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The structure of the potassium channel: molecular basis of K+ conduction and selectivity.

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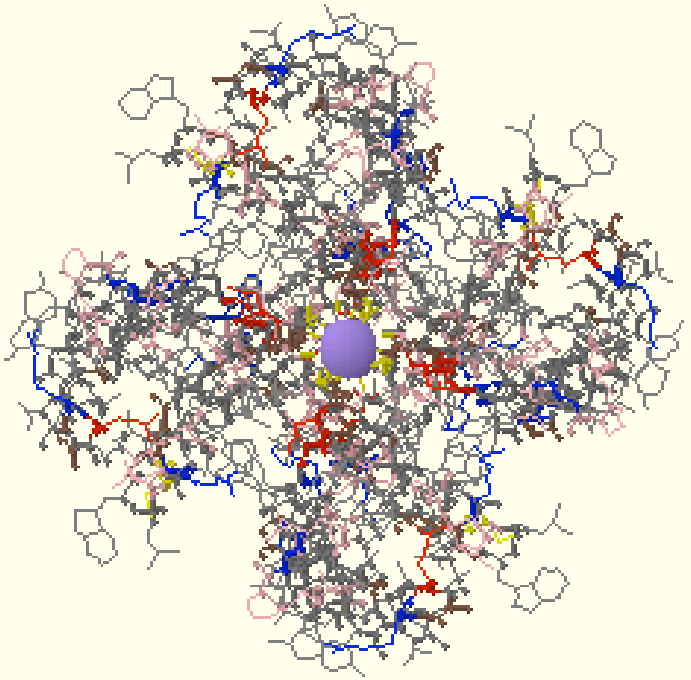
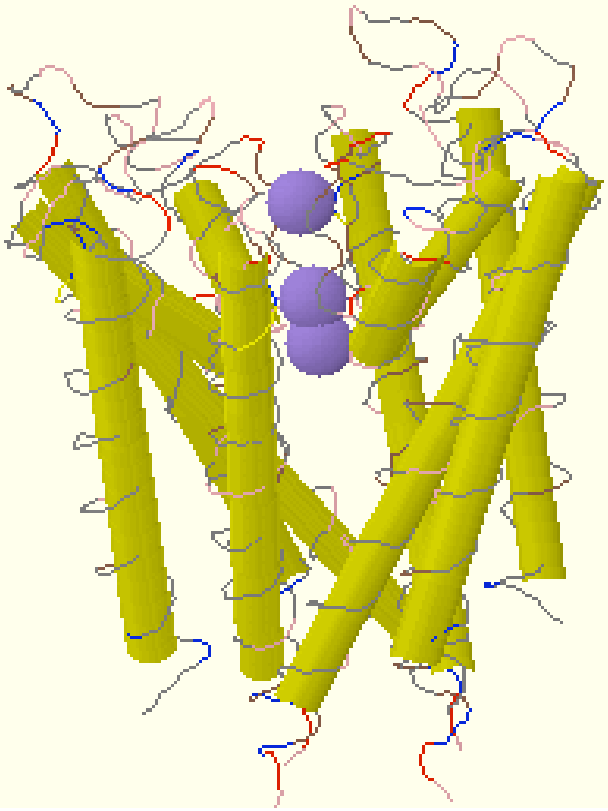


The potassium channel from Streptomyces lividans is an integral membrane protein with sequence similarity to all known K+ channels, particularly in the pore region. X-ray analysis with data to 3.2 angstroms reveals that four identical subunits create an inverted teepee, or cone, cradling the selectivity filter of the pore in its outer end. The narrow selectivity filter is only 12



angstroms long, whereas the remainder of the pore is wider and lined with hydrophobic amino acids. A large water-filled cavity and helix dipoles are positioned so as to overcome electrostatic destabilization of an ion in the pore at the center of the bilayer. Main chain carbonyl oxygen atoms from the K+ channel signature sequence line the selectivity filter, which is held open by structural constraints to coordinate K+ ions but not smaller Na+ ions. The selectivity filter contains two K+ ions about 7.5 angstroms apart. This configuration promotes ion conduction by exploiting electrostatic repulsive forces to overcome attractive forces between K+ ions and the selectivity filter. The architecture of the pore establishes the physical principles underlying selective K+ conduction.

