

the process. But it is relevant, for two main reasons, to devising a homogeneous catalytic process for the production of ammonia. First, although both hydrogen and dinitrogen have been shown to bind at metal centres in solution individually and even at the same time, they have only recently been seen to interact with the formation of one N–H bond<sup>7</sup>. Pool and colleagues' work<sup>2</sup> suggests that these two simple molecules can react to generate a variety of NH<sub>x</sub> ligated species. Second, and more interesting, is the remarkable effect of substituents on the ancillary ligands. The fact that changing from a pentamethylated ligand to a tetramethylated ligand can completely change how the dinitrogen unit coordinates with the metal complex, and then how it reacts with hydrogen, is truly surprising. No one could have predicted such a profound change in outcome with such a small change in ancillary ligands.

In truth, it is unlikely that any homogeneous catalytic process will ever compete on

an industrial scale with the heterogeneous Haber–Bosch reaction and its modern variants. But now that ammonia has been produced from its elements in solution, one can only begin to imagine what other kinds of transformation might be possible for molecular nitrogen. ■

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1. Tamaru, K. in *Catalytic Ammonia Synthesis* (ed. Jennings, J. R.) 1–18 (Plenum, New York, 1991).
2. Pool, J. A., Lobkovsky, E. & Chirik, P. J. *Nature* **427**, 527–530 (2004).
3. Schlögl, R. *Angew. Chem. Int. Edn* **42**, 2004–2008 (2003).
4. Basch, H., Musaev, D. G. & Morokuma, K. *Organometallics* **19**, 3393–3403 (2000).
5. Shaver, M. P. & Fryzuk, M. D. *Adv. Synth. Catal.* **345**, 1061–1076 (2003).
6. Manriquez, J. M. & Bercaw, J. E. *J. Am. Chem. Soc.* **96**, 6229 (1974).
7. Fryzuk, M. D., Love, J. B., Rettig, S. J. & Young, V. G. *Science* **275**, 1445–1447 (1997).

## Ion channels

# Shake, rattle or roll?

Robert O. Blaustein and Christopher Miller

Nerve transmission depends on voltage-gated ion-channel proteins, which in turn depend on the behaviour of a membrane domain called the voltage sensor. Therein lies the latest episode in a continuing story.

The propagation of electrical signals in the nervous system endows animals with moment-to-moment overall coherence. Without it, worms could not wriggle, flies could not find fruit, and we could not read News and Views. Electrical impulses coursing down the nerve axon arise from a molecular minuet in which ion-channel proteins deliver charged particles, Na<sup>+</sup> and K<sup>+</sup>, across the nerve membrane. These proteins possess a special property — voltage dependence, not known in any other macromolecule — that causes their activity to be controlled by the very voltage changes they generate. Voltage dependence arises from the transmembrane movement of charged amino acids on the protein, concomitant with opening of the ion-conducting pore. The part of the protein containing these 'gating charges', the voltage sensor, is known, but the way it moves is highly controversial. Starace and Bezanilla<sup>1</sup> (page 548) now describe a remarkable property of the voltage sensor that sharpens our view of its transmembrane movement.

Voltage-dependent (Kv-type) K<sup>+</sup> channels are tetramers, with each subunit composed of six membrane-crossing  $\alpha$ -helices, S1–S6 (Fig. 1, overleaf)<sup>2</sup>. The last two of these form the K<sup>+</sup>-selective pore, a known structure common to all K<sup>+</sup> channels.

The domain that confers voltage dependence on pore opening is formed from S1–S4, with S4 bearing a regular array of positively charged amino acids, mostly arginines. The outermost three or four arginines on S4 are the gating charges that move from inside to outside to trigger pore opening. The question is, how does S4 move from the 'in' to the 'out' position?

As we see it, three classes of competing model (Fig. 2a–c, overleaf) have evolved to explain this movement, each sufficiently vague as to admit much variation in specifics. The conventional 'sliding-helix' model<sup>3,4</sup> has S4 largely buried in the rest of the membrane protein, and sliding or screwing outwards like a rigid rod through a narrow, proteinaceous gasket. The 'paddle' model<sup>5,6</sup>, evoked by new crystal structures, posits that S4 packs against the outer part of S3 and that this entire 'helix–turn–helix' unit, exposed to membrane lipid and positioned loosely against the periphery of the protein, flips or swivels across the membrane. Finally, the 'transporter' model<sup>1,7</sup> proposes a subtle rearrangement whereby the protein moves around an essentially fixed S4. This rearrangement changes the exposure of the gating charges from the intracellular aqueous solution to the extracellular side, as in the old 'rocking-bananas' cartoons of



## 100 YEARS AGO

It may interest some to know that radium destroys vegetable matter. I happened to replace the usual mica plates, used to keep in the small quantity of radium in its ebonite box, with a piece of cambric, so as to permit the whole of the emanations to pass out, mica stopping the  $\alpha$  rays. In four days the cambric was rotted away. I have replaced it now several times with the same result.

