Today's class:

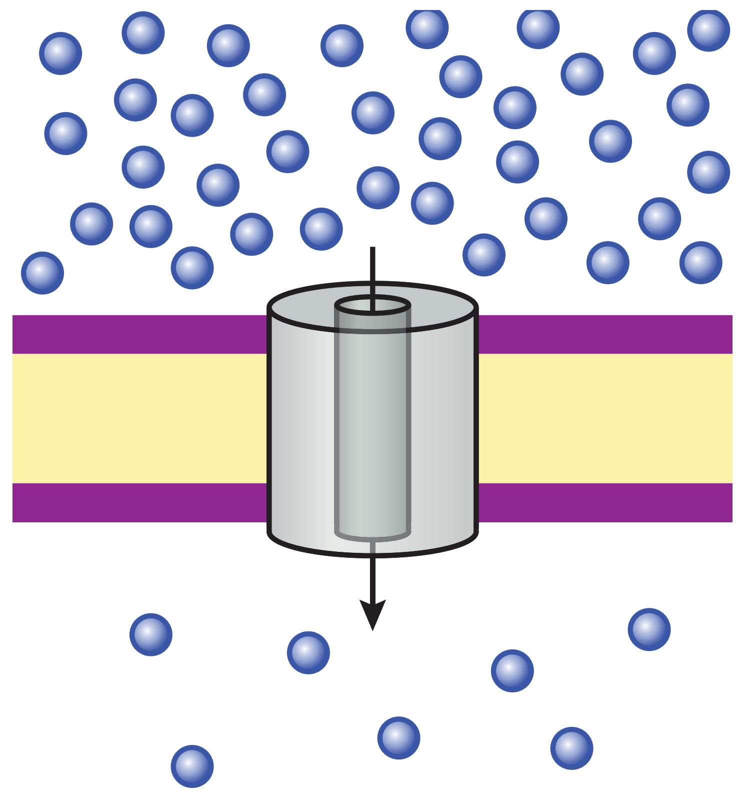
Membrane transporters in the cell

This lecture follows the parts of chapter 11, 14 & 17 in the book 'The Molecules of Life' by Kuriyan et al.

Transmembrane proteins classified by type of transport

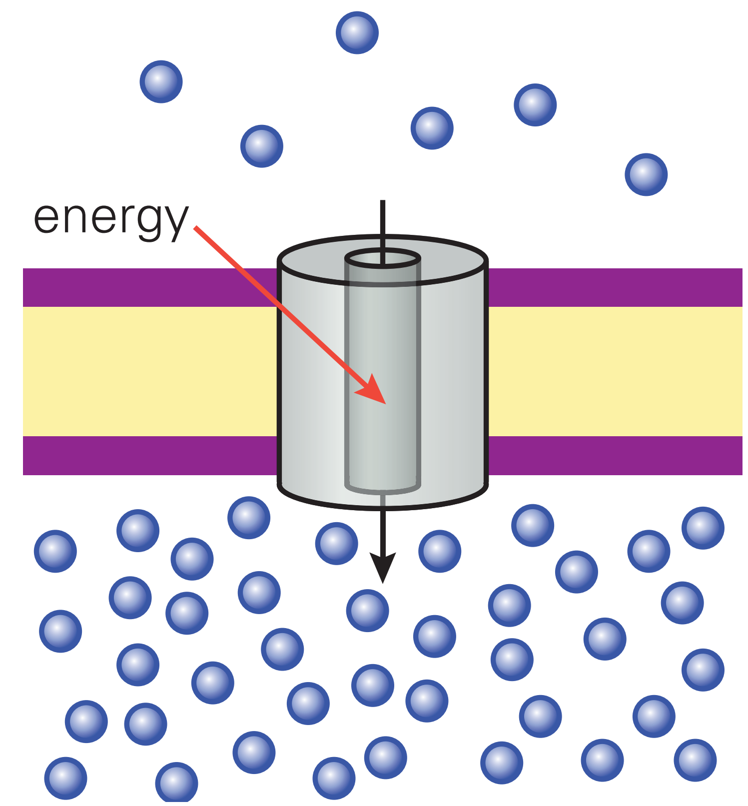
Active and passive transporters

Proteins that form channels in the membrane and facilitate the movement of specific molecules from one side of the membrane to the other are known as transporters. Active transporters are membrane proteins that use energy to move molecules against a concentration gradient. Passive transporters do not use energy to control the flow, and the net flow of molecules is simply from the side of the membrane where they are at higher concentration to the side where they are at lower concentration.



