

Potassium channel gating and structure

Reading:

Hille (3rd ed.) chaps 10, 13, 17

Doyle et al. The Structure of the Potassium Channel: Molecular Basis of K⁺ Conduction and Selectivity. *Science* 280:70-77 (1998).

Miyazawa et al. Structure and gating mechanism of the NACH receptor pore *Nature* 423:949-955 (2003).

Long et al. Voltage Sensor of Kv1.2: Structural Basis of Electromechanical Coupling *Science* 309:897-902 and 309:903-907 (2005).

Payandeh et al. The crystal structure of a voltage-gated sodium channel. *Nature* 475:353-359 (2011).

Voltage gated ion channels show considerable selectivity, inferred from membrane potential experiments.

TABLE 14.2 Permeability Ratios, P_X/P_{Na} , for Na Channels^a

Ion	Frog node ¹	Frog muscle ²	Squid axon ³	<i>Myxicola</i> axon ⁴
H ⁺	252 ⁵	—	>2 ⁶	—
Na ⁺	1.0	1.0	1.0	1.0
Li ⁺	0.93	0.96	1.1	0.94 ⁹
Ca ²⁺	<0.11	<0.093	0.1 ⁵	0.1
K ⁺	0.086	0.048	0.083	0.076 ⁹
Rb ⁺	<0.012	—	0.025	—
Cs ⁺	<0.013	—	0.016	—
TMA	<0.005	<0.008	—	—

TABLE 14.4 Permeability Ratios, P_X/P_{Ca} , for L-Type Ca Channels^a

Ion	P_X/P_{Ca}	Ion	P_X/P_{Ca}
Ca ²⁺	1.0	Li ⁺	1/424
Sr ²⁺	0.67	Na ⁺	1/1170
Ba ²⁺	0.40	K ⁺	1/3000
		Cs ⁺	1/4200

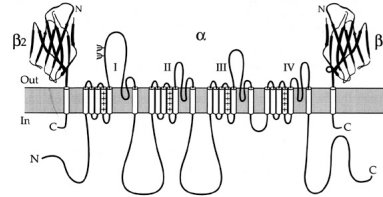
TABLE 14.3 Permeability Ratios, P_X/P_{K} , for Several Types of K Channels^a

Ion	Delayed rectifier			Inward rectifier	M current	BK K(Ca)	SK K(Ca)
	Frog node ¹	Frog muscle ²	Snail neuron ³	Starfish egg ⁴	Frog neuron ⁵	Rat muscle ⁶	Rat chromaffin ⁷
K ⁺	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Rb ⁺	0.91	0.95	0.74	0.35	0.94	0.67	0.81
Cs ⁺	<0.077	<0.11	0.18	<0.03	0.10	<0.05	0.16
Li ⁺	<0.018	<0.02	0.09	—	<0.004	<0.02	<0.005
Na ⁺	<0.010	<0.03	0.07	<0.03	<0.004	<0.01	<0.005

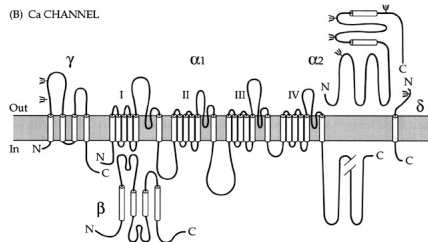
Tables from Hille, 2001

Voltage-gated cation channels consist of four α subunits, each of which has 6 transmembrane segments and a **pore loop**. In sodium and calcium channels, the four subunits are part of the same molecule. In potassium channels, they are different molecules. Also shown are β and γ subunits, separate molecules that bind to the channel and change its properties.

