solute transporters. In this last model, elegant in its minimalism, voltage dependence arises not from movement of the gating charges through the transmembrane electric field, but from the field moving around the charges. The mobile-S4 models rest on evidence variously supporting transmembrane motion on the order of 10–20 Å (refs 3, 4), whereas the transporter picture puts much weight on fluorescence experiments[8] indicating that S4 moves less than 2 Å.

A paroxysm of recent papers[9–12] has examined the proximity of residues near the external end of S4 to the pore domain. On channel opening, the extracellular ends of S4 and S5 come close together, and although this finding fails to distinguish among the three classes of model, it does constrain their individual depictions of the 'out' state. Pictures of the 'in' state are even murkier. The X-ray structure[5] shows S4 in an intracellular position, but this structure, which everyone acknowledges is distorted by crystal-packing forces, is unrepresentative of the S1–S4 domain in a membrane. Nevertheless, electrophysiological studies[4,6] place part of the 'in' paddle near the inside solution. In contrast, a tarantula-venom peptide binds preferentially to the 'in' state of a Kv channel, using receptor determinants on the extracellular ends of S3 and S4 (ref. 13); because the peptide inhibits from the outside, this result would rule out the paddle model if it were established that the toxin encounters its receptor directly from aqueous solution, rather than from within the membrane. But that's a big 'if'.

Against this ambiguous background, Starace and Bezanilla[1] reveal a surprising property of the 'in' configuration of S4: proton conduction. Mutation of the outermost S4 arginine to histidine produces a steady transmembrane leak of protons. This conductance behaves as though it is specifically mediated by the introduced histidine side chain, and most importantly it is present only for the voltage sensor's 'in' state. The authors estimate a unitary turnover rate of some 50,000 protons per second, and conclude that this high value implies that the histidine side chain is exposed to aqueous solution on both sides of the membrane simultaneously. From this they draw several structural inferences: that the 'in' state of the voltage sensor allows the two solutions to approach perilously close to each other, such that protons can access the side chain from both sides, and that the transmembrane voltage therefore falls across an exceedingly short distance (that of a single side chain). Declaring the paddle model inconsistent with such a picture, Starace and Bezanilla assert that voltage-sensor movement is transporter-like, as in Fig. 2c, with the outermost S4 position acting as a narrow 'gate' that separates internal and external solutions in the 'in' state.

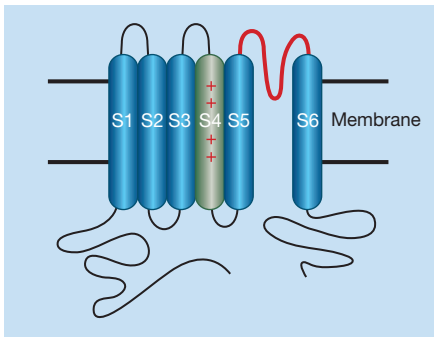


Figure 1 **Composition of one subunit of a voltage-dependent $K^+$ channel. A channel consists of four subunits, parts of which together form a central pore, and each subunit consists of six membrane-crossing α-helices, S1–S6. S5 and S6 are the 'pore domain' (a subunit's contribution to the pore). S1–S4 are the 'gating domain'. It is charged amino acids on S4 that are mainly responsible for voltage sensing, and movement of S4 that is the principal bone of contention.**

In our view, though, it is too big a step to translate proton conductance into a unique structural image of the voltage sensor. A proton leak does not necessarily imply direct access from bulk aqueous solutions; an alternative possibility would be that the histidine residue connects to solvent via narrow crevices formed from protonatable protein groups and individual water molecules. Such pathways could act as proton conduits to the histidine side chain, as seen in proteins containing 'proton wires' as long as 15 Å (ref. 14). The distance separating the two bulk solutions could be further lengthened by about 7 Å if proton transport were also mediated by a histidine side-chain flip. Thus, the separation of internal from external solutions need not be unusually narrow. We agree that the proton current described by Starace and Bezanilla rules out a paddle completely surrounded by bilayer lipid, but a paddle in contact with the pore domain could still be consistent with these observations.

Stepping back from the fray, we should not forget that broad agreement prevails on basic issues of voltage sensing, and that the current controversy is really about fine details at the level of protein chemistry. The jury, we think, is still out, and before a firm choice of model can be made we'll need to see more experiments — and more structures. ■

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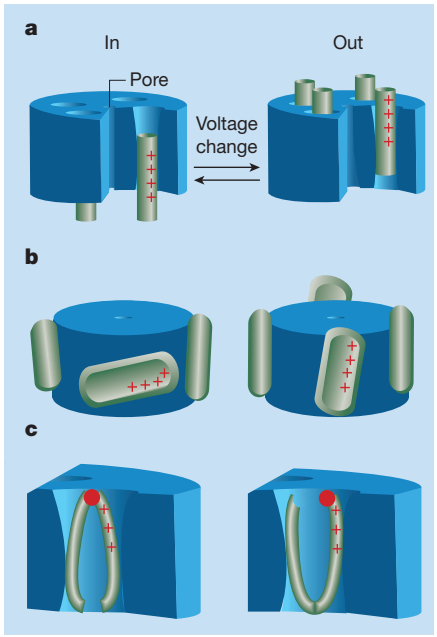


Figure 2 **Models of voltage-sensor behaviour; the voltage sensors' change from the 'in' to the 'out' position triggers pore opening.** a, **The sliding-helix and,** b, **paddle models. These two diagrams show the four subunits, with the voltage-sensing components of each depicted in green.** c, **The transporter-like model proposed by Starace and Bezanilla[1], based on mutation of the outermost S4 amino acid from arginine to histidine (red circle), and depicted in a single subunit. According to this view of events, in its 'in' position the voltage sensor separates the internal and external solutions with a narrow gate that produces a highly focused electric field.**

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### Correction

In "Dreams of a hollow future" by Luis Hueso and Neil Mathur (*Nature* **427,** 301–304; 2004), the third sentence of the figure caption was added in error by an editorial hand: the property of magnetoresistance in manganites has no connection to fuel-cell technology.