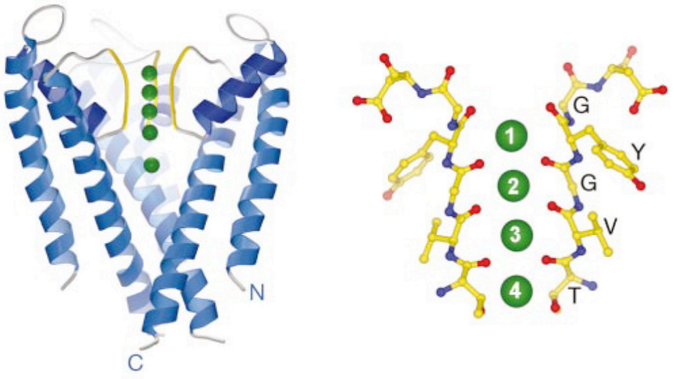
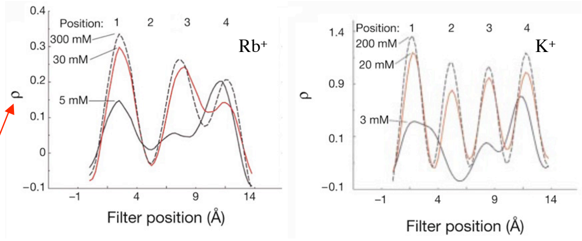
The structure of the KcsA channel selectivity filter. The filter is formed by the amino-acid sequence TVGYG. The oxygen atoms of the amide bonds among these produce four stable binding sites (S1, S2, S3, S4). Potassium ions move in a single-file fashion along this chain of binding sites.



Morais-Cabral et al., 2001

X-ray diffraction studies show that both K⁺ and Rb⁺ ions tend to occupy the four positions identified in the structural study of the selectivity filter.

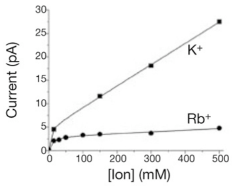
Note that K⁺ ions are seen in all four loci, but Rb⁺ ions only occupy two loci. Presumably this reflects optimization of the channel for K⁺ and explains the lower conductivity of the channel for Rb⁺



electron density

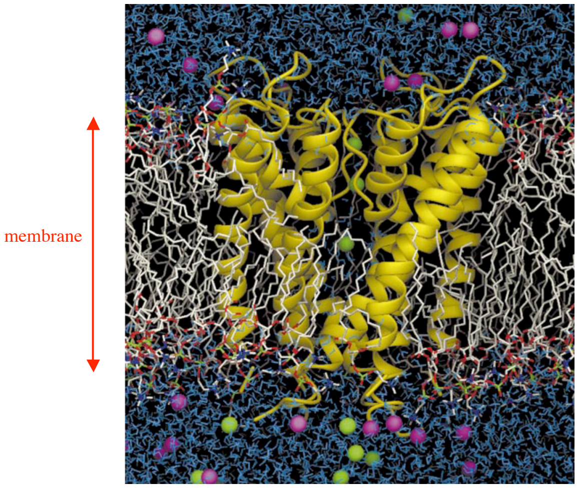
(Note that this doesn't mean that the channel normally contains 4 ions at a time!)

single-channel current



Morais-Cabral et al., 2001

A model of the KcsA channel in a small bit of membrane surrounded by a dilute ionic solution for molecular dynamics (MD) simulations



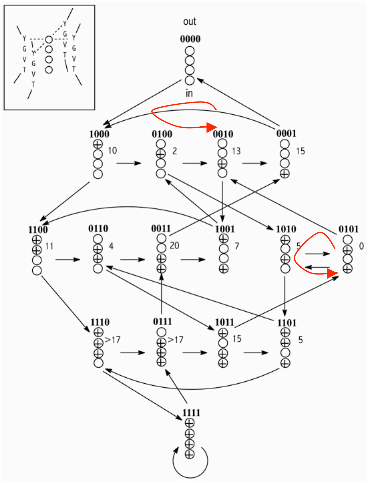
Bernéche & Roux, 2000

There are many possible states of occupancy of the selectivity filter, containing between 0 and 4 potassium ions.