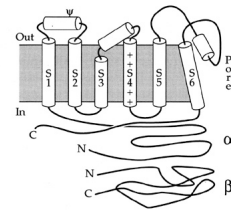
(A) Na CHANNEL



(B) Ca CHANNEL



(C) ONE QUARTER OF A K CHANNEL

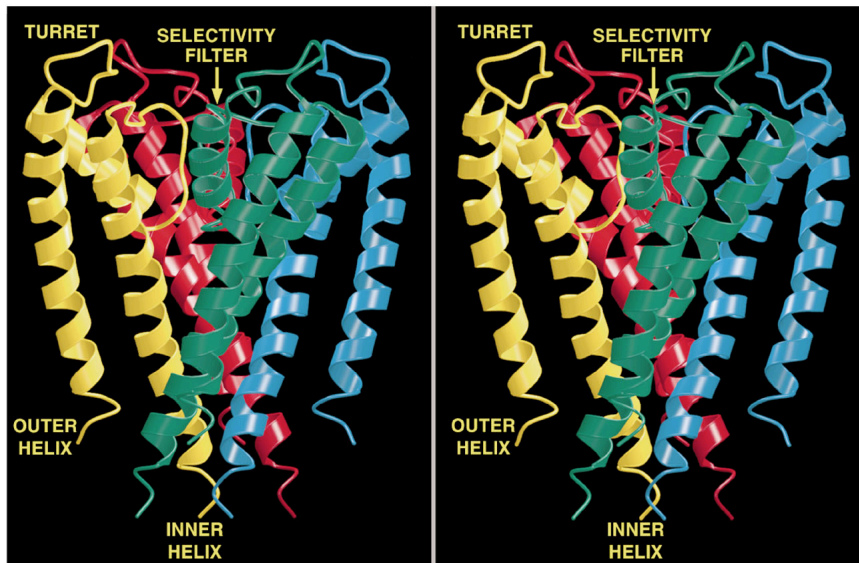


The resulting channel has four-fold symmetry



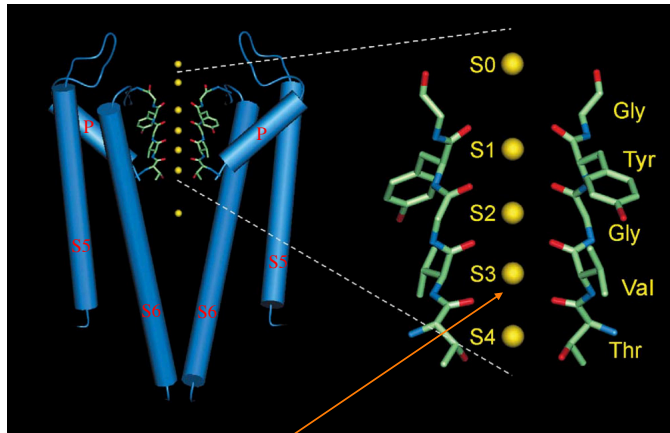
(Hille, 2001)

The structure of potassium channels has been inferred from the KcsA channel, a bacterial K channel having only the S5, S6, and P domains. The pore is formed by the S6 and P domains.



(Doyle et al, *Science* 280:69, 1998)

The **KcsA selectivity filter** consists of five amino acids (TVGYG) on the S6-P connector. The potassium ions (yellow balls) interact with the peptide backbone carbonyl oxygens (small red balls), not the side chains. There are four stable positions for K⁺ ions (S1-S4), plus a fifth, entry, position (S0). Only two are occupied at a time, because of electrostatic interaction among the K⁺s. **Selectivity** is determined by the properties of K⁺ ion interaction with this structure.



Note that the ions are in **single file**. This fact is consistent with a number of previous biophysical observations

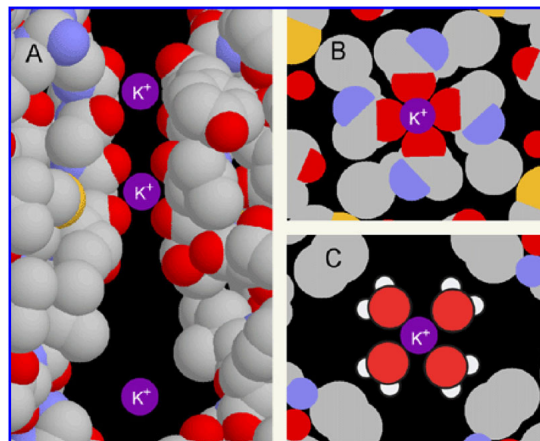
Sansom et al. 2002)

How might the KcsA selectivity filter work?

Potassium ions (dehydrated) are stabilized in the pore region (A) by negatively charged carbonyl groups from the protein making up the wall of the selectivity filter.

