carefully, however, hotspots move with respect to each other and to the Earth's spin axis. Geodynamicists want to resolve these effects independently of changes in relative plate motions.

Mantle plumes are merely upwelling conduits of hot, low-viscosity material in the mantle flow, and clearly must move with respect to each other: the conduit ascends buoyantly while being dragged rather like smoke from a chimney on a windy day. Steinberger *et al.*[1] model the fluid dynamics of this 'mantle wind' by including the observed plate motions. Much of the conduit height is within the very viscous lower mantle, which flows slowly, giving the illusion (and convenient approximation) that hotspots are fixed. They are not, but most of the time move at less than a centimetre per year. Although the Hawaiian hotspot moved faster at some times, it did not do so in a way that would create a sharp bend in the Hawaii–Emperor track.

Steinberger *et al.* then direct their attention to inadequacies in understanding the relative motions between plates. In case you think this has been sorted out to decimal places in the past 30 years, it hasn't. We can calculate relative plate velocities in the past only where plates were in contact at ridge boundaries (where plates are separated by a ridge, creating new crust) or transform boundaries (where they are sliding past one another). At subduction zones, where one plate slides beneath another, the information about past behaviour, encapsulated in palaeomagnetic data in the sea floor, becomes lost. Mathematically, the relative velocity **v** between plates A and B is $\mathbf{v}(A,B) = \mathbf{w}(A,B) \times \mathbf{r}$, where **w** is the rotation 'pole' vector and **r** is the radial vector to the surface point where velocity is measured.

To study the fixity of hotspots, one needs to estimate the velocity of plates, such as the African and Pacific, that are not in contact by ridge boundaries. Formally, this requires summation of rotation vectors around a 'plate circuit', $\mathbf{w}(A,B) + \mathbf{w}(B,C) = \mathbf{w}(A,C)$. This procedure becomes problematic if, at some point in the circuit, two plates have only a short boundary. Then one cannot accurately determine the component of the rotation vector in the direction of **r**, as it produces no velocity. This component, however, produces velocity elsewhere when added to the circuit. In connecting up plate relationships around the circuit, Steinberger *et al.*[1] carry through errors in their analysis and keep this problem in check.

Next, the authors had to take into consideration the fact that some plates are not really rigid, especially within continents, which precludes a simple circuit. For times before 43 million years ago (older than the Hawaii–Emperor bend), they get considerably different results by treating the Antarctic plate as rigid, or alternatively taking the circuit
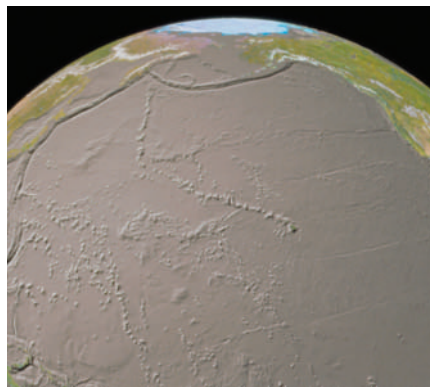

Figure 1 **Spot the bend. Start at Hawaii and follow the features trending west-northwest until they take a sharp turn north.**

through the extinct mid-ocean ridge in the Tasman Sea between Australia and the Lord Howe Rise — a continental fragment that was then attached to New Zealand on the Pacific plate. They prefer the latter solution (see Fig. 3 on page 170) as it gives the bend in the Hawaii–Emperor chain at the right time.

This work makes sufficiently precise predictions to interest the field geologist. For example, the models imply that deformation within the New Zealand plate occurred between 65 million and 83 million years ago, and that there was considerable deformation within Antarctica between 43 million and 83 million years ago. These are surmises that can be checked by field work.