The state diagram at right shows possible paths by which potassium ions could flow through the channel. Two examples are marked in red.

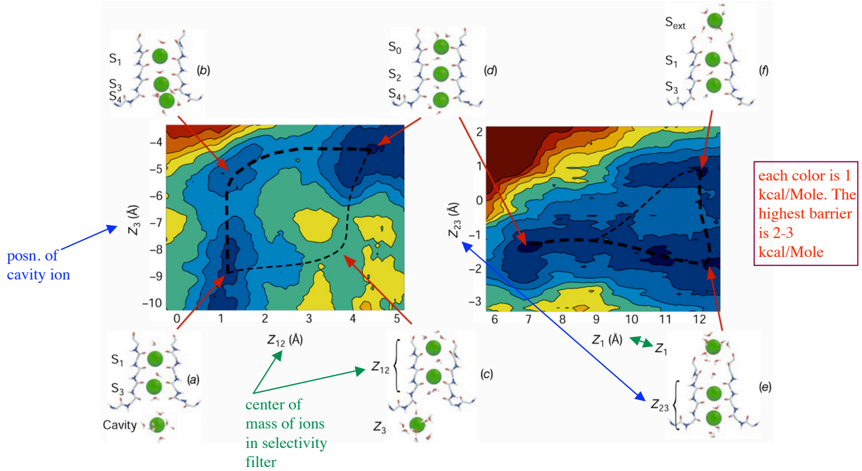
The numbers next to each state are estimates of the free energy of that state. The lowest free energies and the lowest-energy state sequence corresponding to permeation is 1010-->0101-->1010 etc.

The lowest free energy state is 0101, with two ions in the filter. 1010 is second lowest, with two exceptions



Åqvist and Luzhkov, 2000

With MDS, it is possible to compute the free energy of various configurations of the potassium ions in the selectivity filter (assuming 2 ions in the filter plus a third in the cavity). The minimum energy path is *a-b-d-f*.



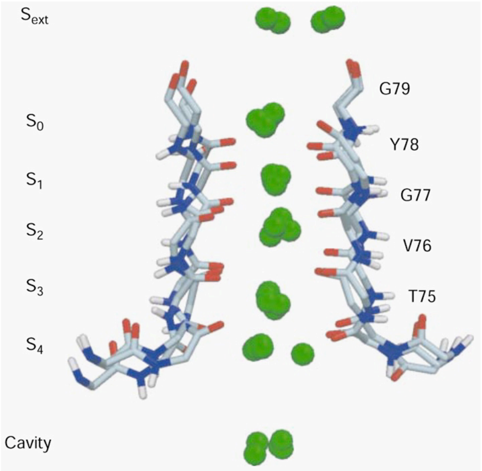
posn. of cavity ion

center of mass of ions in selectivity filter

each color is 1 kcal/Mole. The highest barrier is 2-3 kcal/Mole

Bernéche & Roux, 2000

The positions of the energy minima correspond to the ion sites inferred from the structure. Note the fluctuations in the positions of all parts of the system.

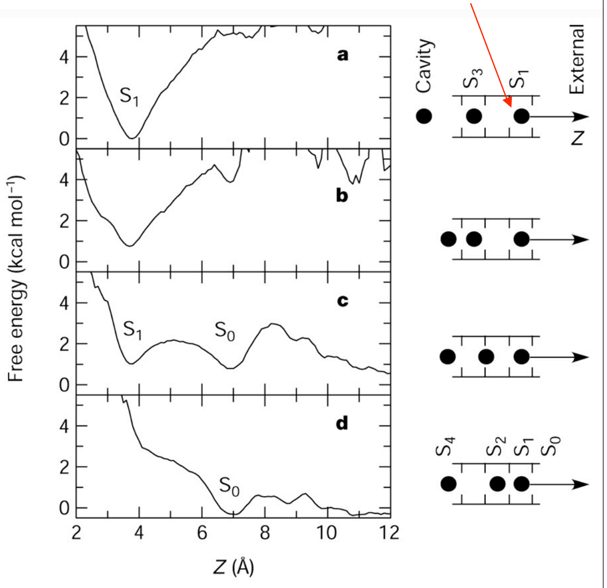


Bernéche & Roux, 2000

When ions are spaced as in the selectivity filter, there should be a repulsive energy corresponding to 10s of kcal/mole, much larger than the apparent energy barriers in this system. Presumably, this reflects shielding by the charges in the protein.

