

Biological membranes and ion channels

Reading:

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

Doyle et al. The Structure of the Potassium Channel: Molecular Basis of K₁ Conduction and Selectivity. *Science* 280:70-77 (1998).

Miyazawa et al. Structure and gating mechanism of the NAc 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.

Ion	Frog node ^b	Frog muscle ^b	Squid axon ^c	Mrixicle axon ^d
H ⁺	25 ²	—	>2 ^e	—
Na ⁺	1.0	1.0	1.0	1.0
Li ⁺	0.93	0.96	1.1	0.94 ^f
Ca ²⁺	<0.11	<0.09	0.1 ^g	0.1
K ⁺	0.006	0.048	0.085	0.076 ^h
Rb ⁺	<0.02	—	0.025	—
Cs ⁺	<0.013	—	0.016	—
TMA	<0.005	<0.008	—	—

Ion	Delayed rectifier			Inward rectifier			M	BK	SK	K(Ca)
	Frog node ⁱ	Frog muscle ^j	Snail neurons ^k	Starfish eggs ^l	Frog neurons ^m	Rat muscle ⁿ				
K ⁺	1.0	1.0	1.0	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	<0.04	0.09	—	<0.008	<0.02	<0.005	—	—	—
Na ⁺	<0.010	<0.03	0.07	<0.005	<0.004	<0.01	<0.005	—	—	—

Ion	$P_x/P_{Ca^{2+}}$	Ion	$P_x/P_{Ca^{2+}}$
Ca ²⁺	1.0	Li ⁺	1/424
Se ²⁻	0.67	Na ⁺	1/1170
Ba ²⁺	0.40	K ⁺	1/3000
Cs ⁺	1/4200	—	—

Tables from Hille, 2001

Ion channels are protein molecules with extracellular and intracellular domains and transmembrane domains. The **nicotinic acetylcholine receptor channel** subunit is diagrammed below. Note the **transmembrane segments**, denoted M1 - M4.

Evidence for channel structure:

1. Hydrophobic plots
2. Binding sites for various ligands

The diagram illustrates the structure of the nAChR channel subunit. It features an extracellular domain with a glycosylation site (N141W) and an intracellular domain with a sulfhydryl group (S119T). The transmembrane domain is shown as a cylinder with four alpha-helices labeled M1 through M4. A hydrophobicity plot shows the hydrophobicity of each residue in the α -subunit across the 400 residues. Key residues are labeled: S119, N141W, C126, C142, Glycosylation, A121, V261, T277, T281, T287, M343, T296, I409, A427, M44, and Ab G437 COOH. Below the plot, a schematic shows the five-fold symmetry of the pentameric complex, with M2 subunits forming the pore. A legend indicates: Parts of backbone, NH₂, COOH, Glycosylation, S119T, N141W, C126, C142, Glycosylation, A121, V261, T277, T281, T287, M343, T296, I409, A427, M44, Ab G437 COOH, Long of pore wall, 12α E⁻, Cap, and Ab.

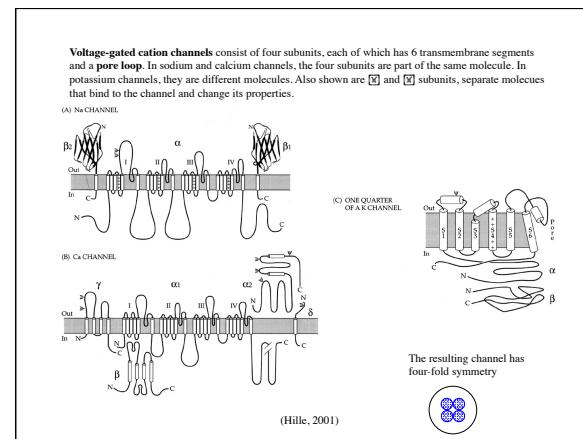
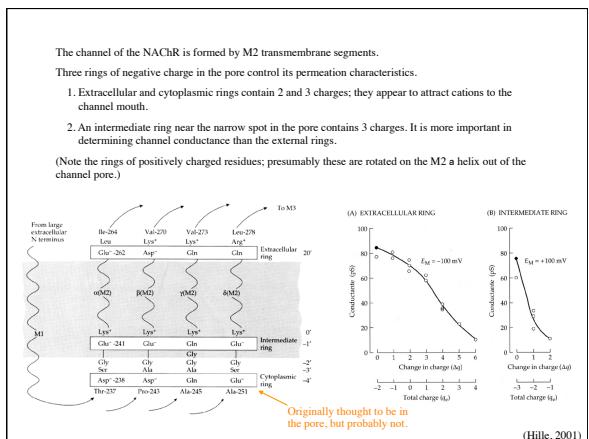
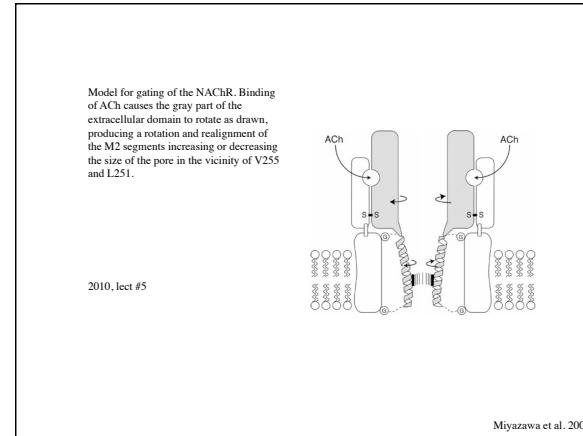
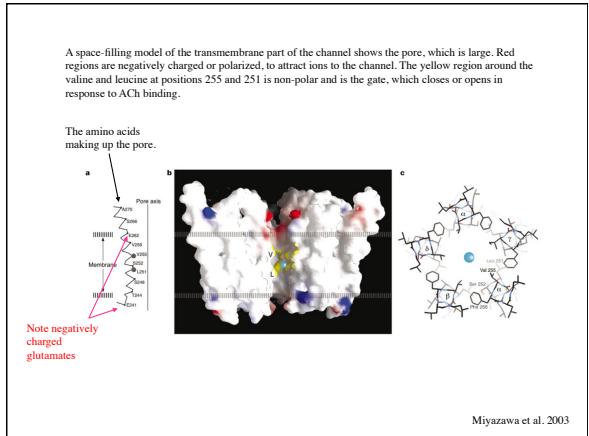
Hille, 2001