Passive transporter
e.g. ion channel, porins

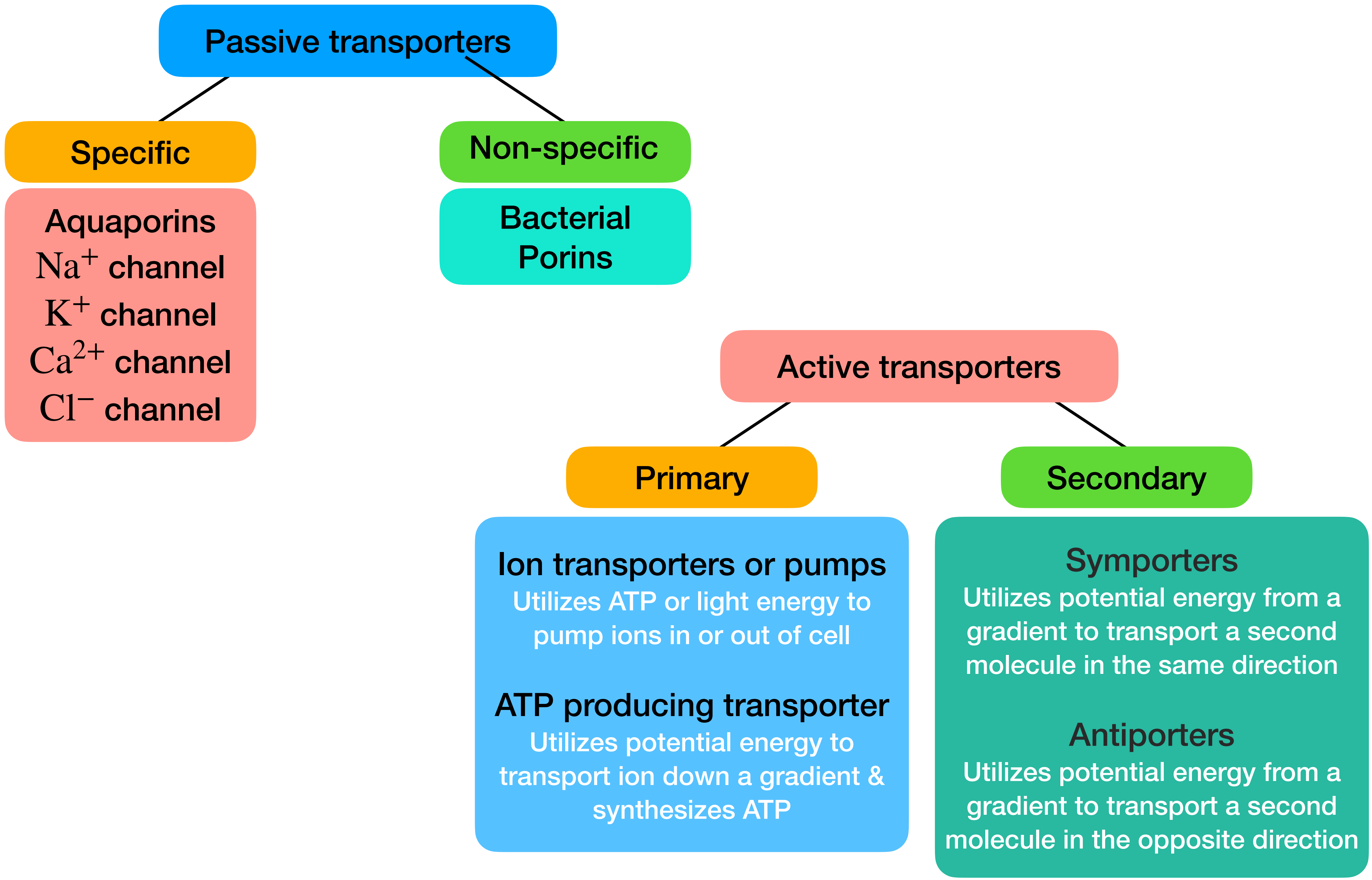
Allows transport 'downhill' a gradient of concentration or electrochemical potential