Ionic repulsion does affect flux through the channel, however. At right are energy diagrams for the ion in the S1 site for four configurations of two other ions in the channel (corresponding to the sequence *a-b-d-f* in the energy diagram). Electrostatic interactions with other ions changes the energy landscape for the index ion.

energy landscape for this ion



Bernéche & Roux, 2000

These are the results of a different calculation of the energy landscape, for two ions moving back and forth between the two favored positions.

The shape is different from the example shown previously, because ions outside the selectivity filter are not included, but the general result is similar.

Note that the barrier system is smooth, relative to models like the Hille sodium channel model, so that permeation is likely to be more of a diffusion process than a hopping-over-barriers process.

Åqvist and Luzhkov, 2000

Time history of K⁺ ion positions in a MD simulation of permeation through the K-channel selectivity filter

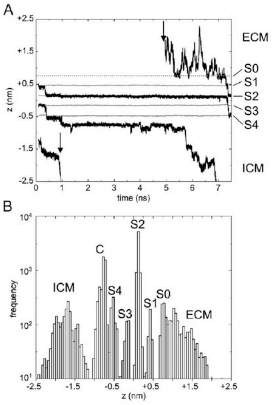


Fig. 4. Simulated movement of K^+ ions through the filter, from a 7 ns MD simulation of KcsA in a POPC bilayer (Shrivastava and Sansom, unpublished data). (A) K^+ ion trajectories projected onto the pore (z) axis, showing the z position of each ion as a function of time. The horizontal grey lines indicate the positions of the centres of sites S0 (dotted line) to S4. The initial configuration of ions in the filter is 01010. There is also a K^+ ion initially in the cavity; at the time indicated by the left-hand arrow, this exits from the pore. The right-hand arrow indicates the same K^+ ion, after exiting the simulation box at negative z and reentering (by virtue of periodic boundary conditions) at positive z. (B) Histogram of K^+ ion positions along the pore (z) axis for the same simulation as in (A). The peaks correspond to distinct 'sites' within the channel, namely S0 to S4, and the cavity (C). ICM and ECM are the intracellular and extracellular mouth regions, respectively.

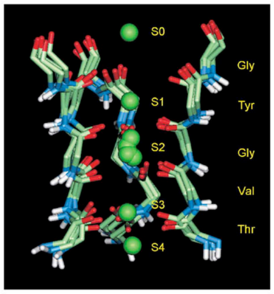


Fig. 5. Potassium ions in the selectivity filter as seen in the same simulation discussed in Fig. 4. Four snapshots from the simulation are superimposed, showing the filter regions of three of the four subunits, and the K^+ ions (green spheres) that occupy (at different times) sites S0 to S4.

Sansome et al., 2002

The following papers are the sources of the figures used in this lecture:

Åqvist, J. and Luzhkov V. Ion permeation mechanism of the potassium channel. Nature, 404:881-884.

Bernéch, S. and Roux, B. Energetics of ion conduction through the K⁺ channel. Nature, 414:73-77 (2001).

Morais-Cabral, J.H., Zhou, Y., and MacKinnon, R. Energetic optimization of ion conduction rate by the K⁺ selectivity filter. Nature 414:37-42 (2001).

Sansom, M.S.P., Shrivastavab, I.H., Bright, J.N., Tatec, J. Capener, C.E., Biggina, P.C. Potassium channels: structures, models, simulations. Biochimica et Biophysica Acta 1565 (2002) 294– 307