To test their calculations relating to the Hawaiian hotspot, Steinberger *et al.* included analyses of three other hotspot tracks in different parts of the world that have produced island or seamount chains — Réunion (in the Indian Ocean), Louisville (in the Pacific) and Tristan (in the Atlantic). As with Hawaii, an important constraint comes from the estimation of palaeolatitudes — shifting latitudinal position in the past — especially of volcanic edifices that are still submerged. The reason that Steinberger *et al.* worked with only four tracks is that, perhaps surprisingly, numerous submarine edifices have not yet been sampled and dated, let alone drilled

for palaeomagnetic studies. But the four that they have worked with provide consistent results, supporting the conclusion that there was a significant change in relative plate motions at the time that the Hawaii–Emperor bend was created.

What does such a change imply for the past and present geodynamic behaviour around the circuit? Plates move far too slowly for inertia to be relevant. Buoyancy forces associated with plate age in the crust and uppermost mantle, and with slab material in the deep mantle, evolve too slowly to realign plate motions quickly. But factors associated with the shallow parts of subduction could have a considerable effect.

In search of a mechanism for an abrupt plate reorganization, Steinberger *et al.* point out that the Antarctic plate may have become strong enough to be rigid around the time the Hawaii–Emperor bend occurred, and that this may have triggered a change in the circuit, with slab subduction being initiated along a transform fault boundary in the Philippine Sea; today this is the Marianas subduction zone. Once started, subduction provides a driving force. The viscosity of the mantle increases with depth, so much of the driving force comes from the upper few hundred kilometres of the slab. That is, once it was under way, subduction beneath the Marianas quickly increased the change in plate motions.

I expect that debate will continue on the relative fixity of hotspots, the rigidity of tectonic plates and mantle dynamics. Meanwhile, more geological data will come in hand, and seismological studies will continue the task, just begun, of resolving the current behaviour of plume conduits[2]. Such work will batten down our understanding of the present-day effects of the mantle wind. ∎

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Ion channels

Gate expectations

Maria L. Garcia

The opening and closing — gating — of ion channels in response to specific stimuli is crucial for cell function. The membrane-partitioning activities of two venom toxins give insights into the mechanisms involved.

The membrane surrounding a biological cell forms a highly selective barrier that allows the cell to control its internal environment. It consists of an assembly of lipids and proteins. Some membrane proteins form channels through which ions

can flow. These ion channels are said to be 'gated' if they can be opened and closed, and the trigger for this can be electrical, chemical or mechanical stimuli. Ion channels are widely distributed throughout the human body, and in many cells different
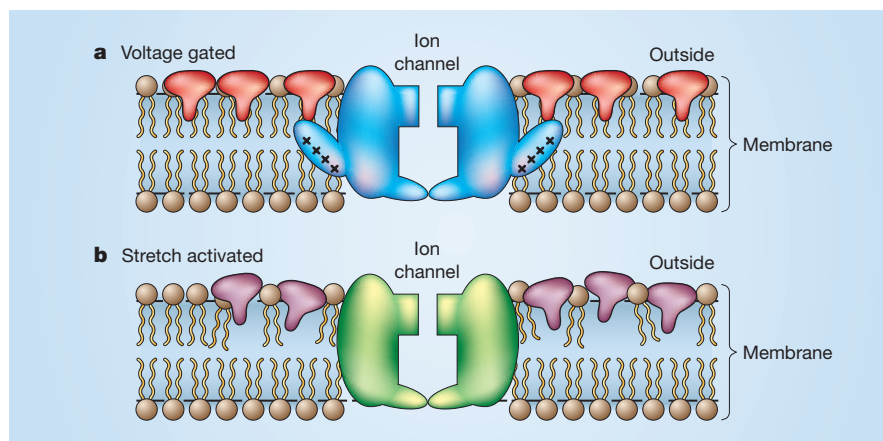
Figure 1 **Inhibition of ion channels by two gating-modifier peptides. Schematic representation of a voltage-gated potassium channel** (a) **and a stretch-activated channel** (b). **The peptides VSTX1** (a, **red**) **and GsMTx4** (b, **purple**) **partition within the membrane. Lee and MacKinnon**[2] **show that the gate in** a **is favoured in the closed conformation when VSTX1 reaches the positively charged voltage sensor through the membrane, whereas Suchyna** *et al.*[3] **show that opening of the gate in** b **is blocked through alterations in lipid packing at the interface between the membrane and channel.**

types of channel coexist. It is their interplay that tunes the cell's electrical activity, enabling it to function properly; even small changes in the balance of activity of the channel proteins can have significant physiological consequences, sometimes leading to severe medical conditions[1]. The development of therapeutic agents that target ion channels is therefore under way.