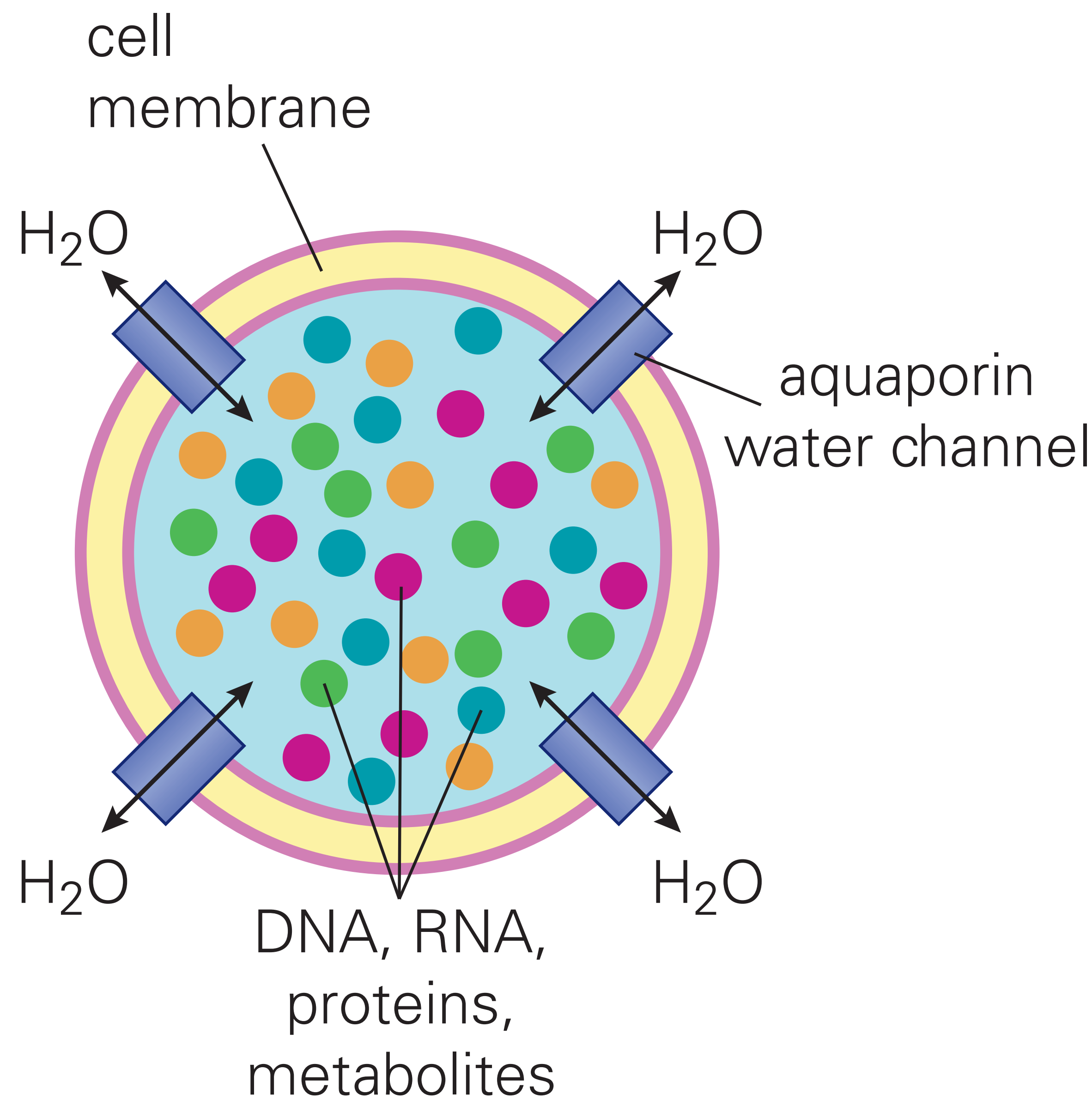
Active transporter
e.g. proton pump,
sodium/potassium pump

Allows transport 'against' a gradient of concentration or even sets up a conc. gradient and utilizes some energy source

Vast array of transporter membrane proteins



Aquaporins are only permeable to water



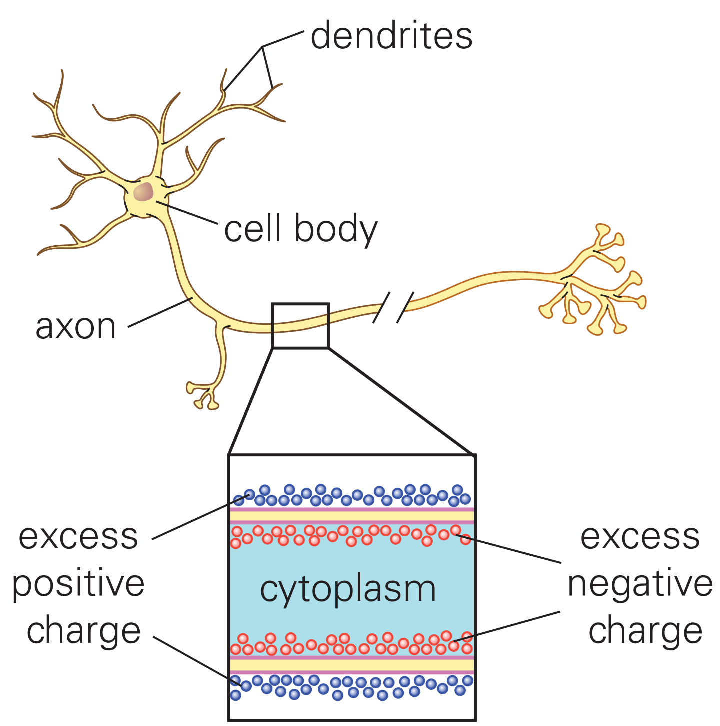
Aquaporins are water channels that allow only water to equilibrate rapidly across the membrane. But the ions can't move through water channels. This leads to the development of an osmotic pressure on the membrane.

