Chem 452 - Lecture 9
Pumps and Channels
111121

With this lecture we begin a unit a that looks at proteins as complex machines. We will look first at the intrinsic membrane proteins that are responsible for moving material across membranes. Those that require a source of free energy to carry out the transport are called active transport systems. Some of these are directly coupled to the hydrolysis of ATP, while others are coupled to a second concentration gradient that flows across the cell in a favorable direction. We will also look at gated passive transport systems, which, while requiring no external source of free energy, are far from from being just simple channels.

Introduction

- Membrane proteins function as
  - Pumps (Chapter 13)
  - Channels (Chapter 13)
  - Signal transducers (Chapter 14)
  - Energy transducers (Chapter 18 & 19)

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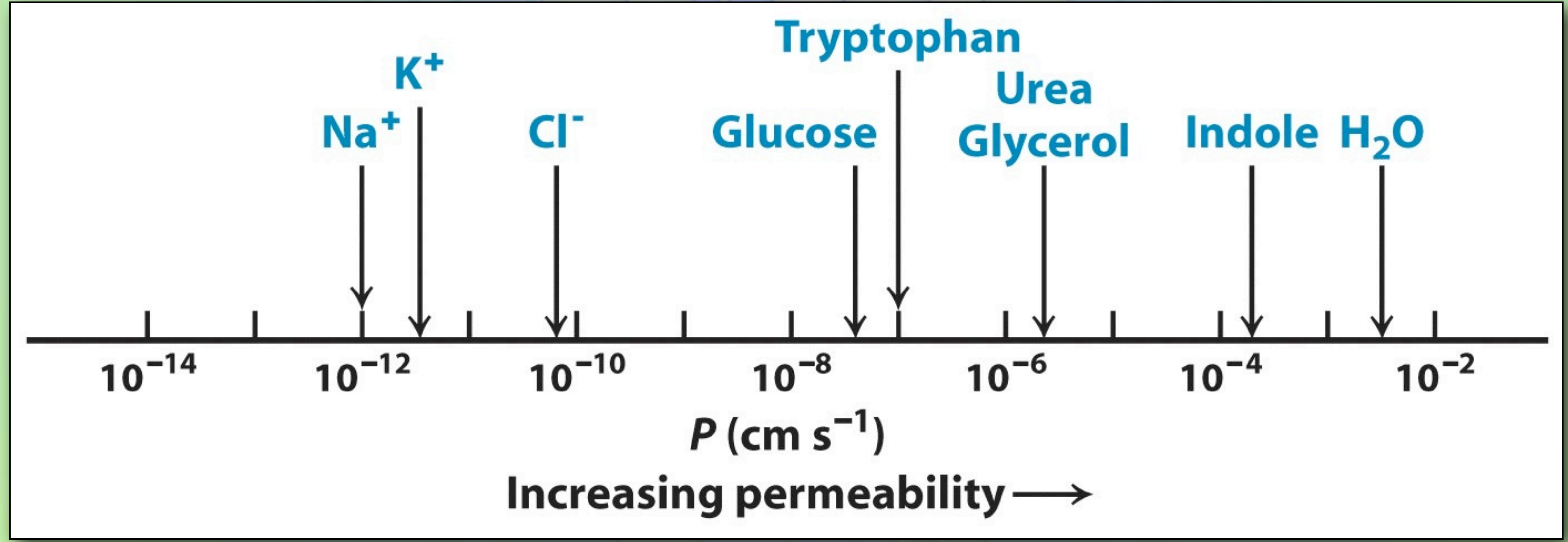
Membrane Lipids and Water

- Lipid membranes display a wide range of permeability's to small molecules.



Introduction

- Pumps and Channels move substances across membranes.
  - Pumps move substances from regions of low concentration to high concentration.
    - Requires a source of energy (**active transport**)
  - Channels allow substances to move from regions of high concentration to low concentration.
    - Does not require a source of energy (**passive transport**)
    - If passive transport requires a channel it is called **facilitated diffusion**.

Introduction

- Some pumps couple transport to the hydrolysis of ATP.
  - P-Type ATPases
  - ATP-binding cassette (ABC) transporters
- Some pumps couple transport to a second concentration gradient (**secondary transport**)

Introduction

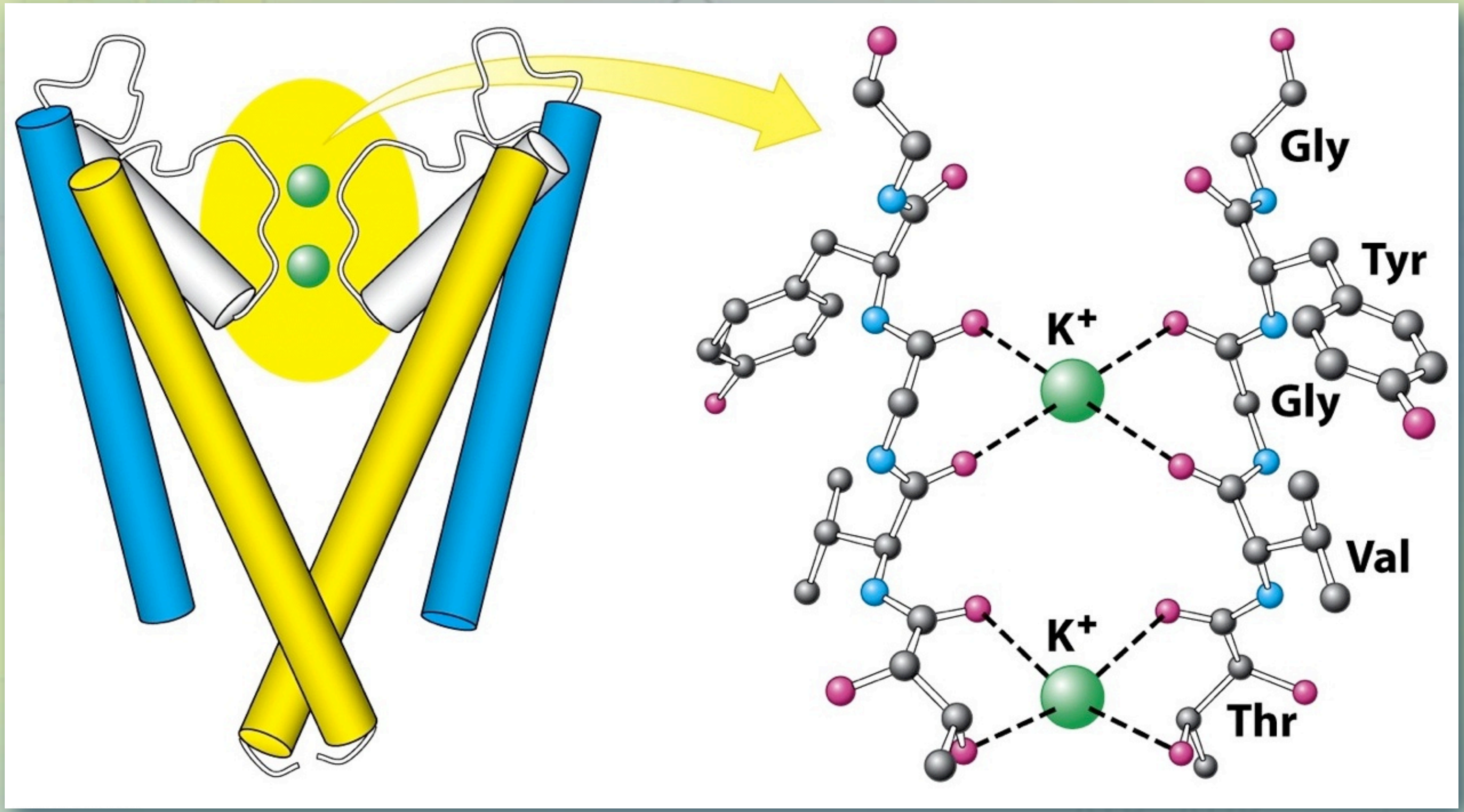
- Transporters are used to regulate the metabolic activity of a cell.
  - e.g. Glucose Transporters

Table 16.4 Family of glucose transporters

Name	Tissue location	K_M	Comments
GLUT1	All mammalian tissues	1 mM	Basal glucose uptake
GLUT2	Liver and pancreatic β cells	15–20 mM	In the pancreas, plays a role in the regulation of insulin In the liver, removes excess glucose from the blood
GLUT3	All mammalian tissues	1 mM	Basal glucose uptake
GLUT4	Muscle and fat cells	5 mM	Amount in muscle plasma mem-
brane			
			increases with endurance training
GLUT5	Small intestine	—	Primarily a fructose transporter

Introduction

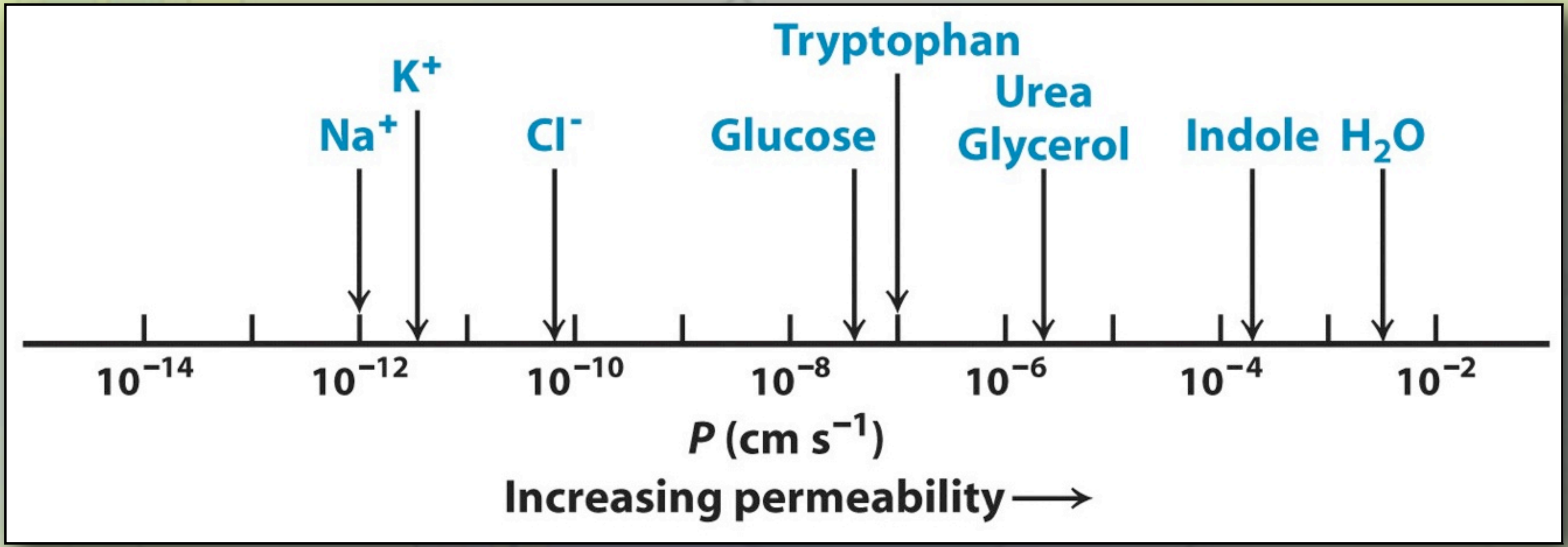
- Gated channels, while requiring not energy for transport, can be highly specific.



