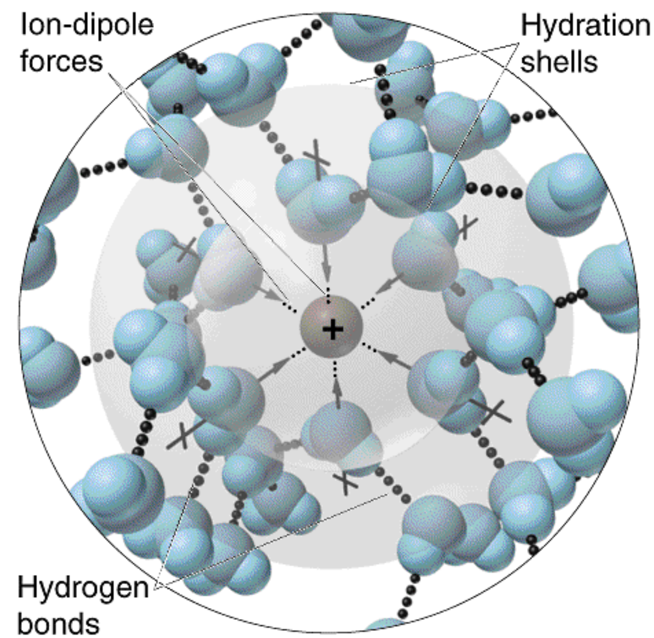
Hydrophobic barrier

Born-Formula

$$\Delta E = \frac{1}{2}\frac{Q^2}{r}\left(\frac{1}{\varepsilon_m} - \frac{1}{\varepsilon_w}\right)$$

- There are about 7 water molecules in the first hydration shell of potassium ion.

- Each water molecule stabilizes the ion by approximately 24 kT.



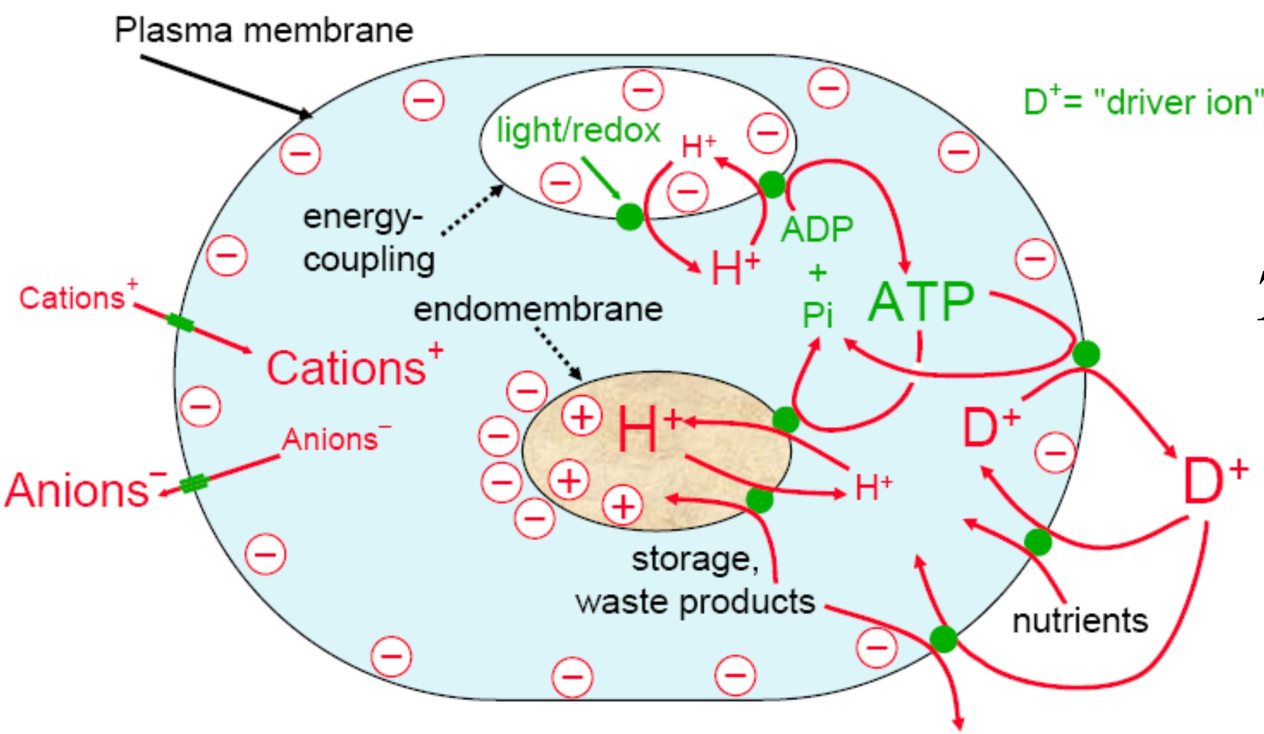
Roux & McKinnon, Science (1999)

Completion and 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



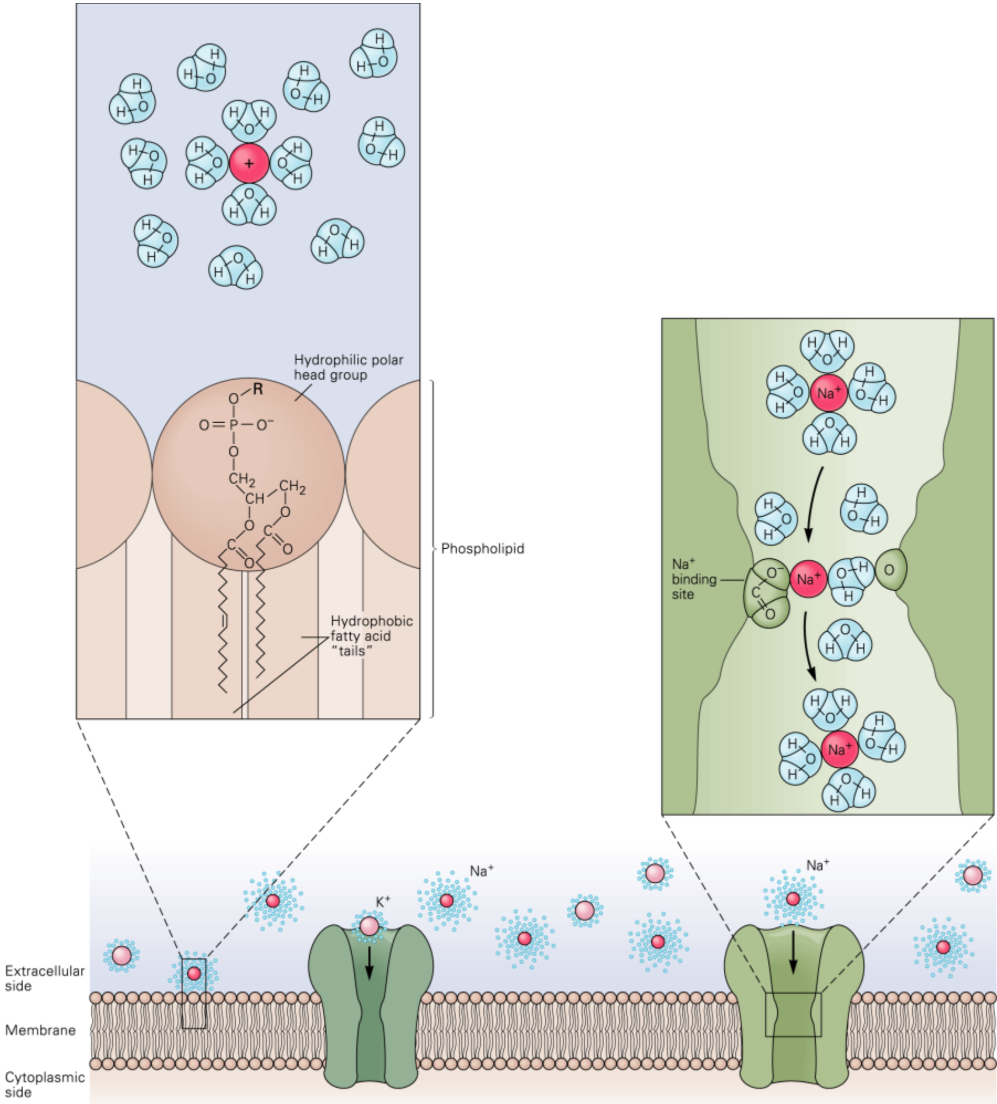
Transport Processes in an Idealized Eukaryotic Cell

Ion channels are enzymes that catalyze the flow of ions across cell membranes causing picoamp current.