How is this osmotic pressure balanced? By the membrane potential

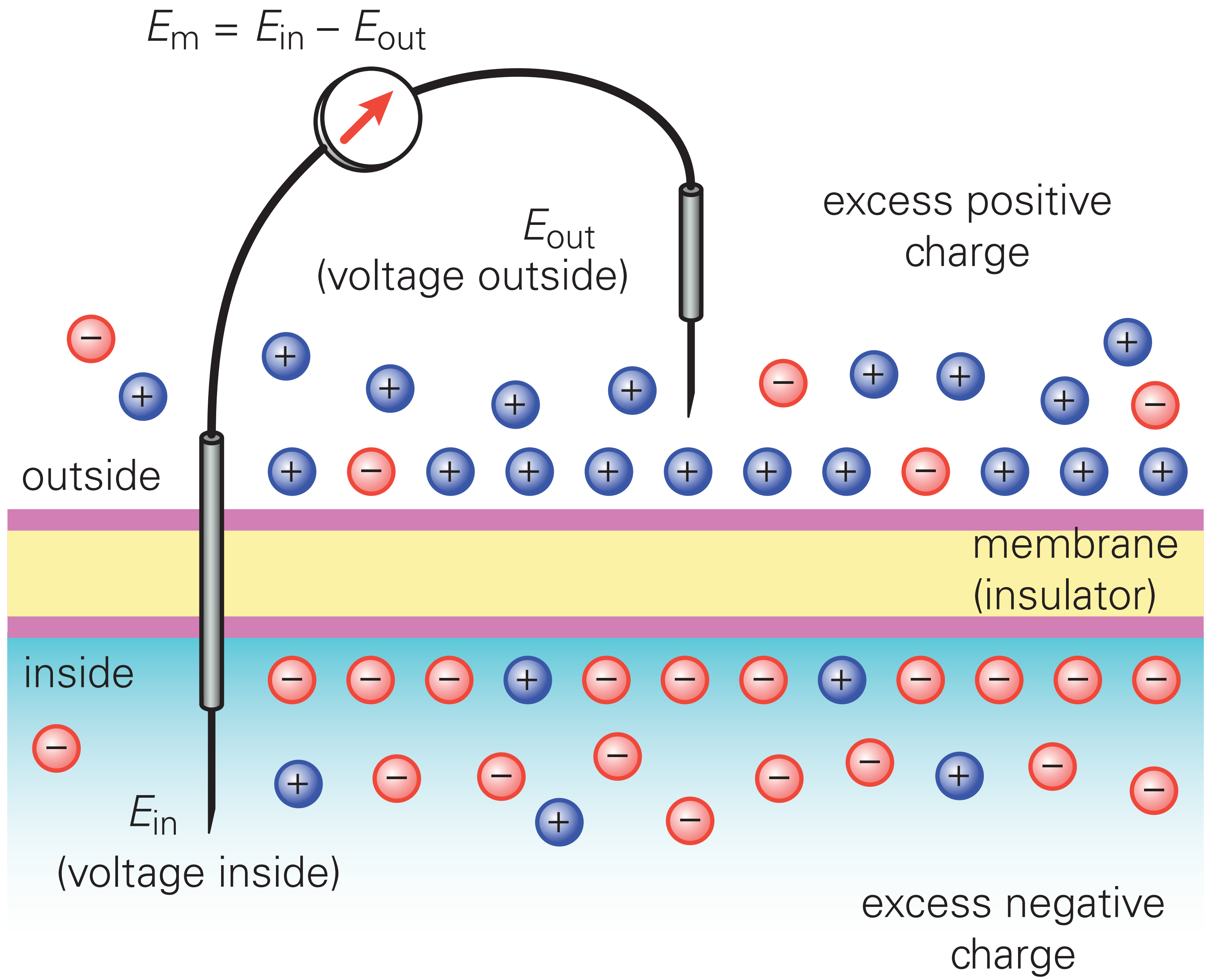
What is membrane potential?

Membrane potential

The electrical potential difference across the cell membrane (that is, the difference between the potential inside the cell and the potential outside the cell) is known as the membrane potential. Resting mammalian cells have a membrane potential that is approximately –70 mV, with the interior of the cell at a negative potential with respect to the outside.