TABLE 3. IONIC PERMEABILITY RATIOS, P_X/P_K, FOR SEVERAL TYPES OF POTASSIUM CHANNELS

	Delayed rectifier			Inward rectifier	K(Ca)	Light-activated
Ion	Frog node[1]	Frog muscle[2]	Snail neuron[3]	Starfish egg[4]	*Aplysia* neuron[5]	Scallop eye[5]
Tl^+	2.3	—	1.29	1.5	0.99	1.07
K^+	1.0	1.0	1.0	1.0	1.0	1.0
Rb^+	0.91	0.95	0.74	0.35	0.69	0.71
NH_4^+	0.13	—	0.15	0.035	0.11	0.11
Cs^+	<0.077	<0.11	0.18	<0.03	0.03	<0.023
Li^+	<0.018	<0.02	0.09	—	<0.011	<0.013
Na^+	<0.010	<0.03	0.07	<0.03	<0.009	<0.008
$H_2NNH_3^+$	<0.029	—	—	—	<0.04	<0.06
Methylammonium	<0.021	—	—	—	<0.04	<0.027

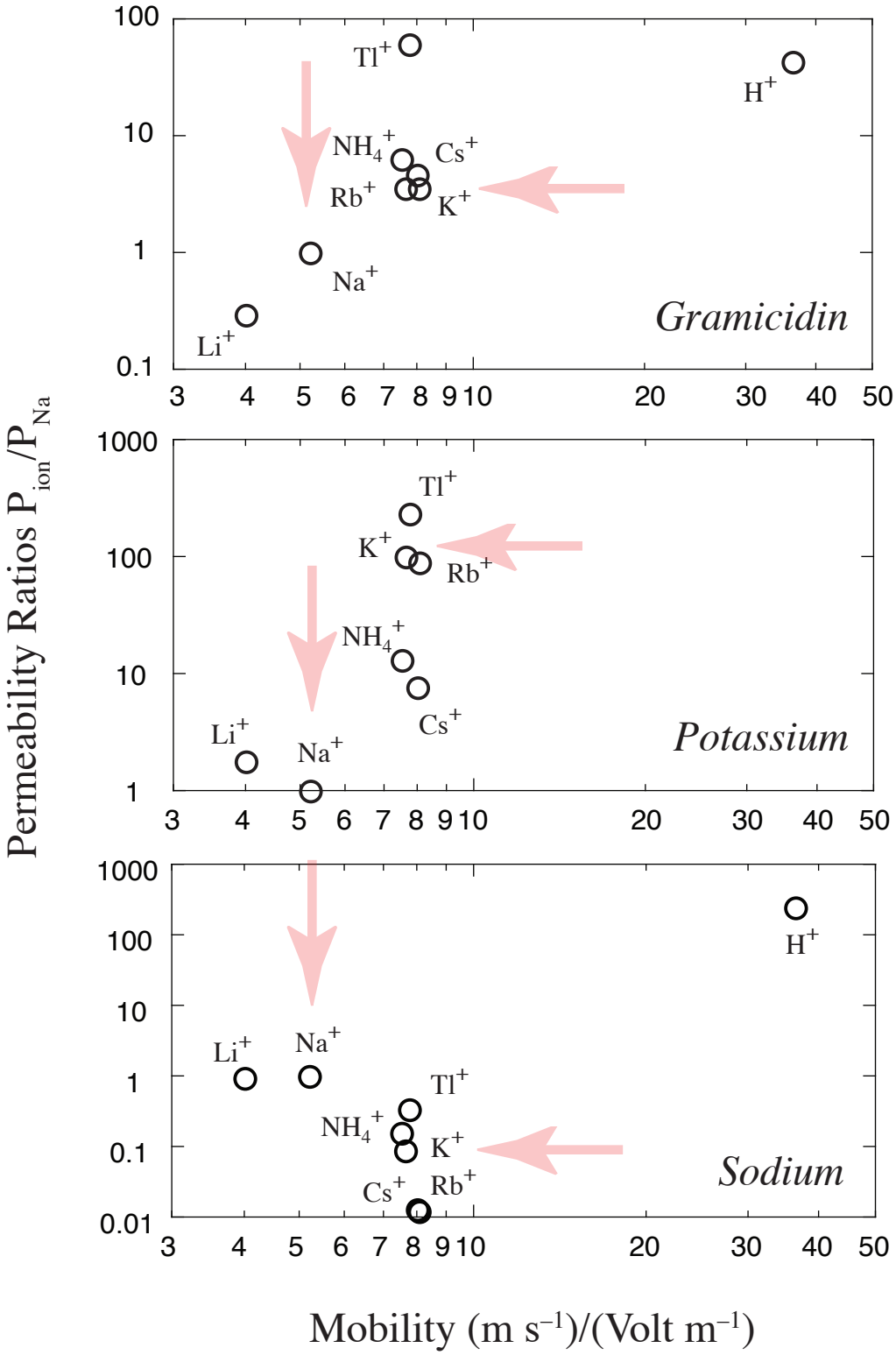
Permeability ratios calculated from reversal potentials using Equation 1–13, 10–14, or 10–15.
References: [1]Hille (1973), [2]Gay and Stanfield (1978), [3]Reuter and Stevens (1980), [4]Hagiwara and Takahashi (1974a), [5]Gorman et al., (1982).

