along the Hawaiian island chain, with the help of new seismometers deployed further to the northwest. This might reveal the rethickening of the lithosphere that should eventually occur as the plume material cools. A second task is to test the conclusions of Li *et al.* against new measurements of heat flux on the Hawaiian swell. Thermally induced thinning of the lithosphere to 50–60 km should produce measurable anomalies of the heat flux at the ocean floor, starting about 10 million years later, or after about 900 km of motion by the Pacific plate. However, attempts to detect such anomalies[10] have so far been unsuccessful. It seems the Hawaiian swell still has much to teach the Earth scientist. ■

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Ion transport

Spot the difference

David C. Gadsby

Common wisdom holds that ion channels and ion pumps, with their obvious functional differences, should have visibly dissimilar structures. It seems that's not necessarily so.

The two kinds of membrane protein that control movements of ions such as Na^+, K^+ and Cl^- into and out of cells have very different jobs. Ion channels let these charged atoms flow down chemical and electrical gradients; pumps build up the gradients. Hence the view that channels and pumps must be cut from different cloth.

In a startling dismissal of that idea, on page 803 of this issue Accardi and Miller[1] show that a protein called CLC-ec1, a prokaryotic forebear of the large CLC family of eukaryotic Cl^- channels, isn't a channel as presumed[2–5]. After reconstituting purified protein in an environment mimicking a cell membrane, the authors show that CLC-ec1 is an exchange pump that can harness an energetically favourable gradient of protons to move Cl^- ions against their electrochemical gradient. This reclassification would excite only diehard transport specialists were it not for the fact that a high-resolution X-ray structure[5] of CLC-ec1 has proven an illuminating model for understanding how CLC Cl^- channels work. So we're forced to conclude that we can't yet distinguish a channel from a pump by simply staring at a crystal structure.

But what are the functional characteristics of channels and pumps that might demand structural differences? Ion channels need a membrane-spanning pore through which ions diffuse, and a gate that opens only as needed (lest perpetually open channels dissipate the gradients upon which their function depends). The pore of a selective ion channel must include a selectivity filter that allows speedy passage — 10 million to 100 million ions per second through the open pore — of the appropriate ions while keeping others out[6]. Ions move more slowly through pumps than through channels. For instance, the ATP hydrolysis-driven sodium–potassium pump, a so-called 'primary' transporter, exchanges three intracellular Na^+ ions for two extracellular K^+ ions only 100 times per second. The secondary transporter CLC-ec1 exchanges two Cl^- ions for a single proton[1], up to 100,000 times per second[1,7].

In principle, the difference between an ion channel and an ion pump, or transporter, boils down to this: an ion channel needs no more than a single gate, and a pump needs at least two gates that ought never to be open at the same time (Fig. 1, overleaf). A practical limit on 'never' is set by the ratio of throughput rates for uphill versus downhill ion transport. A pump such as the sodium–potassium pump moves roughly 100 ions per second uphill, but would let 10 million ions per second flow downhill if both gates were open, so the probability of finding both gates open must be far less than one in 100,000 for the pump to be useful. To achieve such low probabilities, the pumps ensure that one gate closes before the other opens, temporarily trapping ions inside the protein (Fig. 1b). Although secondary transporters such as CLC-ec1 tend to have somewhat faster transport rates than the sodium–potassium pump, the same principle applies.

A CLC-ec1 exchange pump might therefore differ from a CLC Cl^- channel by little more than an additional gate. So what constitutes a gate? Although, in theory, a