Now Lee and MacKinnon[2] and Suchyna *et al.*[3] (pages 232 and 235 of this issue) describe how two toxins isolated from the venom of tarantulas interact with two different types of ion channel. Remarkably, they find that the toxins' high-affinity block of these channels is not due to a complementary interaction between channel and toxin surfaces, but to the toxins' ability to partition into the membrane.

The deadly effects of spider venoms are generally thought to result from the high-affinity binding of their toxin components to membrane ion channels. Many toxins are peptides — small assemblies of amino acids — that specifically modulate ion-channel activity. Several peptides that modify the gating of ion channels have been identified. Members of this class interact with the families of voltage-gated channels for sodium, calcium or potassium ions, and with mechanosensitive channels, whose gating can be altered by mechanical forces[4]. Gating-modifier peptides seem to have a common structural feature in that one face is almost exclusively hydrophobic, which seems to be important for affinity[5]. The peptides are thought to access their receptor on the channel from the outer, extracellular, side of the membrane and to bind to regions on the protein that are normally involved in the conformational changes, triggered by a given stimulus, that lead to channel opening[6].

But gating-modifier peptides have two characteristics requiring special considera-

tion. First, whereas the kinetics of other channel-inhibitory peptides that bind at the outer, surface-exposed region of the channel pore are generally consistent with a diffusion-controlled process, gating-modifier peptides act far more slowly. And second, the interaction surface on the channel for gating-modifier peptides seems to be too small to account for their high affinity.

In an attempt to explain these discrepancies, Lee and MacKinnon[2] investigated the interaction of a voltage-sensor toxin, VSTX1, with a voltage-dependent potassium channel known as KvAP. The structure of this channel has been determined from high-resolution X-ray crystallography by MacKinnon's laboratory[7,8], making it a good study candidate. Suchyna *et al.*[3], meanwhile, looked at the venom peptide GsMTx4, which inhibits stretch-activated ion channels.

Lee and MacKinnon found that if the KvAP channel is removed from the membrane using detergent, VSTX1 binds to the solubilized protein with a 10,000-fold lower affinity than when the channel is present in the membrane. Suchyna *et al.* show that GsMTx4 has the same efficacy as its enantiomer — its mirror-image structure — in modifying native stretch-activated channels. They obtained similar results with artificial membranes consisting of lipid bilayers and channels formed by a peptide called gramicidin. These results fly in the face of the traditional 'lock-and-key' model of ligand–receptor binding, and instead suggest that the peptide not only acts on the ion channel but also alters the lipid packing at the interface between the channel and the membrane. Thus, much of the binding energy of VSTX1 and GsMTx4 is derived from the nonspecific free energy of membrane partitioning, whereas the actual peptide–channel interaction is rather weak (Fig. 1).

The high-resolution X-ray structure of

KvAP has led to a controversial proposal for voltage-dependent gating that involves a 'voltage-sensor paddle', a positively charged voltage sensor (Fig. 1a). The paddle model is very different from conventional gating models[9] in both the shape of the channel in the closed state and the mechanism by which membrane depolarization leads to opening of the ion pathway. Studies of another gating-modifier peptide called hanatoxin have shown that, when this peptide is applied extracellularly, it can bind to closed channels. This has been interpreted as evidence that the voltage sensor lies on the outer part of the membrane in the channel's closed state, thereby limiting its movement within the membrane during activation[10]. Furthermore, the slow kinetics of hanatoxin-induced block suggested that it remains bound to the channel during gating. However, these observations must be reconsidered in the light of Lee and MacKinnon's results[2]. If hanatoxin can diffuse into the membrane, previous results would be compatible with a paddle model of gating whereby the voltage sensor moves within the membrane during depolarization. Moreover, membrane partitioning combined with low-affinity binding could allow the peptide to dissociate and rebind rapidly during gating.