The Potassium Channel

Active versus Passive Transport

- Transport across membranes
  - Simple Diffusion (passive transport)



  - Facilitated diffusion (passive transport)
  - Requires energy (active transport)

Active versus Passive Transport

- The free energy change required for active transport depends on
  - Concentration differences
  - Voltage differences

$$\Delta G = RT \ln\left(\frac{c_2}{c_1}\right) + ZF\Delta V$$

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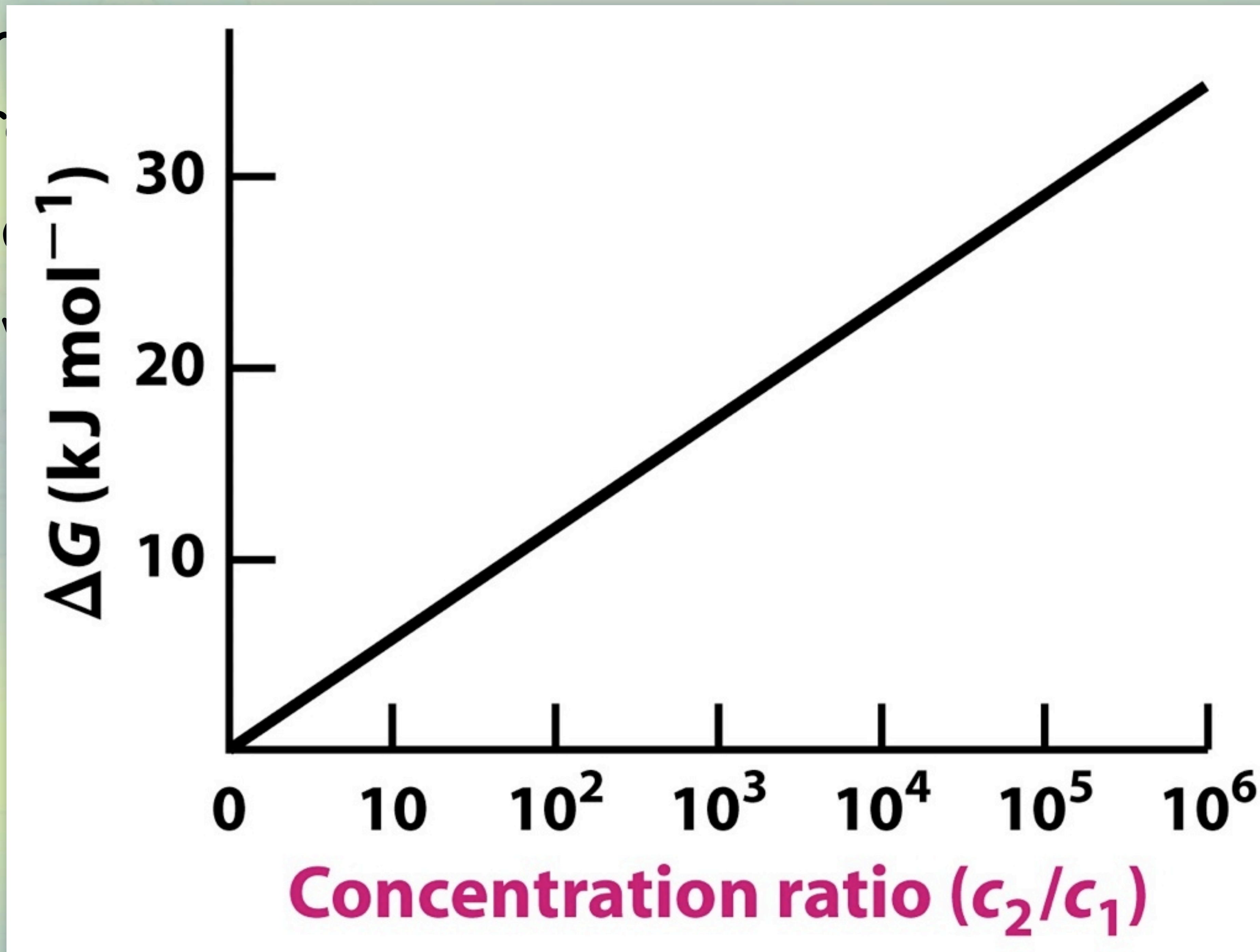
Concentration

Active versus Passive Transport

- Th
  tr



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Concentration Voltage

Active versus Passive Transport

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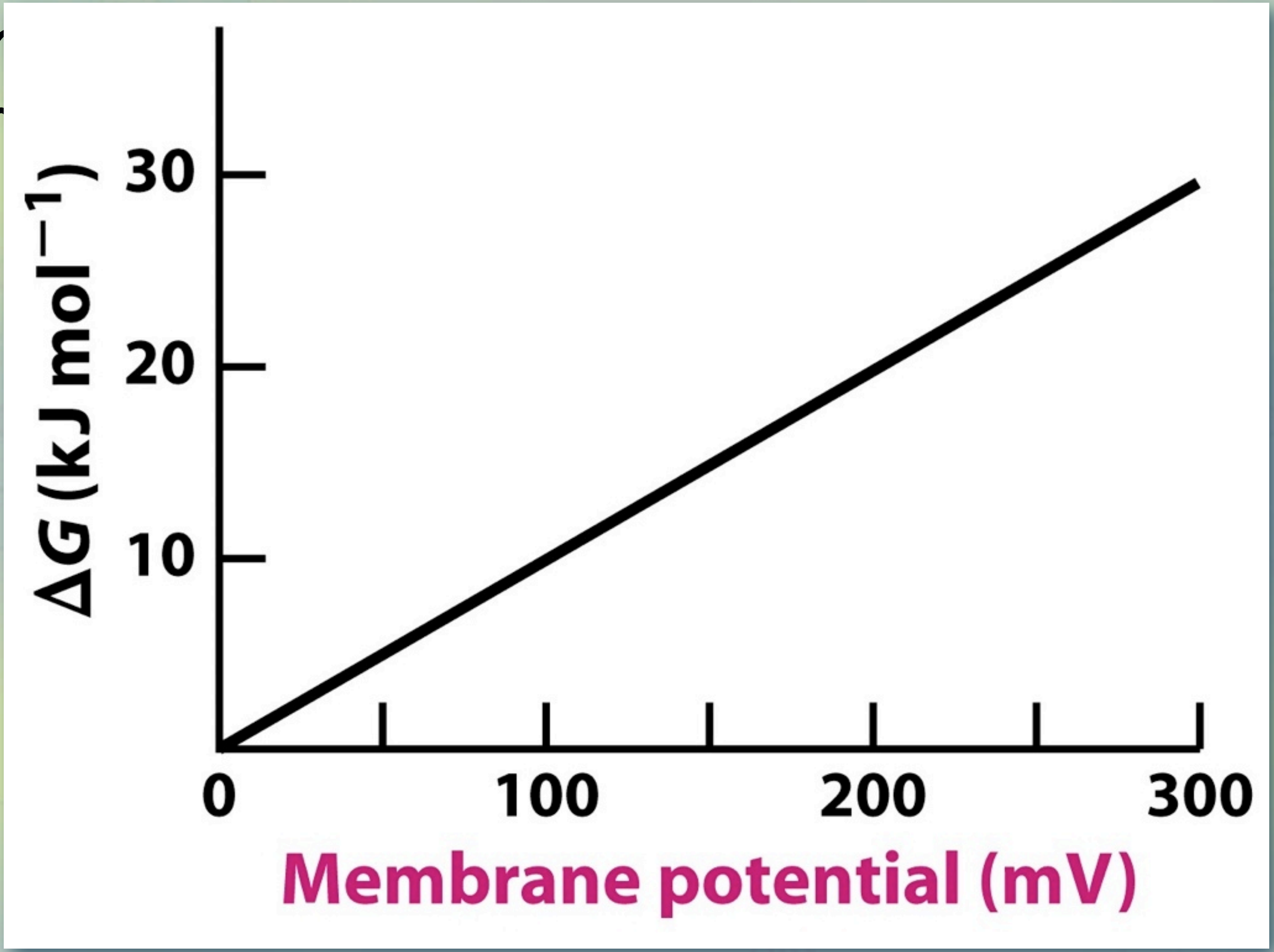
  tr
  -
  -



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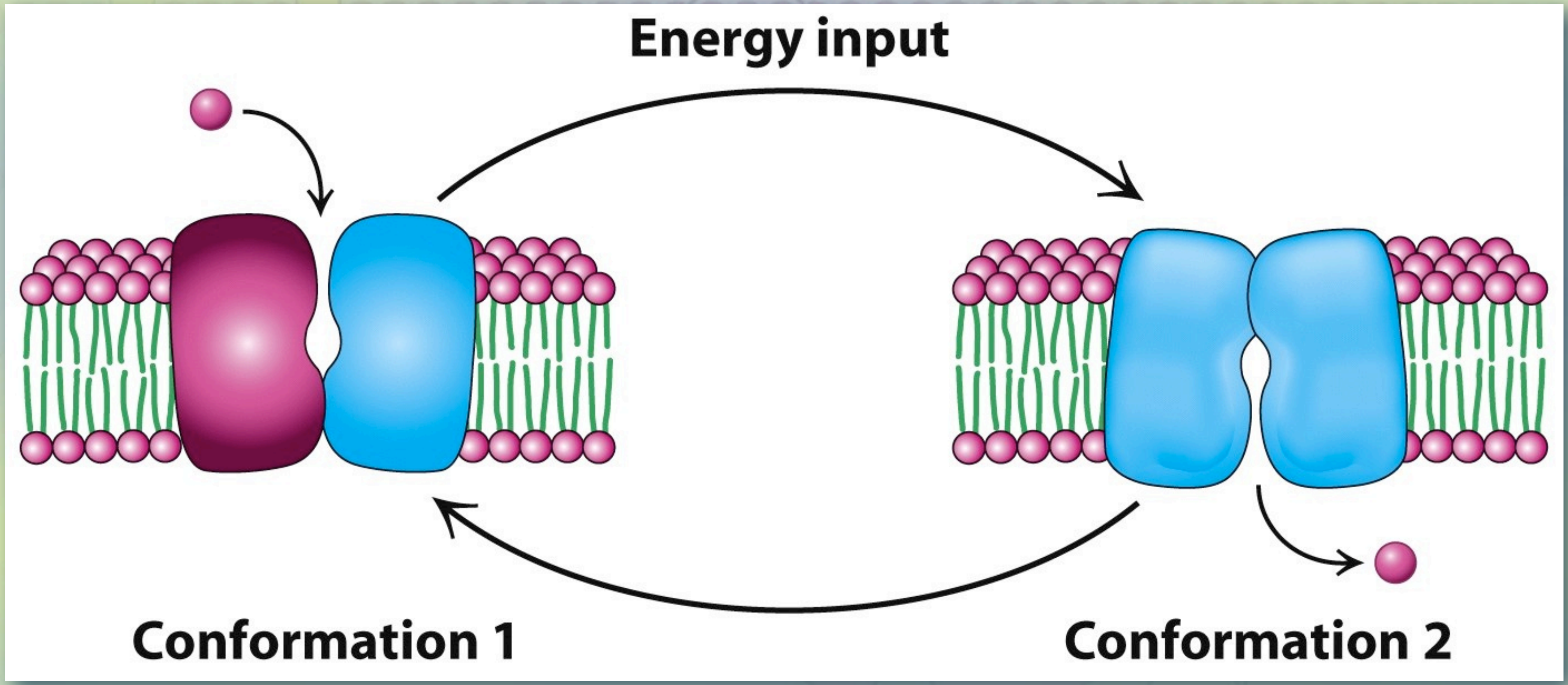
Concentration   Voltage

ATPase Pumps (Active Transport)