Presumably, the K⁺ ions “just fit” into the cross section of the pore (B). The electrostatic binding between the K⁺ and the carbonyls replaces the H-bonding in the aqueous environment, facilitating entry of K⁺ into the channel.

In the cavity of the KcsA channel, there is room for the potassium ions to carry a hydration shell, facilitating transport of ions in and out of the channel on the cytoplasmic side.



At the level of thr 75

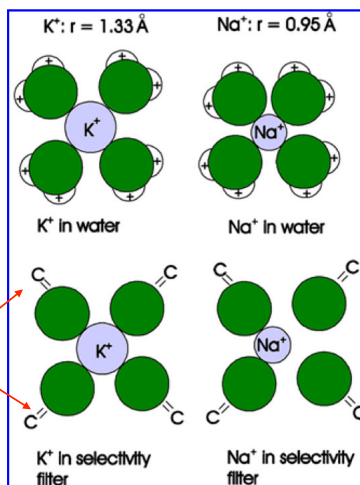
In the aqueous cavity

Armstrong, 2003

By contrast, Na⁺ ions, which have a smaller ionic radius, do not bind efficiently to all four carbonyls, as shown in the schematic cross sections at right.

Because the binding energy varies inversely with the distance between charges, Na is less stabilized in the selectivity filter than K, and is less likely to escape from an aqueous hydration shell into the pore.

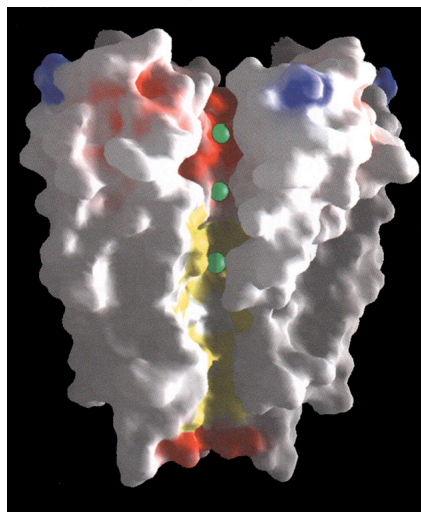
Interactions with surrounding moieties stiffen the selectivity filter so it can't collapse on the Na⁺ ion



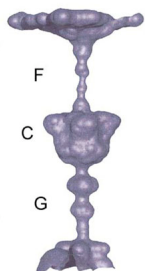
Armstrong, 2003

At right is a space-filling model of the KcsA channel, showing the pore. Ions (green balls) tend to occupy three sites in the channel, two (of the four spaces) in the **selectivity filter** and one in a **pool of water** in the center of the channel. Note the negative charges (red) at the two ends of the pore, which attract ions to the channel's entrance. Subsequently, it has been shown that the hydrophobic (yellow) narrow spot on the cytoplasmic side of the channel is the **gate**.