100 YEARS AGO

Studies in Heterogenesis. **By H. Charlton Bastian. Heterogenesis means, in these studies, the *per saltum* origin of forms of life from other quite different forms, e.g. of a ciliated infusorian from a rotifer's egg, or of a sun-animalcule from a chlorophyll corpuscle. It is long since Dr H. Charlton Bastian first suggested this heresy; and many years of industrious observation have resulted in this large and expensive volume describing and (with 815 figures) illustrating those cases in which the author thinks he has detected the heterogenetic process at work. One cannot but admire the doggedness with which Dr Bastian has persisted — *contra mundum* — in maintaining his thesis; and even those who feel quite sure that he has misinterpreted what he saw may find it interesting to discover by repetition of his experiments what did actually occur and was actually photographed. Others, again, who would not turn round to look at slides supposed to demonstrate that the egg of a rotifer may resolve itself into infusorians or into one large ciliate, may be more tolerant of the suggestion that Protistan evolution is still going on, retracing some of its ancient steps, or making new ones. It may be that Proteus still frisks a little among the Protists, or that there are mutations among unicellulars just as among De Vries's evening primroses.**

From *Nature* 25 February 1904.

50 YEARS AGO

I wish to direct attention to the large amount of scientific work carried out at the public expense but only reported in brief summary terms or published after long delay… It seems that an example is furnished by some of the work carried out under the Colonial Research Council. Under that Council is a committee dealing with insecticides which met first in January 1947. [This work] is lavishly financed and has received 7.5 per cent of the £12,000,000 allocated to the Colonial Research Council up to 1953, namely, £900,000. As most of the work carried out by the Insecticide Committee appears not to be very expensive, we conclude that the air spraying has cost about three-quarters of a million pounds. It is difficult to see why work should be done and paid for, if it is not made available or if it is to be published after it is out of date.

From *Nature* 27 February 1954.

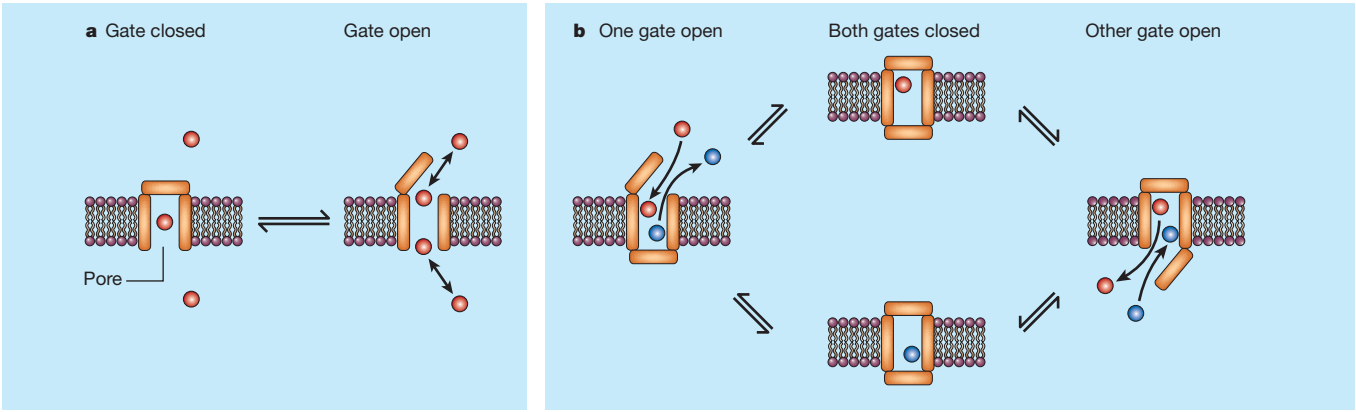

Figure 1 **Functional differences between ion channels and ion exchange pumps.** a, **Ion channels need only a single gate, which can be open or closed. When closed, ions (red circles) cannot pass through the pore but when open, ions can enter and flow through freely.** b, **By contrast, ion-exchange pumps need two gates, which are never both open. Each gate can open only if the other is closed, to prevent unrestricted ion flow. When one gate is open, one type (red) of ion enters, and another (blue) leaves. Continuing clockwise, closing the gate temporarily traps red ions inside the pore, until the second gate opens to release them to the other side of the membrane and allow blue ions in. Clockwise exchange of red for blue ions across the membrane is completed after the second gate closes, entrapping blue ions until the first gate opens to release them at the opposite side.**