- P-type ATPases
- ATP-Binding Cassette Transporters



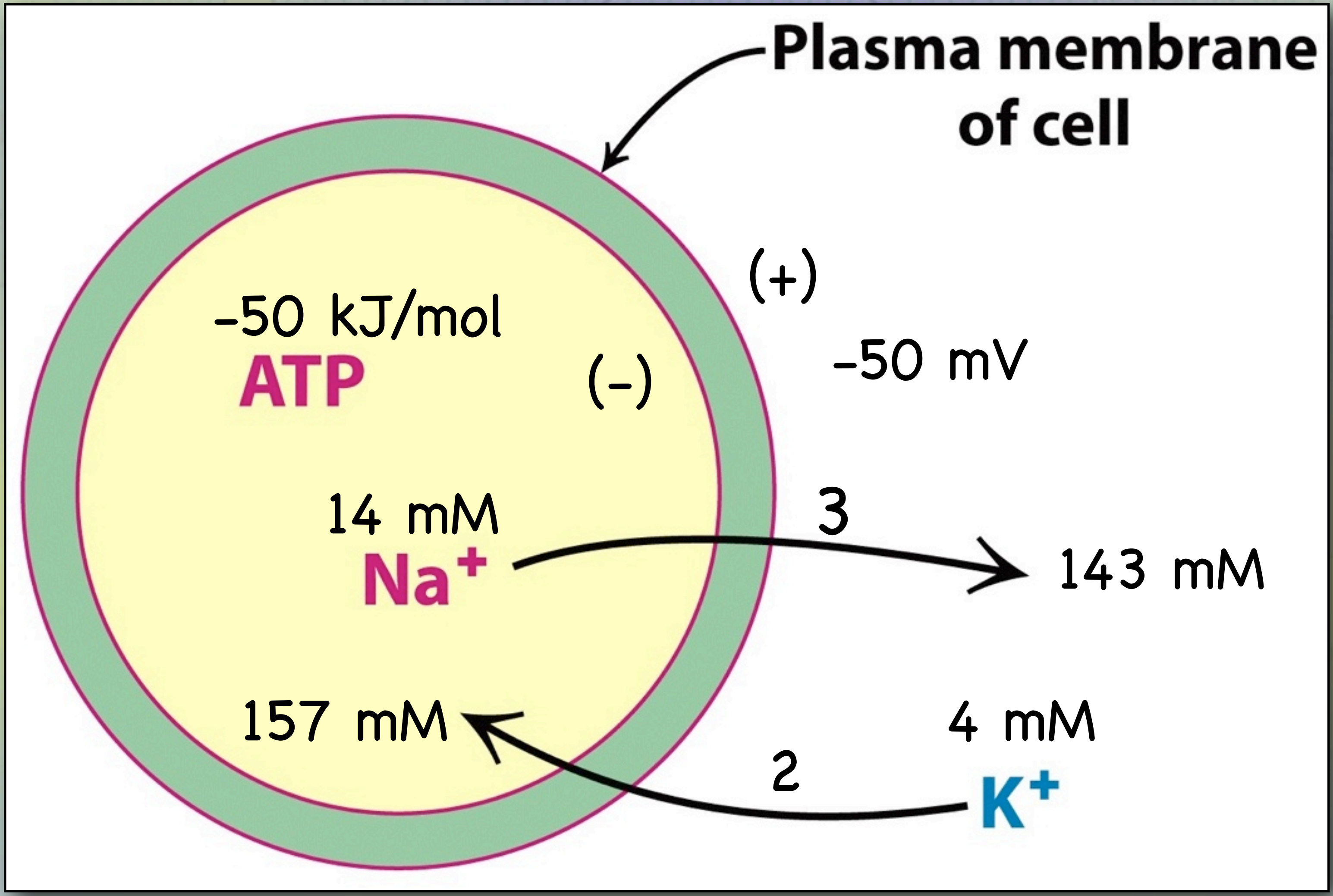
Conformational changes are coupled to ATP hydrolysis

ATPase Pumps

- P-type ATPases
  - Na^+/K^+ ATPase
    - Pumps 3 Na^+ out while pumping 2 K^+ in.
  - Gastric H^+/K^+ ATPase
  - Sarcoplasmic Ca^{2+}ATPase (SERCA)

ATPase Pumps

- The energetics of active transport
  - Na^+/K^+ ATPase
    - Pumps 3 Na^+ out while pumping 2 K^+ in.



ATPase Pumps

- The energetics of active transport
  - Na^+/K^+ ATPase
    - Pumps 3 Na^+ out while pumping 2 K^+ in.

$$\Delta G = RT\ln\left(\frac{c_2}{c_1}\right) + ZF\Delta V$$

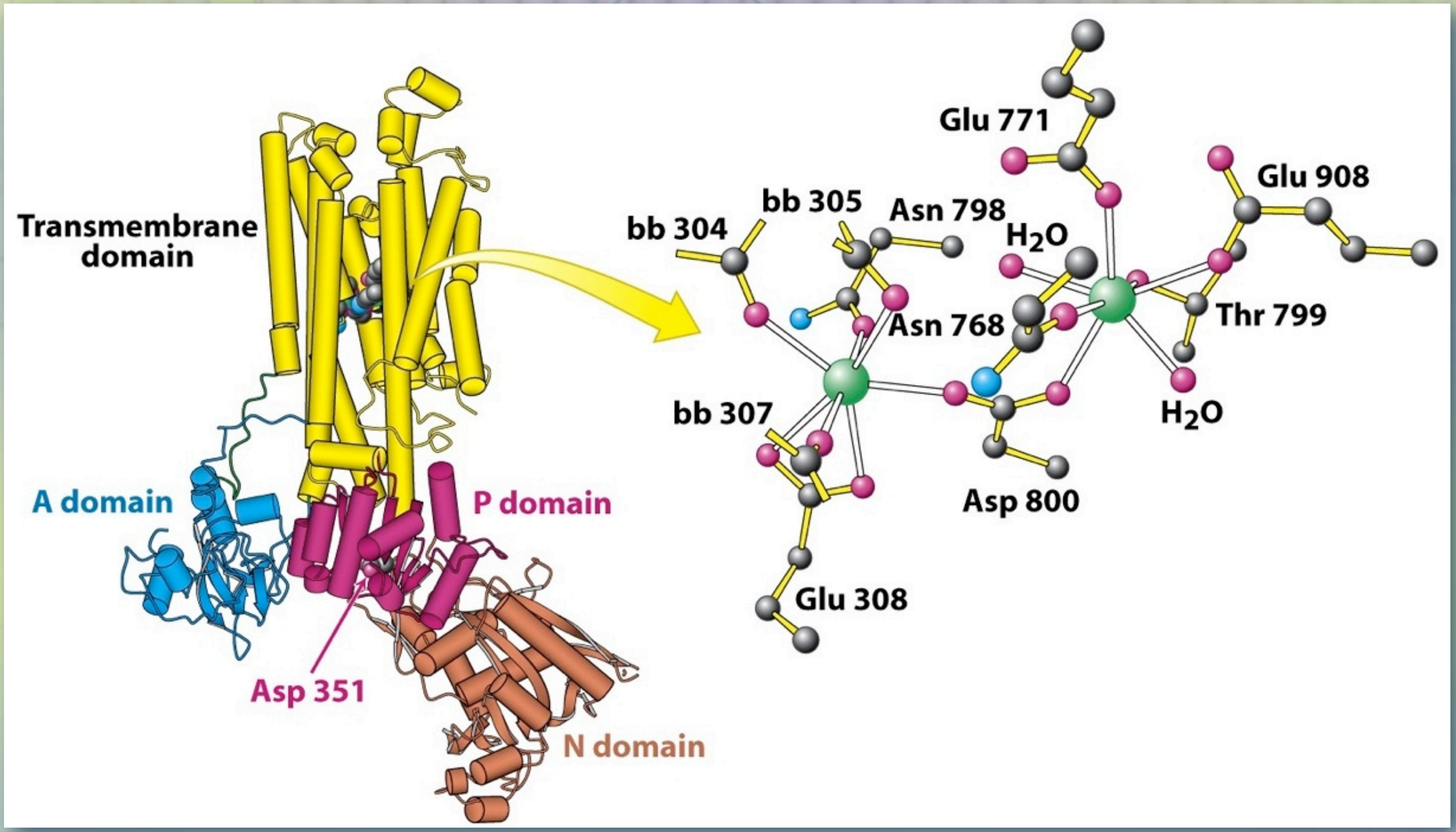
$$= \left(8.314 \text{ x } 10^{-3}\,\frac{\text{kJ}}{\text{mol•K}}\right)(310\text{ K})\ln\left(\frac{(0.143)^3(0.157)^2}{(0.014)^3(0.004)^2}\right) + (+1)\left(96.5\,\frac{\text{kJ}}{\text{mol•V}}\right)(+0.050\text{V})$$

$$= 36.9\ \frac{\text{kJ}}{\text{mol}} + 4.8\ \frac{\text{kJ}}{\text{mol}}$$

$$= 41.7\ \frac{\text{kJ}}{\text{mol}}$$

ATPase Pumps

- SERCA (Sarcoplasmic Reticulum Ca^{2+} ATPase)
  - Have crystal structure for each step in pumping cycle



