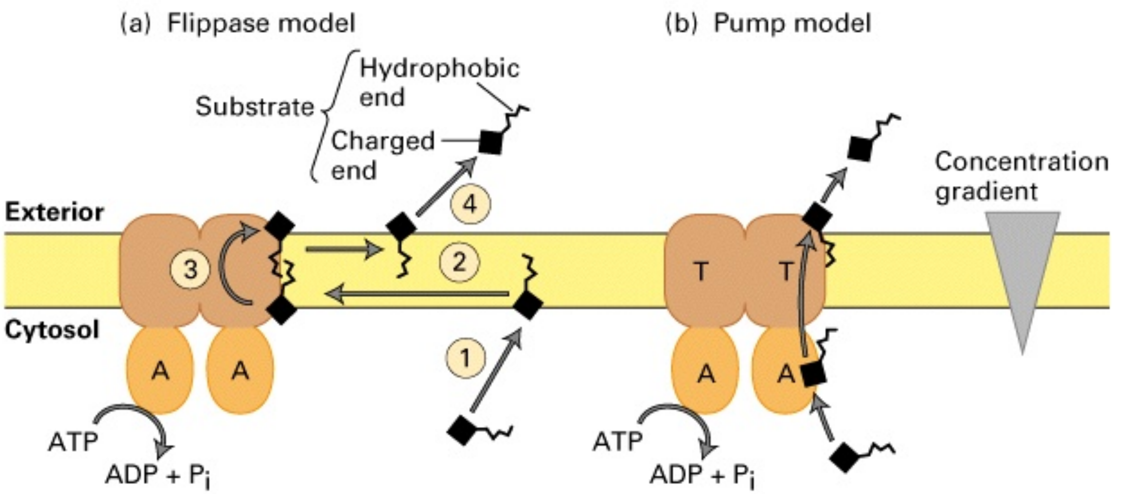
ABC Transporter: transport ATPase

1. ***Largest transport ATPase family (> 50 members)***
2. ***In procaryotes, the transporter locates in the inner membrane to carry nutrients into the cell***
3. ***In eucaryotes: multidrug resistance (MDR) protein, which produce resistance to drug.***
4. ***Cyctic fibrosis: a mutation on one ABC transporter (cyctic fibrosis transmembrane regulator [CFTR] protein) that function as a Cl^- channel in the epithelial***

ABC Transporters Translocate a Wide Variety of Solutes

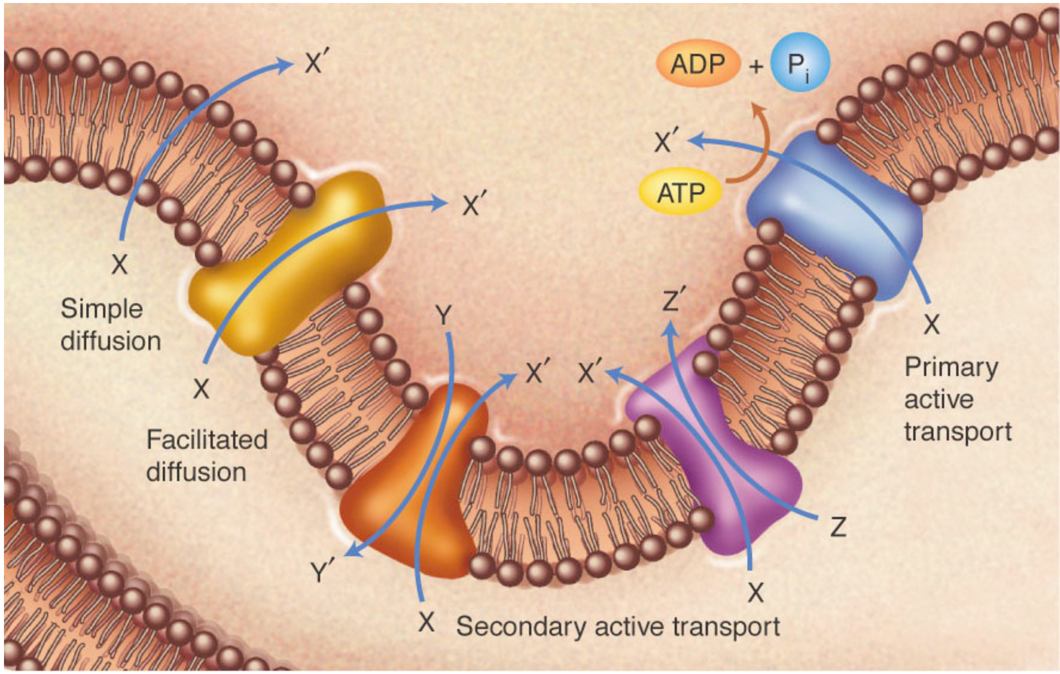
Some examples:

Species	System	Substrate	Direction
Streptococcus pneumoniae	AmiABCDEF	Oligopeptides	In
E coli	HisJQMP	Histidine	In
E coli	PstABC	Phosphate	In
Erwinia chrysanthemi	PrtD	Proteases	Out
Yeast	STE6	a-mating peptide	Out
Human	MDR1	Hydrophobic drugs	Out
Human	CFTR	Chloride	Out
Human	RING 4-11	Peptides	Into E.R.



The master pump concept

- *Creates transmembrane gradient of a selected ion.*
- *Other ions and molecules are transported across the membrane by coupling their movement to the movement of the selected ion.*
- *The electrochemical potential energy is stored only across the membrane in which the pump is located.*
- *Ion gradients generally store smaller packets of energy than ATP - coupled transporters (increased efficiency).*
- *Coupling transport to a single master pump serve a **control function**.*

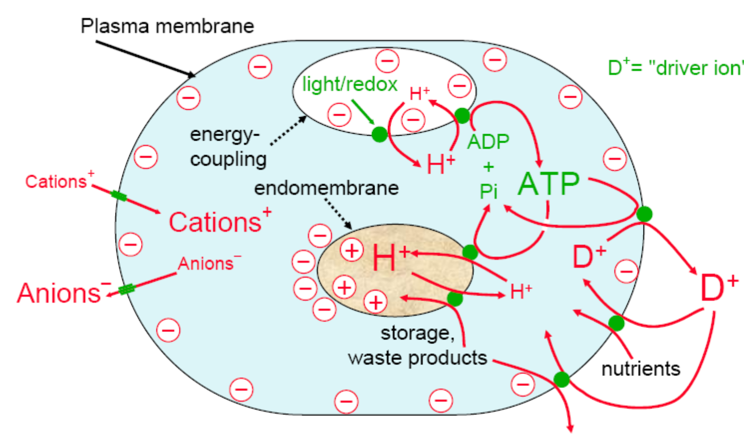


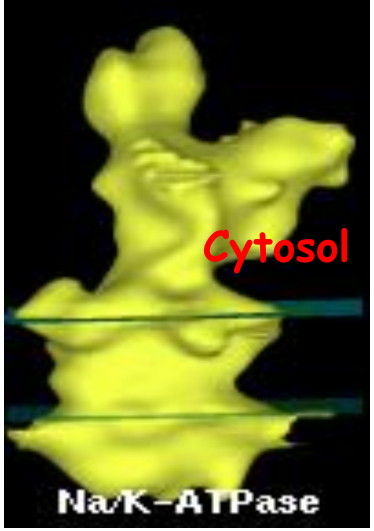
Atributes of a master pump

- ***Low dissipation (leakage current)*** is the reason that pumps almost exclusively transport the relatively impermeant inorganic cations.

- ***High capacity*** – the ion gradient involve concentrations that are relatively large compared to the concentrations of the compounds that are to be transported.