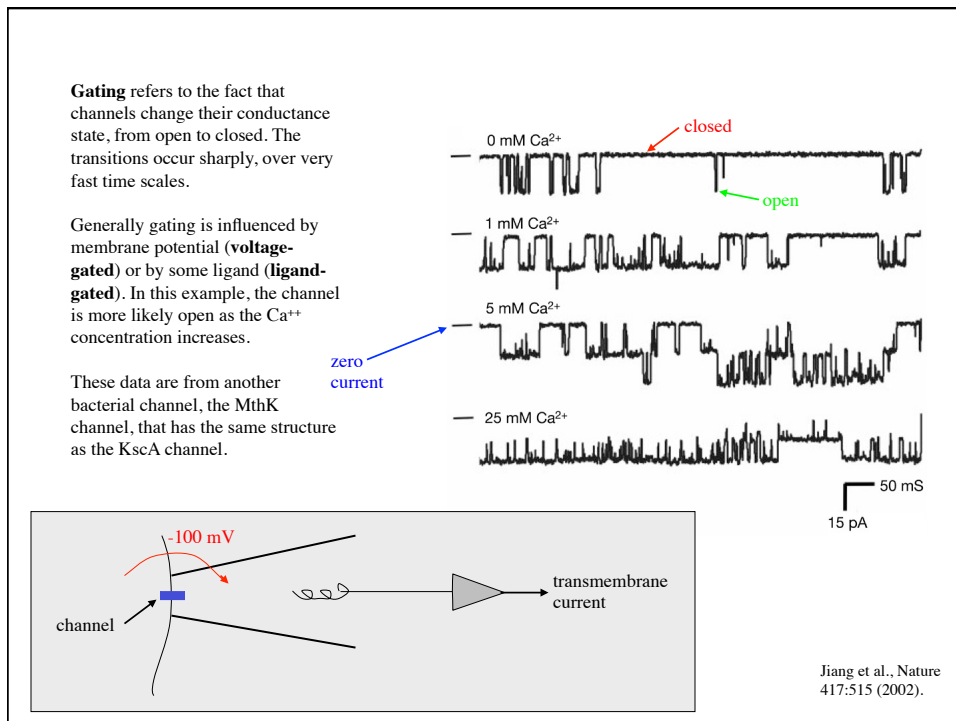
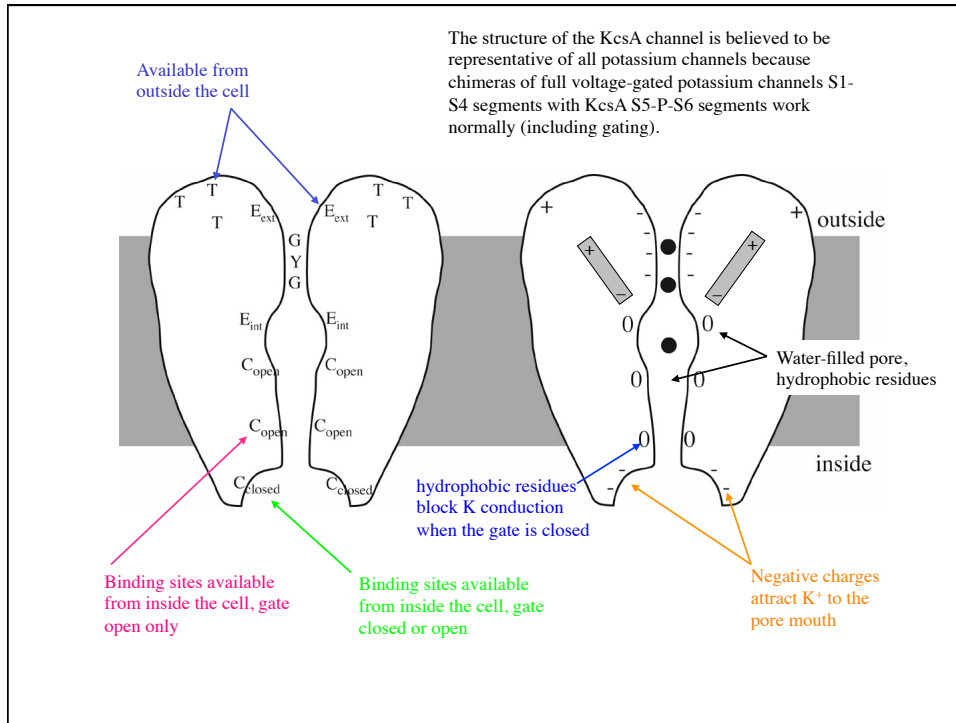
(Doyle et al, *Science* 280:69, 1998)



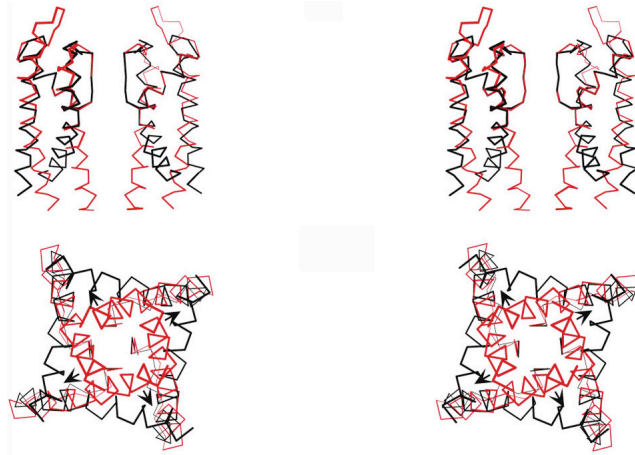
red - charge; blue + charge; yellow hydrophobic



