

tumour cells, the bulk of Hsp90 exists in such an assembly, whereas most of the Hsp90 in normal cells exists in a free form. The Hsp90 in tumour cells also had higher ATPase activity (required for its chaperone function) — a finding that supports the view that tumour Hsp90 is present in fully active chaperone complexes.

So the affinity of 17-AAG for Hsp90 seems to depend on the incorporation of the chaperone into a multi-protein machine. Strikingly, Kamal *et al.* were able to increase the weak affinity of purified Hsp90 for 17-AAG roughly 50-fold by adding components of the chaperone machine. Data on drug levels achieved in patients support these findings — intravenously administered 17-AAG is present in the circulation for many hours at concentrations far exceeding its apparent affinity for tumour Hsp90, but only transiently reaches the high concentration that would allow binding to the free form of the protein found in normal cells⁷. This might partly explain the relative lack of toxicity of 17-AAG in patients.

What makes Hsp90 better able to bind 17-AAG when the protein is part of the super-chaperone complex? At present we can only speculate. An intriguing possibility is that the chaperone complex might catalyse a conformational change in the drug. Indeed, it has been suggested^{8,9} that the structurally similar drug geldanamycin (the 'parent' of 17-AAG) must undergo a conformational change from an open, planar structure to a more compact 'C-clamp' shape before it can bind to Hsp90 (Fig. 1). The energetics of the spontaneous conversion between these two forms is highly unfavourable⁸ (Y.-S. Lee, M. G. Marcu and L. Neckers, unpublished observations). So one or more components of the super-chaperone machine might be much more efficient than free Hsp90 at catalysing a conformational change in drugs such as 17-AAG; alternatively, the complex might potentiate the ability of Hsp90 itself to do so. Both possibilities are feasible. For example, association with other chaperones has been shown to stimulate the normally weak ATPase activity of Hsp90 (ref. 10). And other components of the Hsp90 multi-chaperone complex possess an intrinsic ability to modulate client-protein conformation¹¹. Does the Hsp90 super-chaperone machine view 17-AAG as a protein in need of refolding? Further experiments will be needed to answer this question.

Meanwhile, modifications of 17-AAG and other geldanamycin derivatives are being developed that spontaneously form the C-clamp conformation in solution. It will be interesting to compare their affinity for tumour Hsp90 with that for Hsp90 from normal cells — if they do not retain preferential binding to tumour Hsp90, will they also lose their tumour-cell-specific toxicity? The

study by Kamal *et al.*² suggests that subverting the natural rules of attraction that determine 17-AAG binding to Hsp90 might prove to be counter-productive. Instead of developing drugs with a higher affinity for Hsp90, what might be needed are compounds that have bigger differences in the affinities with which they bind the two forms of Hsp90.

Kamal and colleagues' findings will undoubtedly affect the future design of Hsp90 drugs, but the study also has general implications for anticancer drug development. It suggests that it is not enough to identify a potential molecular target — the drugs directed against that target must also be assessed in an appropriate cellular context. ■

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Applied physics

Spintronics gets a magnetic flute

Jonathan Sun

Magnetic-memory devices of the future could be based on 'spintronics', through switching the directions of electron spins. New work confirms the physics behind a spin-switching mechanism.

Progress in understanding the microscopic behaviour of electrons continues to open up new frontiers for materials and device research, and vice versa. Watching how electrons move, at high current density, through structures that are less than 100 nm in size has revealed a wealth of new physics based on the 'spin' properties of these particles, and

potentially a new class of electronic device: a spin-transfer switch for magnetic-memory 'spintronics'. Experiments reported by Kiselev *et al.*¹, on page 380 of this issue, have now proved the nature of the physics at play.