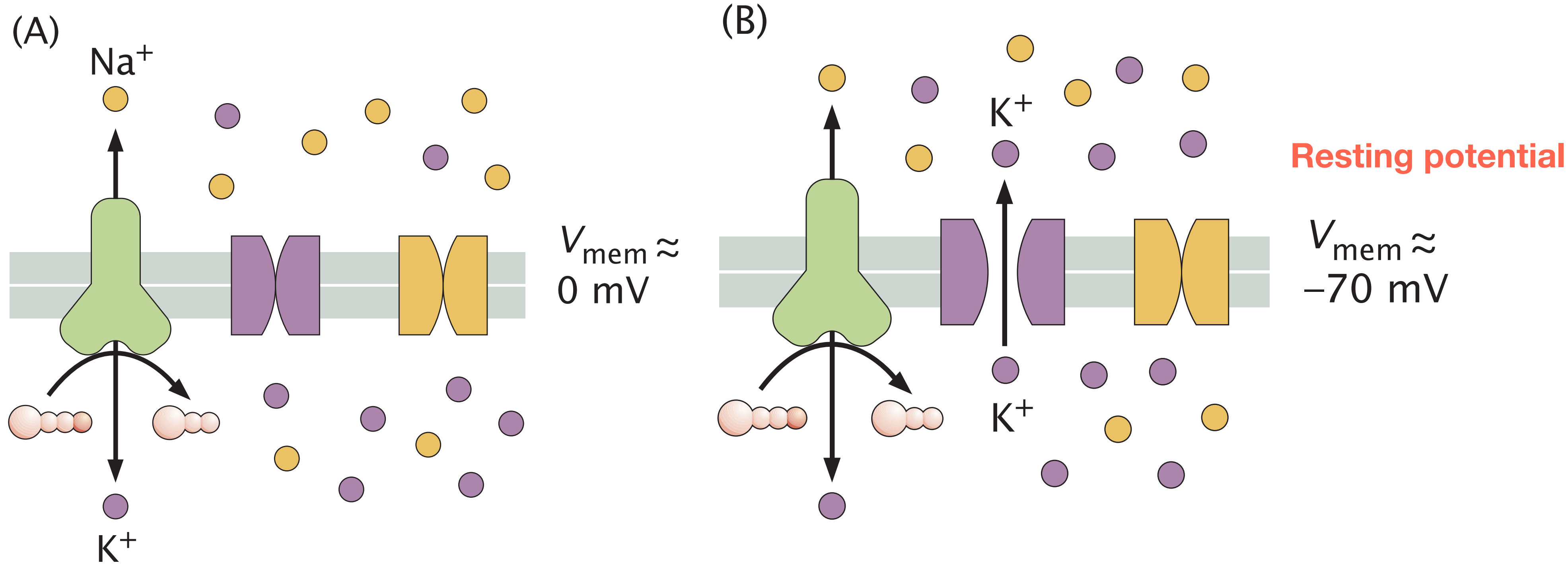


Measuring membrane potential using electrodes

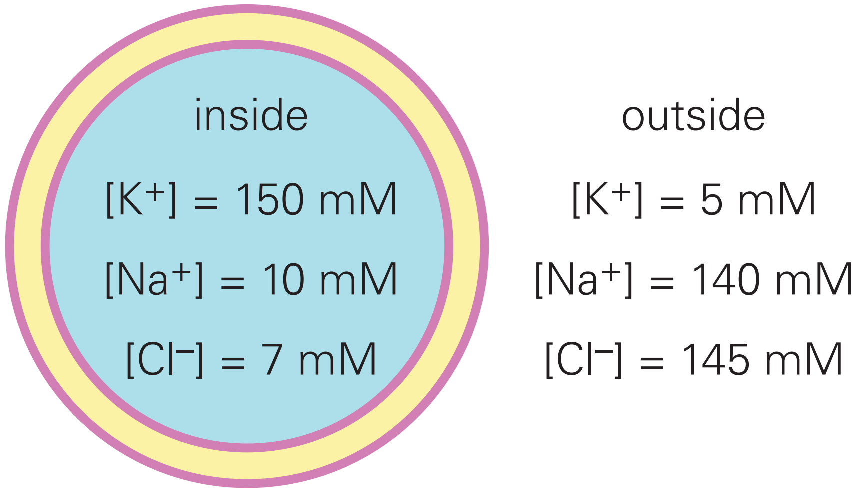


How is this potential created?