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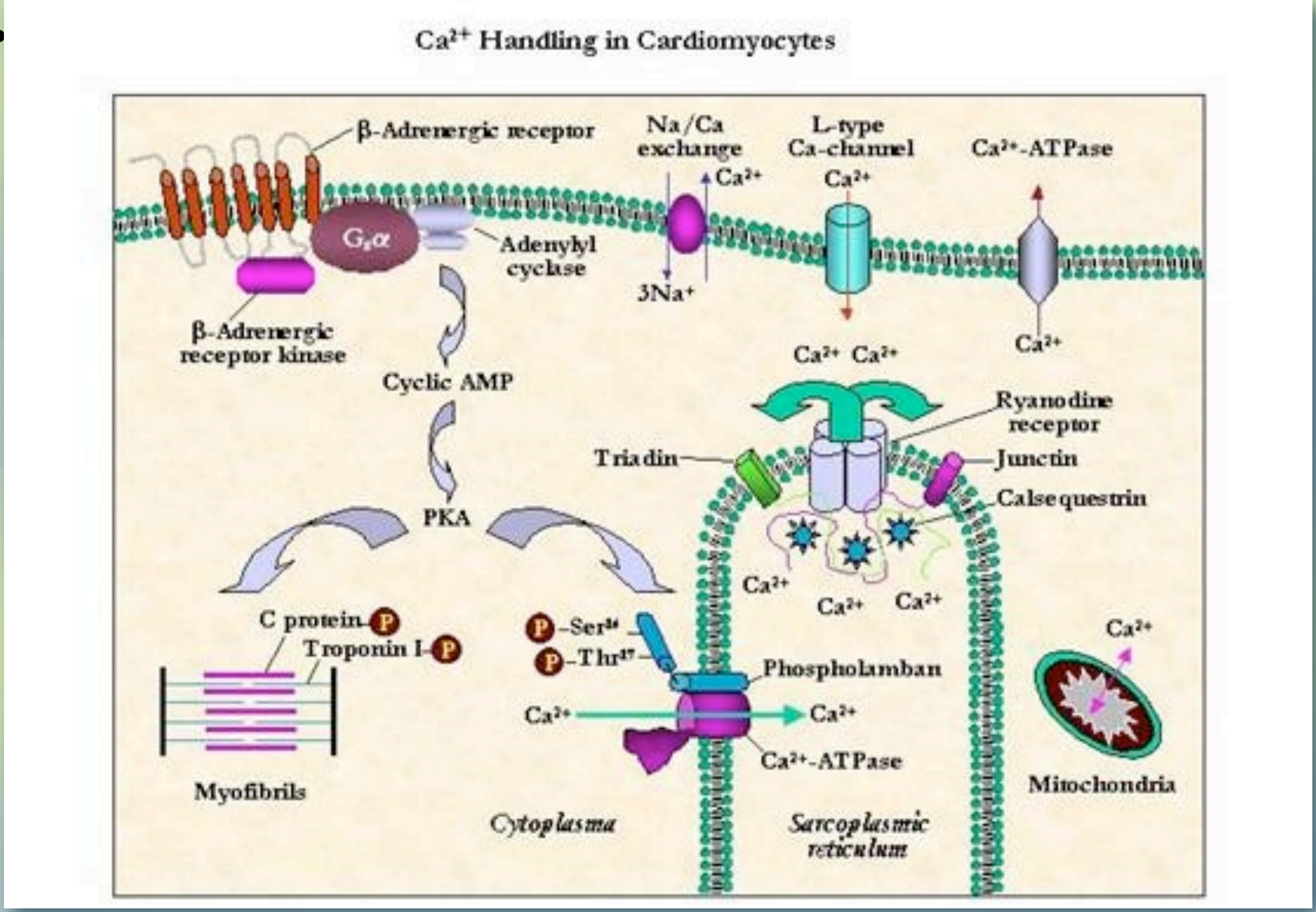
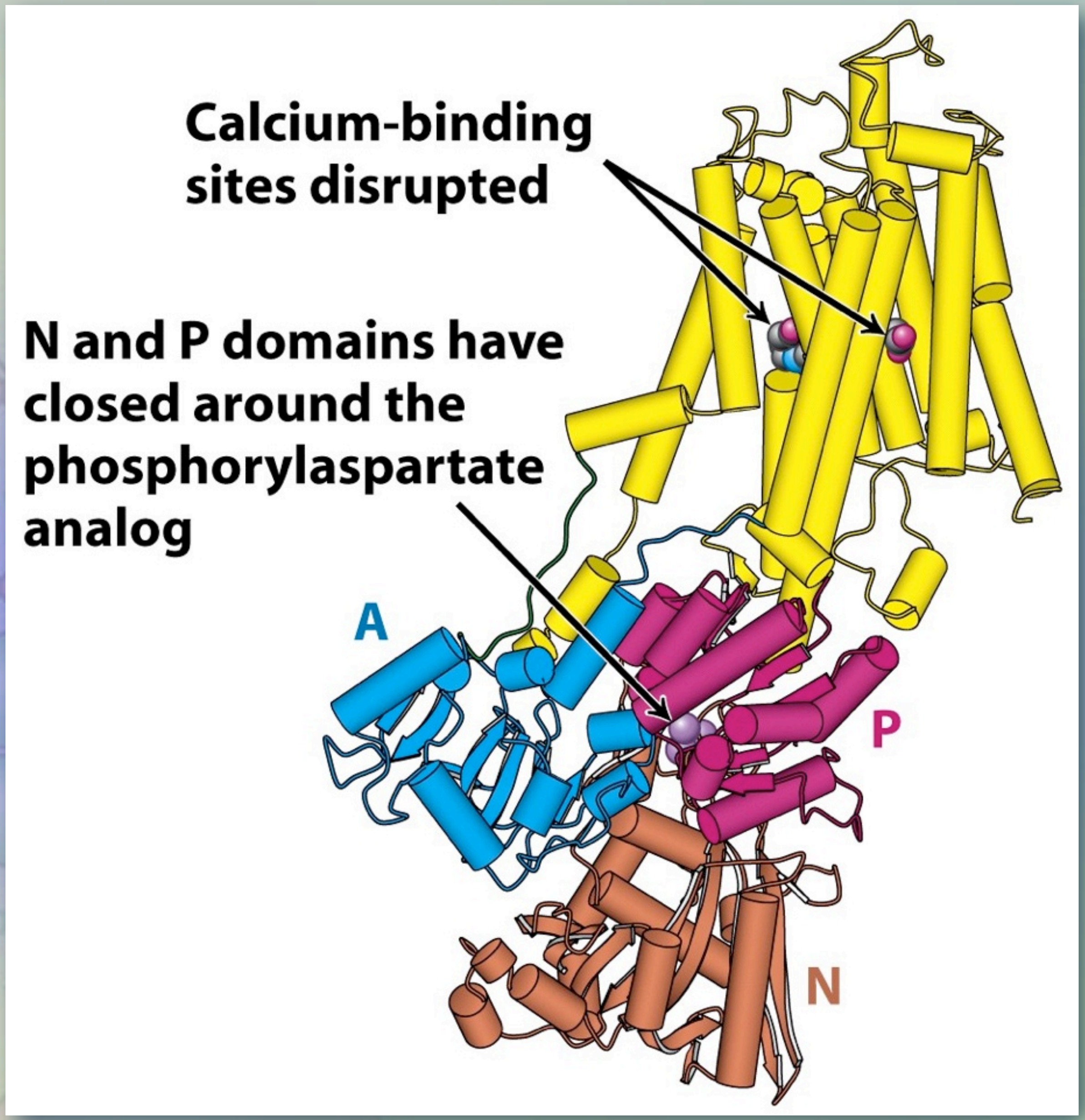


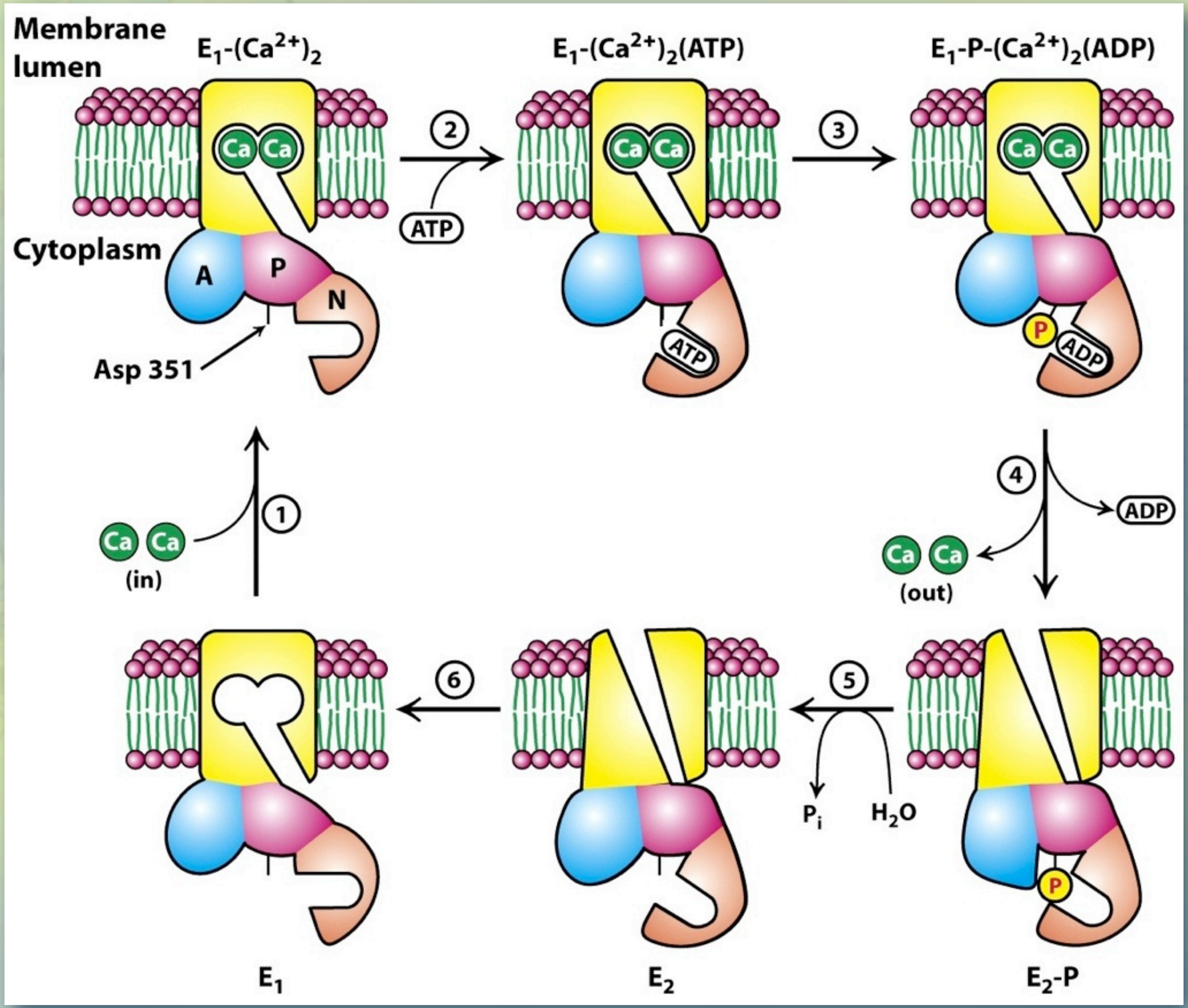
ATPase Pumps

- SERCA
  - Phosphorylation of an aspartate (A351) causes a conformational change that disrupts the Ca^{2+} binding sites.



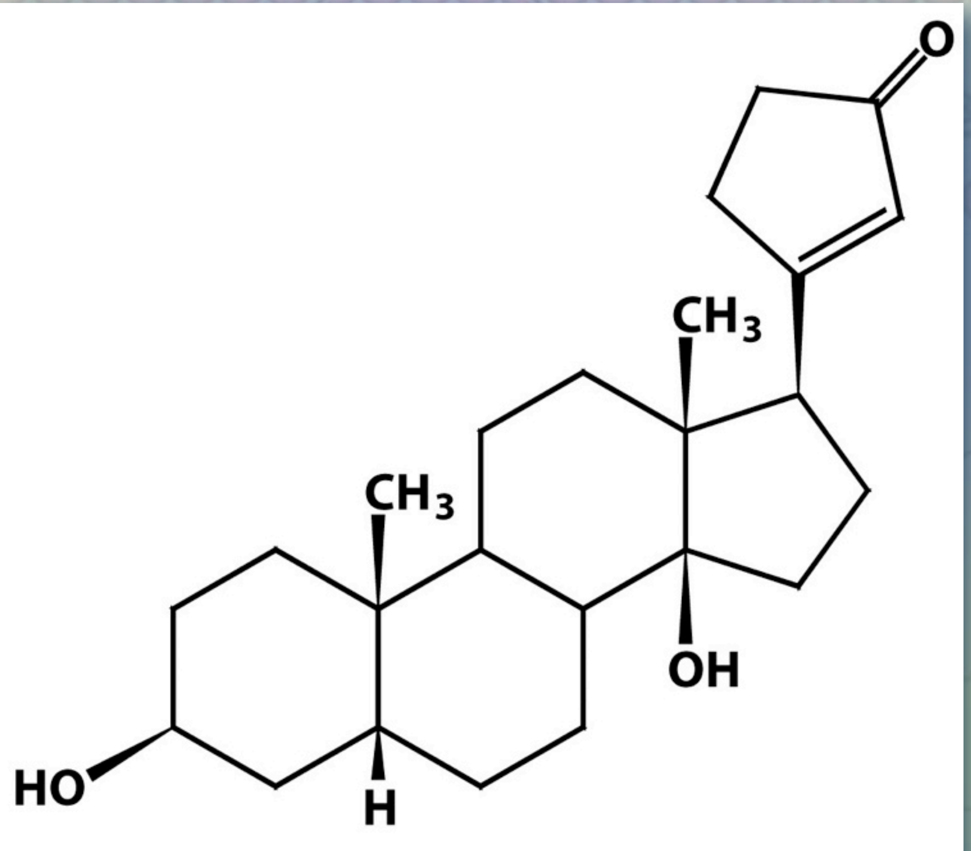
ATPase Pumps

- SERCA



ATPase Pumps

- The drug digitoxigenin (digitalis), which is used to treat congestive heart failure, inhibits the Na^+/K^+ ATPase.