- ***High efficiency***





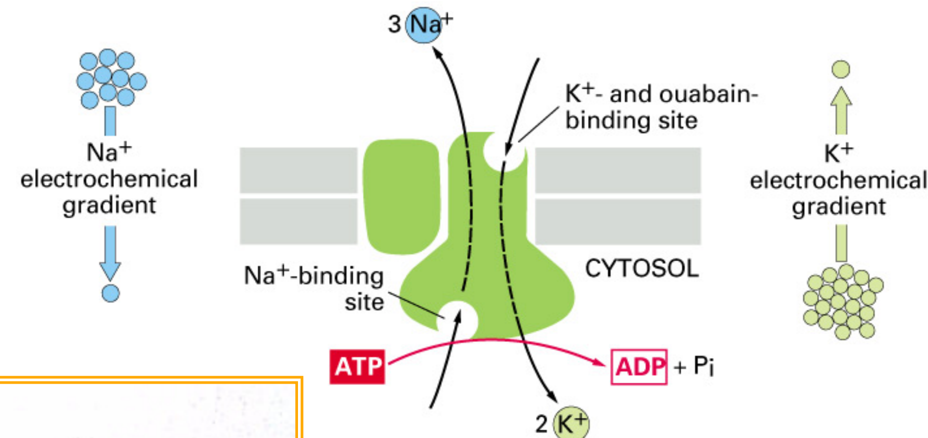
David Stokes, Univ. Virginia

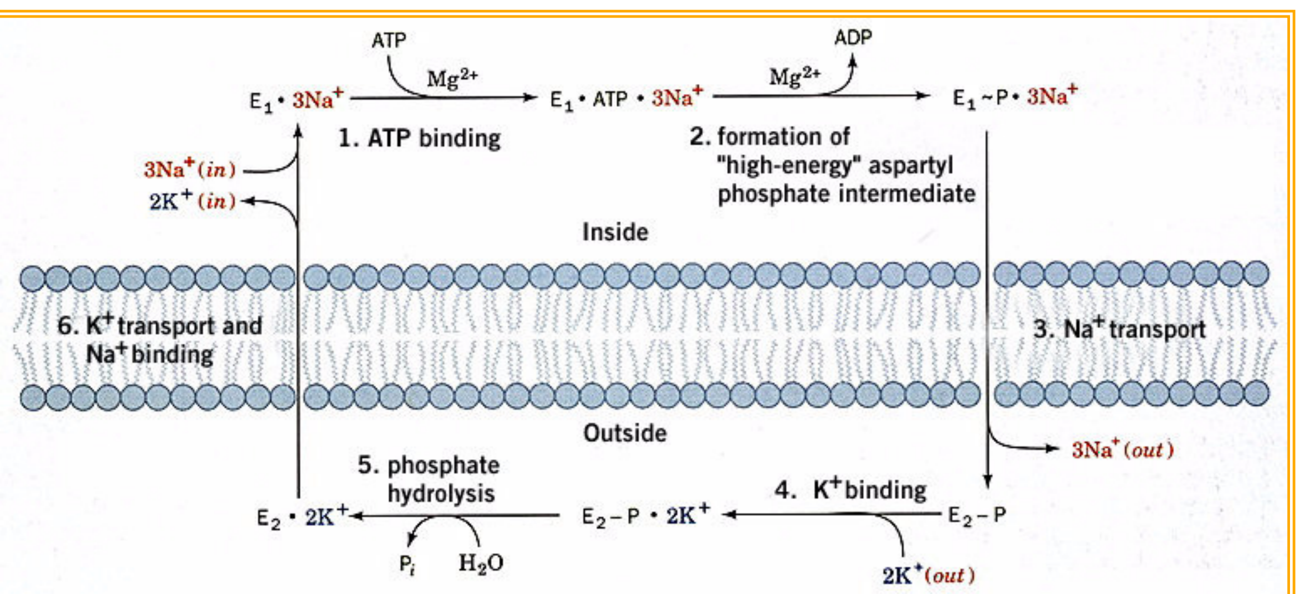
Na⁺,K⁺-ATPase

Abundance reflects importance

- *Erythrocyte = 20-30 copies*
- *Heart cell or neuron > 100,000 copies*

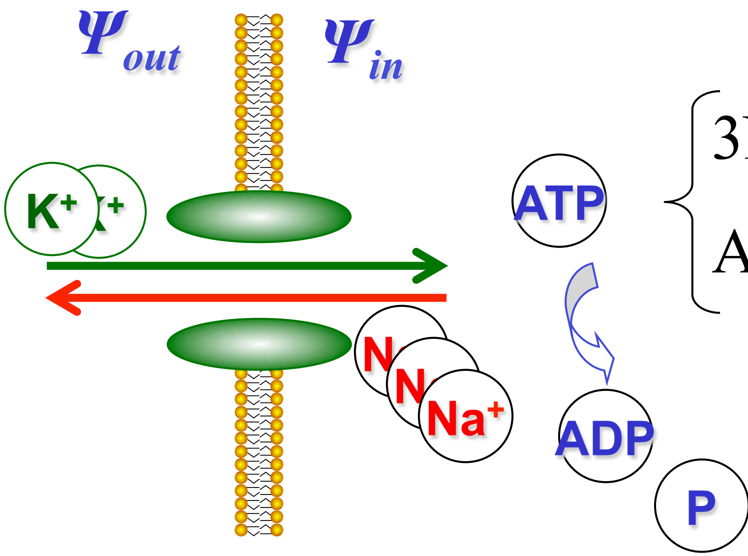
Pump Activity is Electrogenic





Primary active transport

$$3Na^+(in) + 2K^+(out) + ATP + H_2O \longleftrightarrow 3Na^+(out) + 2K^+(in) + ADP + Pi$$



$$\begin{cases} 3Na^+(in)+2K^+(out)\leftrightarrow 3Na^+(out)+2K^+(in) \\ ATP + H_2O \leftrightarrow ADP + Pi \end{cases}$$

$$\Delta G_{net} = \Delta G_{ion} + \Delta G_{ATP}$$

$$\Delta G_{ion} = RT\ln\left(\left(\frac{[Na^+]_{out}}{[Na^+]_{in}}\right)^3\left(\frac{[K^+]_{in}}{[K^+]_{out}}\right)^2\right) - F\Delta\Psi_{in-out}$$

$$\Delta G_{ATP} = \Delta G^0{}_{ATP} + RT\ln\frac{[ADP][Pi]}{[ATP]}$$

394 BIOCHIMICA ET BIOPHYSICA ACTA VOL. 23 (1957)

THE INFLUENCE OF SOME CATIONS ON AN ADENOSINE TRIPHOSPHATASE FROM PERIPHERAL NERVES

JENS CHR. SKOU

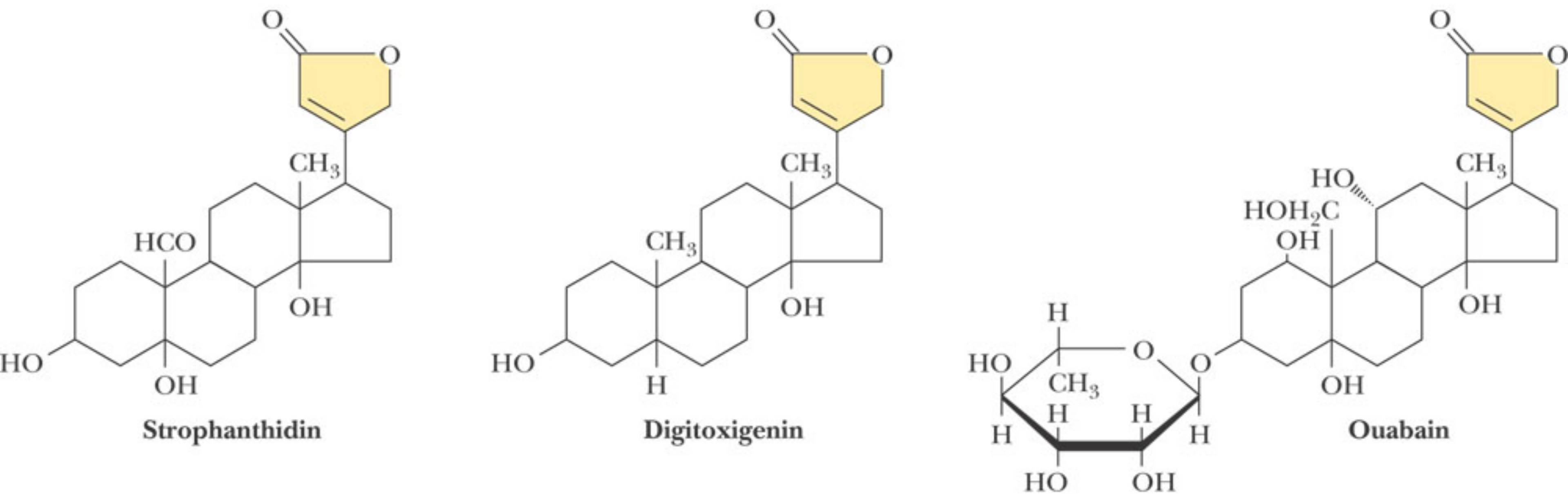
Institute of Physiology, University of Aarhus (Denmark)

Jens Skou Receives 1997 Nobel Prize for Discovery of Na,K-ATPase

Na^+,K^+-ATPase Functions

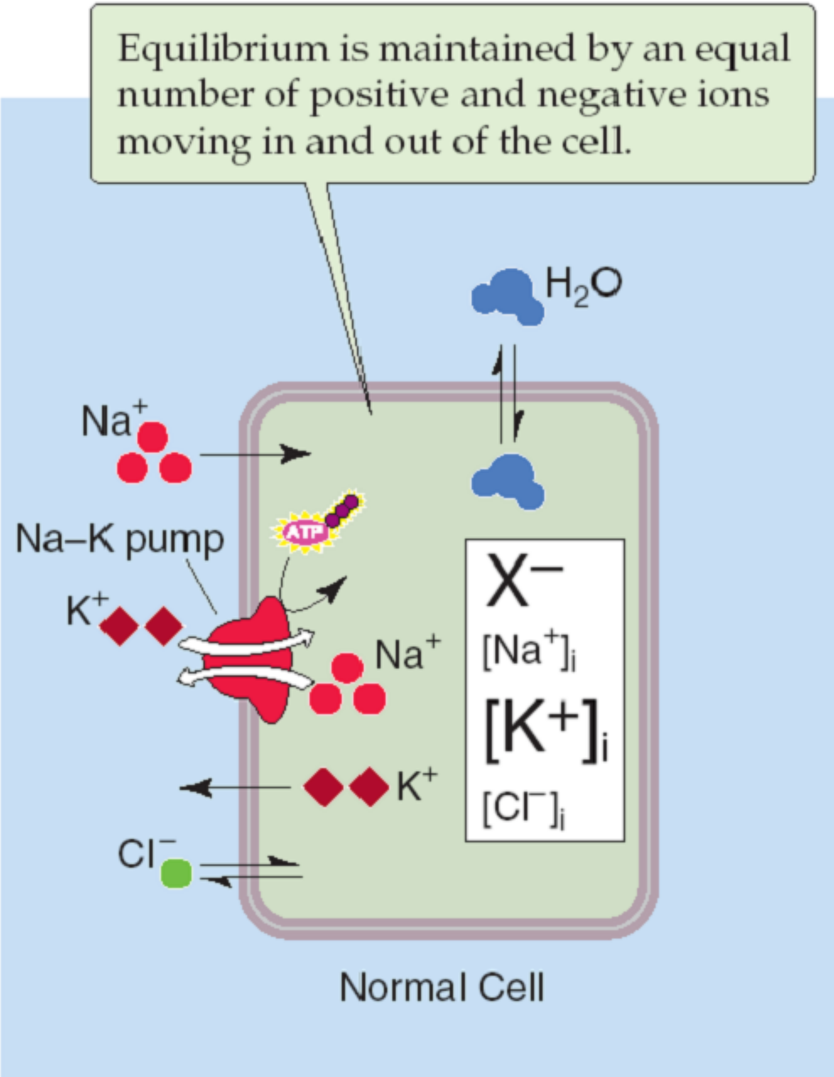
- ***20% of body heat in mammals is from the basal activity of Na^+,K^+-ATPase.***