Membrane potential created by ion transporters balances the osmotic pressure

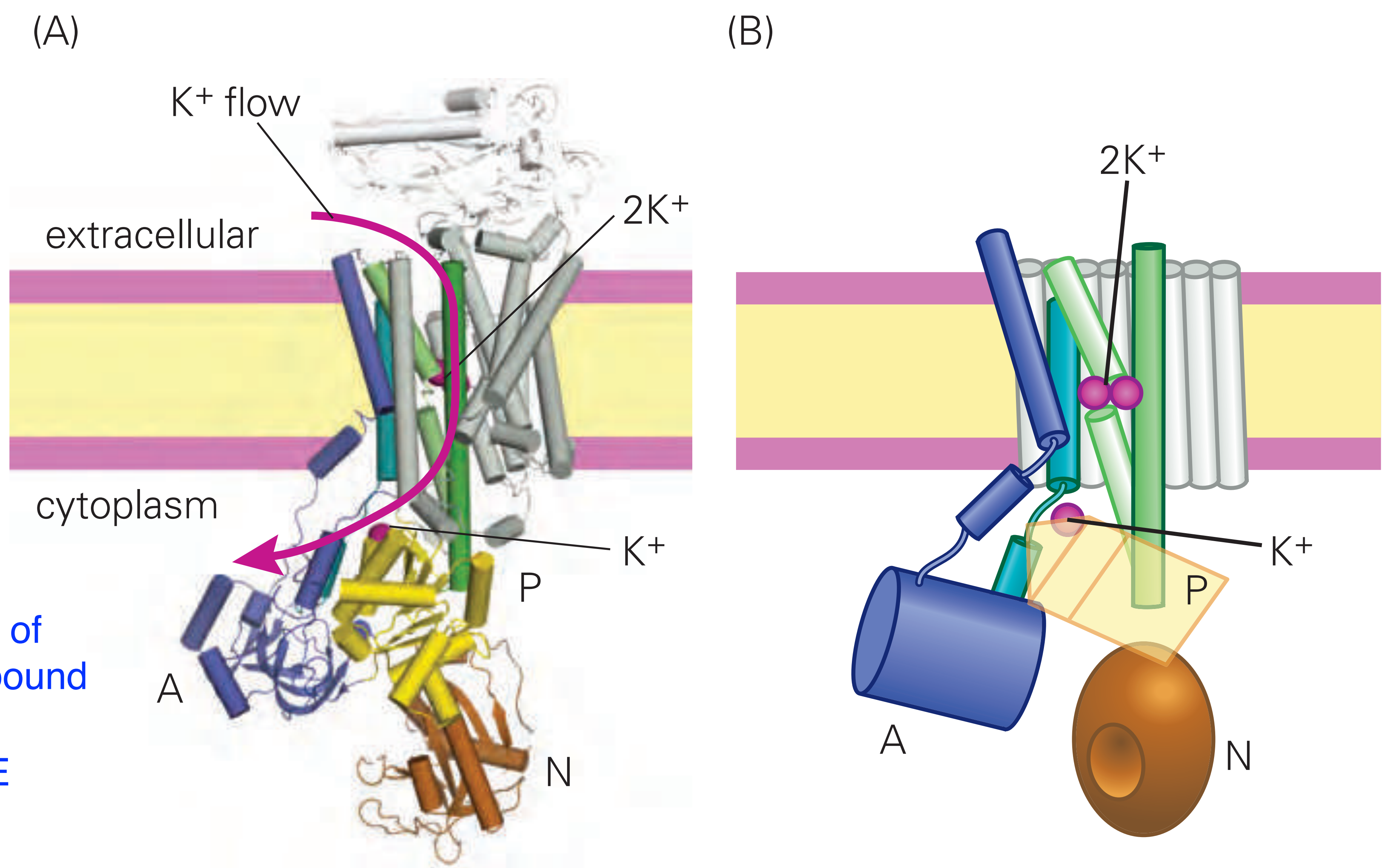


- The cell contains sodium–potassium pumps that uses energy of ATP hydrolysis to transport **three** Na^+ **ions out** of the cell for every **two** K^+ **ions in.** When ion channels are closed this creates steep gradients of conc of these ions.
- Under normal circumstances, K^+-specific “leak channels" (purple) are in an open state, allowing K^+ ions to exit the cell. The exit of K^+ ions renders the membrane potential negative on the inside.



Due to the negative electrical potential inside the cell, there is a net outflow of chloride ions through Cl^- channels. This balances the osmotic pressure on the membrane.

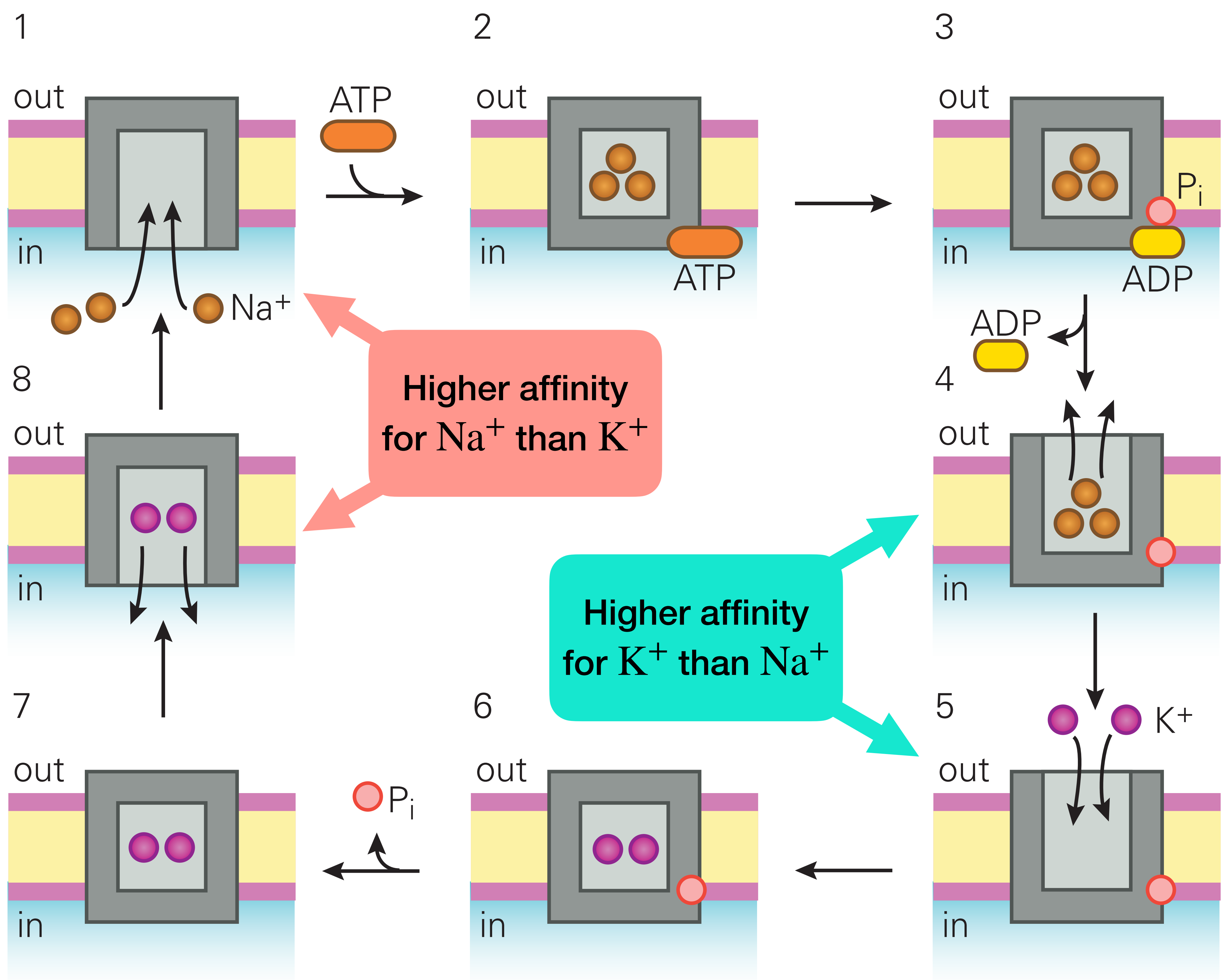
The sodium/potassium pump is a two subunit protein