Digitoxigenin

ATPase Pumps

- The P-type pumps are homologous.
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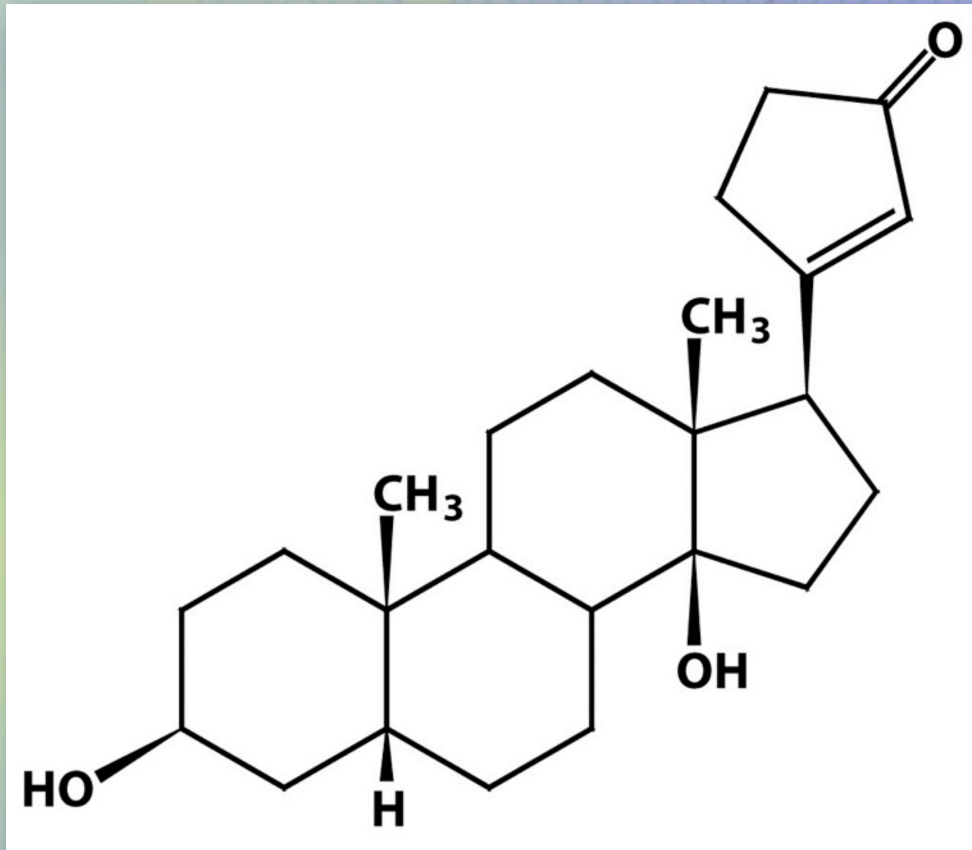
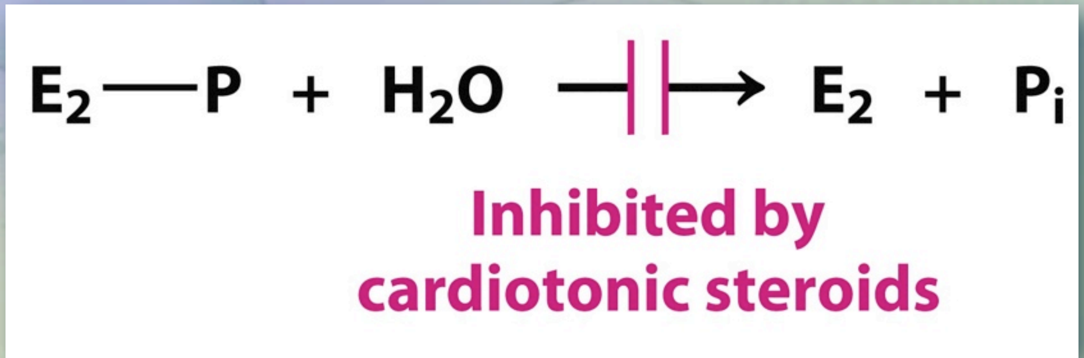


Digitoxigenin



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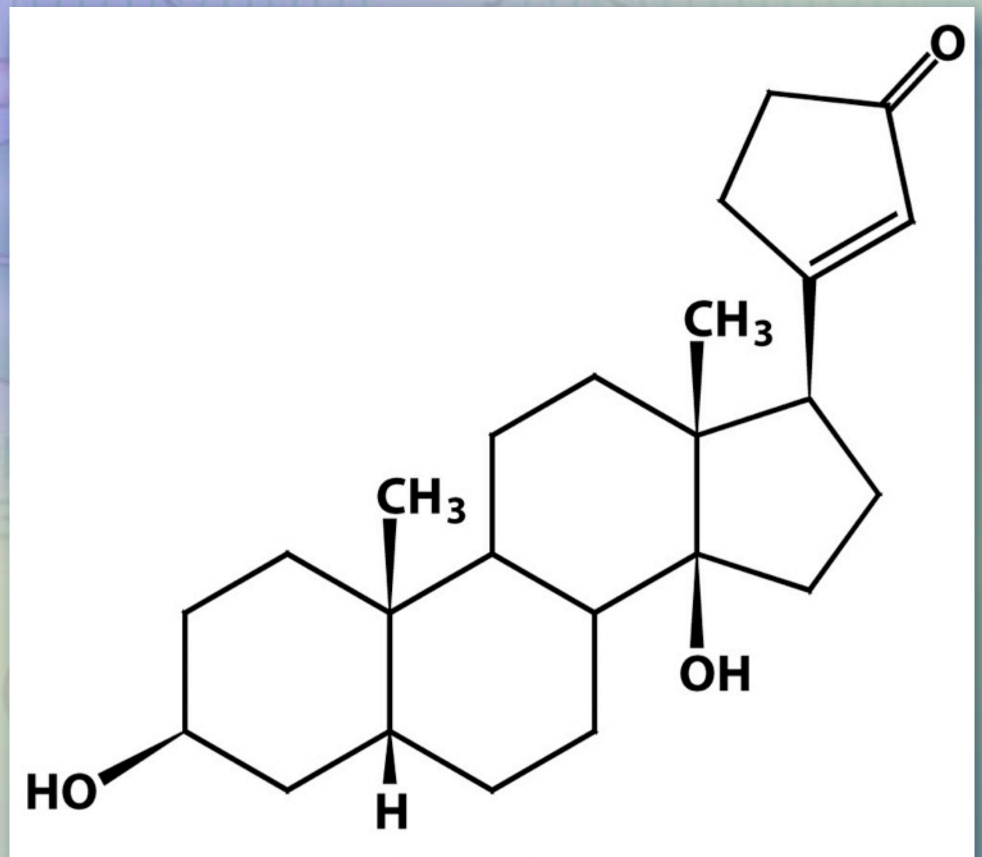
Foxglove (Digitalis purpurea)

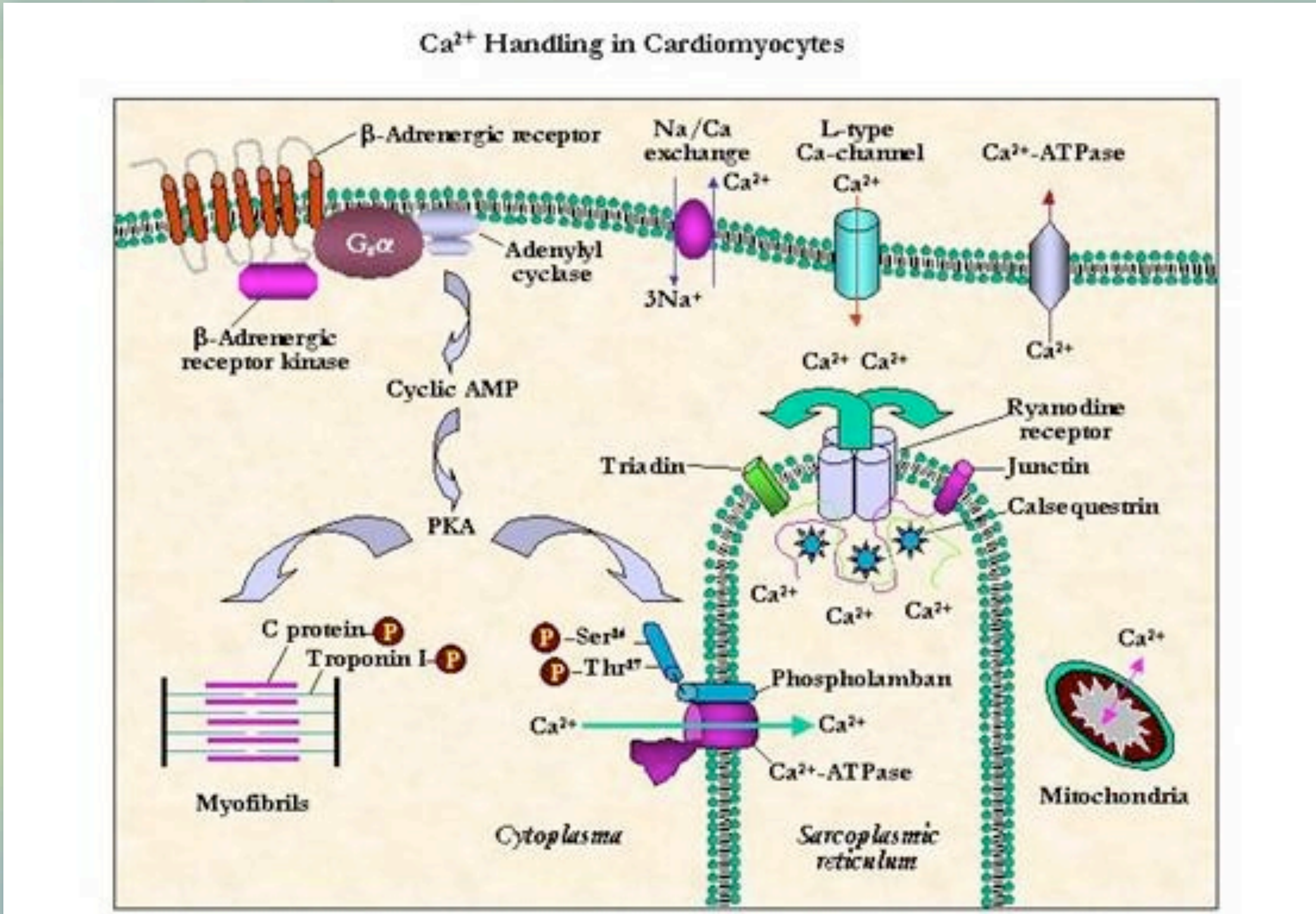


Digitoxigenin

ATPase Pumps

- The P-type pumps are homologous.
- The drug digitoxigenin (digitalis), which is used to treat congestive heart failure, inhibits the Na^+/K^+ ATPase.
- With higher cellular Na^+ levels, the Ca^{2+} pump is slower to remove the Ca^{2+} from the cytoplasm, leading to a stronger contraction.