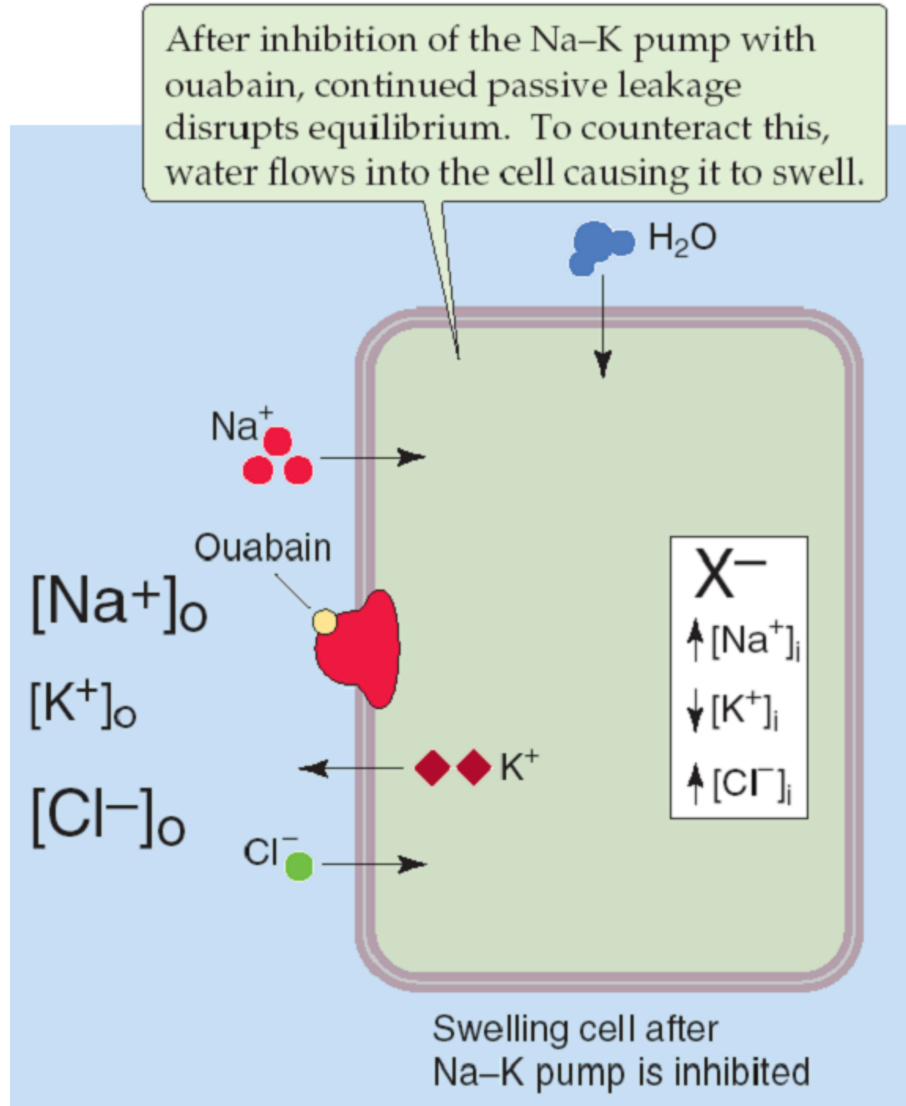
- ***> 30% of metabolic energy in resting mammals is consumed by Na^+,K^+-ATPase.***



Cardiac glycosides bind exclusively to the extracellular surface of Na^+,K^+-ATPase when it is in the E_2-P state.

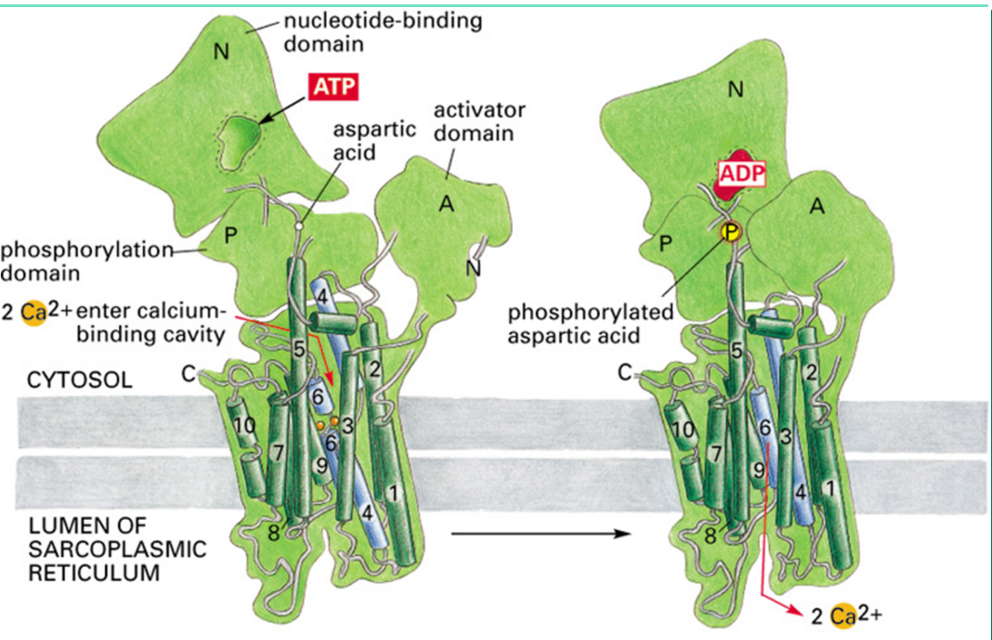
When pump is stopped ……





A transport system might not be coupled to the master pump

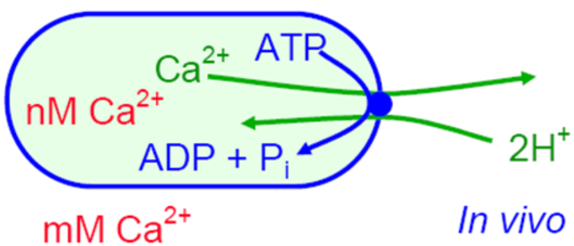
Ca^{2+}-ATPase



Calcium homeostasis

Cytoplasmic Ca^{2+} is regulated by a Na^{+}/Ca^{2+} antiporter in plasma membranes and by P-type Ca-ATPases in plasma membranes and endoplasmic reticulum.

Plasma membrane Ca^{2+}-ATPase

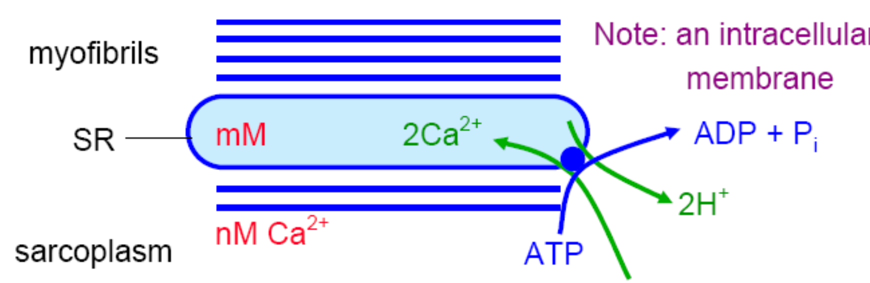


Ubiquitous in eukaryotes

In vivo activity ~ 5% of (Na^{+}/K^{+})-ATPase

Sarcoplasmic Reticulum Ca^{2+} - ATPase

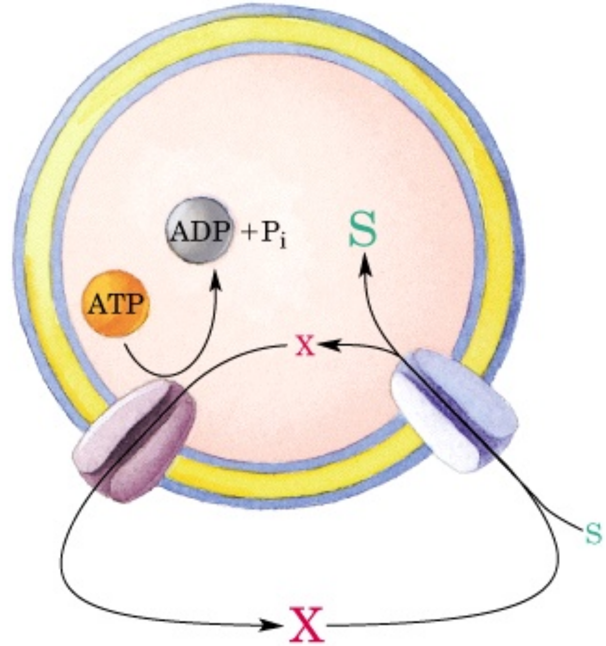
[also on ER, hence "SERCA" pump]



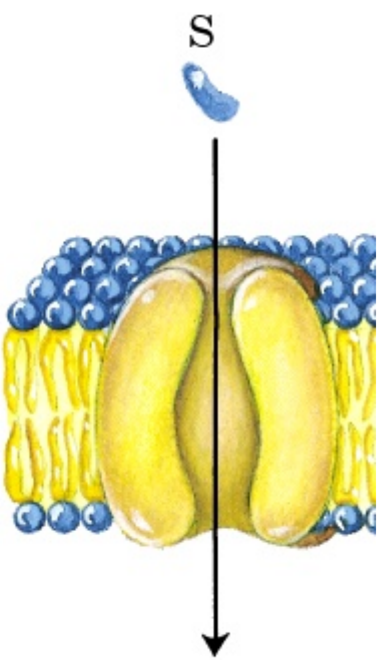
Secondary Active Transport

(Coupled Transport)

Utilizes ion-gradients generated by primary transporters.



Secondary active transport



Uniport

***Uniport* – transport of a single solute driven only by $\Delta\Psi$**

$$\log_{10}\frac{[S_I^{+Z}]}{[S_O^{+Z}]} = -z\frac{\Delta\Psi}{B}$$

Nerst equation

2.3RT/F = 59 mV ≡ B at 25^{0}C

Symport (cotransport) amino acids and sugers

Et the equilibrium

$$\Delta G_{S^{Z+}} = n\Delta\tilde{\mu}_{H^+} + \Delta\tilde{\mu}_{S^{Z+}} = 0$$

n is the number of moles of H^+ that would have to move down the $\Delta\tilde{\mu}_{J+}$ gradient to generate the accumulation.