FROM: Hille. B Ionic Channels of Excitable Membranes

TABLE 2. IONIC PERMEABILITY RATIOS, P_X/P_{Na}, FOR Na CHANNELS

Ion	Frog node[1]	Frog muscle[2]	Squid axon[3]	*Myxicola* axon[4]
H^+	252[5]	—	>2[6]	—
Na^+	1.0	1.0	1.0	1.0
$HONH_3^+$	0.94	0.94	—	—
Li^+	0.93	0.96	1.1	0.949
$H_2NNH_3^+$	0.59	0.31	—	0.85
Tl^+	0.33	—	—	—
NH_4^+	0.16	0.11	0.27[7]	0.20
Formamidinium	0.14	—	—	0.13
Guanidinium	0.13	0.093	—	0.17
Hydroxyguanidinium	0.12	—	—	—
Ca^{2+}	<0.11	<0.093	0.1[8]	0.1
K^+	0.086	0.048	0.083	0.076[9]
Aminoguanidinium	0.06	0.031	-	0.13
Rb^+	<0.012	—	0.025	—
Cs^+	<0.013	—	0.016	—
Methylammonium	<0.007	<0.009	—	—
TMA	<0.005	<0.008	—	—

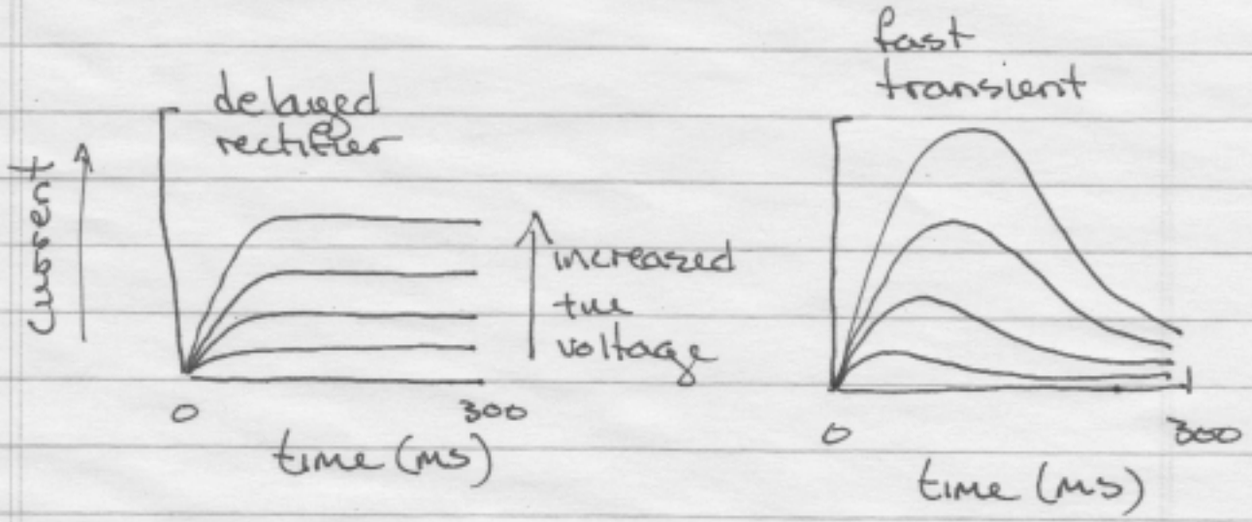
Permeability ratios calculated from reversal potentials using Equation 1–13, 10–15, or 10–16.
References: [1]Hille (1971, 1972), except where noted, [2]Campbell (1976), [3]Chandler and Meves (1965), except where noted, [4]Binstock (1976), except where noted, [5]Mozhayeva and Naumov (1983), [6]Begenisich and Danko (1983), [7]Binstock and Lecar (1969), [8]Meves and Vogel (1973), [9]Ebert and Goldman (1976).