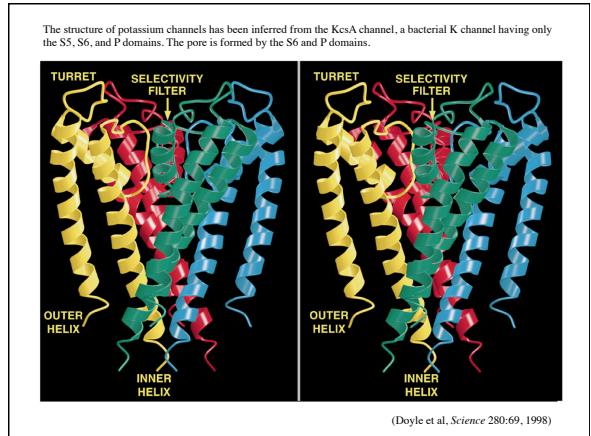
Using electron diffraction the structure of the NAcR was determined at 4 Å resolution. The M2 segments form a loose pore (blue) with substantial aqueous space in the membrane (between blue and red). The large extracellular domain contains the ACh binding site (green).

The figure shows three panels (a, b, c) of electron density maps. Panel (a) is a 3D surface plot of the density, with axes for 0 to 60 Å in the vertical direction and 0 to 30 Å in the horizontal directions. Panel (b) shows a schematic of the pentameric structure with individual subunits labeled M1 through M5 and their respective helical regions (α, β, δ, γ, δ). The extracellular domain is green, the membrane region is red, and the pore region is blue. Panel (c) is another view of the structure, highlighting the ACh binding site in green.

The M1-M4 domains are alpha helices, but the extracellular domain is mostly beta sheets.

Miyazawa et al., 2003



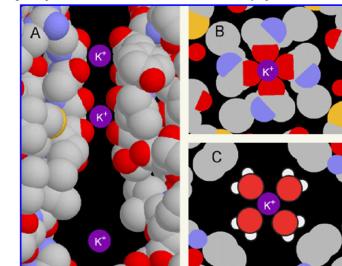


How might the KcsA selectivity filter work?

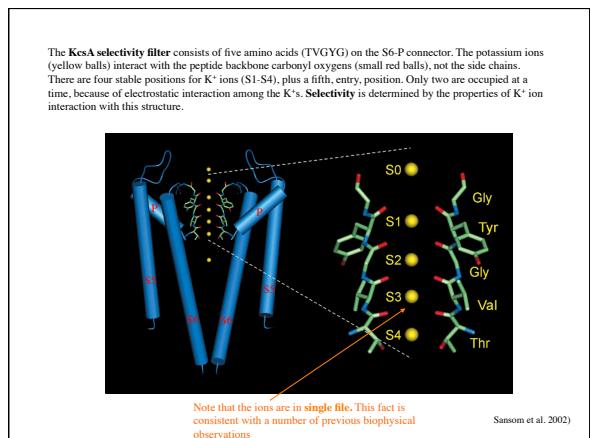
Potassium ions (dehydrated) are stabilized in the pore region (A) by negatively charged carbonyl groups from the protein making up the wall of the selectivity filter.

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.

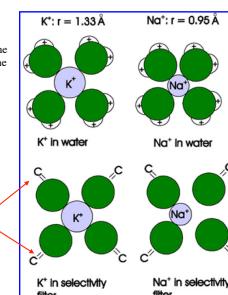


Armstrong, 2003



By contrast, Na⁺ ions, which have a smaller ion 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.



Armstrong, 2003