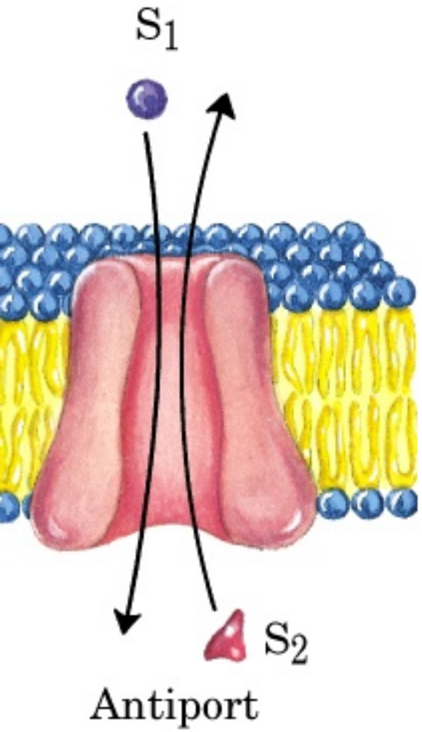
$$\Delta\tilde{\mu}_{H^+} = F\Delta\Psi - 2.3RT\Delta pH$$

$$\Delta\tilde{\mu}_{S^{Z+}} = 2.3RT\log_{10}\frac{[S_I^{+Z}]}{[S_O^{+Z}]} + zF\Delta\Psi$$

$$\Delta G_{S^{Z+}} = \Delta\tilde{\mu}_{S^{Z+}} + \Delta\tilde{\mu}_{H+} = 2.3RT\log_{10}\frac{[S_I^{+Z}]}{[S_O^{+Z}]} + zF\Delta\Psi + n(F\Delta\Psi - 2.3RT\Delta pH) = 0$$

$$\log_{10}\frac{[S_I^{+Z}]}{[S_O^{+Z}]} = n\Delta pH - (n+z)\frac{\Delta\Psi}{B}$$

$2.3RT/F = 59\ mV \equiv B$ at 25^0C



Antiport ***(counter-transport)*** *restricted to ions*

$$\Delta\tilde{\mu}_{S^{+Z}} = 2.3RT\log_{10}\frac{S_0^{+Z}}{S_I^{+Z}} - zF\Delta\Psi$$

$$\Delta\tilde{\mu}_{H^+} = F\Delta\Psi - 2.3RT\Delta pH$$

- Combining $\Delta\mu^{\sim}_{H+}$ and $\Delta\mu^{\sim}_{S+Z}$

$$\log_{10}\frac{S_I^{+Z}}{S_O^{+Z}} = (n-z)\frac{\Delta\Psi}{Z} - n\Delta pH$$

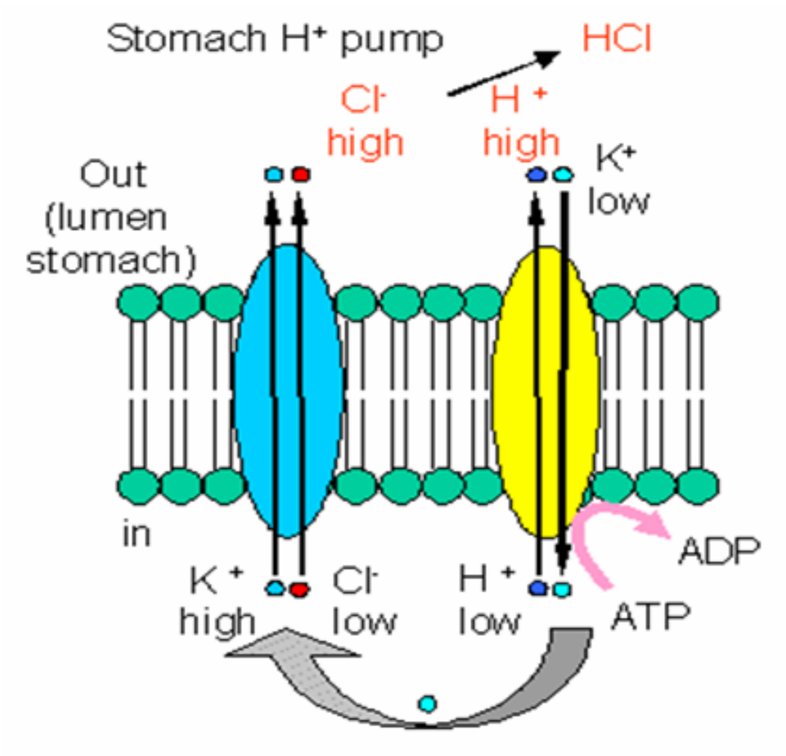
n is the number of moles of H^+ that would have to move againsty the $\Delta\mu^{\sim}_{J+}$ gradient to generate the accumulation.

- If n = z, then the charge movement would be neutral and ΔΨ has no effect.

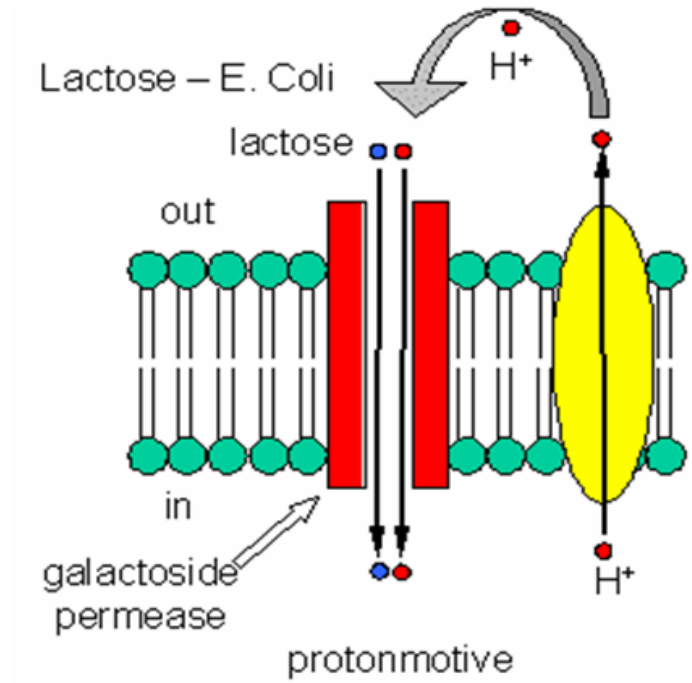
$$\log_{10}\frac{S_I^{+Z}}{S_O^{+Z}} = -n\Delta pH$$

The consequence of the transfer of charged malecules

Electroneutral



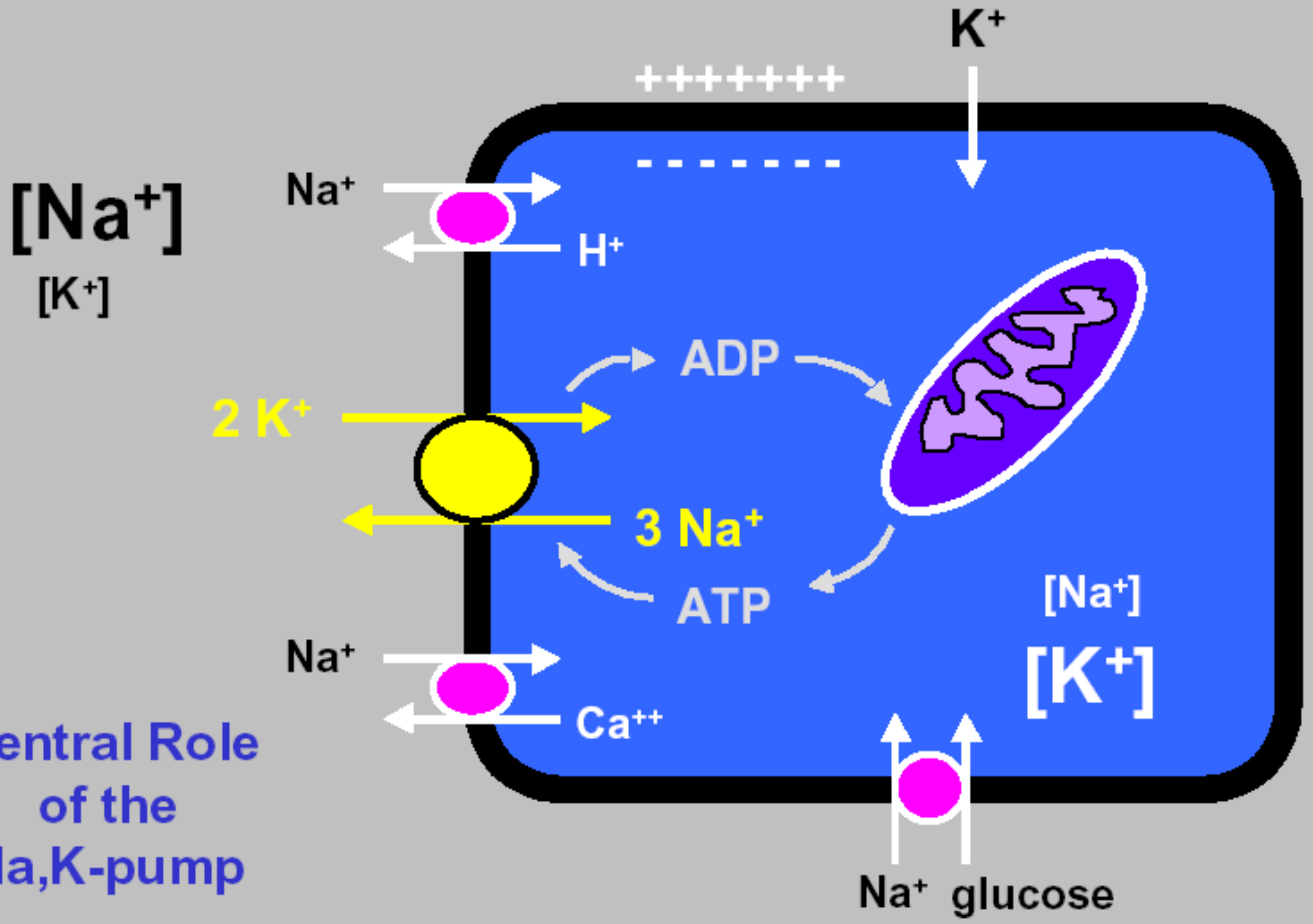
Electrogenic



A potential difference across a biological membrane: ~70 mV

The voltage gradient is ~ 20,000,000 V/m.

Integration of a transport systems !!!