For every ion that crosses the membrane through the lipid bilayer, 10^{13} do so by traversing an ion channel.

The downhill diffusion of ions through biological membranes occurs through ion channels;

- an ion channel has a resistance of ~ $\mathbf{10^{10}\ \Omega}$,
- a patch of lipid bilayer of similar cross section has a resistance of ~ $\mathbf{10^{23}\ \Omega}$.



Physical Characteristics of Ion Channels

Natural Nanodevices

Ion channels have **Selectivity.**

K channel selects K^+ over Na^+ by ~10^4.

Ion channels Gate/Switch in response

to pH, voltage, chemical species and mechanical force from conducting to nonconducting state.

Ion channels have **VERY Large Charge Densities**

critical to I-V characteristics and selectivity (and gating?)

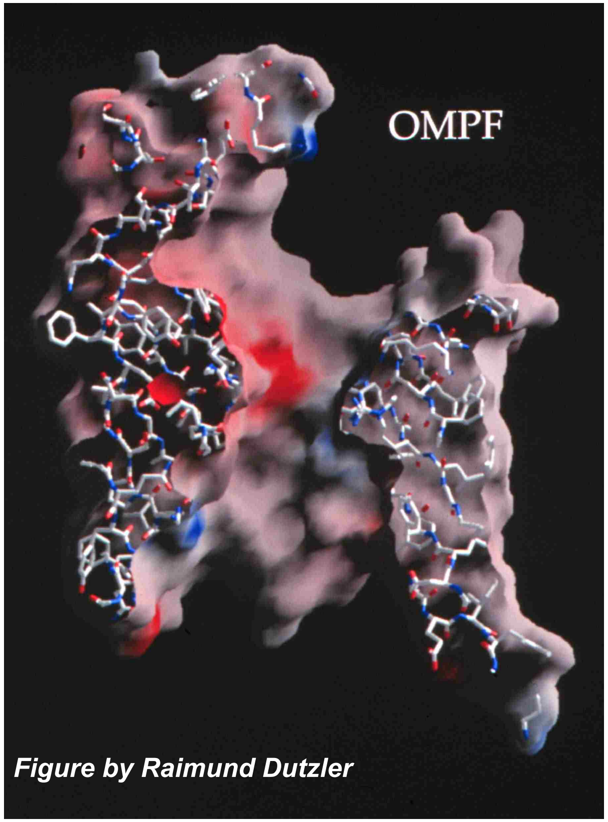
Ion channels allow **Mutations**

that modify conductance, selectivity, and function.

Ion channels are **Device Elements**

that self-assemble into perfectly reproducible arrays.

Ion channels form **Templates for design of bio-devices and biosensors.**



~30Å

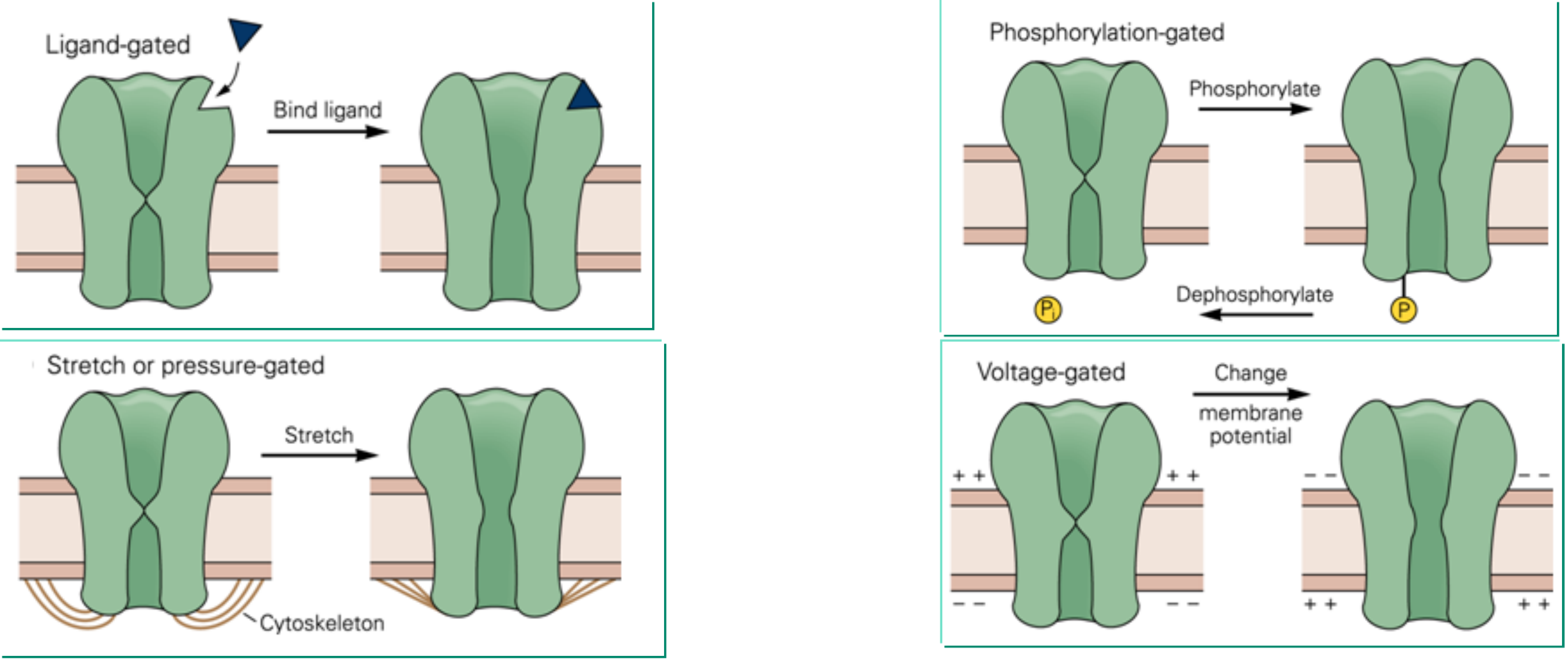
Ion channel

ion-permeation pathway through the membrane

Selectivity filter
(narrowest constriction in the 'open' conformation)

Gate
(narrowest constriction in the 'closed' conformation)

Elements that control the gate
(ligand-binding sites, voltage-sensor, pH-sensor, temperature-sensor, mechanical-deformation sensor)

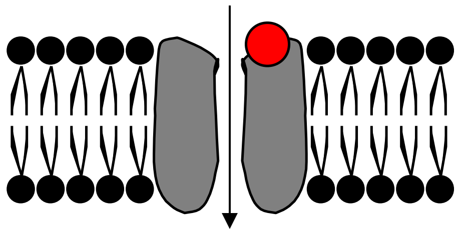


Depending on the type of the channel, this gating process may be driven by:

- ligand binding (ligand-gated channels)
- changes in electrical potential across cell membrane (voltage-gated channels)
- mechanical forces acting on cellular components (mechanosensitive channels)

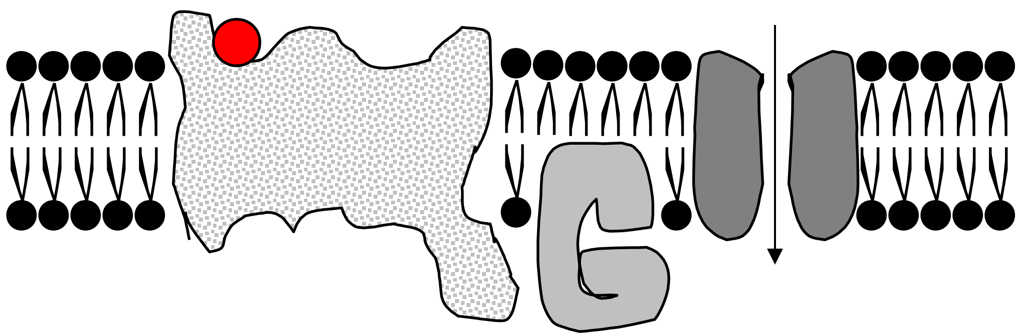
Ligand-gated ion channels

Receptor with integral ion channel



(Nicotinic ACh receptors)