How do the findings in these two papers[2,3] bear on our understanding of therapeutic agents that target ion channels? Traditional pharmacological methods provided the ion-channel drugs currently in use, but drug development is now based on a more rational approach. An ion channel is usually selected as a potential therapeutic target, and possible channel modulators are then screened for activity. Ideally, however, structural information would be used to increase the potency and specificity of lead candidates. Knowledge of the conformations that ion channels assume during gating, as well as the precise nature of drug–channel interactions, will lead to more effective drugs. Because gating-modifier peptides seem to bind to a region of the channel that differs between channel families and even within the same family, it was assumed that drug specificity might be achieved by using a small molecule that mimics the peptide's effect on its target channel. But these two papers suggest that such an approach might not work because nonspecific membrane partitioning contributes greatly to the high affinity of these peptides.

There is one piece of good news, though. The observation that the two enantiomers of GsMTx4 are equally effective in blocking stretch-activated channels has major implications for the use of peptides in drug therapy. This is because, generally, only one of the two enantiomers is susceptible to the body's breakdown enzymes, so the alternative form might be stable in the circulation. Finally, although other small organic

molecules seem to modify gating by accessing the channel through the lipid membrane, it remains to be determined whether membrane partitioning is a common mechanism for all ion-channel gating modifiers. ∎

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Condensed-matter physics

Charge-ordering in oxides

Michael Coey

Transition metals form mixed-valence oxides that are expected to have ordered arrangements of *d*-shell electrons. But the ionic picture must be rethought to include oxygen 'holes' in the charge-ordered patterns.

The crystal chemistry of oxides seemed as solid as a rock; indeed, most rocks *are* oxides, in which 90% of the ions involved — Si^{4+}, Al^{3+}, Mg^{2+}, Na^+, O^{2-} — adopt a stable configuration with just ten electrons. To form ionic bonds, the electrons transfer their allegiance from metals to oxygen, filling up the $2p$ shell to arrive at a $1s^2 2s^2 2p^6$ configuration. This transfer in oxides of transition metals possessing $3d$ shells can lead to multiple charge states for the metal cations. For example, TiO_2 contains Ti^{4+} ($3d^0$), but Ti_2O_3 contains Ti^{3+} ($3d^1$) and Ti_4O_7 has a mixture of both, in the formula $Ti_2^{3+}Ti_2^{4+}O_7$. At low temperature, the extra electrons associated with Ti^{3+} should be driven by their mutual Coulomb repulsion into some sort of ordered arrangement. But, in *Physical Review B*, Herrero-Martín *et al.*[1] throw doubt on physicists' favourite model of electrons in solids by calling cation charge-ordering into question, at least in manganites. The manganites are a family of compounds that have provided harmless pleasure to generations of solid-state physicists and chemists since their discovery at the Philips Research Laboratories in the Netherlands more than 50 years ago.

Charge-ordering in solids was first envisaged by Eugene Wigner in the late 1930s. The concept was applied by E. J. W. Verwey to the transition that occurs in magnetite (Fe_3O_4) at 120 K, now known as the Verwey transition. Verwey suggested that the electrons belonging to Fe^{2+} and Fe^{3+} ions order themselves over octahedral sites coordinated by oxygen[2]. Magnetite is nature's most common mixed-valence mineral. The charge-ordered state below a Verwey transition is less conducting than the disordered state above it, where electrons can hop or tunnel from one cation site to the next. The charge order–disorder transition is driven, at least in part, by the entropy of disorder.

The mixed-valence manganites[3] are solid solutions — compositionally random mixtures of two perovskite-structure oxides that have the general formula ABO_3. Examples include $LaMnO_3$, for which the presence of the La^{3+} charge state implies a Mn^{3+} $3d^4$ configuration; and $CaMnO_3$, for which the Ca^{2+} charge state implies the smaller Mn^{4+} $3d^3$ configuration. Many rare-earth elements can replace La, and other alkaline earths can replace Ca — providing a large chemical playground that filled in the mid-1990s with researchers who had become bored with the structurally related superconducting cuprates. The manganites offered a bewildering profusion of crystallographic, magnetic and electronic ground states, as well as catchy physical phenomena such as magnetic melting of charge order and colossal magnetoresistance — where the resistance of the material drops dramatically as a magnetic field is applied.

