rest of the channel, as the authors show by comparison with another crystal structure, of segments S1 to S4 alone. This flexibility explains the difficulty that the authors encountered in crystallizing the protein; it also suggests a mechanism for voltage sensing. The paddle is a hydrophobic, charged particle that can move in the membrane interior, transporting its four positive charges from one membrane surface to the other (Fig. 1b).

It is the location of S4—not embedded in the protein core, but loose in the membrane—that is the big surprise here. It explains an old puzzle, that small lipid-soluble molecules somehow have ready access to ion-channel voltage sensors. Such molecules include local anesthetics, the alkaloid nervetoxins and the well-known insecticides allethrin and DDT.

It is now easy to imagine them diffusing up to the voltage-sensor paddle from within the lipid membrane interior.

An X-ray crystal structure is like a posed photograph; in the KvAP crystal, for instance, the voltage-sensor paddle is held firmly in place by an antibody scaffold. What can be learned about the paddle's natural conformation and movements? A few years ago, Horn and colleagues1 showed for sodium channels that a bulky moiety, attached by chemical modification to an S4 amino acid on the outside of the membrane, can actually be dragged through to the inner surface in response to an inside-negative voltage. In their second paper2, MacKinnon and colleagues showed that a much larger molecule—biotin plus a 17 Å linker—flips across the membrane in a voltage-dependent manner when it is attached to an S4 amino acid in KvAP. They conclude that the S3–S4 paddle moves through a quite unrestricted space. They go on to attach this biotin-linker molecule to various other sites in the paddle, to map its position relative to the membrane surfaces at positive and negative voltages.

After all this, MacKinnon and co-workers have still left a few questions to be answered. The actual conformation of the channel in the membrane will need to be clarified, because in the crystal the membrane is replaced by a blanket of detergent molecules. Questions also remain about the disposition of the amino-terminal end of the protein (thought to be intracellular) and of the loop between the S3 and S4 segments in related channels (in the well-studied Shaker potassium channel, this loop is always accessible from the outside surface). Moreover, details of the motions of the voltage sensor—in some channels the charge movement occurs in several discrete steps—remain to be worked out, as does the energetic issue of moving the quadruply charged paddle through the membrane interior. But the structure of KvAP’s voltage sensor, so simple and, with hindsight, so obvious, is a wonderful end to a 50-year-old mystery.

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Genomics

Relative pathogenic values

Julian Parkhill and Colin Berry

The bacterium that causes anthrax has several close relatives. Comparison of their genome sequences should provide insight into the biology of these organisms as agents of disease — and of terrorism.

Particular notoriety has been accorded to Bacillus anthracis of late. As the causative agent of anthrax, this bacterium was used in the 2001 postal attacks in the United States, and it has reportedly been “weaponized” as a warfare agent on at least one occasion. On pages 81 and 87 of this issue, Read et al. and Ivanova et al. bring the power of genomics to bear on efforts to understand this pathogen and its close relatives.

Bacillus anthracis is a member of a group of closely related organisms that includes B. cereus, an opportunistic pathogen of humans, and B. thuringiensis, an insect pathogen that has been used worldwide as a biological control agent of agricultural pests. The bacterium that causes anthrax has several close relatives.