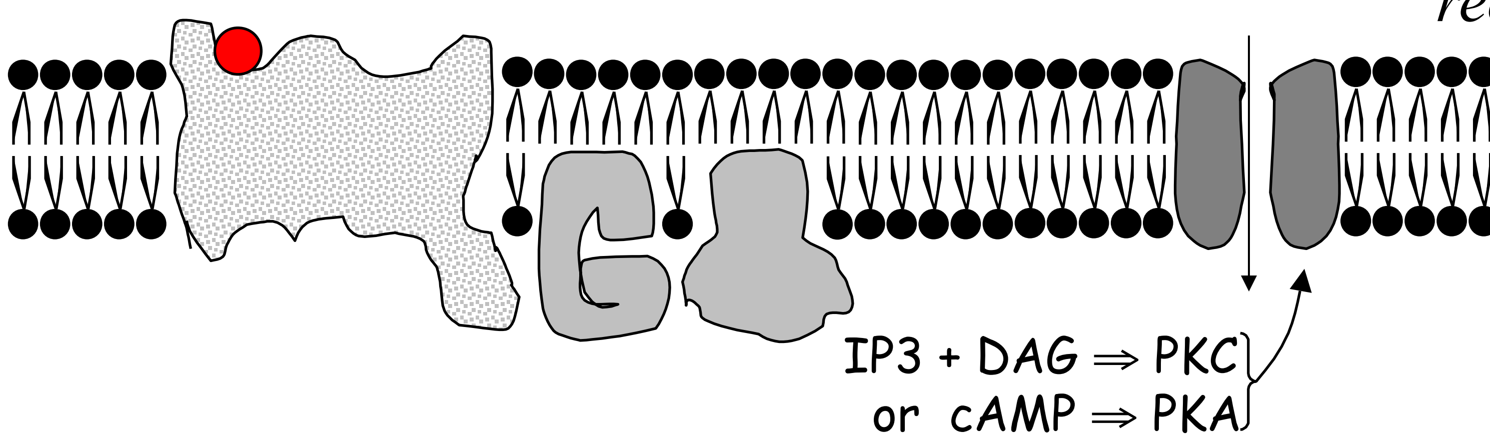
Receptor linked to ion channel via g-protein



K^+ channel

($GABA_B$ receptors)

Receptor linked via g-protein & 2nd messenger



Methods for Studying Ion Channels

Biochemistry

– agonist, antagonist or drug binding
– isolation and purification
– reconstitution
– radioactive ion flux

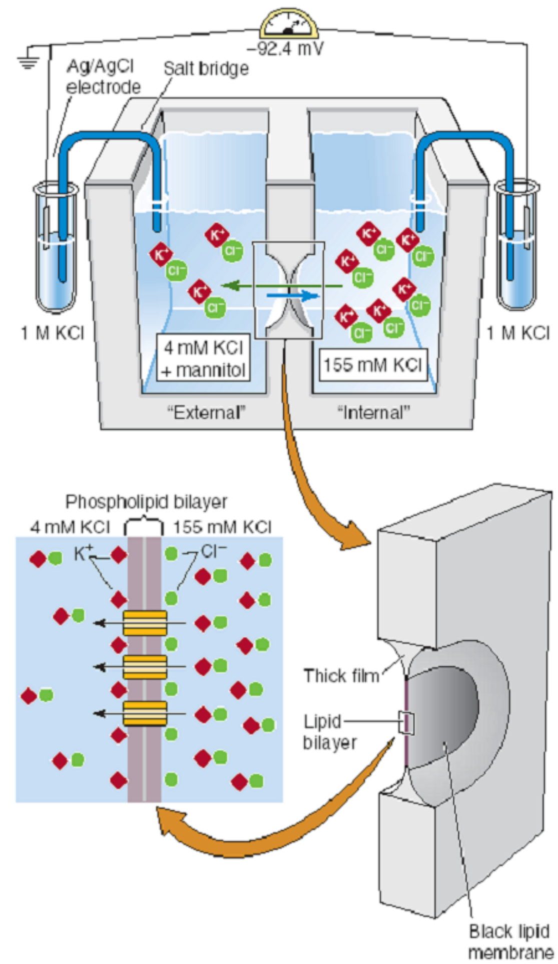
Molecular biology

– sequencing, cloning, mutagenesis

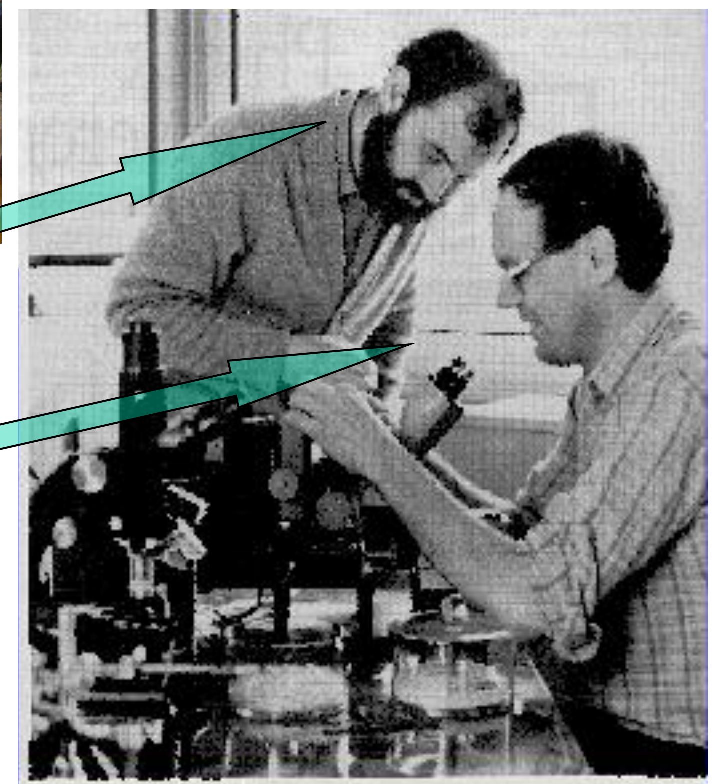
Structural biology

– microscopy, crystallography, NMR, ...