ATPase Pumps



ATPase Pumps

- The P-type pumps are homologous.
  - Yeast contain 16 examples
    - H^+
    - Ca^{2+}
    - Na^+
    - Cu^{2+}
    - phospholipid (flipases)

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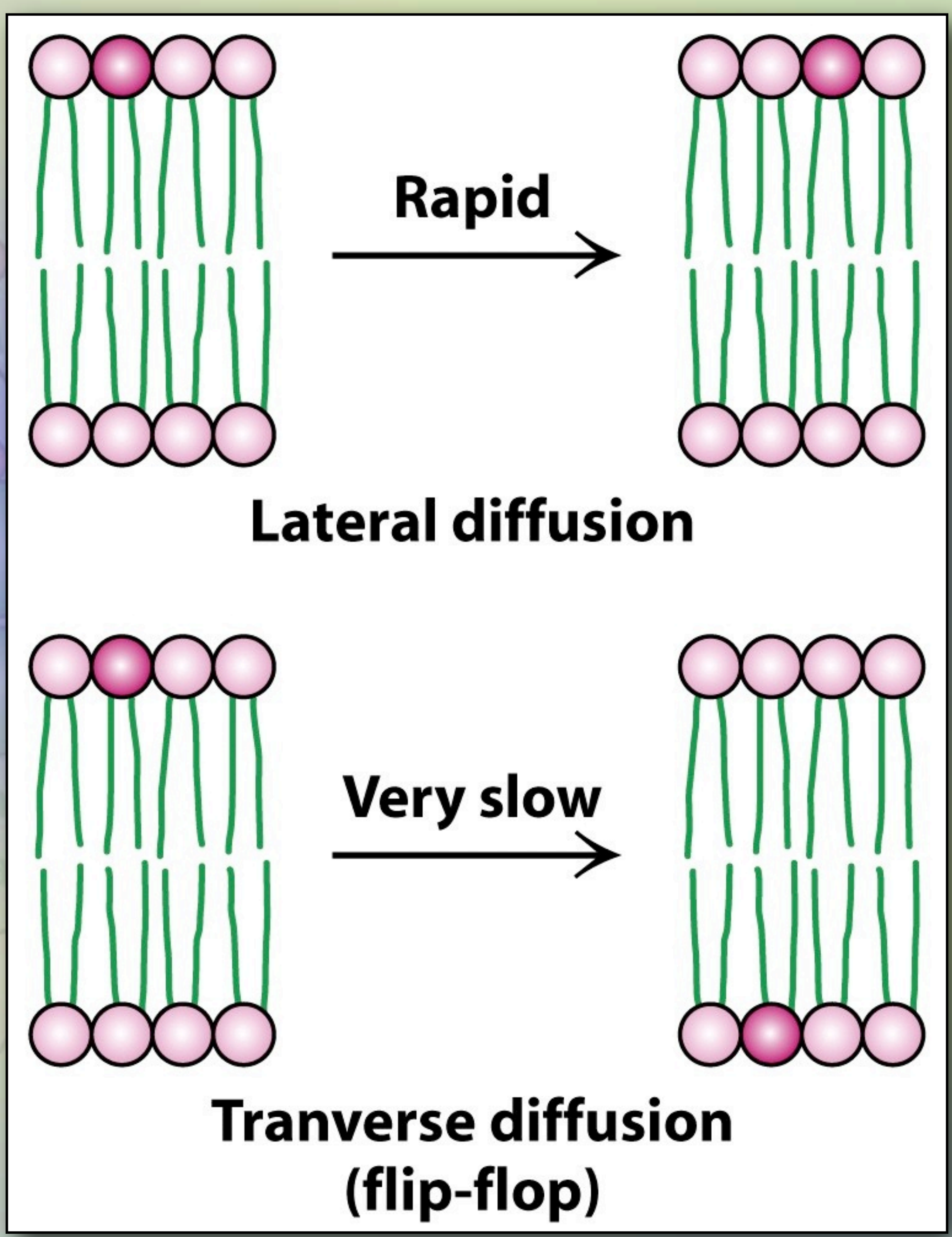
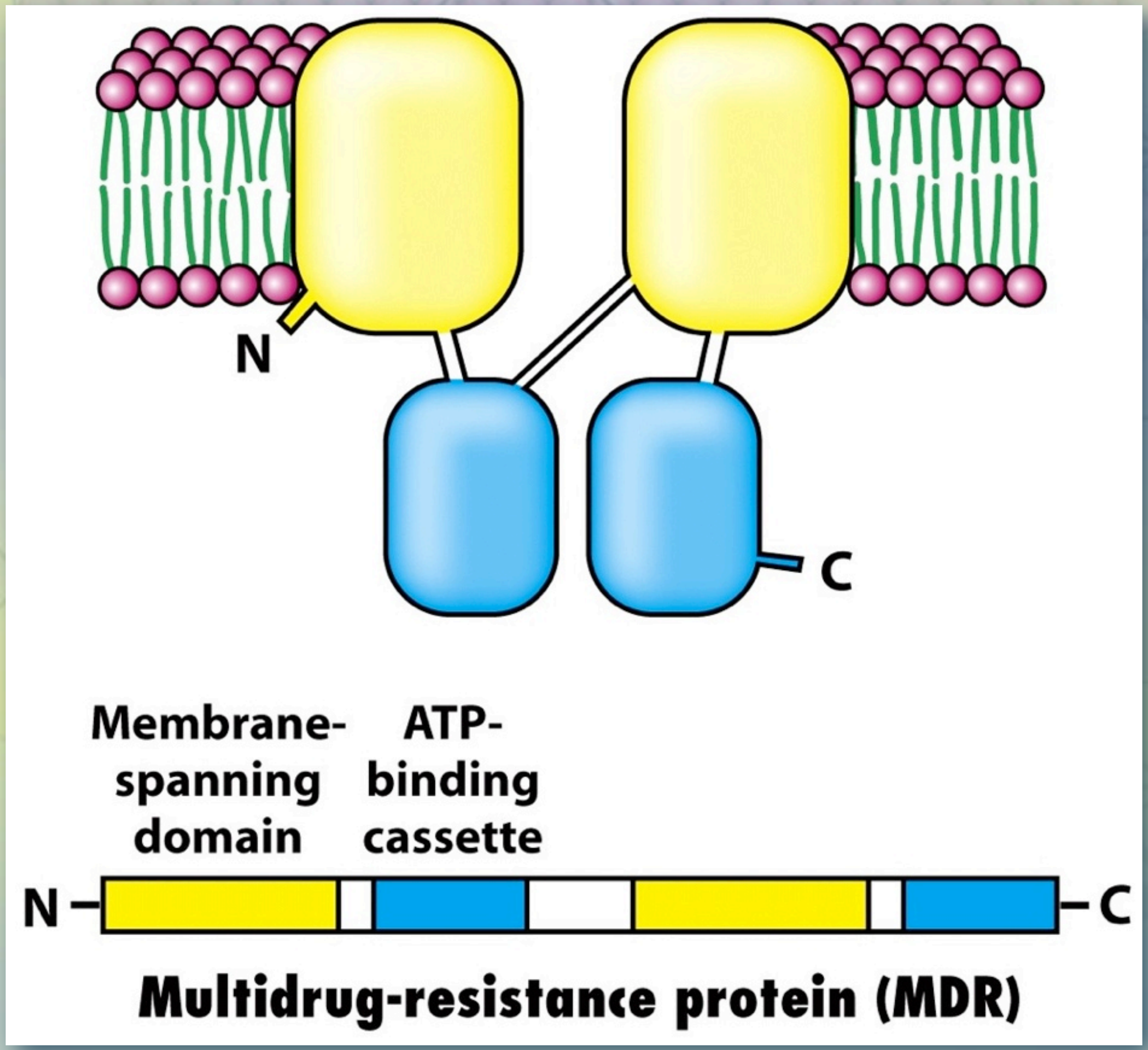


ATPase Pumps

- The ATP-binding (ABC) Transporter.
  - Uses a slightly different strategy from the P-type ATPases.



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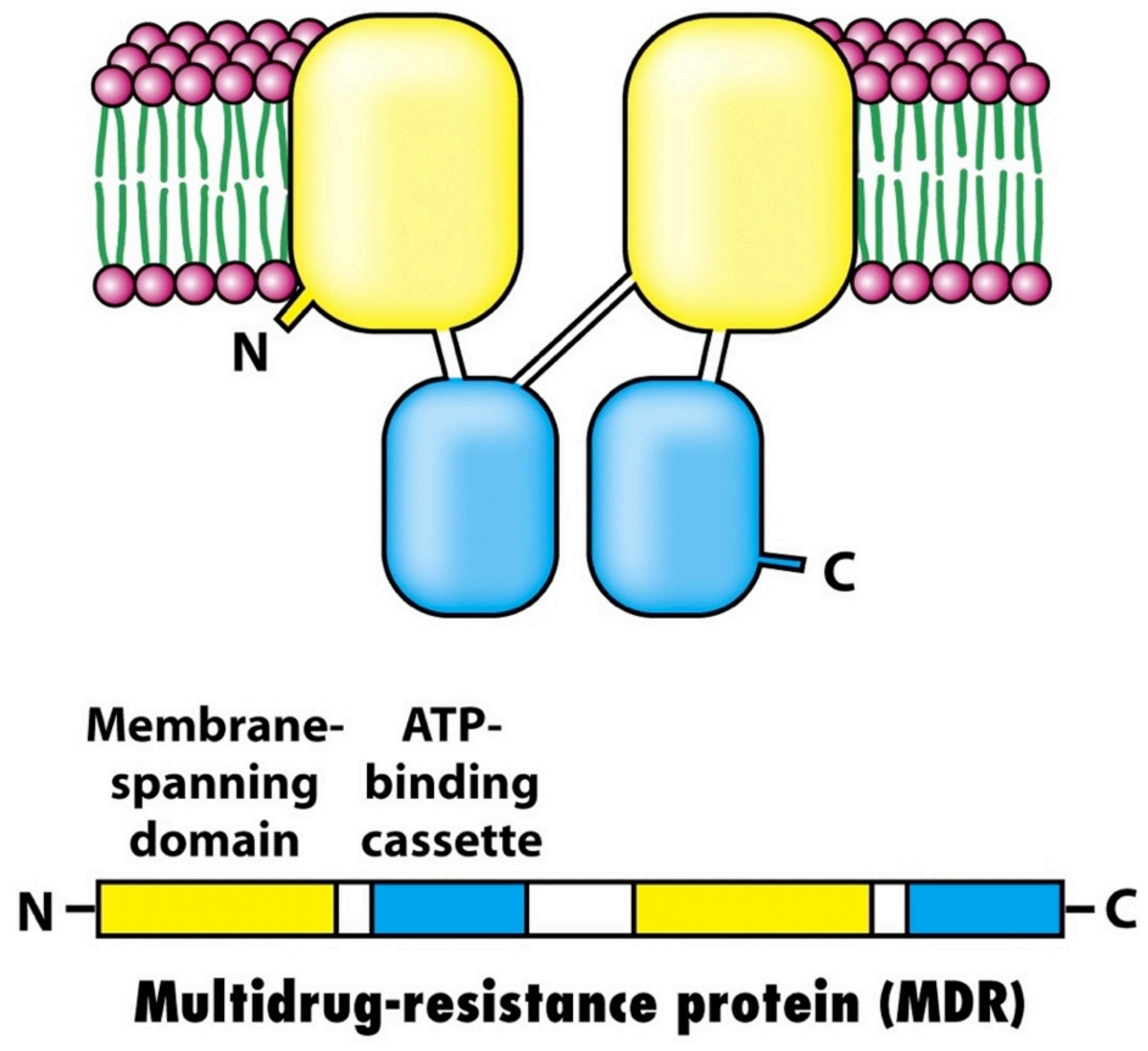