Permeability Ratios P_{ion}/P_{Na}
Mobility (m s^{-1})/(Volt m^{-1})
Gramicidin
Potassium
Sodium
Tl^+
H^+
NH_4^+
Cs^+
Rb^+
K^+
Na^+
Li^+
100
10
1
0.1
1000
0.01
3
4
5
6
7
8
9
10
20
30
40
50

In addition, gating is quite variable:

Voltage-gating [delayed rectifier / fast transient / inward rectifier]

Ca^{2+}-activation
light-activation
ATP-activation
→ ligand-gated.



(the inward rectifier behaves like the delayed rectifier except increased -ve voltage increases inward current).

Now, there is fairly high homology between various K^+ channels, especially in a region known as the selectivity filter.
In fact, this homology holds for the procaryotic K^+ channel, KcsA, isolated from Streptomyces lividans.

x-ray crystallographic determination of the channel structure of the procaryotic channel represented a significant breakthrough in understanding the mechanism of selectivity.

→ The selectivity motif:

$\begin{matrix} T \\ S \end{matrix}$ TVGYGD

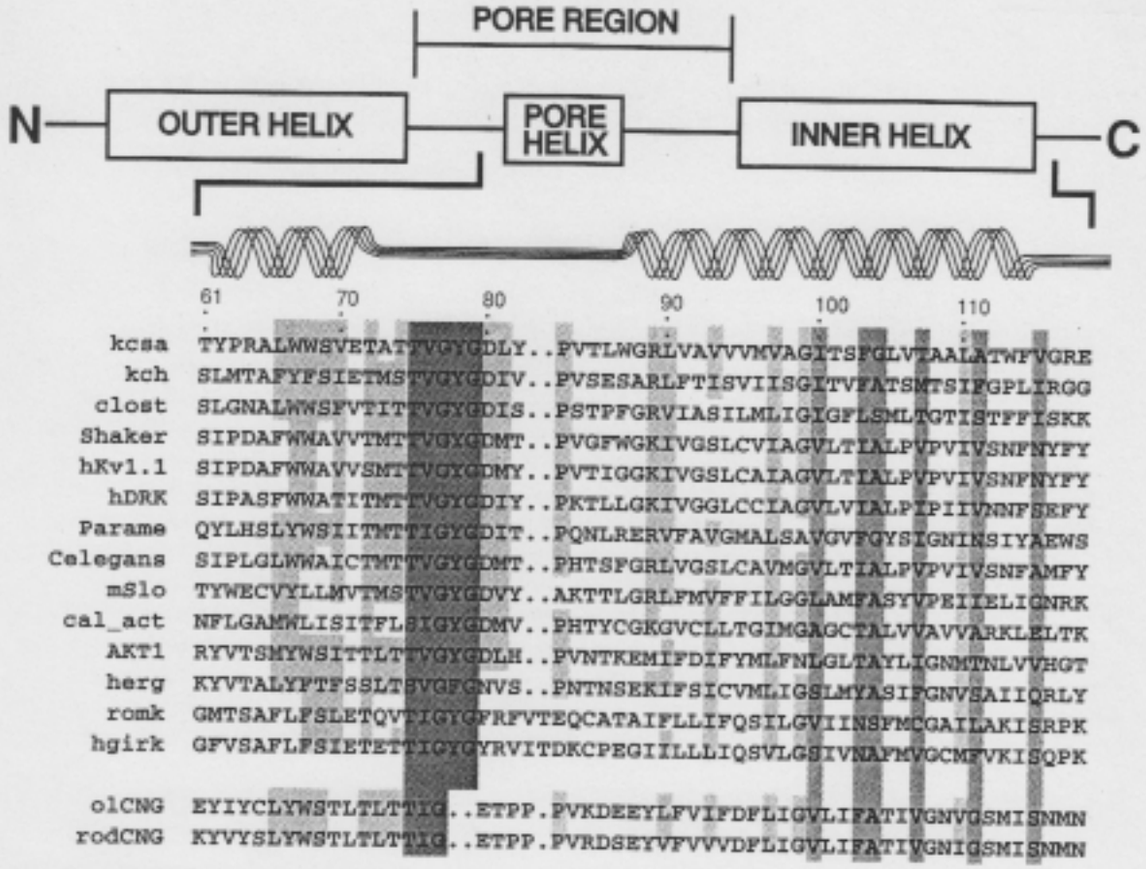


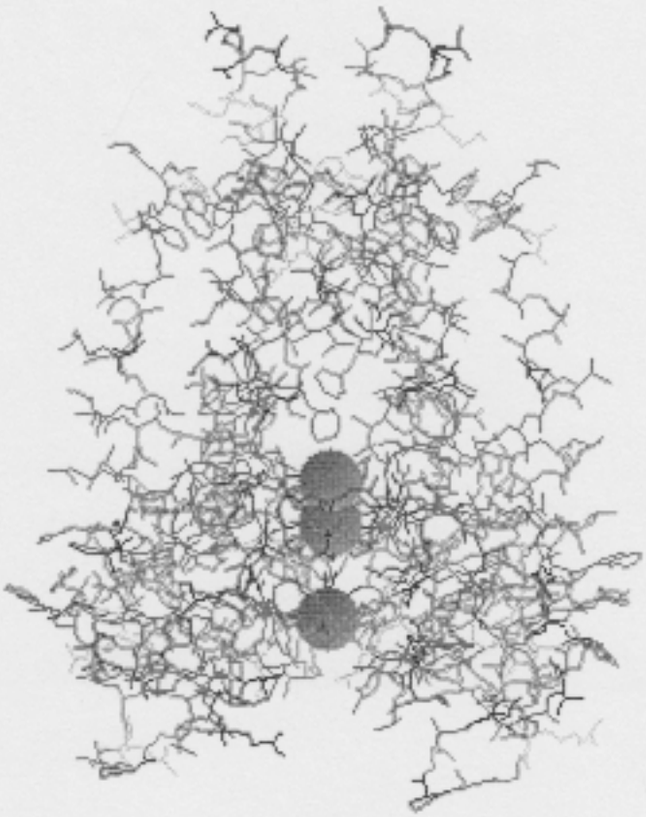