## ALSO

What Mr. J. Y. Buchanan says (p. 293) about the French Academy is to me much more wonderful than the revelations of radium. It appears that there is a happy land close by where a scientific man of recognised standing can indulge in the luxury of original research, and then send in an account of his work, *not* to have it rejected by the opinion of, say, a couple of fellow-men, but actually to have it published as a right! This seems impossible. It is the encouragement of original research. Perhaps it is hopeless to expect such freedom in this stick-in-the-mud country, which is so much in love with tradition and antiquated forms. Oliver Heaviside

From *Nature* 4 February 1904.

## 50 YEARS AGO

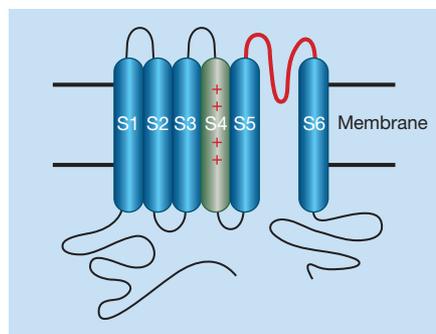
Readers of the *Bulletin of the Atomic Scientists* will have noticed that the hands of the clock which forms the distinctive coverpiece of the *Bulletin* have been moved forward so that they now stand at two minutes to midnight. This is to direct attention to the recent announcement that an atomic test involving both fission and thermonuclear reactions was conducted by the U.S.S.R. on August 12 and to warn members of all nations of the great danger of an untoward event acting as a trigger for the eruption of atomic or thermonuclear warfare. In an article in the October number of the *Bulletin* entitled "The Narrowing Way", the editor, Dr. E. Rabinowitch... considers that unless special care is taken it may only be a few more swings of the pendulum before atomic explosions strike midnight for Western civilization... Dr. Rabinowitch maintains that the Western countries are faced with the inevitable prospect of a "cold peace", precariously supported by a mutual threat of atomic and thermonuclear annihilation.

From *Nature* 6 February 1954.

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<sup>8</sup> indicating that S4 moves less than 2 Å.

A paroxysm of recent papers<sup>9–12</sup> 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<sup>3</sup> 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<sup>4,6</sup> 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<sup>1</sup> 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



**Figure 1** Composition of one subunit of a voltage-dependent K<sup>+</sup> channel. A channel consists of four subunits, parts of which together form a central pore, and each subunit consists of six membrane-crossing  $\alpha$ -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.

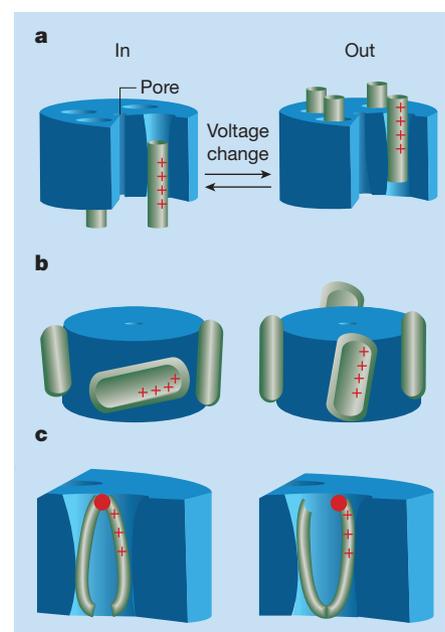
mediated by the introduced histidine side chain, and most importantly it is present only for the voltage sensor’s ‘in’ state. The authors estimate a unitary turnover rate of some 50,000 protons per second, and conclude that this high value implies that the histidine side chain is exposed to aqueous solution 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.

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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1. Starace, D. M. & Bezanilla, F. *Nature* **427**, 548–553 (2004).



**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<sup>1</sup>, 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.

2. Yellen, G. *Nature* **419**, 35–42 (2002).  
3. Yang, N., George, A. L. & Horn, R. *Neuron* **16**, 113–122 (1996).  
4. Larsson, H. P., Baker, O. S., Dhillon, D. S. & Isacoff, E. Y. *Neuron* **16**, 387–397 (1996).  
5. Jiang, Y. et al. *Nature* **423**, 33–41 (2003).  
6. Jiang, Y., Ruta, V., Chen, J., Lee, A. & MacKinnon, R. *Nature* **423**, 42–48 (2003).  
7. Yellen, G. Q. *Rev. Biophys.* **31**, 239–295 (1998).  
8. Cha, A., Snyder, G. E., Selvin, P. R. & Bezanilla, F. *Nature* **402**, 809–813 (1999).  
9. Gandhi, C. S., Clark, E., Loots, E., Pralle, A. & Isacoff, E. Y. *Neuron* **40**, 515–525 (2003).  
10. Laine, M. et al. *Neuron* **39**, 467–481 (2003).  
11. Broomand, A., Mannikk, R., Larsson, H. P. & Elinder, F. *J. Gen. Physiol.* **122**, 741–748 (2003).  
12. Neale, E. J., Elliott, D. J., Hunter, M. & Sivaprasadarao, A. *J. Biol. Chem.* **278**, 29079–29085 (2003).  
13. Lee, H. C., Wang, J. M. & Swartz, K. J. *Neuron* **40**, 527–536 (2003).  
14. Luecke, H., Schobert, B., Richter, H. T., Cartailleur, J. P. & Lanyi, J. K. *J. Mol. Biol.* **291**, 899–911 (1999).

**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.