Central Role
of the
Na,K-pump

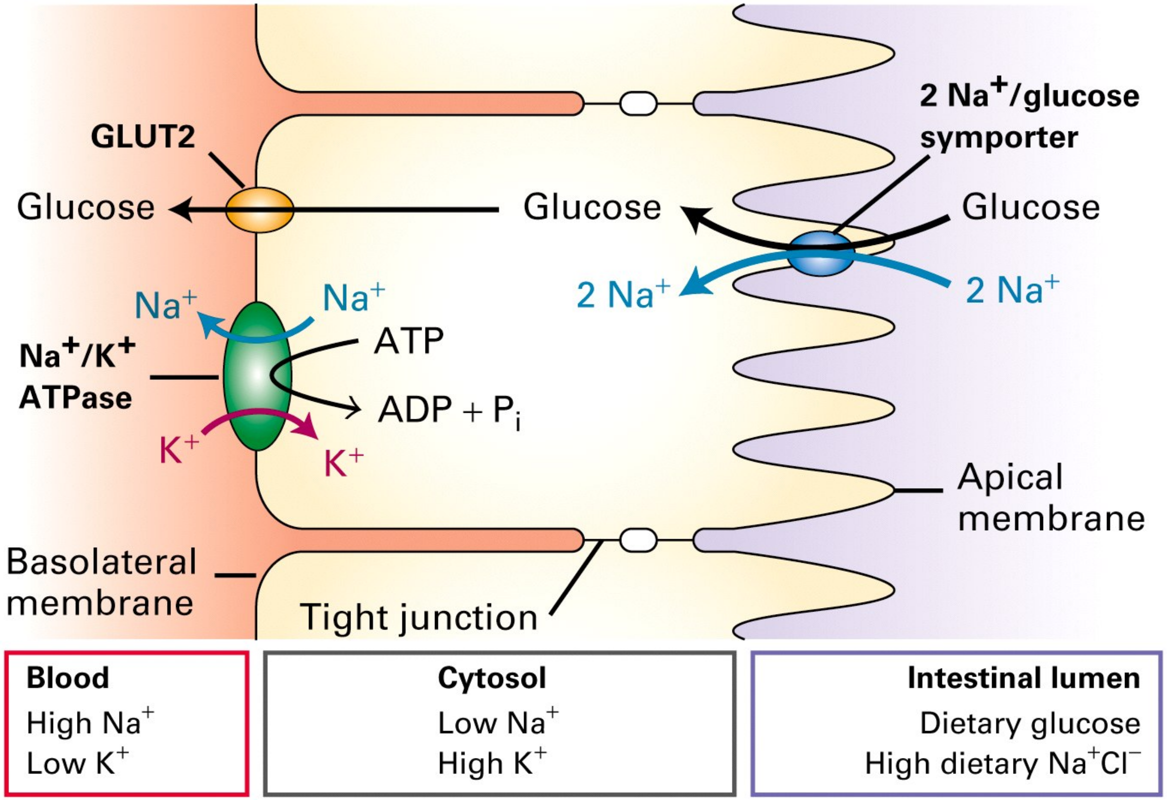
Secondary active transport example

- Works if $\left| n_{ions} \Delta G_{driving\,ion} \right| > \left| n_{transportee} \Delta G_{transportee} \right|$

- Sodium-Glucose cotransporter (1:1)
- Intestinal glucose around 0.5 mM
- Intestinal epithelial intracellular glucose >5 mM

- $\Delta G_{\text{glucose IN}} = +1{,}418$ cal/mol
- $\Delta G_{\text{sodium IN}} = -3{,}261$ cal/mol

- **So one sodium CAN drive the import of one glucose from the interior of your intestine!**



Na^+/glucose cotransporter

Energetics of transport:

Entry of 1 sodium contributes about 2.2-3 kcal/mol

For uncharged glucose

$$\Delta G = RT\ln([C_2]/[C_1])$$

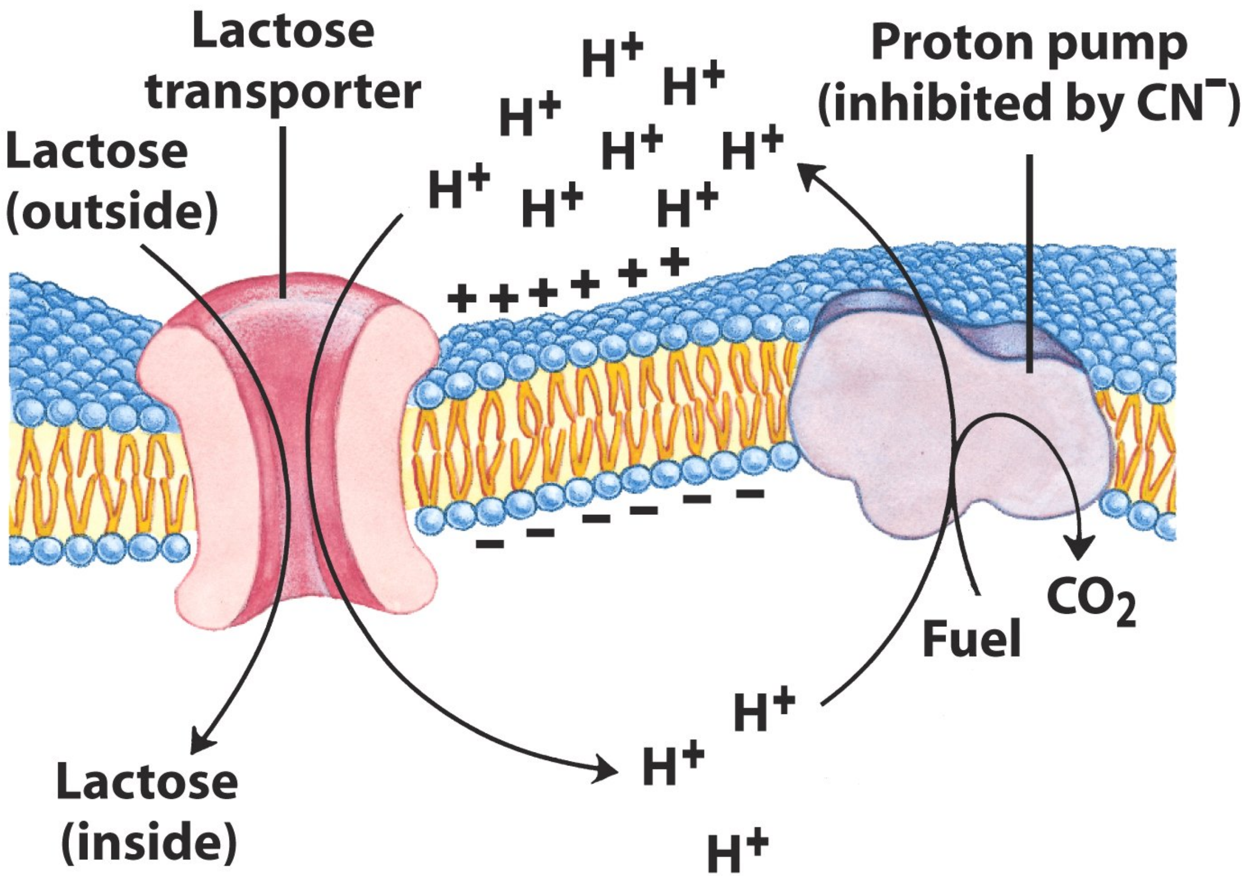
Therefore co-transport with 2 Na^+ allows to generate about 1000 fold higher concentration of glucose inside the cell

$$\Delta G = \sum_i n_i \Delta\mu_i = \sum_i n_i(\mu_i^{in} - \mu_i^{out}) = \sum_i n_i\left[RT\ln\left(\frac{C_{in}}{C_{out}}\right) + z_i F\psi_m\right]$$

At equilibrium:

$$\Delta G = RT\ln\left(\frac{[G]_{in}}{[G]_{out}}\right) + RT\ln\left(\frac{[Na^+]_{in}}{[Na^+]_{out}}\right) + F\psi_m = 0$$

$$\frac{[G]_{in}}{[G]_{out}} = \left(\frac{[Na^+]_{out}}{[Na^+]_{in}}\right)\exp(-F\psi_m / RT)$$



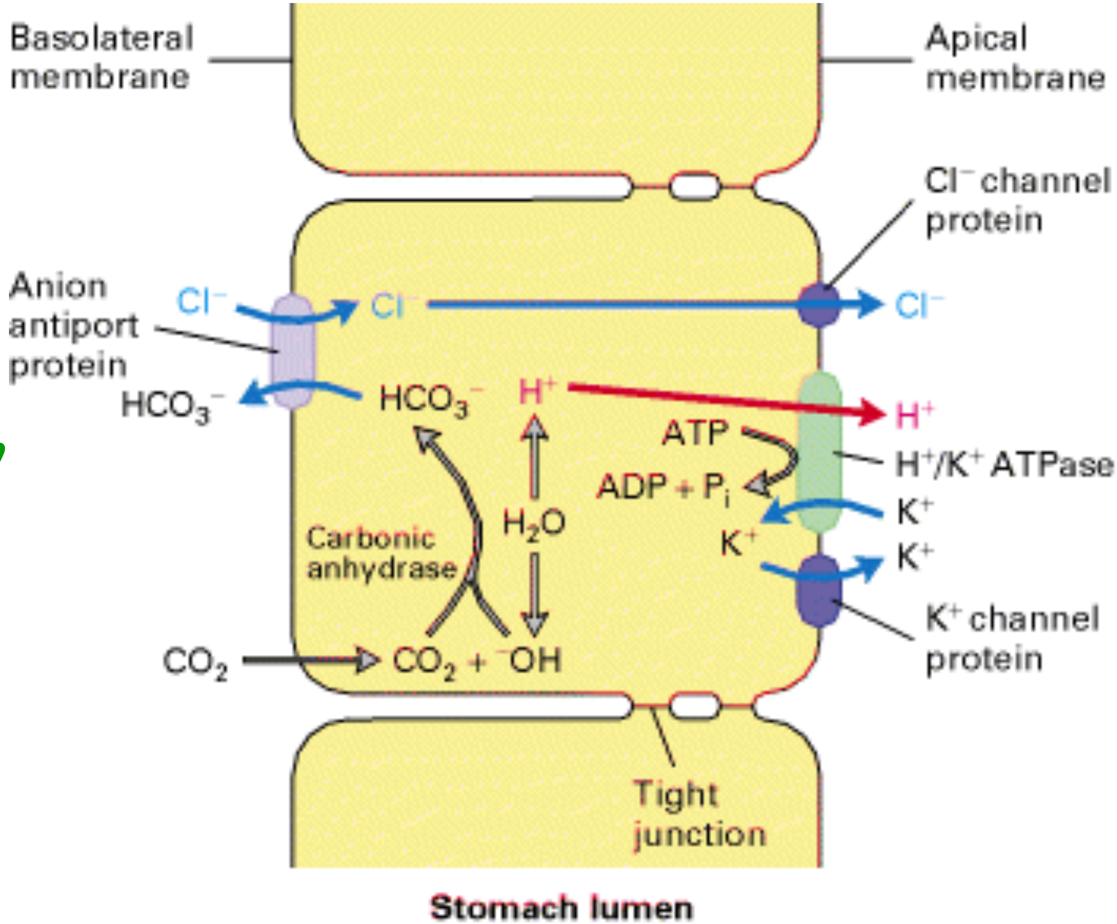
E. coli **lactose transporter**

Acidification of the stomach lumen

The role of H^+/K^+ ATPase

This is the largest concentration gradient (pH = 1.0; pH = 7.5)

across a membrane in eukaryotic organisms!



