New and Notable

Subtle Shades of Permeability

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Na^+ and K^+ ions differ in diameter by only a few tenths of an Å, but that is enough for a channel to select one ion over the other by factors that can exceed 1000. Physiologists have been wondering how this can take place for several decades, and now that we are starting to see crystal structures, some answers are emerging. Before the crystal structure, we knew that ion permeation depended on the energetics of ions interacting with water versus the channel protein. We suspected, and in some cases knew, what some of the contributions were. They included dehydration of the permeating ion, image forces due to the different polarizabilities of the water and membrane, interactions with charged residues, and interactions with the dipoles of protein carbonyls and hydroxyls. The crystal structure of the KcsA K^+ channel showed that the right groups are in the right place for these various interactions, and revealed that α-helices were situated so that their large macrodipoles also enter into the equation (Doyle et al., 1998; Roux and MacKinnon, 1999).

Now we can ask two questions: How much does each specific interaction help an ion glide through a channel? How much does each interaction confer selectivity for one ion over another? Theoretical modeling can make a valuable contribution to both of these questions, but there are some daunting problems. Both long-range and short-range forces act on ions, and incorporating this into a force field of the entire protein makes energy computation very time consuming. Detailed force fields yield energies that can easily be off by >10 kT. The dielectric environment is highly inhomogeneous. How does one make reasonable estimates of the various energetic contributions to ion channel interactions without fully sampling an energy surface that has 50,000 dimensions?

A general strategy that holds promise for addressing these problems is to make judicious choices in selecting parts of the problem for detailed treatment, and resorting to reasonable coarse-grained representations for the other parts of the problem. Such ''microscopic-mesoscopic hybrid'' models have been developed recently by Chung et al. (1999, 2002) and Burykin et al. (2002), and have been very instructive in relating protein structure to ion permeation mechanisms. In this issue of the *Biophysical Journal*, Garofoli and Jordan take this approach to a new level and estimate the energies of cations in the KcsA K^+ channel. The authors focused on the selectivity filter formed by the signature TVGYG sequence present in all K^+ channels. An atomic-level potential energy function was developed for the single-file chain of water molecules contained within this rigid pipelike structure. The backbone carbonyl oxygen atoms that form a linear sequence of four ion binding sites are treated as mobile partial charges tethered by their flexible covalent bonds to rigid partially charged carbon atoms. The rest of the system is represented with macroscopic models. In an especially bold stroke, the polarizability (a particularly vexing problem with ion channels) is represented by the flexible parts of the detailed potential energy function superimposed on a background high-frequency component with a dielectric constant of 2.

Energies were then computed for binding K^+, Rb^+, Cs^+, Na^+, and Ba^{2+} to each of the four sites in the selectivity filter. The results illuminate a wide range of experimental data on permeability and channel blockade. The high preference for K^+ and Rb^+ over Na^+ is reproduced, as well as other features of selectivity among cations. Ba^{2+} and Na^+ interact strongly with the innermost site in the filter, leading to channel block. Some questions remain, however, because the pattern of site occupancy for K^+ and Rb^+ deviates in significant ways from the crystallographic analysis (Morais-Cabral, 2001). One of the important insights to emerge from this work is that each of the energetic terms makes a substantial contribution, but the contribution that varies between ions, and thus generates the channel's selectivity, is the reorientation of the backbone carbonyls that form the ion binding sites. K^+ fits in these sites nearly perfectly, with minimal distortion of the carbonyl bonds. The slight compression of these bonds with Rb^+ is easily accommodated, the larger compression with Cs^+ is far more difficult, and the stretching of the bonds to coordinate to a smaller Na^+ ion entails a major energetic cost. From this perspective, the energetics of ion permeation depends on large opposing forces balancing out to near zero. Most of these large terms are constant and unselective among cations, but the interaction of ions with the oxygen atoms of the selectivity filter is very sensitive to the size of the ion and this dictates which ions can permeate the channel.

The present theoretical framework for analysis of channels can be readily modified to explore the consequences of deviations from the KcsA structure. The authors ended with a tantalizing suggestion that changes in protonation of two acidic residues can transform the channel into one that is selective for divalent cations. One wonders more broadly whether the approach of combining coarse- and fine-grained theories in computer models might be a generally useful strategy in the study of relations between structure and func-

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tion not only in channels, but in other proteins as well.

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