A magnet usually responds to an electric current because of the magnetic field generated by the current. But if the magnet is

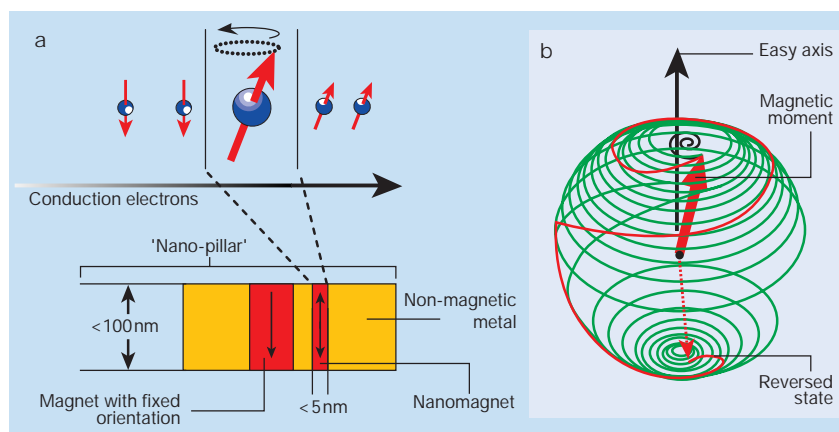


Figure 1 **Magnetic excitation and switching through spin transfer.** a, As conduction electrons pass a magnet, their spins preferentially align in the magnet's direction. As the electrons encounter a nanomagnet, sandwiched between layers of non-magnetic material close to the fixed-orientation magnet, the direction of their spins is repolarized to match that of the nanomagnet. As a result, the nanomagnet's magnetic moment begins to precess, turning like a spinning-top about its axis. b, If the current (that is, the rate of electrons passing) is below a threshold value, the nanomagnetic moment relaxes back to its 'easy' axis (black); if the current is just above threshold, the moment follows many cycles of precession until its direction is reversed (green); when the current is well above threshold, the moment quickly reaches its reversed state (red).

smaller than 100 nm or so in size, a new force is expected to emerge²⁻⁴. When the electrons that constitute the current pass through a magnetic conductor, their spins will become preferentially aligned to the magnetic direction — that is, they are ‘spin-polarized’. These spins may be repolarized into a new direction when they encounter another magnet (Fig. 1a). In repolarizing the current, the nanomagnet experiences a torque (or turning force) associated with the change in angular momentum that occurs from the rotation of the electron spins. This spin-transfer torque can pump enough energy into the nanomagnet for its magnetic moment to precess — that is, it moves at microwave frequencies around the symmetry axis with ever-increasing amplitude until it reverses its orientation, accomplishing a magnetic switch (Fig. 1b).

The spin-transfer mechanism is both unique and efficient. It is unique because it relies on the amplification of magnetic precession. Under spin-transfer excitation, such precession can even become persistent under balanced conditions with a steady current and a static magnetic field. The mechanism is efficient because, theoretically, it would need a current of only a few hundred microamperes to reverse the moment of a nanomagnet whose reversal would otherwise

require the action of a very strong magnetic field (of the order of a tesla)⁵. This makes the spin-transfer mechanism very interesting as a means of writing magnetic memory.

The current-driven reversal of a nanomagnet has been seen in experiments⁵⁻⁸, with observations that are consistent with a spin-transfer mechanism. The presence of spin-transfer dynamics at microwave frequencies has also been implied by earlier work⁹ in which a spin-transfer junction was irradiated with microwaves. To definitively prove the presence of a spin-transfer mechanism, however, the reverse microwave effect should be sought — that is, the persistent emission of microwaves (generated as the nanomagnet moment precesses) from a device through which current is flowing. This would be a unique signature for spin transfer and impossible for a current-induced magnetic field to produce.

This is exactly what Kiselev *et al.*¹ have done. They attached a broadband microwave receiver to a painstakingly fabricated, magnetic ‘nano-pillar’ — two interleaved layers of magnetic and non-magnetic materials, 70 nm by 130 nm in lateral size. The electron spin direction is set as the current passes through the thicker (fixed) magnetic layer, about 40 nm thick (Fig. 1a). As the current then moves into the much thinner magnetic

layer (3 nm thick), it creates a spin-transfer torque on the magnetic moment of this layer, which emits microwaves as its moment precesses continuously under spin-transfer excitation. By detecting this microwave radiation, Kiselev *et al.* were able to map out the oscillation strength at different frequencies as a function of the electric current and magnetic field, and then to compare this map quantitatively with a model calculation.