Chris Miller
Brandeis University



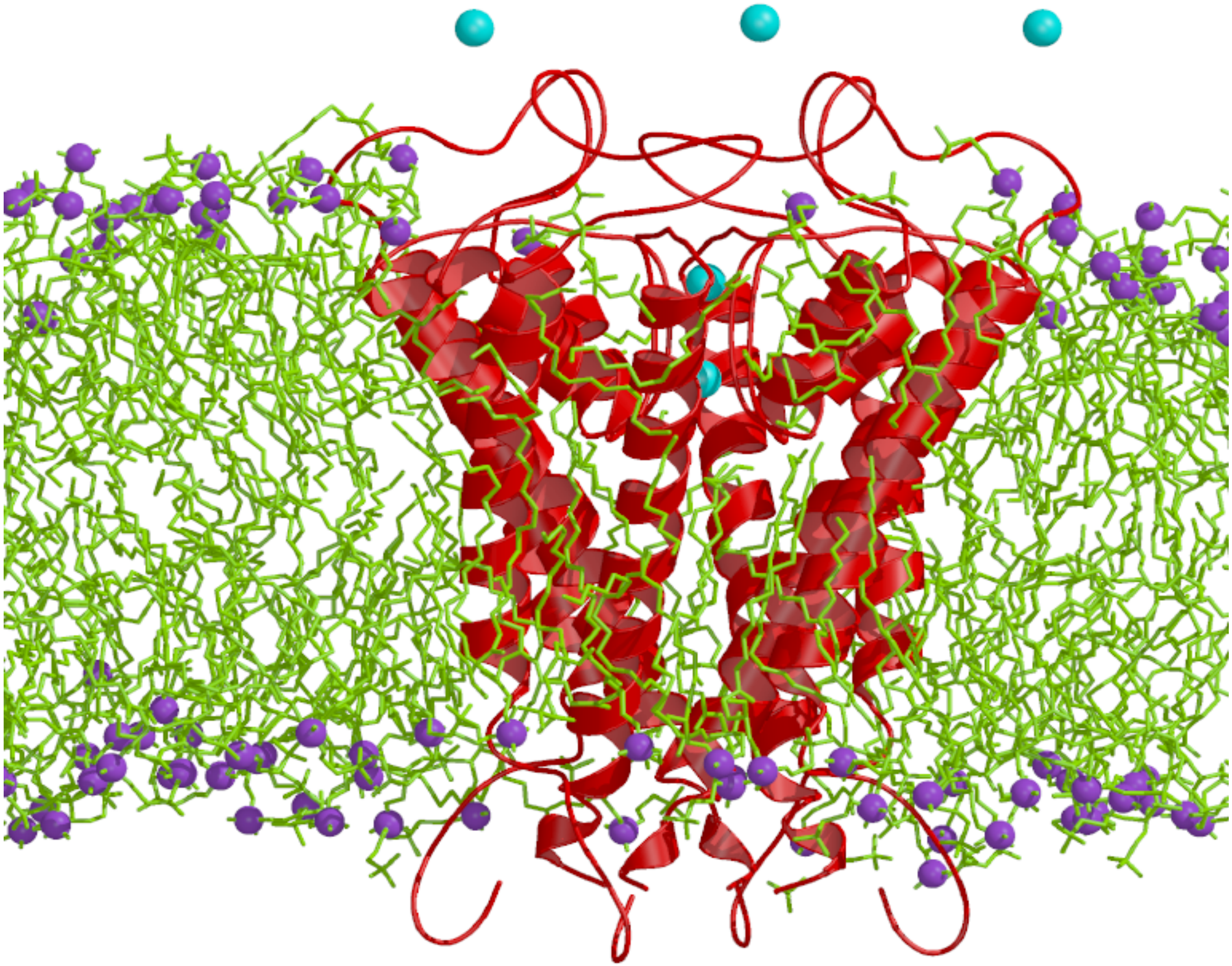
Patch clamp technique



Erwin Neher

Bert Sakmann

Germany
(1991 Nobel Laureates)

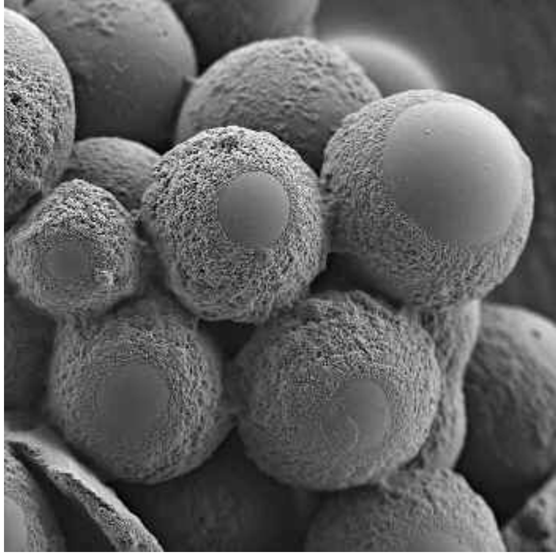


Potasium channel

Potasium channel KcsA

The 3D-structure of KcsA from Streptomyces lividans was the first X-ray structure of an ion channel.

For the Atomic Basis of Selective Ion Conduction in Potassium Channels



Streptomyces lividans

Advanced information on the Nobel Prize in Chemistry, 8 October 2003

KUNGL. VETENSKAPSAKADEMIEN
THE ROYAL SWEDISH ACADEMY OF SCIENCES

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Membrane channels

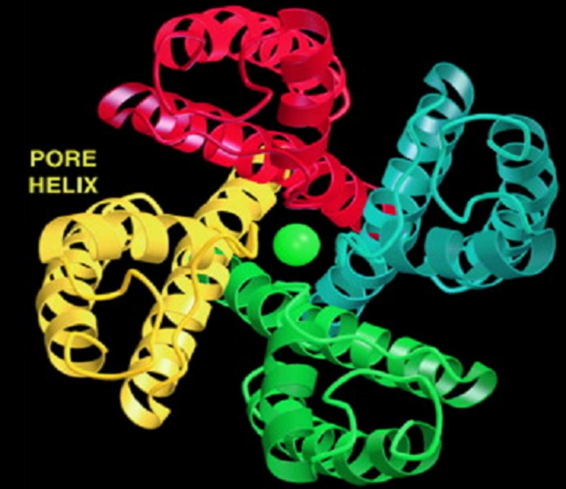
Introduction

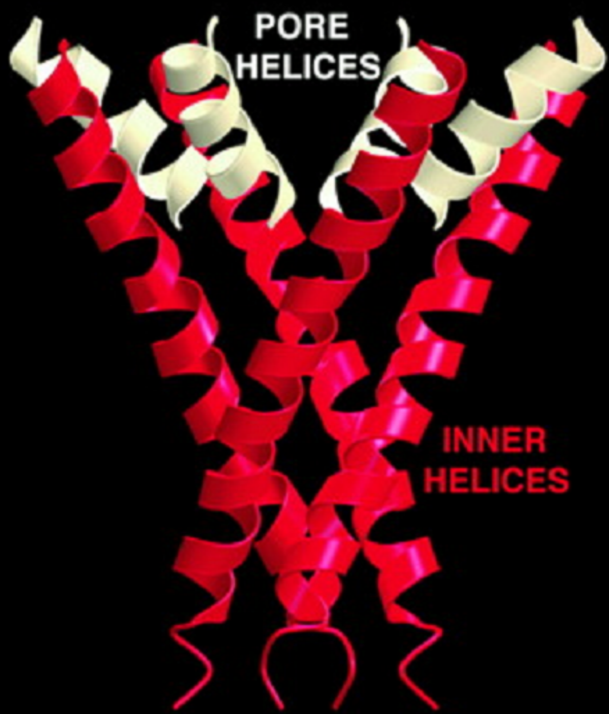
The Nobel Prize in Chemistry for 2003 is shared between two scientists who have made fundamental discoveries concerning how water and ions move through cell membranes. Peter Agre discovered and characterized the first water channel protein and Roderick MacKinnon has elucidated the structural and mechanistic basis for ion channel function.

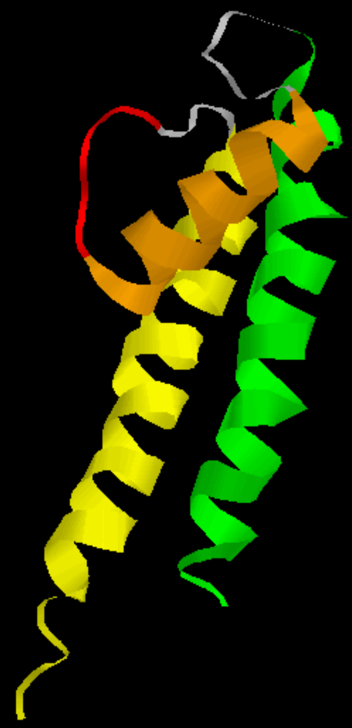
The Potassium Channel (KcsA)

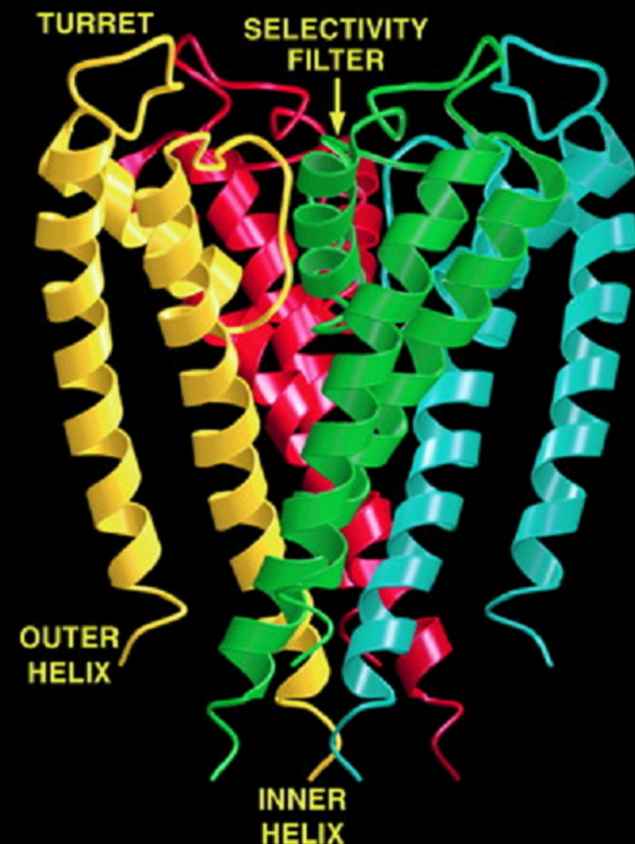
It is a **tetramer**.