Fig. 1. Sequence alignment of selected K^+ channels and cyclic nucleotide-gated channels. The numbering and secondary structural elements for the *Streptomyces lividans* K^+ channel (KcsA) is given above the sequences. Selectivity filter, red; lining of the cavity and inner pore, blue; residues in which the nature of the side chain is preserved (>50% similarity), grey. The sequences are: KcsA, *Streptomyces lividans*, accession number (acc) PIR S60172; kch, *Escherichia coli*, acc GenBank U24203; clost, *Clostridium acetobutylicum* (Genome Therapeutics Corp.); Shaker, *Drosophila melanogaster*, acc PIR S00479; hKv1.1, *Homo sapiens*, acc Swissprot Q09470; hDRK, *H. sapiens*, acc PIR S31761; Parame, *Paramecium tetraaurelia*, acc GenBank U19908; Celegans, *Caenorhabditis elegans*, acc GenBank AF005246; mSlo, *Mus musculus*, acc PIR A48206; cal_act, *H. sapiens*, acc GenBank AF031815; AKT1, *Arabidopsis thaliana*, acc PIR S62694; herg, *H. sapiens*, acc PIR I38465; romk, *Rattus norvegicus*, acc Swissprot P35560; hgirk, *H. sapiens*, acc GenBank S78684; olCNG, *H. sapiens*, acc Swissprot Q16280; rodCNG, *H. sapiens*, acc PIR A42161. The last two sequences, separate from the rest, are from cyclic nucleotide–gated channels, which are not K^+ selective.