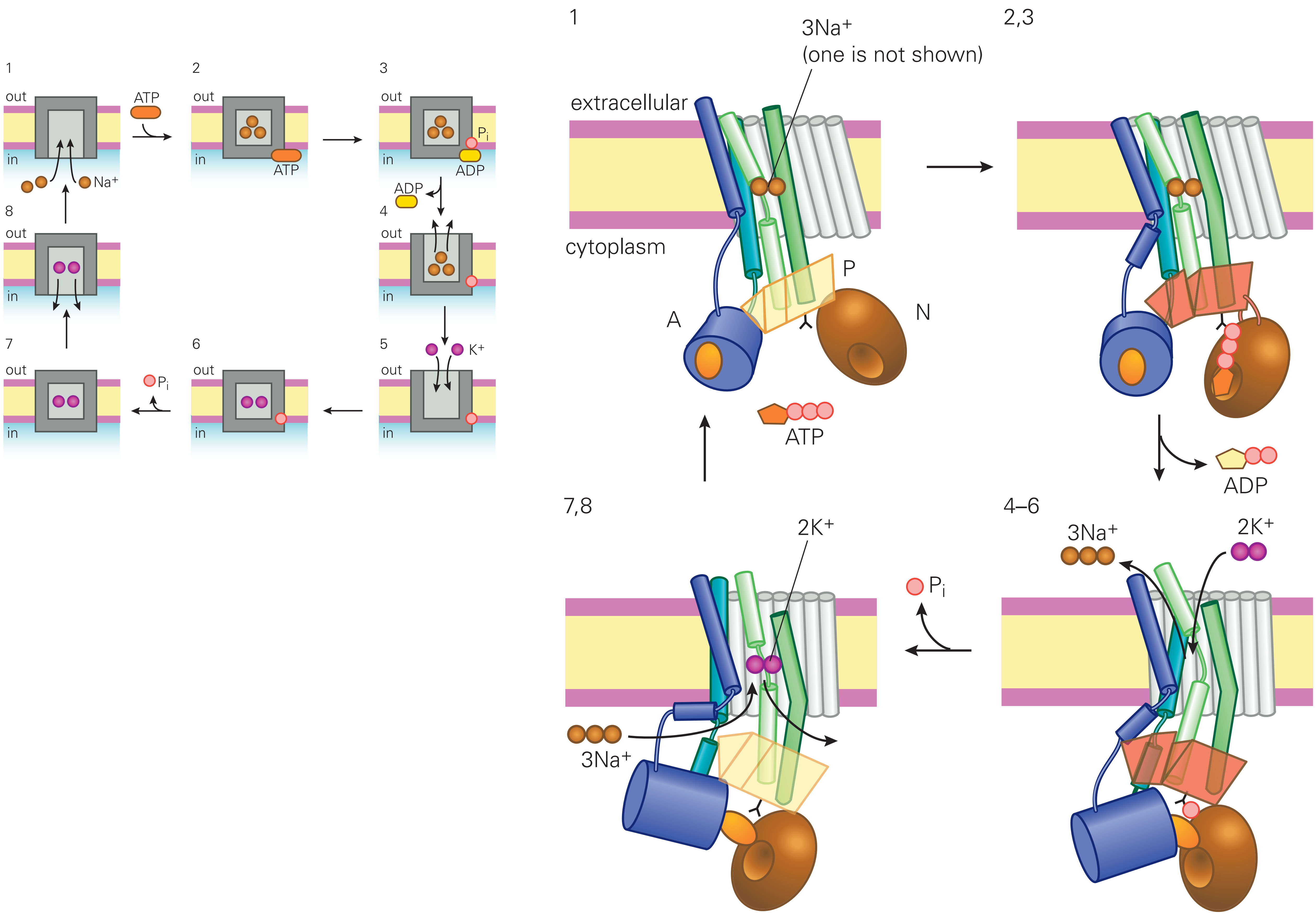
Crystal structure of Na^+/K^+ pump bound to three K^+ ions
PDB code: 2ZXE