Each monomer is 96 amino acids long and consist of 3 helices.









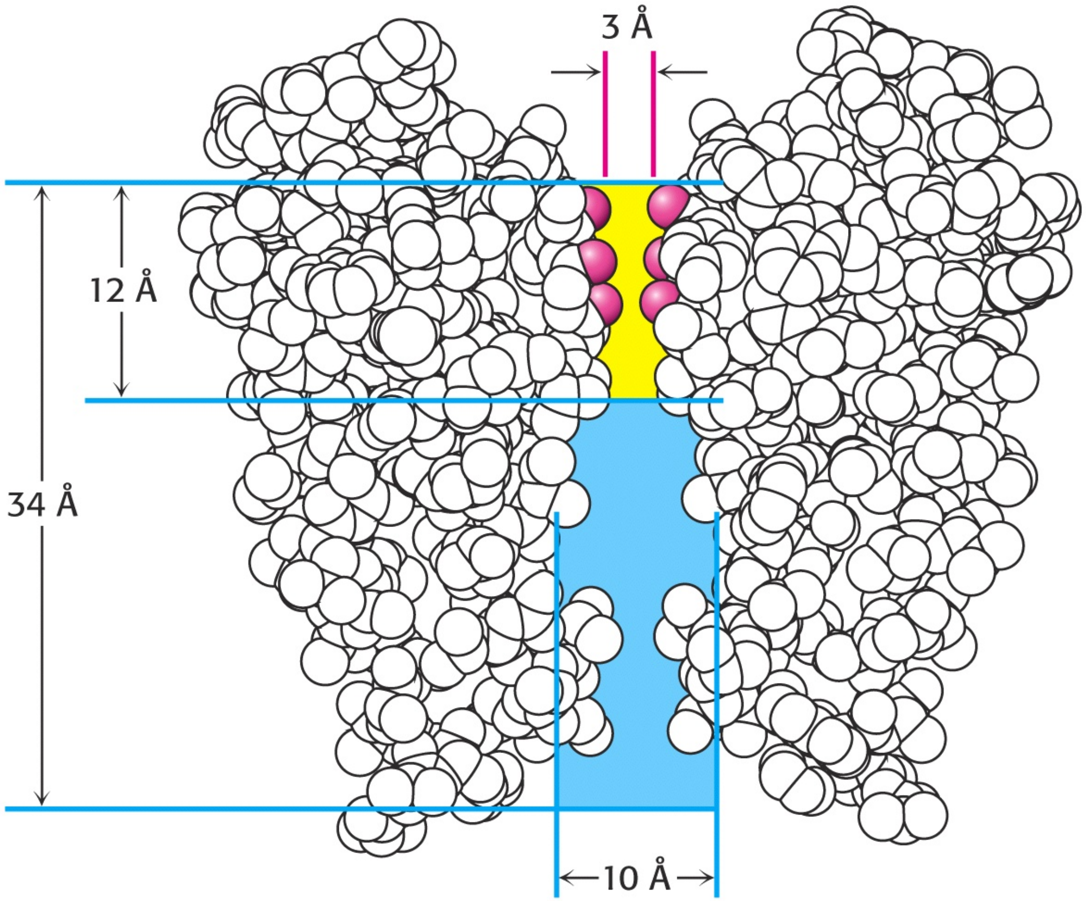
Doyle *et al.* Science (1998)

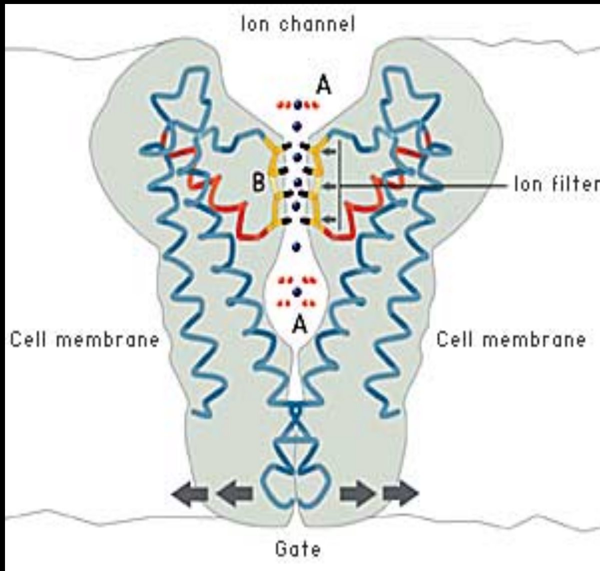
Potassium channel

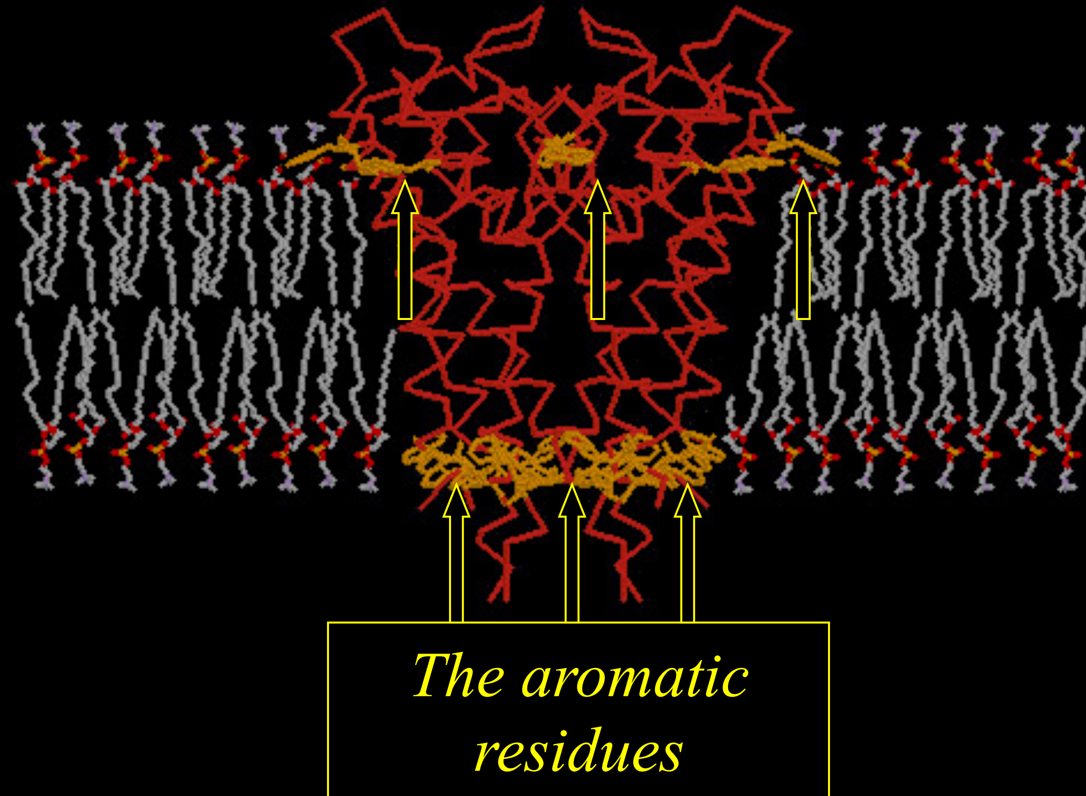
Potassium channels are a class of ion channels, managing to distinguish between K^+ and Na^+ ions while maintaining a very high throughput of K^+ ions when gated.

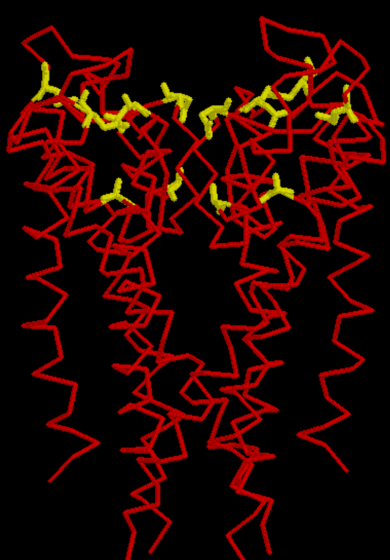
It has a diffusion rate of 10^8 ions per second.

One K^+ ion is dehydrated, transfered, and rehydrated every 10 ns.