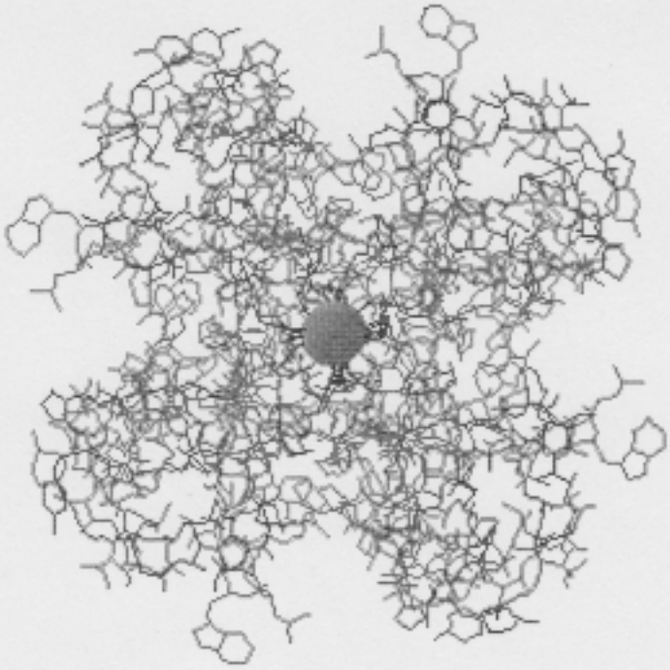
The first structural portrait shows a wire frame representation of the channel structure.

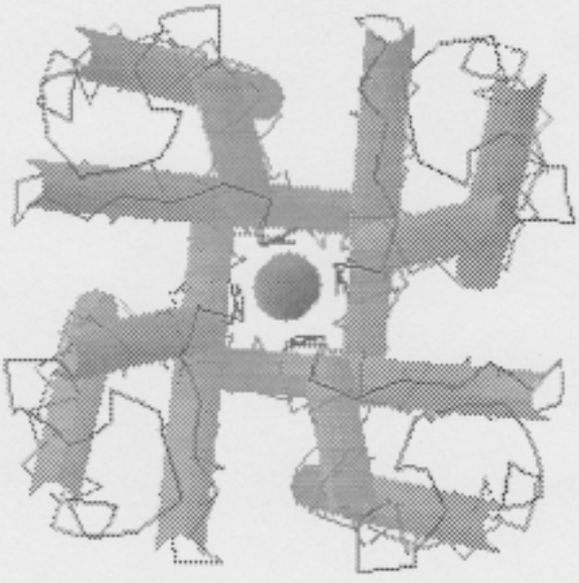
The level of complexity is quite high.

A simpler representation that focuses on the major structural motifs is shown in the next overhead.

The clearest representation comes directly from the paper.







K^+ Channel Structure
- K^+ ion selectivity.