- One subunit is in color and another is in gray
- It has 3 cytoplasmic domains A, P and N.
- N is the ATP binding domain
- P domain receives the phosphate group from ATP hydrolysis.
- A domain is an actuator that undergoes large conformational changes that are coupled to changes in the structure of the transmembrane segments

Sodium/potassium pump hydrolyzes ATP to move ions



Structural basis of sodium/potassium pump



The sodium/potassium pump is quite slow while the channels are fast

The Na^+/K^+ pump is slow for two reasons

- The ATP hydrolysis is time consuming
- The cytoplasmic domains undergo large conformational changes ← **Slowest step!**

Typical speed of the second step $= 50\ /\text{second}$

Thus the typical ion transport speed $= 150\ Na^+ - \text{out}\ \ \&\ 100\ K^+ - \text{in}\ /\text{s}$

The ion channels are not limited by such complicated steps, they depend on diffusion

For a K^+ channel typical length $= 40\ \text{Å}$

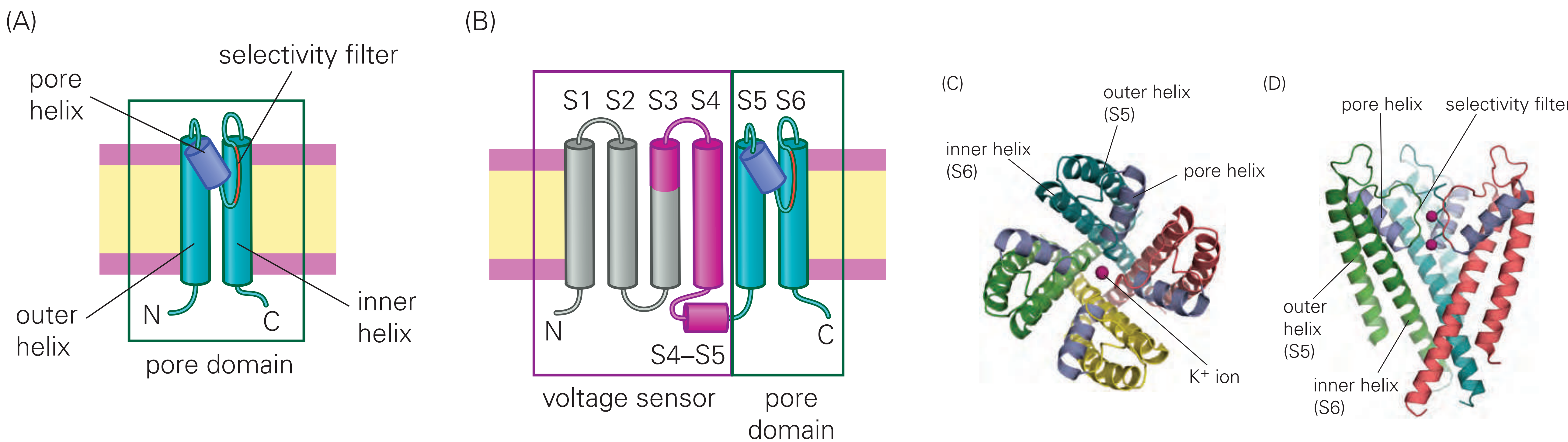
Diffusion constant of K^+ in water $\approx 10^{-5}\ \text{cm}^2\ \text{s}^{-1}$

Speed of transport?

Time taken to move across the channel $\tau_{transport} \approx \dfrac{L^2_{channel}}{D} = \dfrac{(40\ \text{Å})^2}{10^{-5}\ \text{cm}^2\ \text{s}^{-1}} = 16\ \text{ns}$

Ion transport speed $\approx 6 \times 10^7\ \text{ions/s}$ ← **Lot higher**

Sodium, potassium, calcium channels have a highly conserved structure



Bacterial potassium channel

- Such channels open in a particular direction
- They have voltage-sensor domains that undergo conformational change upon changes in membrane voltage
- They have a tetrameric pore domain that has a similar structure across K^+, Na^+ and Ca^{2+} channels
- The pore contains a selectivity filter that preferentially binds one type of ion
- They may also have domains that undergo conformational change to inactivate the channel

The sodium channel responds to sudden change in membrane potential

Illustration using action potential transmission across axons

Action potential

A transient change in the voltage difference across the plasma membrane of an axon is called an action potential, also called a *nerve impulse*. Action potentials move along the axon with essentially no attenuation. They are the currency of signal transmission through the axon.