Sansom et al. 2002)

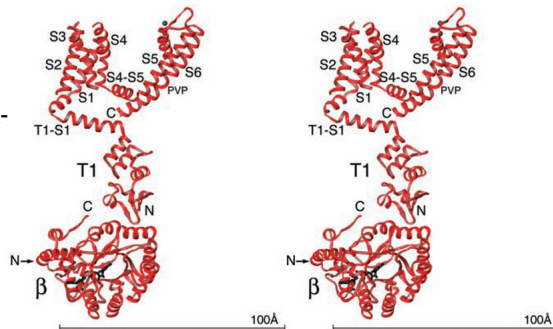


For the KcsA-like potassium channels, the gate opens by a splaying of the S5 and S6 domains, thus opening the pore at the inner side of the membrane. Below the KcsA channel (red) is shown in comparison to a similar bacterial channel, MthK (black), which is gated open by calcium. The S6 domain hinges at a glycine residue at the point shown.



Jiang et al., Nature 417:523, 2002.

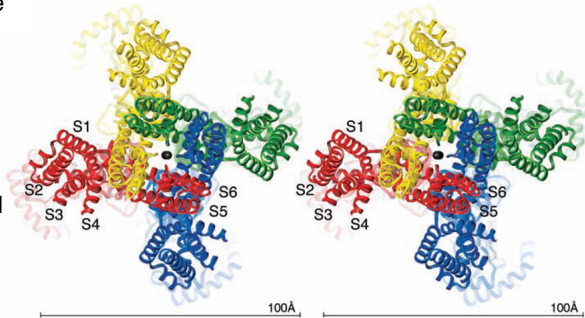
Structure of a Kv1.2 potassium channel, with a modulatory β subunit (an A-channel with N-terminal inactivation). Note the position of the S4 voltage sensor and the S5-S6 pore forming domains. In this case the channel is open.



Top: side view of one of the 4 subunits of the channel.

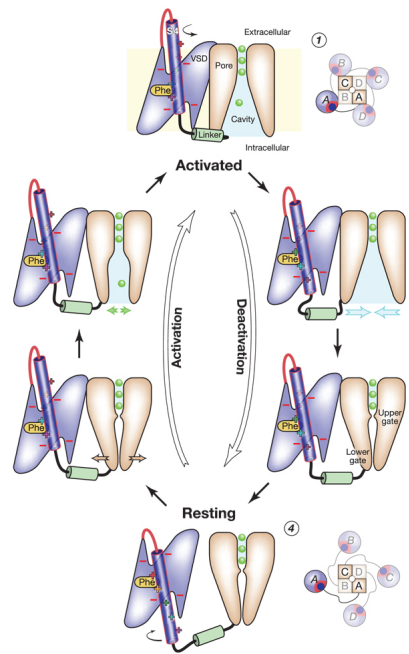
Bottom: membrane view of the whole transmembrane domain of the channel.

Note the location of S5 and S6 shifted 90° w.r.t. the location of S1-4.



Long et al. 2005a

Voltage-dependent gating in the Kv1.2 channel is driven by a motion in the membrane of the (- charged) S4 domain as shown. The linker between S4 and S5 drives the pore open and closed