Regulation of intracellular pH

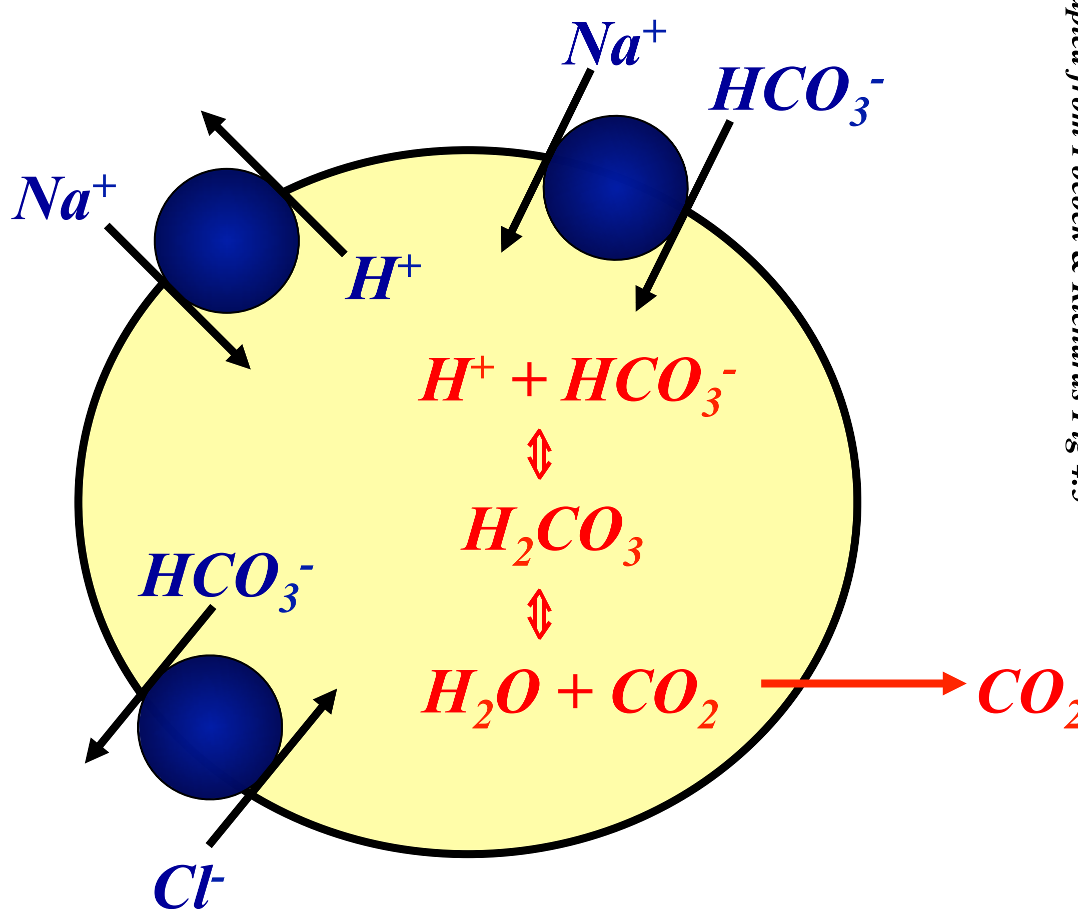
- *Intracellular pH (pH_i) ~ 7.0-7.2*
- *Extracellular pH (pH_e) ~ 7.4*
- *Metabolic processes produce acidic byproducts ⇒ ↓pH_i*
- *Require regulatory mechanisms to maintain pH_i*

Principal mechanisms:

Na^+/H^+ exchange

Cl^-/HCO_3^- exchange

Na^+-HCO_3^- co-transport

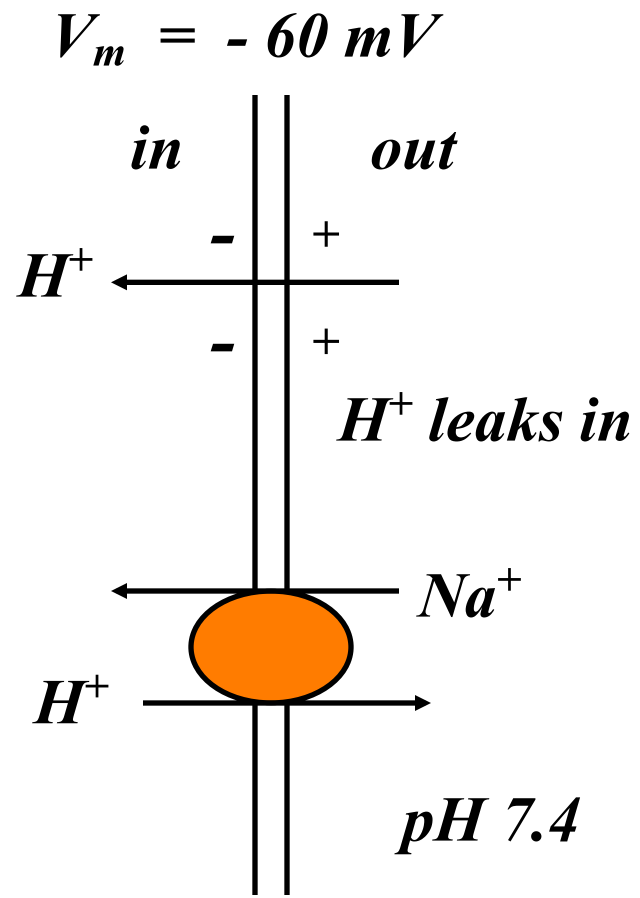


Adapted from Pocock & Richards Fig 4.5

Na/H exchanger

Because of V_m, pH_{in} would equilibrate at ~ 6.4 without a mechanism to move H^+ out.

- Exchanges H^+ for Na^+ *electroneutrally*, unaffected by membrane voltage.
- Direction of exchange is determined by concentration ratios of the ions in and out.



At equilibrium,

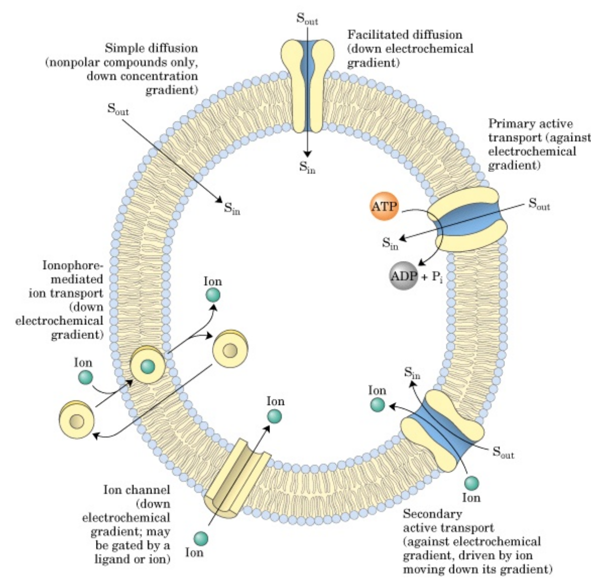
$$[Na^+]_{out}/[Na^+]_{in} = [H^+]_{out}/[H^+]_{in}$$

pH_{in} would be ~ 8.4, but exchanger turns off when pH_{in} rises into the range of 7.0 - 7.4.

$[Na^+]_{out}$ is ~10^6 times greater than $[H^+]_{in}$, one-for-one exchange of H^+ for Na^+ can substantially change $[H^+]_{in}$ with almost no change in Na^+ concentrations, so $\Delta[Na^+]$ driving force remains strong as $\Delta[H^+]$ diminishes.

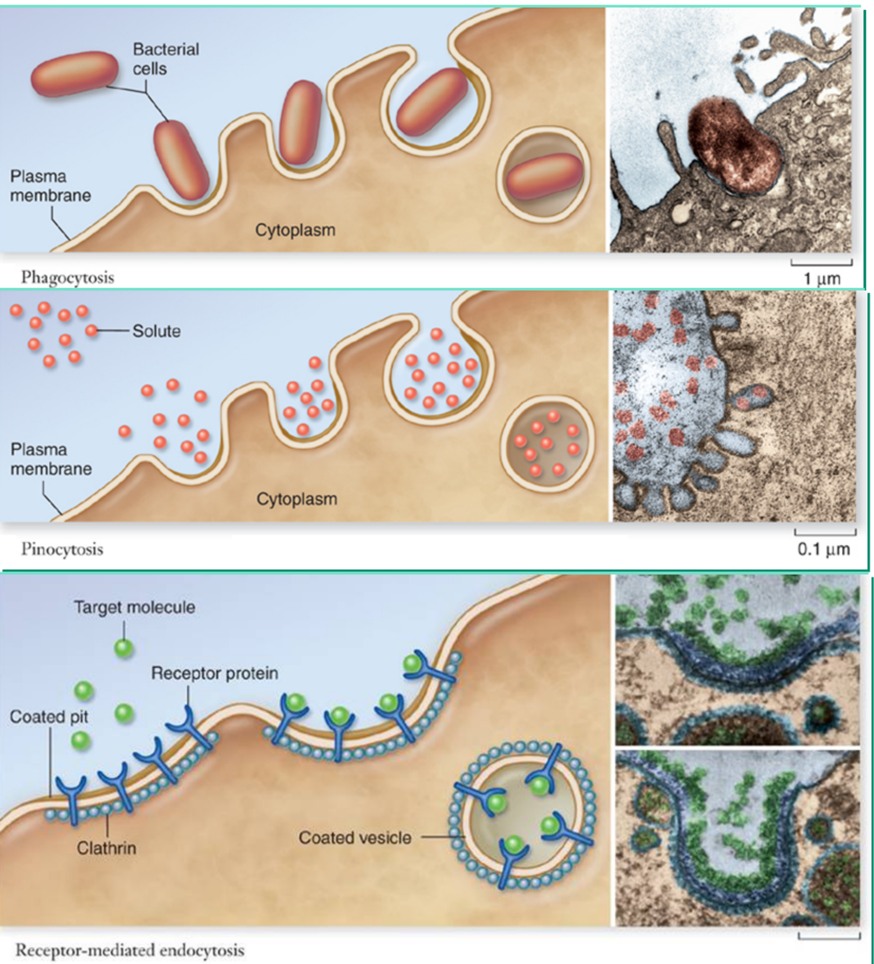
Comparison of transport mechanisms

	Transport rate [s^{-1}]
Channels/Pores - Often very high rate (when open)	
Sodium Channel	10^7
Gramicidin A (H^+)	10^8
Acetylcholine receptor channel	10^7
Passive Permeases (Carriers, Transporters)	
valinomycin (carrier)	10^4
H^+ - Lactose permease (*E. coli) - symport*	*30*
Glucose transporter (erythrocytes) - *uniport*	*300*
Band 3 anion transporter (erythrocytes) - Cl^-/HCO_3 - *antiport*	*10^5*
Primary Active Transporters	
Bacteriorhodopsin (H^+), Halorhodopsin (Cl^-)	100
Na^+/K^+-ATPase (P-type)	450
H^+-ATPase (F-type)	500
Cytochrome c oxidase (H^+)	1000

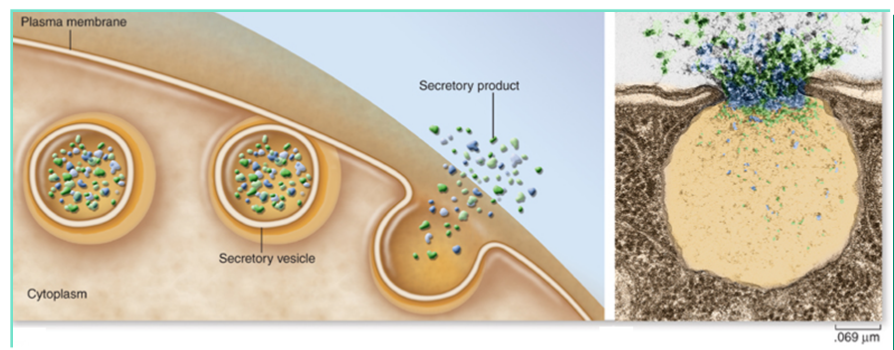


Bulk transport

Endocytosis



Exocytosis



Cystic Fibrosis and Membrane Transport

Cystic Fibrosis

CF causes the body to produce an abnormally thick, sticky mucus on epithelial surfaces.