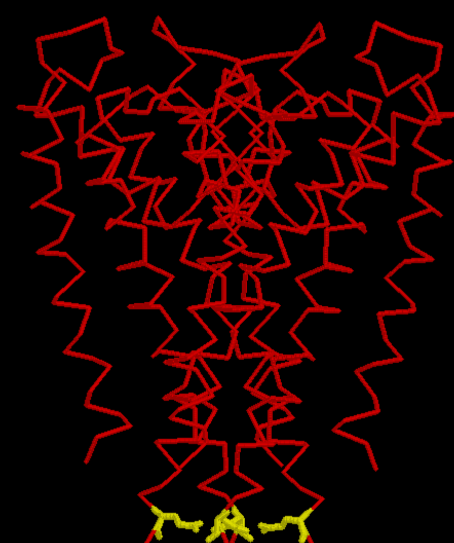




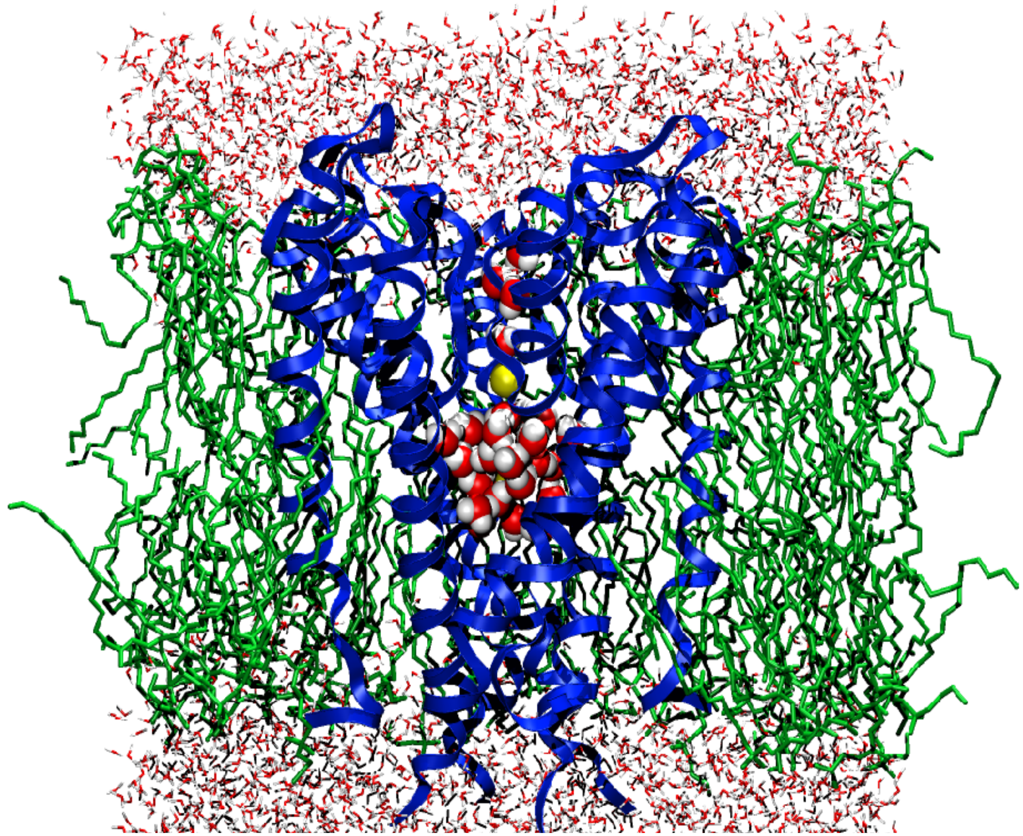




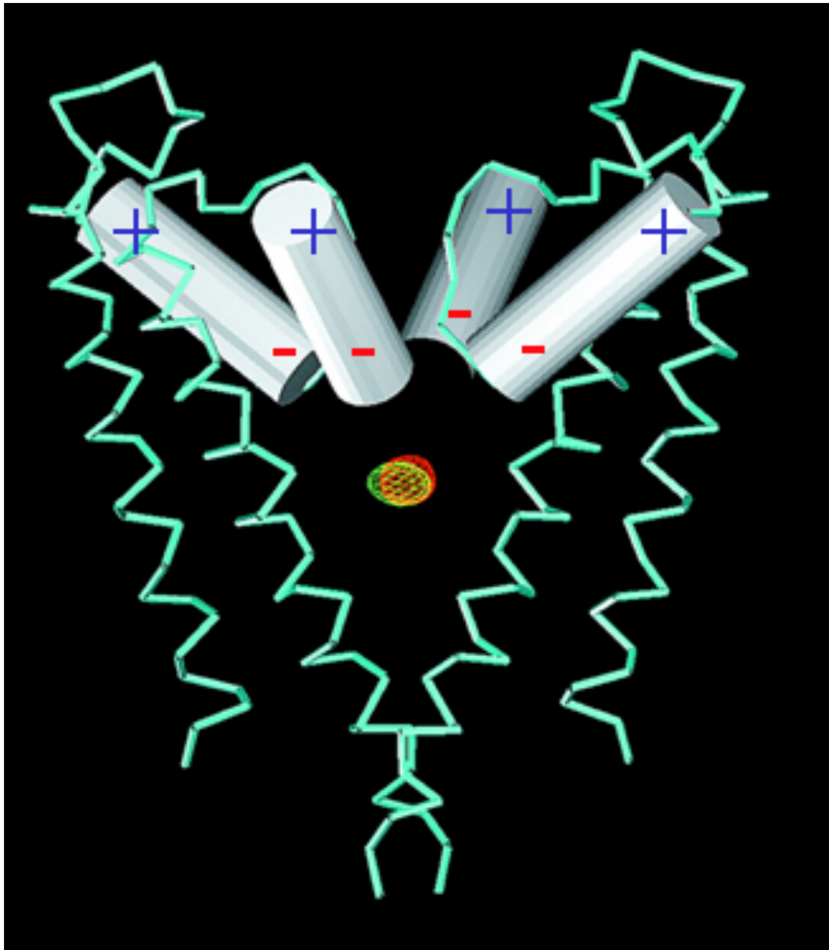
***Negativel
charged
acidic
residues
are on to
attract K⁺***

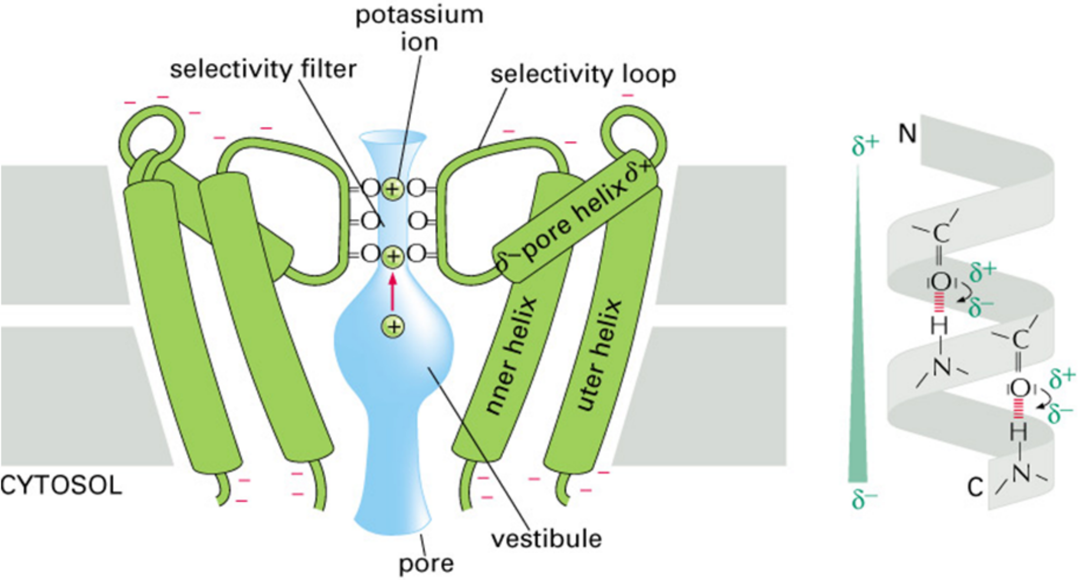


The negative charges on the bottom help to pull the K^+ ion through the pore.



The central cavity is lined with hydrophobic residues.