gate can comprise any impediment to ion transit, structural studies in primary ion pumps[8] and cation channels[9–11] indicate that large domain movements probably control ion transport. But in CLC proteins (channels and pumps), a more subtle structural change — rotation of a single amino-acid side chain — seems to regulate ion passage[5]. This side chain, of a well-conserved glutamate at position 148 (E148), visibly obstructs the extracellular entrance to the ion pathway in the normal CLC-ec1 protein. But if this glutamate is replaced by alanine or glutamine (E148A or E148Q) the side chain swings out of the pore, and is replaced by a Cl^- ion[5]. CLC-0-type Cl^- channels are, in effect, permanently open when they have the same mutations at their corresponding residue (E166). So the negatively charged side chain of the glutamate functions as a gate that blocks ion passage until it is displaced by a permeating Cl^- ion. An enhanced opening of CLC-0 channels is seen at low pH[5,12], and this is probably because the protons neutralize the glutamate side chain — the same effect achieved by the mutations.

According to the simple principle outlined above, this conserved glutamate might represent the sole gate sufficient for a CLC-0 channel pore, and one of the two gates needed by a CLC-ec1 exchange pump. Indeed, Lin and Chen[13] showed that there is no gate at the cytoplasmic end of the CLC-0 channel pore, consistent with it needing no more than one gate. On the other hand, CLC-ec1 exchange pumps are expected to contain a second gate, and the X-ray structures[3,5] suggest that two residues — serine at position 107 and tyrosine at 445 — contribute to such a gate. The side chains of both interact with the Cl^- ion found in the normal, as well as the E148-mutant, CLC-ec1 near the intracellular end of the route that the Cl^- ions take[3,5].

If we pursue this simple analysis, the external gate ought to be largely absent from the E148A mutant of CLC-ec1. It might therefore be expected to behave like a Cl^- channel, gated only by the intracellular-end gate. But does it? Well, in new reports in this issue and elsewhere[1,7], Accardi and Miller show that currents flowing through this CLC-ec1 mutant are perfectly Cl^- selective, just as they are in CLC channels[1]. Also, as anticipated, neither currents nor labelled Cl^- fluxes respond to changes in pH[1,7], confirming that Cl^- ion movements through this mutant transporter are no longer coupled to proton movements. However, no more than 100,000 Cl^- ions flow, on average, through a mutant E148A CLC-ec1 molecule in a second[1,7], whereas Cl^- flow through a single open E166A CLC-0 channel is 100 times faster[5].

Despite this tiny average current, could the E148A mutant CLC-ec1 exchange pump still behave like a channel? Could, perhaps, the still-remaining internal gate keep the pathway shut 99% of the time, and undergo only brief (as yet undetected) openings that allow Cl^- ion flow through the mutant transporter as rapidly as through an open CLC-0 channel? Probably not, because, at least in the normal exchange pump, both external and internal gates must open and close very frequently to account for the observed rapid exchange of two Cl^- ions for each proton[1]. Well, perhaps the internal gate does open and close frequently in the mutant transporter but, when open, Cl^- ion flow is 100-fold slower than through open CLC-0 channels? This doesn't seem likely either, as the equivalent mutation in CLC-0 (E166A) leaves the open-channel current unaltered[5]. More likely, as inferred by the authors[1], discrete movements of Cl^- ions, perhaps still two at a time, 100,000 times each second, persist in the mutant transporter, albeit uncoupled from protons. Clearing this up will require higher resolution current recordings, as well as information on the whereabouts and workings of the exchange pump's inner gate.

Answers to questions like these, long the stuff of dreams for transport buffs, now seem tantalizingly within reach. There can be no doubt that CLC-ec1 is an exchange pump, just as CLC-0 is undoubtedly a channel. Moreover, a lot of evidence — not just the conserved glutamate gate — makes the structure of CLC-ec1 a reliable template for the architecture of CLC channels[3,14–16]. The strong implication is that when the structure of the CLC-0 pore is eventually determined it will closely resemble that of CLC-ec1. In the meantime, we can think hard about the functional distinction between a slowly conducting channel and a rapidly gating transporter, when both translocate just one kind of ion. Anyone for ping-pong? ■

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