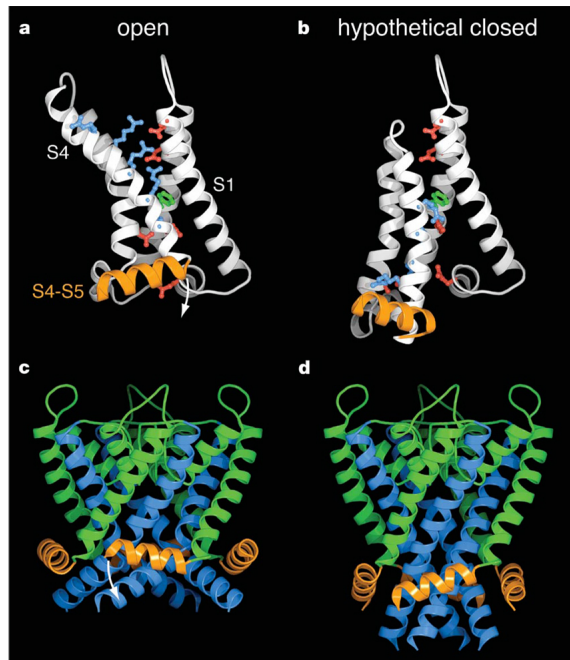


Jensen et al. 2012

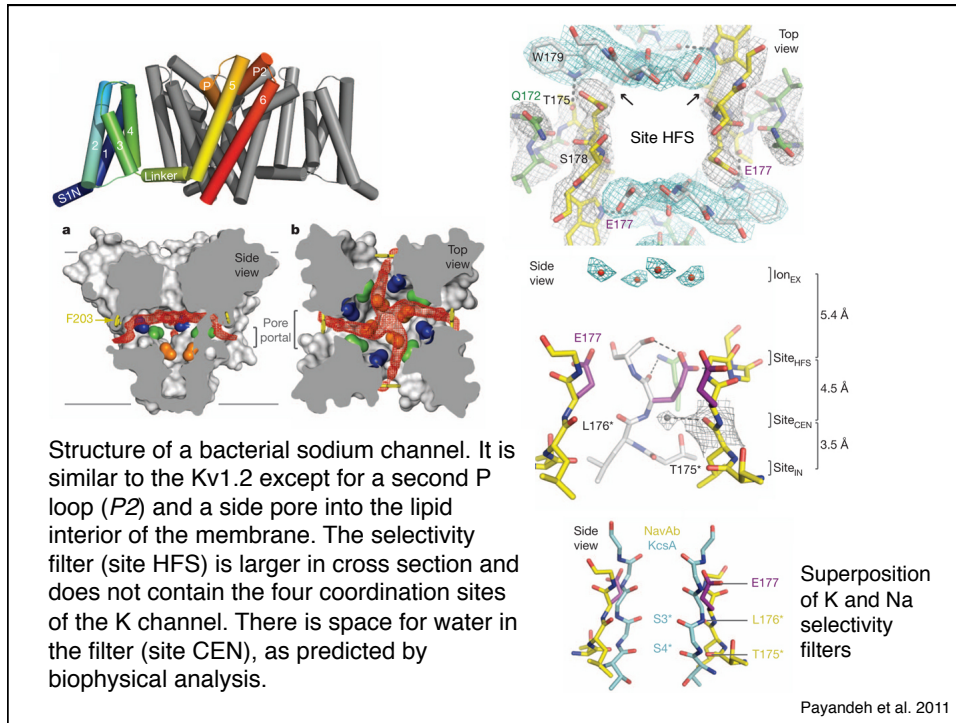
At top is the motion of the voltage sensor (S4). Blue are the + charges. Red are - charges on S1 that help to stabilize S4. (view from the pore)

Note the vertical movement of S4 and the change in orientation of the S4-S5 linker.

At bottom is the motion of the pore domain as the S4-S5 linker (orange) changes orientation. The S6 helices (blue) splay out when the channel opens and are presumed to be roughly straight when the channel closes.



Long et al. 2007



The structure of other channels can be quite different.

The stereo pairs at right show a type of **chloride channel** which consists of two channels in parallel.

Note that the structure is completely different from the voltage-gated cation channels discussed previously.

The channel is voltage-gated, presumably by electrostatic attraction of Cl⁻ ions into the channel where they displace a glu residue that blocks the extracellular access to the pore.

Dutzler et al. Nature 415:287 (2002)

Cl⁻ moves between two pool of water that extend into the channel. E148 is the glutamate that forms the channels gate.

In between, the ion is stabilized by the dipole fields of three alpha helices . . .

. . . and by electrostatic interactions with polar residues and the peptide bonds of the protein backbone. The stereo pair shows a Cl⁻ ion (red ball) making electrostatic interactions (dashed white lines) with several parts of the molecule.

Dutzler et al. Nature 415:287 (2002)