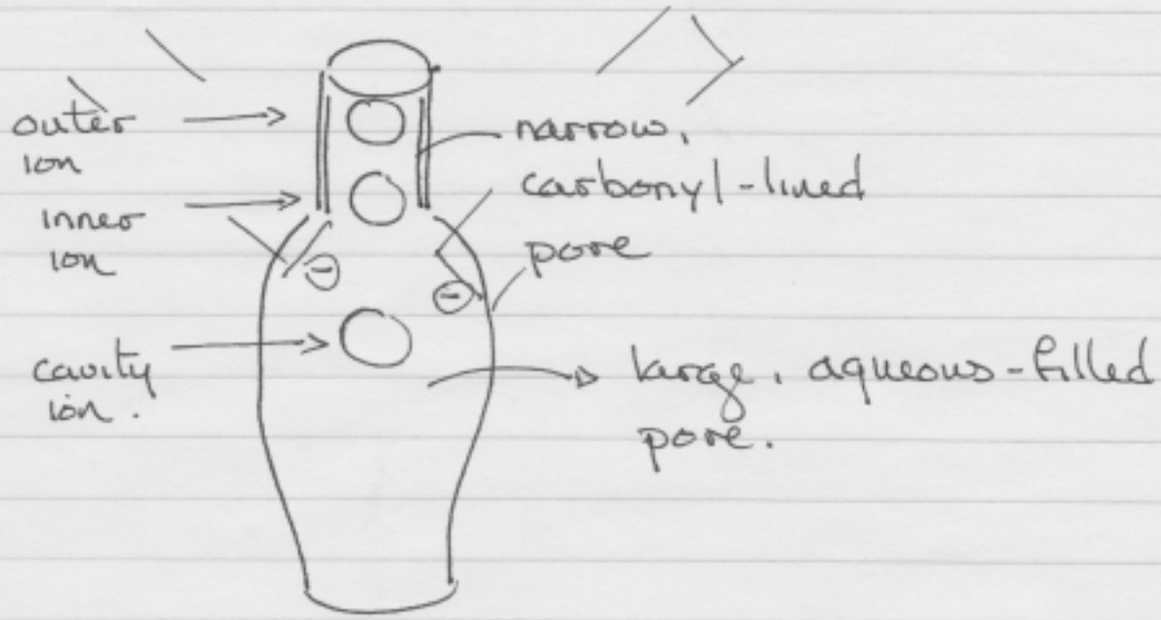
The K^+ channel represents a remarkable increase in functional complexity compared to the gramicidin channel.

In the gramicidin channel, ion selectivity depends solely on the size of the pore. Gating involves a simple intercalation into the membrane followed by the 'coupling' of two monomers end-to-end to form the functional dimer transmembrane pore.

By contrast, the selectivity of the K^+ channel does not match expectations based on ionic mobilities:

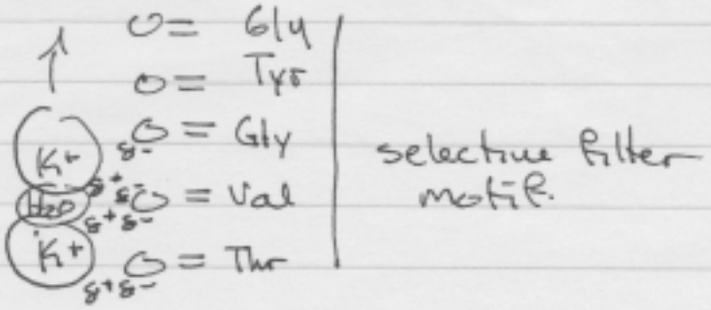
Ion	Gramicidin P_{ion}/P_{Na}	K^+ channel P_{ion}/P_{Na}	mobility	Na^+ channel P_{ion}/P_{Na}
Tl^+	60.0	230	7.74	0.33
H^+	43.0	—	36.25	252
NH_4^+	6.3	13	7.52	0.16
Cs^+	4.6	7.7	8.01	0.013
Rb^+	3.6	91	8.06	0.012
K^+	3.5	100	7.62	0.086
Na^+	1.0	1	5.19	1.0
Li^+	0.29	1.8	4.01	0.93

The general structure of the pore:



The ions were "mapped" using diffraction patterns in the absence/presence of various ions

The ions in the ~~stee~~ se narrow pore structure are completely dehydrated - the "naked" ion is coordinated with oxygens



This allows a 'best-fit' which would explicitly exclude the smaller 'naked' Na^+ ion.