The 50–50 solid solutions, such as $(La_{0.5}Ca_{0.5})MnO_3$, seemed relatively straightforward. They undergo two transitions on cooling, the first at about 220 K to a ferromagnetic — spontaneously magnetic — conducting state, and the second near 160 K to an insulating antiferromagnetic state. At this second transition, the Mn^{3+} and Mn^{4+} ions were thought to adopt the charge-ordered chequerboard arrangement[4] shown in Fig. 1. Another wrinkle is that the fourth $3d$ electron can occupy one of two different orbitals, a wasp-waisted cigar and a four-leaved clover. A pattern of orbital order may exist independently of charge order[5]. The octahedral sites occupied by $3d^4$ ions tend to distort in response to the orbital shape so as to lower the electrostatic energy. This site distortion is known as the Jahn–Teller effect.

Herrero-Martín *et al.*[1] have probed the local structure around the manganese ions in the 50–50 solid solution $(Nd_{0.5}Sr_{0.5})MnO_3$ by using resonant scattering of an intense synchrotron-generated X-ray beam. They do indeed find two manganese sites, and one of them is distorted as expected. However, the charge difference between the two configurations is only 0.16 electrons[1] — a far cry from $3d^3$ and $3d^4$, but in line with other experimental[6–10] and computational[11,12] evidence that there is little difference in manganese charge or magnetic moment on different sites. An alternative model is the Zener polaron[9], in which pairs of Mn^{3+} cations share a 'hole' on a bridging O^- ion. These oxygen holes may form a soft charge-density wave[10,12].

Doubts about charge-ordering are also circulating for magnetite, the archetypal mixed-valence oxide. García and Subías argue in a topical review[13] that no good evidence for distinct Fe^{2+} and Fe^{3+} charge states below the Verwey transition has ever been found. This is probably an overstatement; nuclear magnetic resonance and Mössbauer probes of the iron hyperfine fields reveal many distinct components below 120 K that are associated with more than two charge configurations, intermediate between
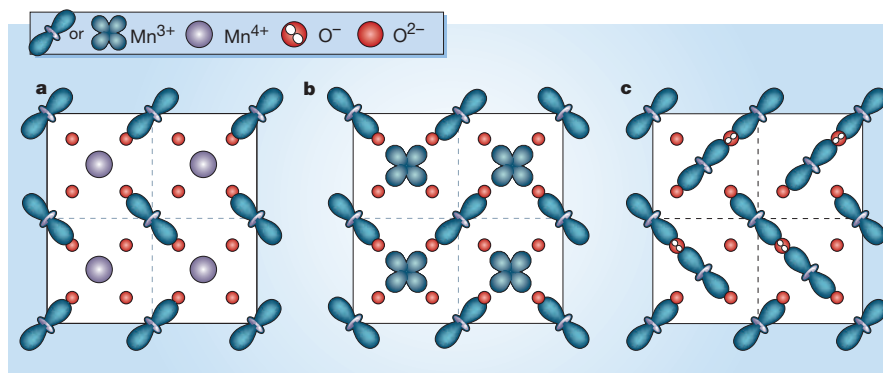

Figure 1 **Called to order.** a, The chequerboard charge-ordered arrangement of Mn^{3+} and Mn^{4+} ions, originally proposed for $(La_{0.5}Ca_{0.5})MnO_3$ by Goodenough[4]. b, A pattern of orbital order for Mn^{3+} ions[7], which implies that there is incomplete occupancy of the oxygen $2p$ shell. c, The ordered arrangement of O^- ions between Mn^{3+} pairs in the Zener polaron model[9,11]. Four of the six oxygen ions forming an octahedral cage around each of the manganese sites are shown; the other two lie above and below the plane.