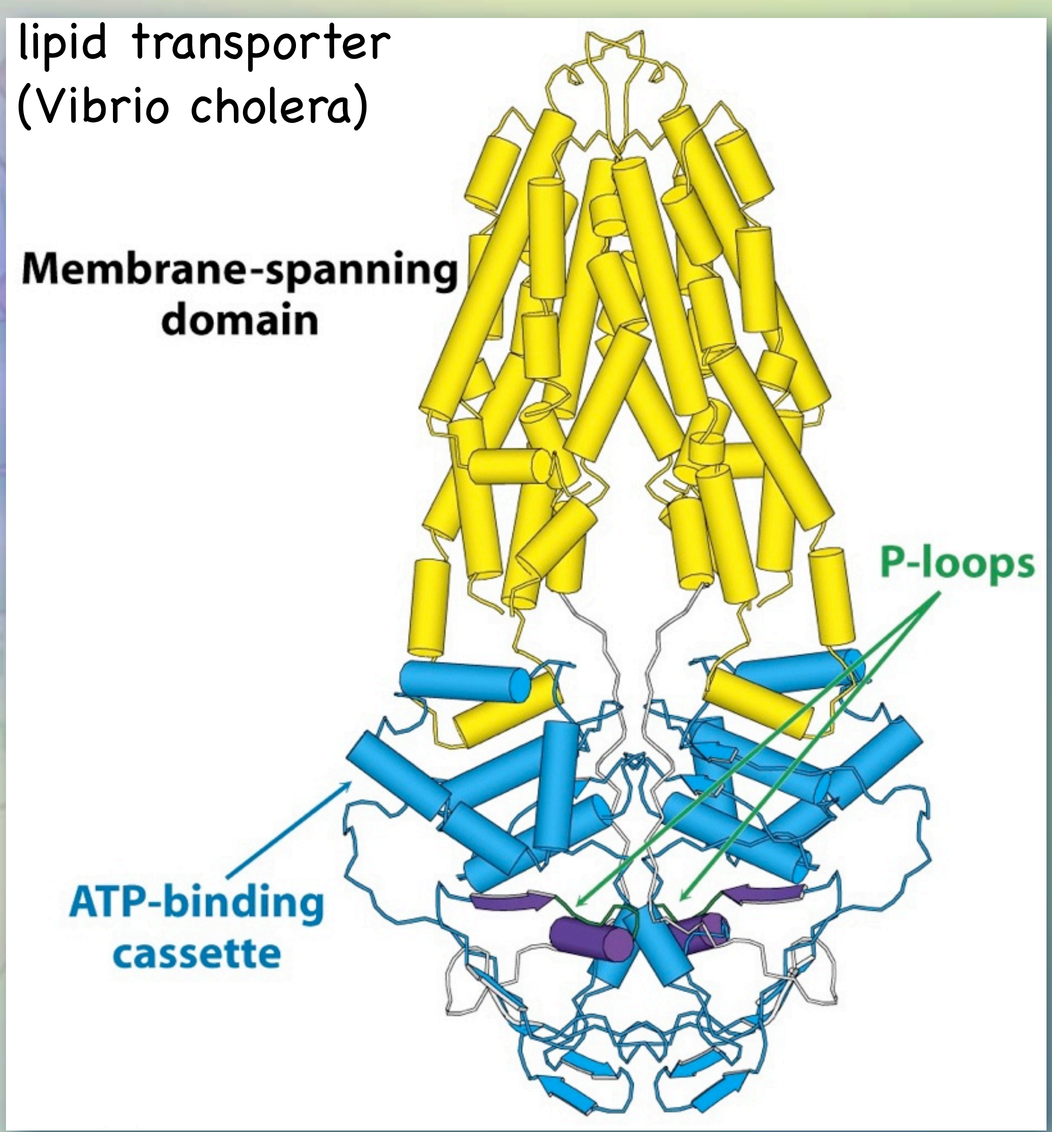

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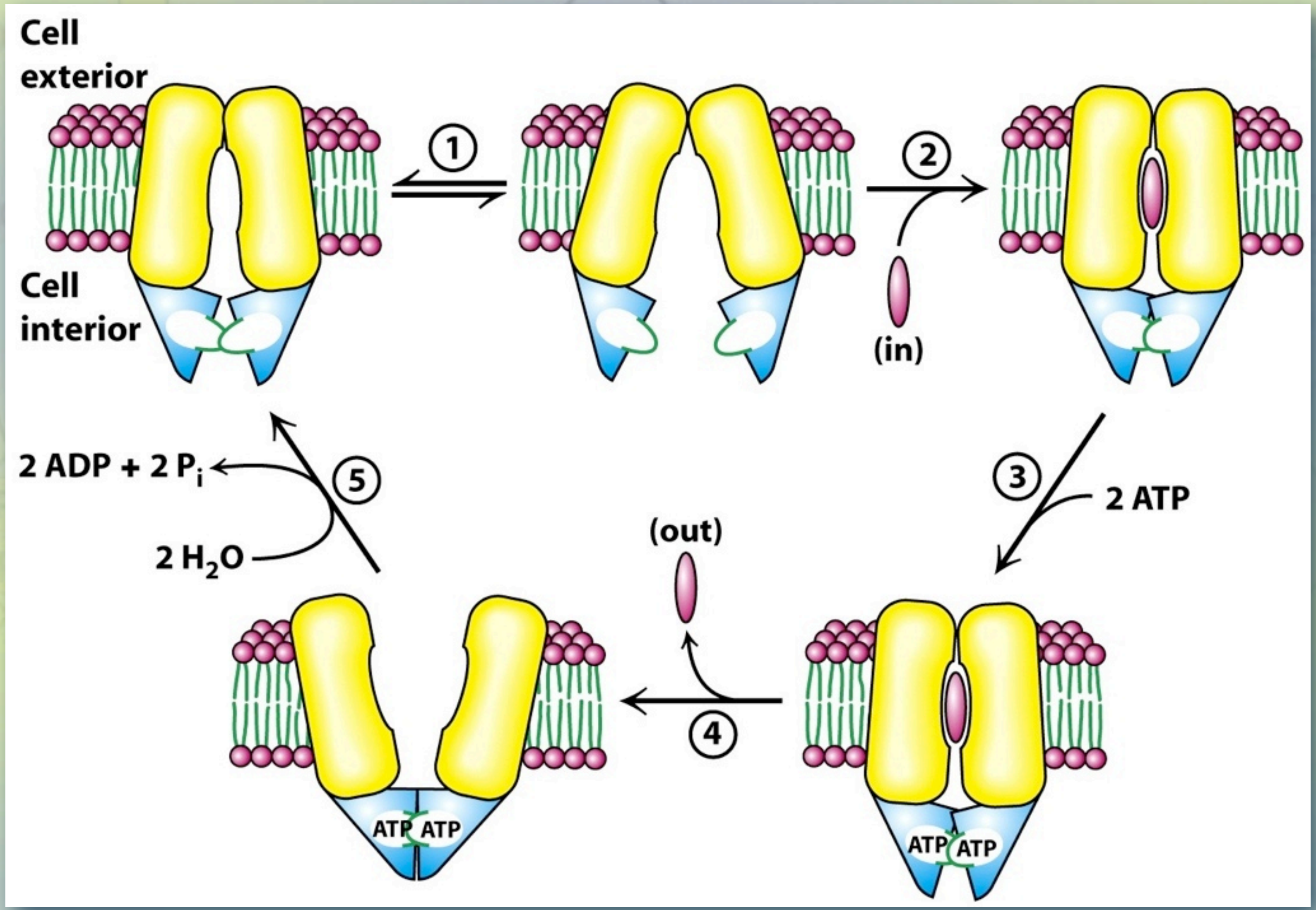
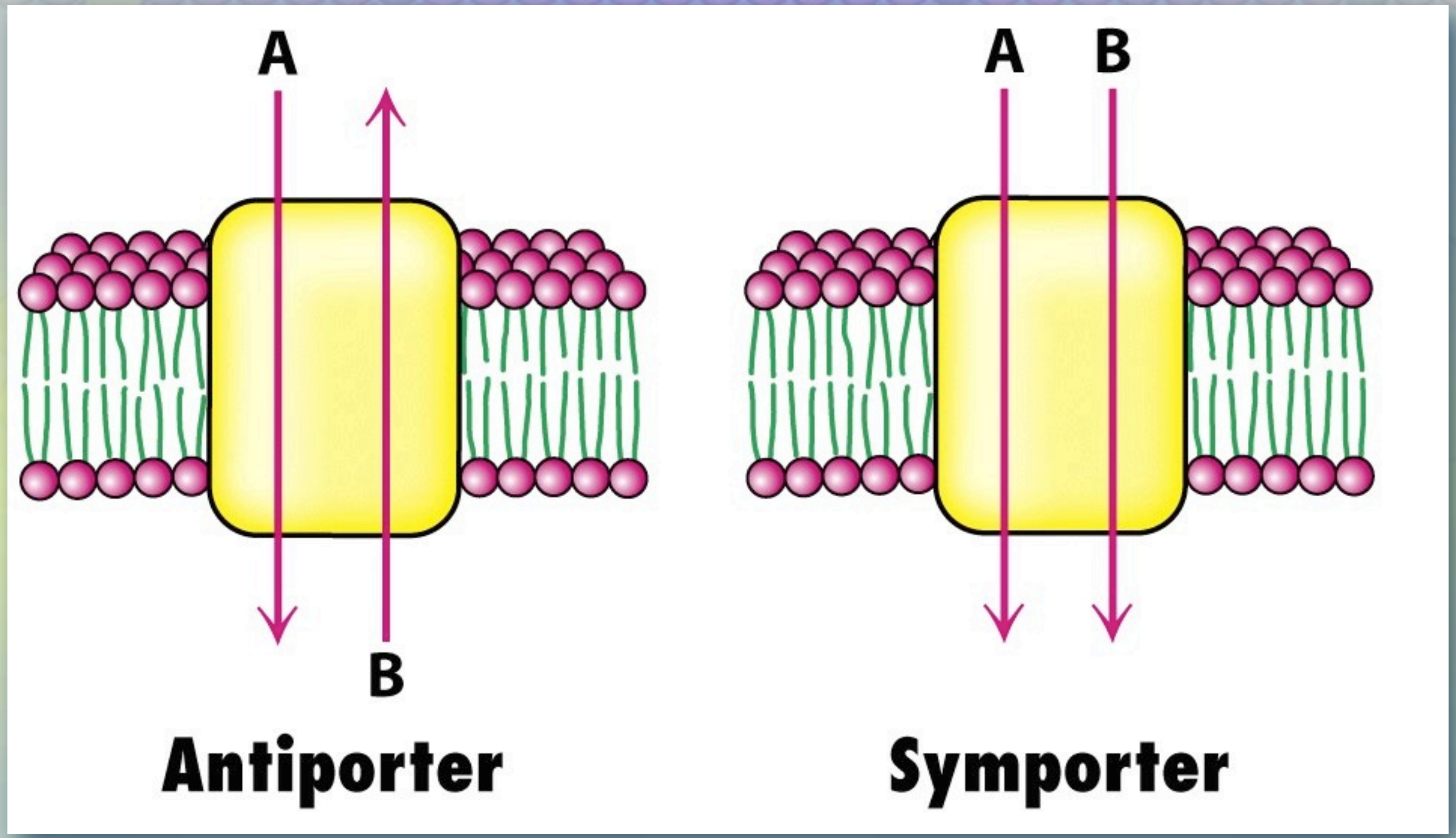