It is one of the most common lethal inherited disorders among caucasians.

One in 28 Caucasians - is an unknowing, symptom-less heterozygous carrier of the defective gene

Symptoms and complications

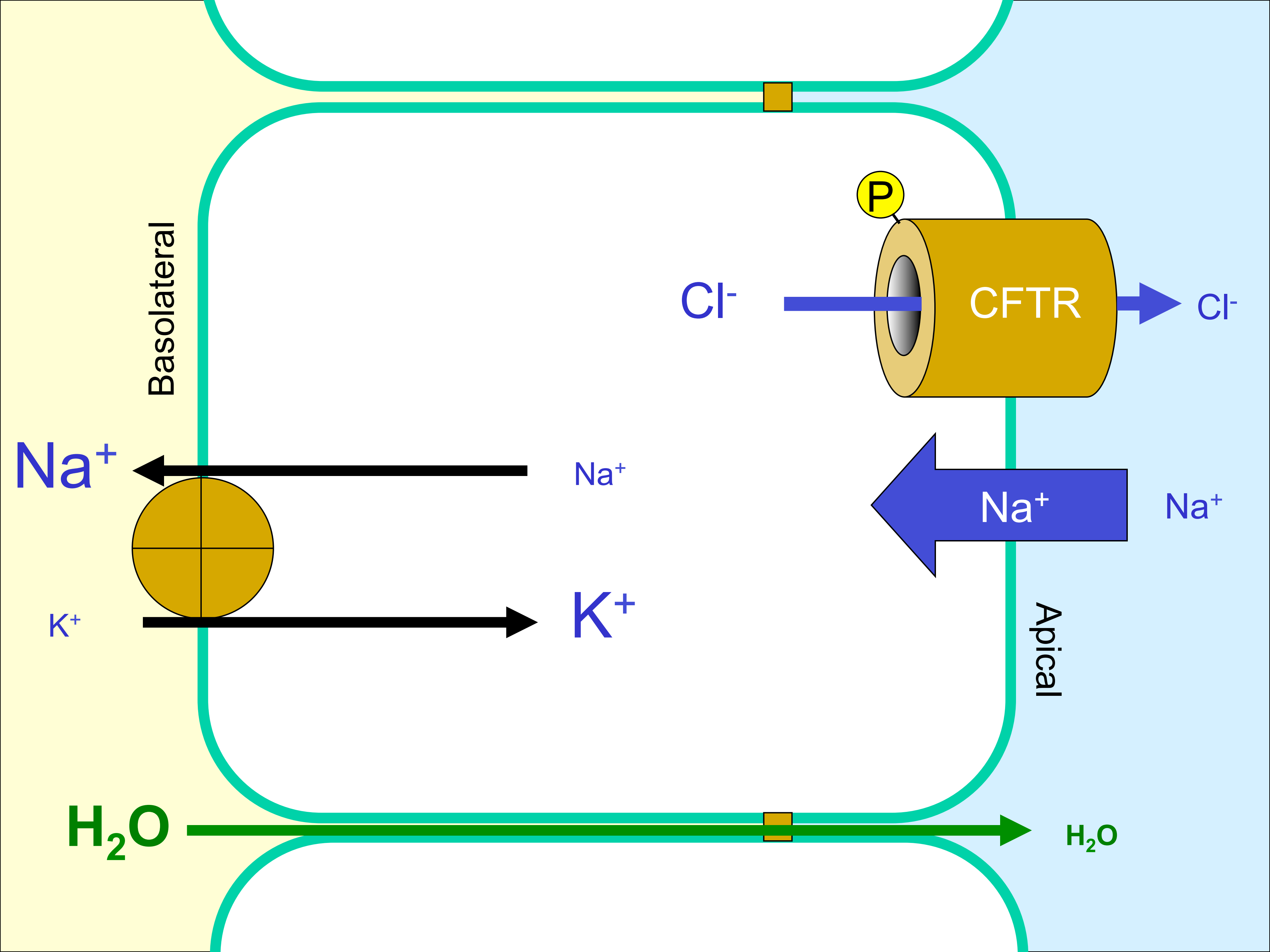
- Decreased mucociliary clearance of sputum leads to chronic endobronchial bacterial colonization, and…
  - Production of large amounts of sputum
  - Wheezing
  - Dyspnea
  - Limited exercise tolerance
  - Death

- Pancreatic insufficiency in 85% of patients, leading to malabsorption of fat and malnutrition.
- Also diabetes mellitus, bowel obstructions, arthritis, and infertility.

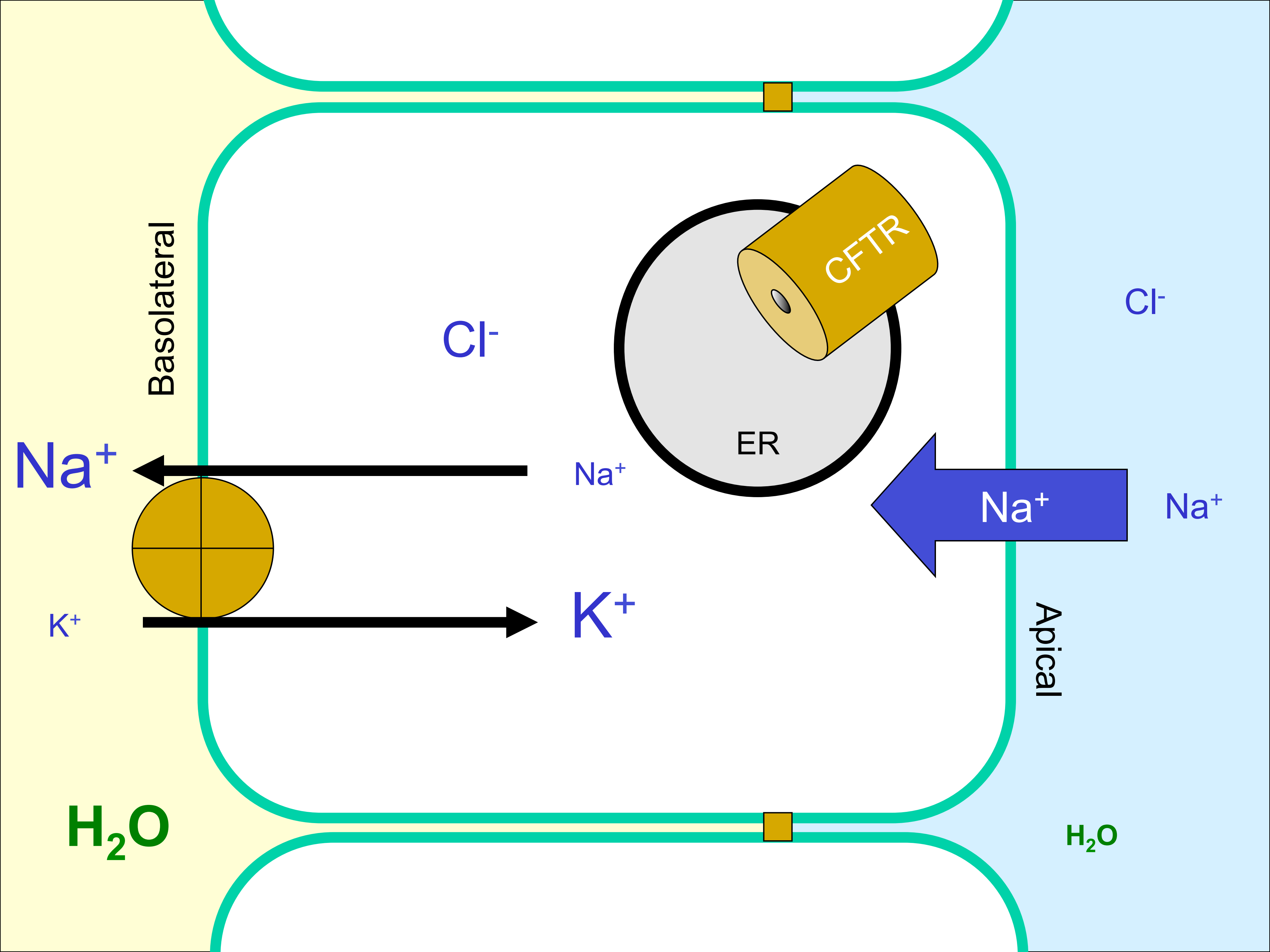
Cystic Fibrosis Transconductance Regulator (CFTR)

- A member of the ABC superfamily of transport proteins
- However, it does not appear to act as an *active* transporter
- A chloride channel – facilitated diffusion
- Activated by phosphorylation
- Permits chloride movement to the epithelial surface.
- This results in osmotic flux of water to the apical surface, diluting mucus.

- In about 70% of CR cases, a mutated form of the CFTR is reaches the ER, but is then degraded.