It is a very convincing experiment. The only input is a steady electric current. The output undeniably contains microwave emission, in the expected frequency range. Through the spin-transfer mechanism, a current is seen to excite high-frequency magnetic precession, much like the flow of air through a flute excites an audible air vibration.

A magnetic flute sounds like music to the ear for spintronics. What future will it hold for computer memory? In the short term, this will depend critically on two factors. First, the threshold current density needs to be lowered: integration with existing electronic technology would require switching currents of less than 10⁵ to 10⁶ amperes per square centimetre, but for present spin-transfer switches these are more than 10⁷ amperes per square centimetre. Second, read-out signals need to be larger, which means that the resistance of a spin-transfer

Zoology

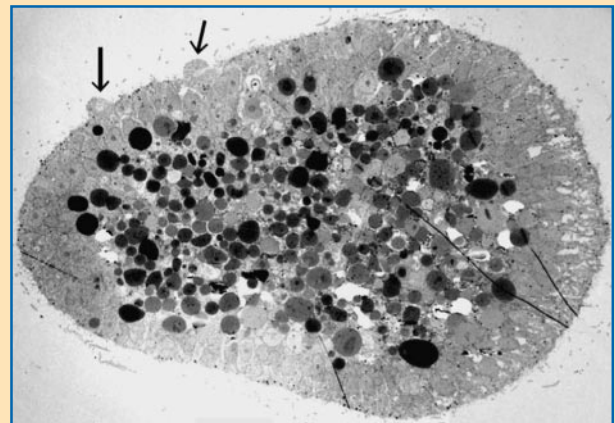
Light touch on the rudder

The larva of the box jellyfish *Tripedalia cystophora* is an uncomplicated creature: it consists of only five cell types. But studies of the animal and of one cell type in particular, the light-sensitive ‘ocellus’, have produced an intriguing set of observations. Most strikingly, the larvae seem not to have a nervous system of any kind to which the photoreceptors could be connected. In the words of Karin Nordström and colleagues, whose work it is, the photoreceptors are “self-contained sensory-motor entities” (*Proc. R. Soc. Lond. B* doi: 10.1098/rspb.2003.2504).

The life cycle of box jellyfish has three phases: a swimming larval stage; a stationary polyp; and the medusa, the familiar jellyfish form, again free-swimming, which in this case is square in cross-section (hence the name of the group). The larva is pear-shaped, but only about 200 µm in length. Tooled up with a transmission electron microscope, Nordström *et al.* set about looking at it in detail.

An individual larva has 10–15 ocelli, two of which are arrowed in this micrograph of the whole organism. Each consists of a single cell, and together they form an array around the rear-end of the animal relative to the direction of movement. The cell contains a ‘cup’ of screening pigment, which is filled with structures that Nordström *et al.* argue are the light-sensing devices. The cups point out at an angle towards the front of the animal. In swimming, the animal also rotates continually (at about two turns per second), so the photoreceptors constitute a scanning system of the light conditions ahead of it.

Another feature of each ocellus is a protruding hair-like cilium. Certain cilia can themselves act as photoreceptors. The authors think that that’s not the case here: such a function requires heavy modification, not evident in the ocellar cilia of the *Tripedalia* larva. So could the cilium be functioning as an active motor? Again no, it seems. Another larval cell type bears cilia for propulsion;



and the ocelli don’t have the extra power packs, in the form of mitochondria, that would be expected in a system that has the dual functions of light-sensing and propulsion.