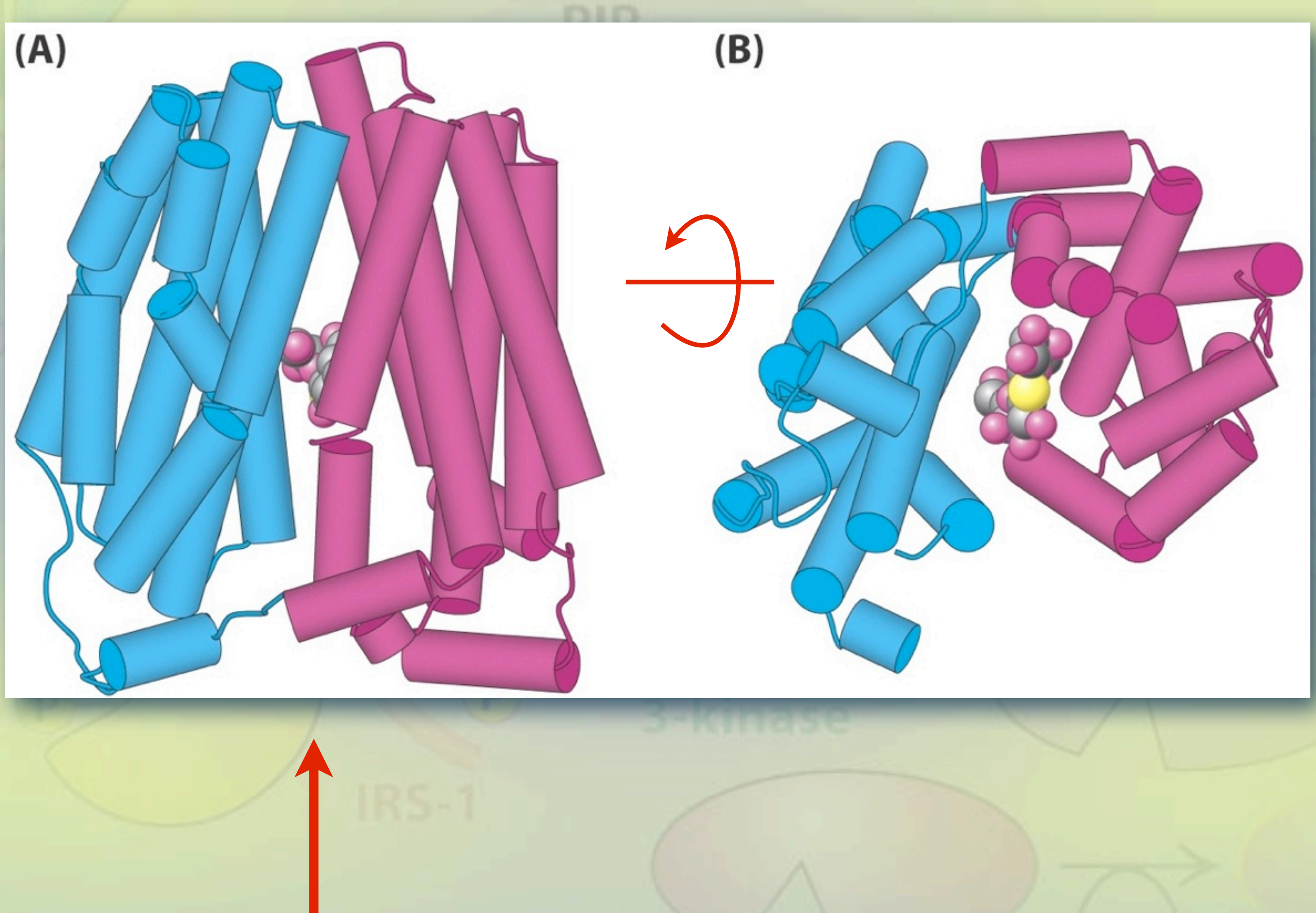
Secondary Transporters

- Secondary transporters are active transport systems that do not derive their energy directly from the hydrolysis of ATP
  - Instead, the active transport is coupled to the passive transport of a second metabolite



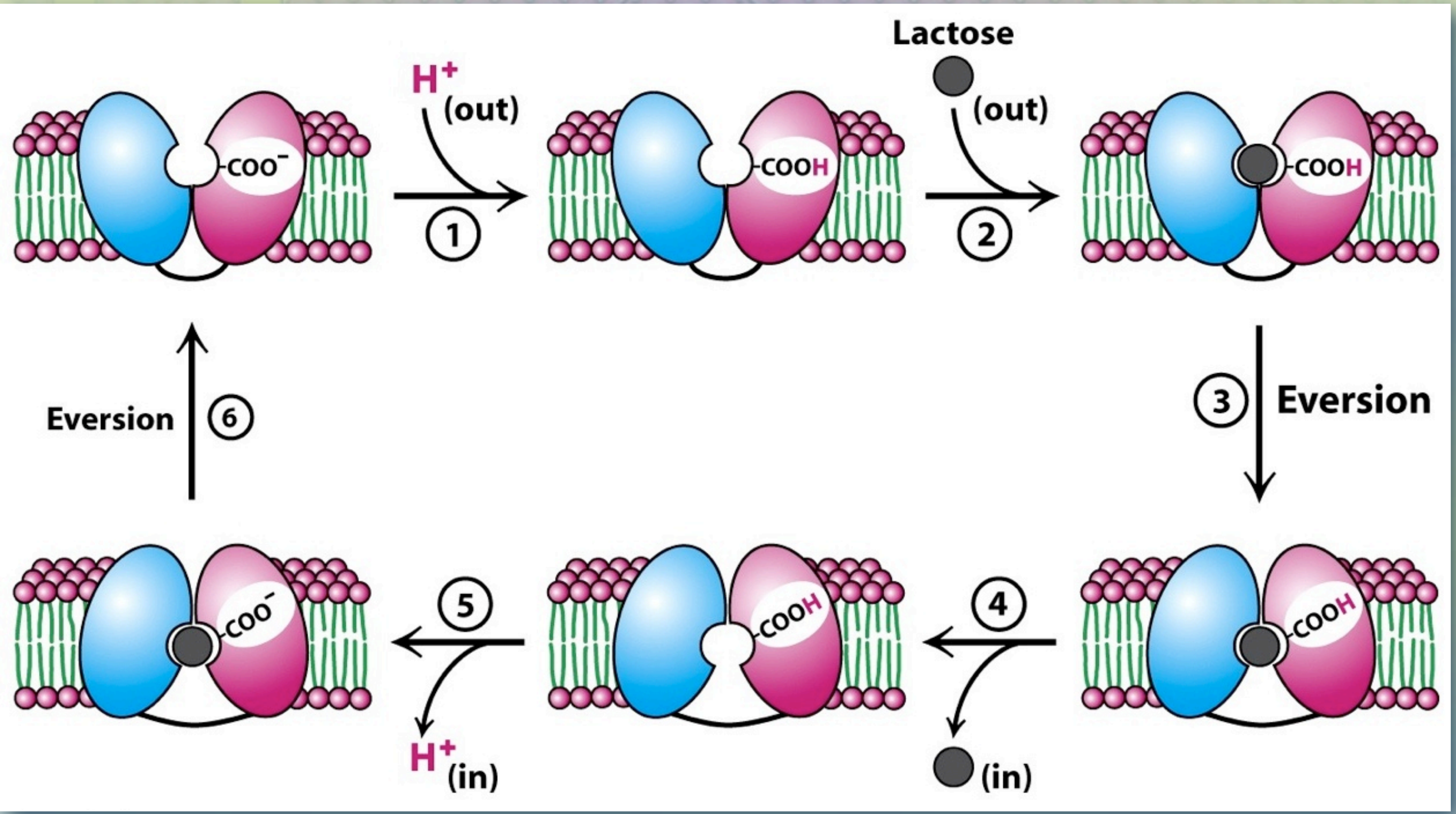
Secondary Transporters

- Lactose Permease is a well-studied example.



Secondary Transporters

- The transport of lactose up a concentration gradient is coupled to the transport of protons down a concentration gradient.



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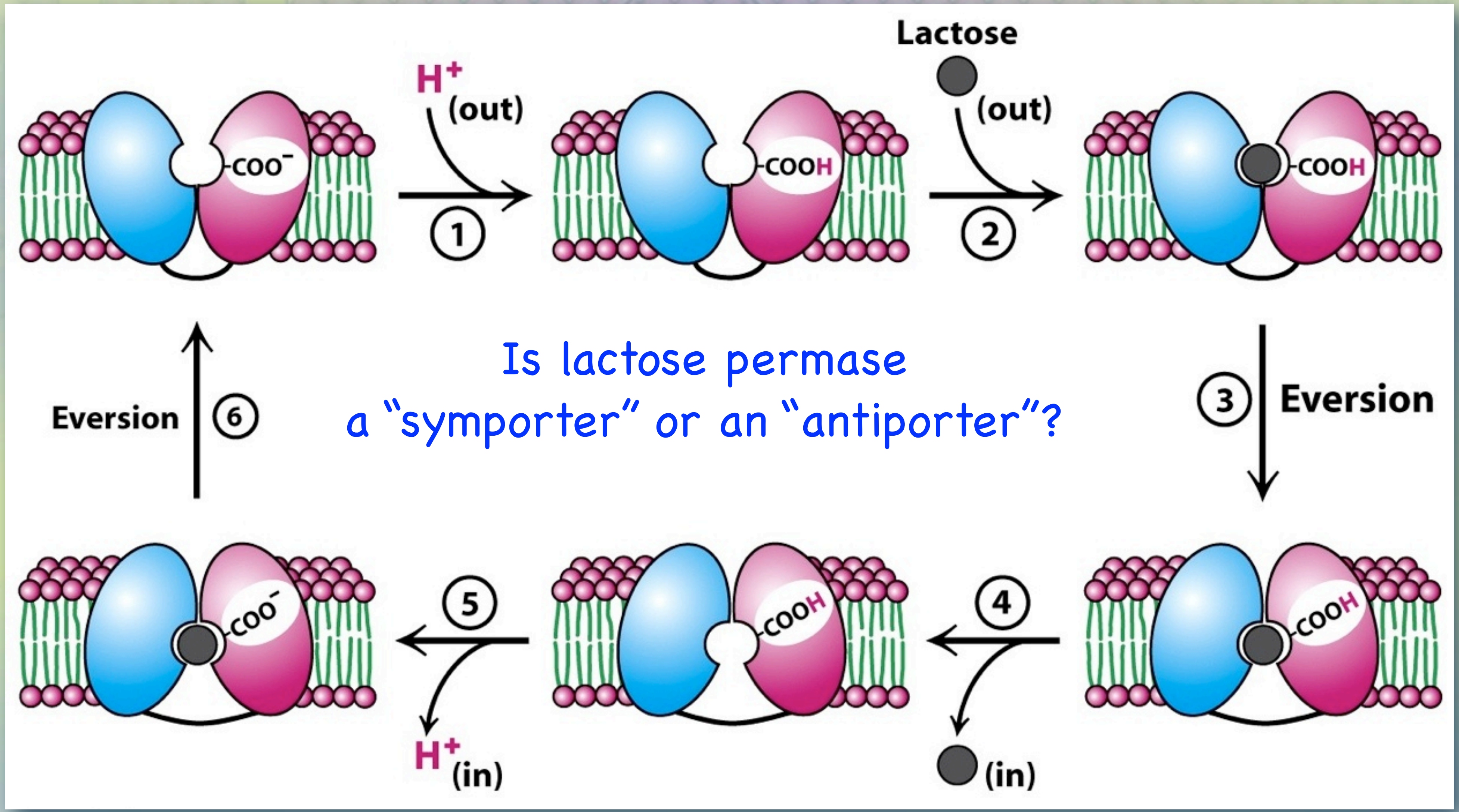

Next up

- Unit V, Lecture 9, con'd - Membrane Channels and Pumps. (Chapter 13)
  - K^+ channel and the action potential