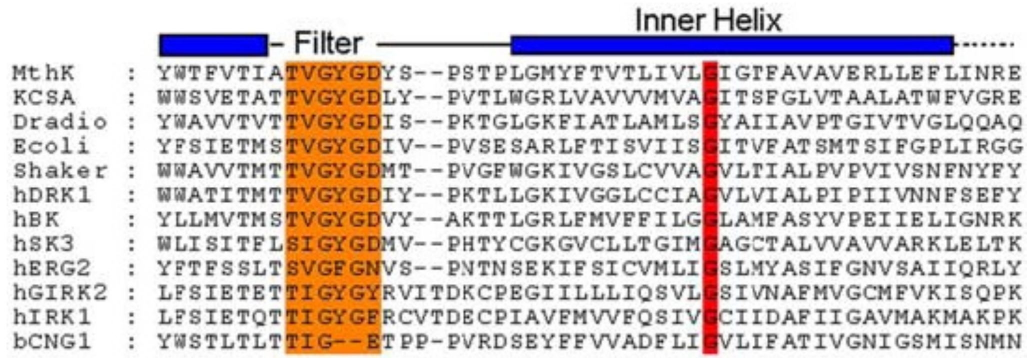




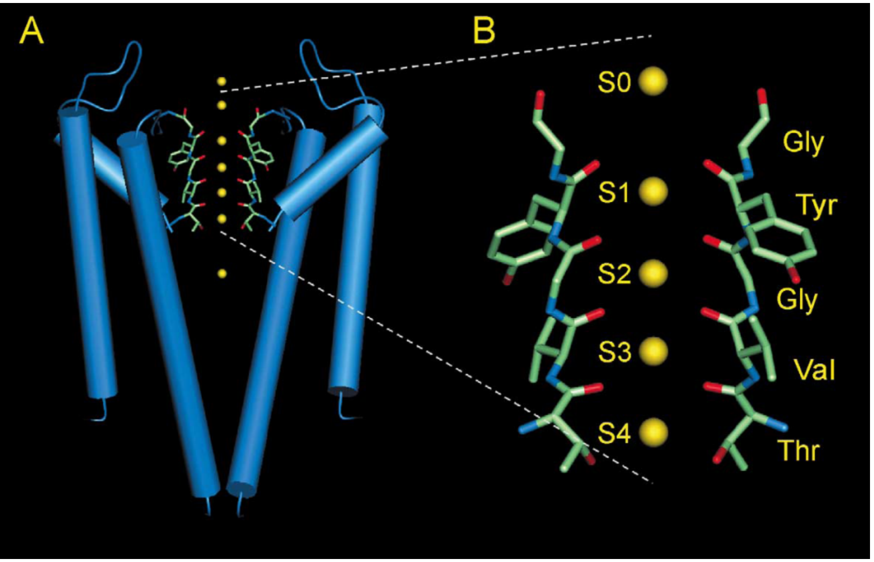
Selectivity filter

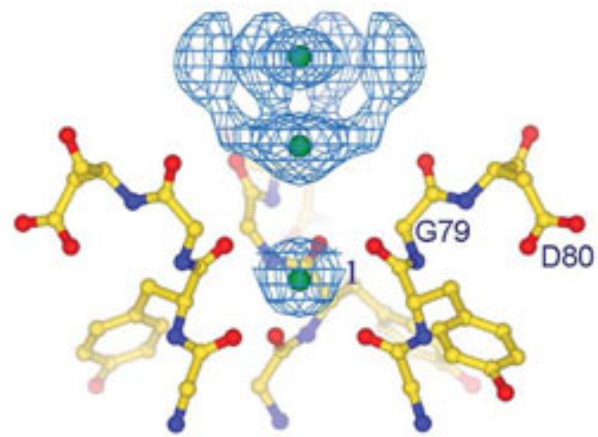
***C=O** atoms of the protein backbone form selectivity filter (4 × Tyr-Val-Gly-Tyr-Gly).*

The sequence is **conserved** in all K^+-channels.



❑ *Four K^+ ion binding sites.*

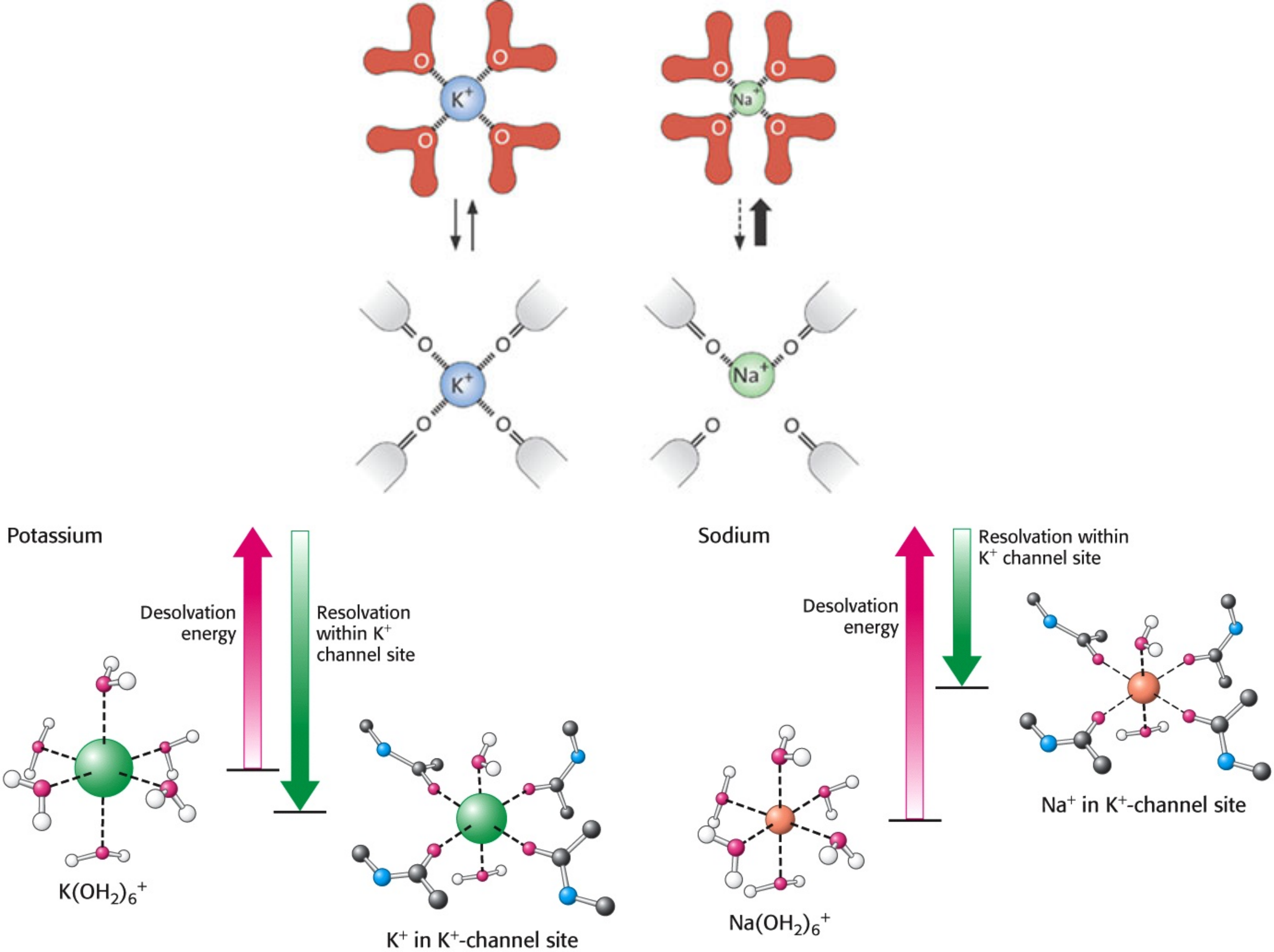




❑ *K^+ is surrounded by eight oxygen atoms from the protein*

- four 'above' and four 'below'.