Basolateral
Apical
P
CFTR
Cl^-
Cl^-
Na^+
Na^+
Na^+
Na^+
K^+
K^+
H_2O
H_2O

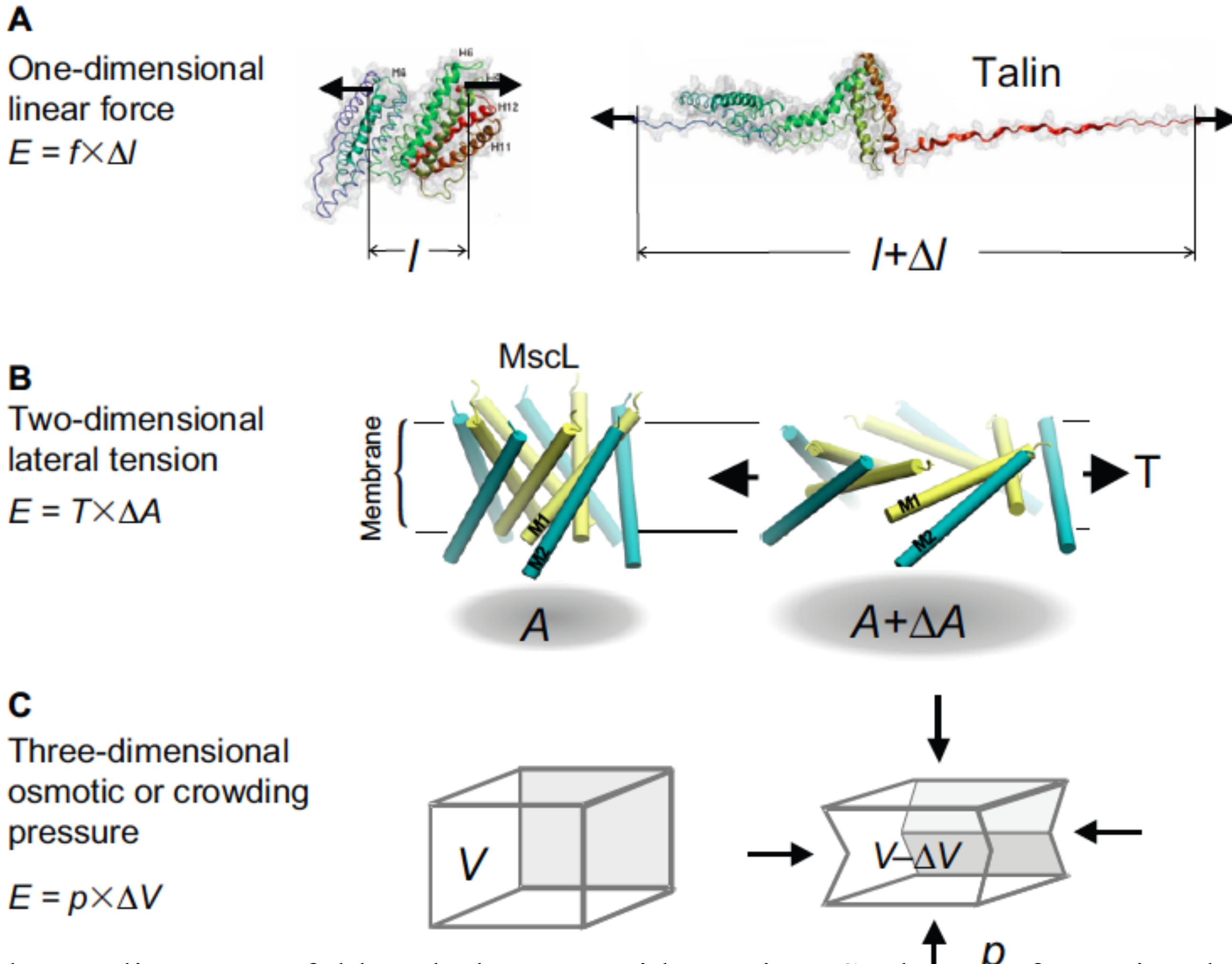


Basolateral
Cl-
CFTR
Cl-
ER
Na+
Na+
Na+
Na+
K+
K+
Apical
H2O
H2O

Current treatments

- Treatment for Lung Problems
  - Antibiotics
  - Chest physical therapy (like percussion)
  - Exercise
  - Other medications
    - Anti-inflammatory medications
    - Bronchodilators,
    - Mucus-thinning drugs
  - Oxygen Therapy
- Lung Transplantation
- Management of Digestive Problems
  - Oral pancreatic enzymes
  - Fat-soluble vitamins A, D, E, and K
  - Feeding tube
  - Enemas and mucus-thinning medications to treat intestinal blockages

Mechano-sensing in different dimensions.

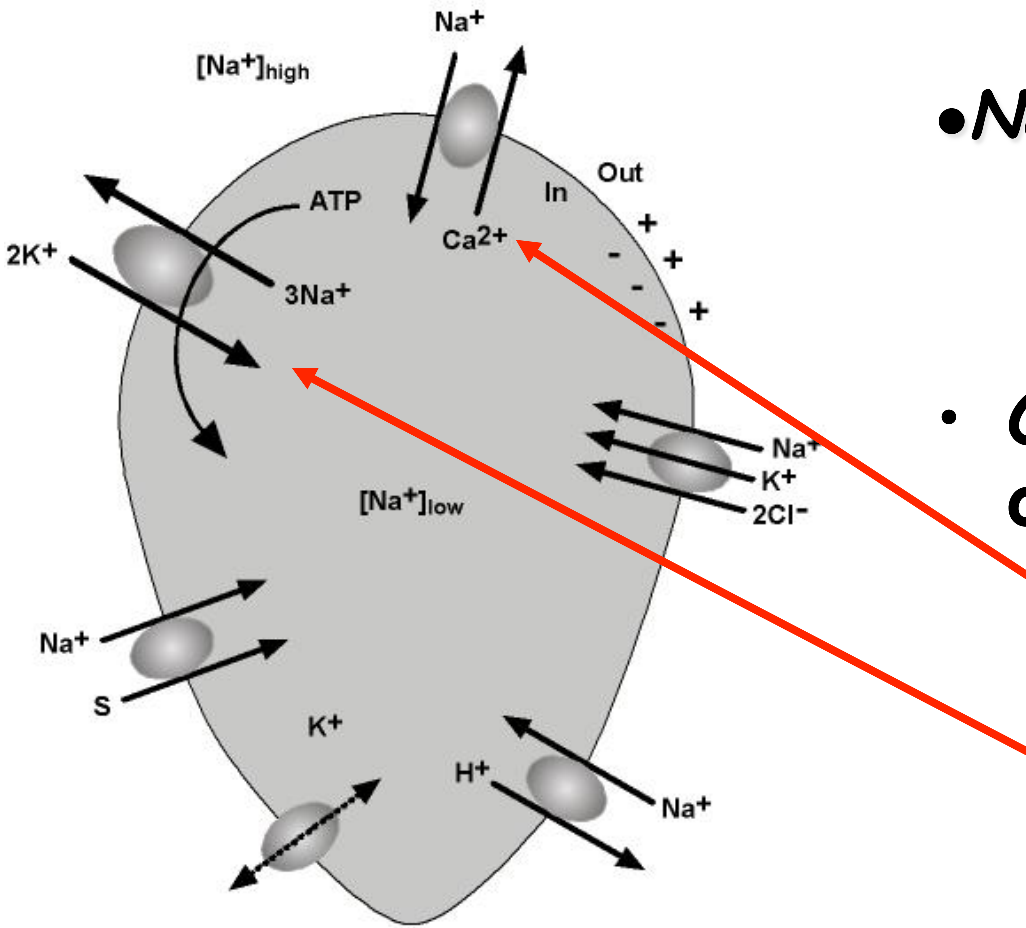


(A) A one-dimensional sensor, such as talin, can unfold and elongate with tension. Such a conformational change could expose cryptic binding sites within the protein.

(B) A membrane channel that opens in response to membrane tension is an example of a two dimensional sensor that increases its in-plane area (A). The panel shows the predicted tilting motion of pairs of transmembrane helices of the bacterial mechanosensitive channel MscL, which are associated with a ,20 nm^2 change of in-plane area expansion.

(C) A hypothetical elastic structure that decreases its volume under osmotic pressure is an example of a three-dimensional mechanosensor.

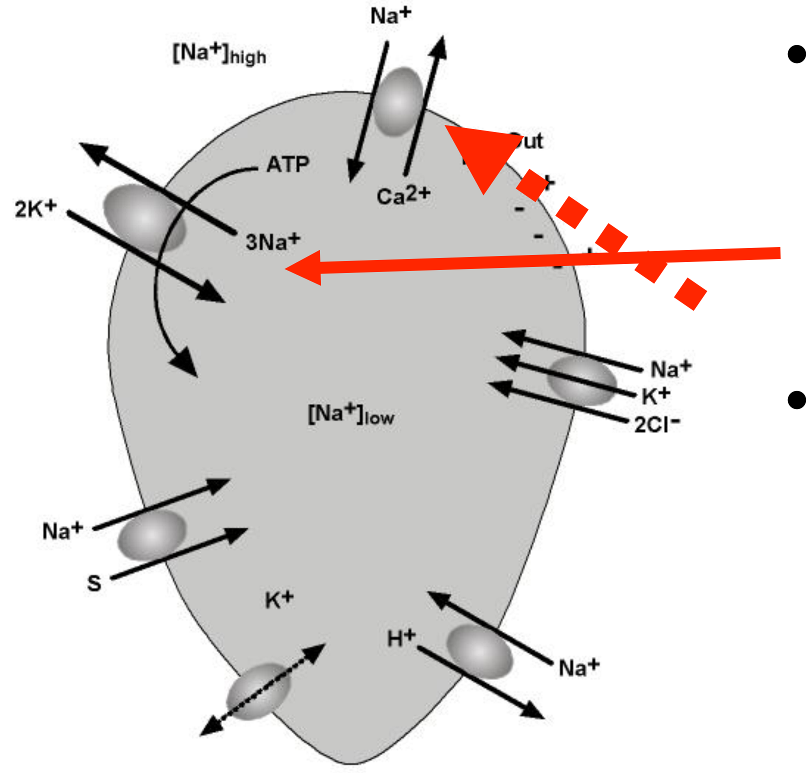
Transport System Integration



Examples of Types of Na+-coupled Transporters

- *Na^+ Homeostasis*
  - Multiple interacting systems
- Consider interaction of:
  - Na^+,Ca^{2+} antiporter
  - Na^+,K^+-ATPase

Transport System Integration



Examples of Types of Na+-coupled Transporters

- ***When the Na$^+$,K$^+$-ATPase is inhibited***
  - *[K$^+$] decreases in cytosol.*
  - *[Na$^+$] increases in cytosol.*
- ***At the Na$^+$,Ca^{2+} antiporter,***
  - *Affinity of transporter for Na$^+$ at cytosolic binding site is close to intracellular [Na$^+$].*
  - *If intracellular [Na$^+$] increases, Na$^+$ will compete more effectively with Ca^{2+} at transporter.*
  - *Increased Na$^+$ competition results in less Ca^{2+} efflux.*
  - *Less Ca^{2+} efflux results in increased intracellular free Ca^{2+}.*