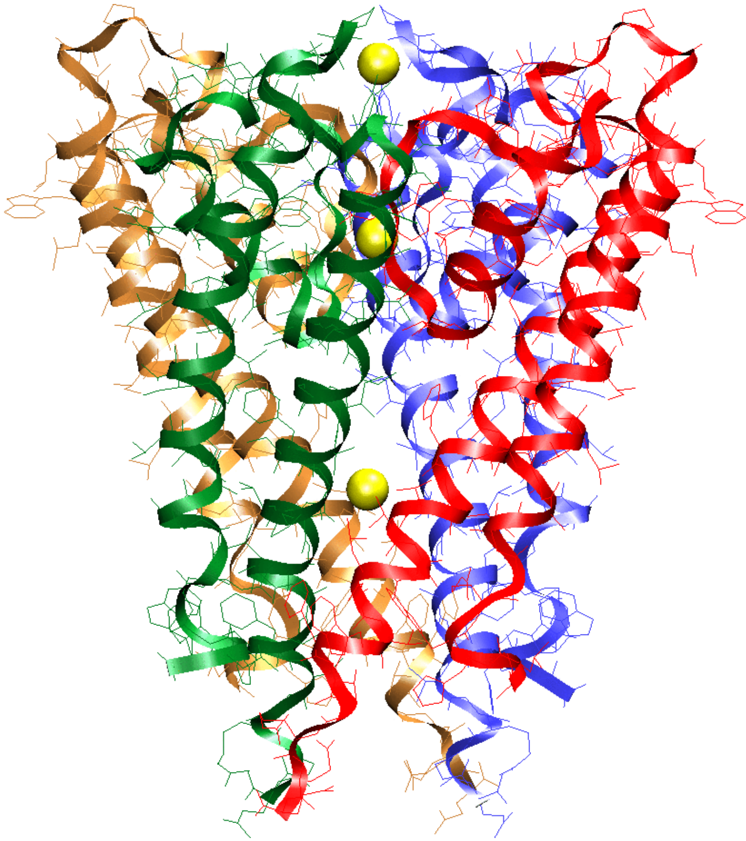
- very similar to water molecules around hydrated K^+.



O
K+
Na+
Potassium
Desolation energy
Resolvation within K+ channel site
K(OH2)6+
K+ in K+-channel site
Sodium
Desolvation energy
Resolvation within K+ channel site
Na(OH2)6+
Na+ in K+-channel site

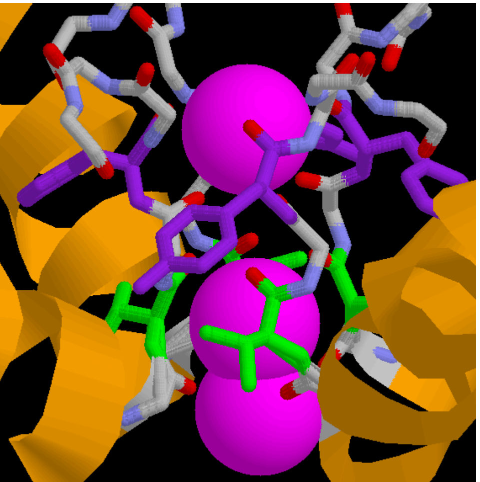
The selectivity filter needs to be rigid

KcsA Potassium Channel from *Streptomyces lividans*



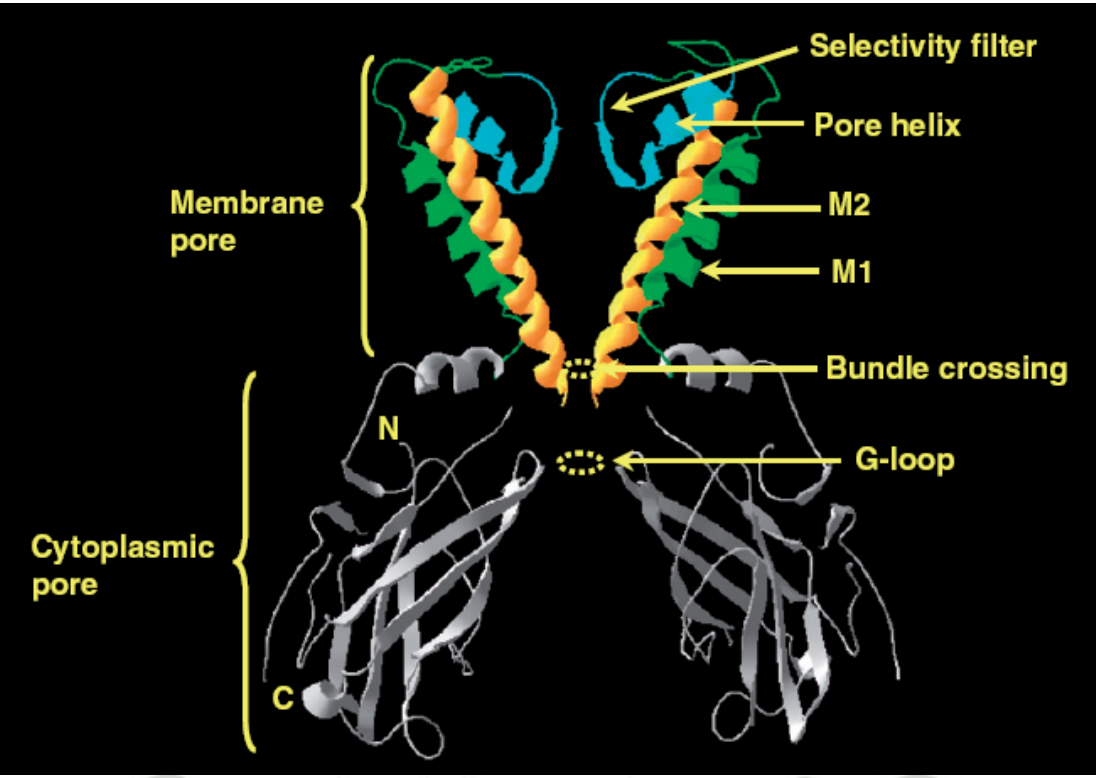
- The Val and Tyr hold the selectivity filter at a certain diameter by hydrogen bonding with the inner helix.

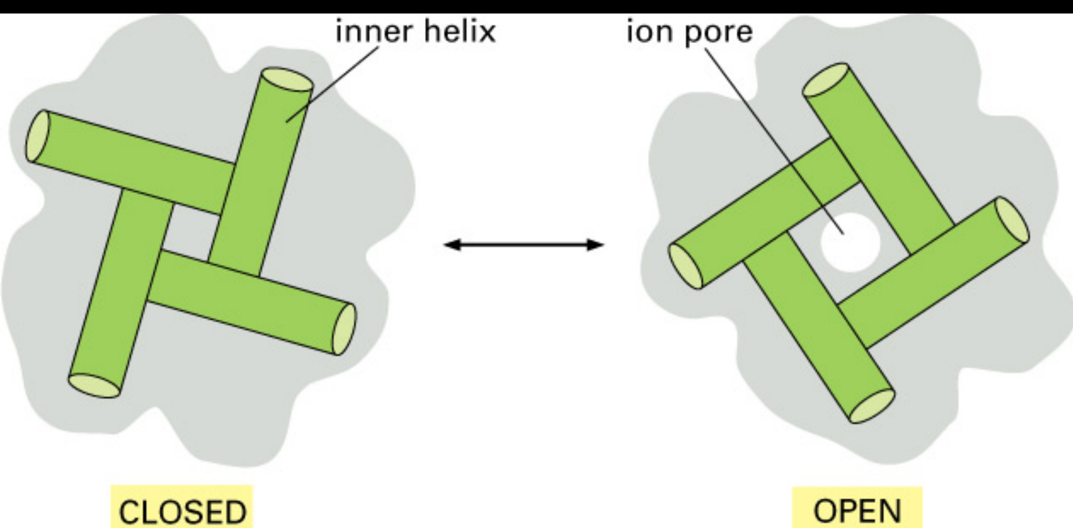
- They form hydrogen bonds which acts as tight springs that will not allow the pore to collapse.



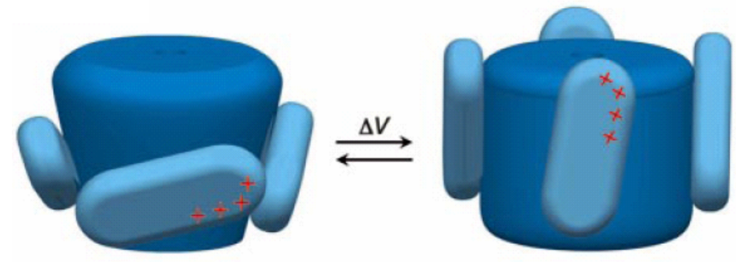
- The "springs" prevent the selectivity filter from interacting with cations smaller than K^+.

Topology of a Kir subunit.





The bacterial voltage-gated K^+ channel KvAP



The gate