The explanation that Nordström *et al.* plump for is that the function of the ocellar cilia is that of rudders. They control a larva’s swimming direction by flexing and stretching, steering it towards (or away

from) desirable (or undesirable) conditions signalled by the light regime.

There remains the question of why an array for sensing light conditions ahead of an organism should be set at the back of the body, rather than at the front. Nordström *et al.* have an explanation for that too. It’s because the sensor is also a rudder, and rudders work best at the stern. **Tim Lincoln**

switch must be increased while still keeping its magnetic response at an adequate level. There is no lack of challenges ahead, but Kiselev *et al.*¹ have shown that we are on the right path. ■

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Plant biology

Water gate

N. Michele Holbrook and Maciej A. Zwieniecki

Flooding reduces the ability of roots to absorb water. The molecular basis for this paradox involves the regulation of water-channel proteins by the pH inside root cells.

Plants are among the thirstiest of creatures. Of the more than 60 trillion tonnes of water that cycles each year from the land to the atmosphere, nearly two-thirds passes through the bodies of living land plants¹. Plants require these large amounts of water because their mode of acquiring carbon dioxide exposes their interior to the drying power of the atmosphere. Without water, forests become stunted, agricultural yields decline, and house plants shrivel and die. Yet, as is so often the case, too much of a good thing can also be a problem. Flooding typically reduces both photosynthesis and growth, and, in the short term, can even cause plants to wilt. This paradox of famine in the midst of plenty arises from the fact that flooding causes roots to become less permeable to water. On page 393 of this issue², Tournaire-Roux and colleagues elucidate a cascade of molecular events that links the low oxygen levels associated with flooding, via changes in the pH inside cells, to this decrease in root permeability.

The large-scale movement of water from roots to leaves takes place almost entirely through spaces that are not bounded by cell membranes. Only as water enters roots is there substantial evidence that this 'transpiration stream' flows through living cells. The ease with which water can traverse root cells is, to a large degree, governed by the presence of highly selective channel proteins known as aquaporins, specifically those of a subgroup known as 'plasma membrane intrinsic proteins' (PIPs). These proteins are present in the plasma membranes of root cells and enhance the membranes' permeability to water³.

Because of the key role of aquaporins in water uptake by roots⁴, changes in the conductance of individual water channels — a process referred to as 'gating' — are likely to be involved in mediating the effects of flooding. Previous studies have shown that aqua-

porins can be gated by various factors, including enzymatic modification with phosphate groups⁵, intracellular calcium levels^{5,6} and, most recently, protons^{5–8}. But the molecular mechanisms that underlie the regulation of aquaporin permeability — including how it might be connected to flooding — have until now remained elusive.

Gases diffuse around 10,000 times more slowly through water than through air, with the result that roots in flooded soils quickly become exposed to conditions of low oxygen. Early cellular responses to oxygen deprivation include a marked decrease in pH in the cell interior, or cytosol. Tournaire-Roux *et al.*² have now investigated whether these changes are linked to changes in the permeability of roots to water. Using roots of the model plant *Arabidopsis thaliana*, the authors manipulated the pH in the cytosol of root cells in one of three ways: by decreasing the availability of oxygen; by inhibiting respiration; and by loading the roots with acid. In all cases, decreases in cytosolic pH were associated with a decrease in root permeability. Altering the pH outside root cells did not have this effect.

Do decreases in cytosolic pH alter root permeability by affecting the conductance of PIP-type aquaporins? To test this hypothesis, Tournaire-Roux and colleagues inserted aquaporins into the plasma membrane of immature frog eggs. Osmotic swelling assays showed that water influx through most PIP-type aquaporins was selectively blocked by cytosolic acidification. In contrast, the activity of an aquaporin from vacuoles (an intracellular compartment) was insensitive to changes in pH. By using a series of mutant proteins, Tournaire-Roux *et al.* demonstrated that charged amino acids (particularly histidine at position 197) in the cytosolic vestibule of the aqueous pore are responsible for the observed pH sensitivity of the PIPs. These findings provide a detailed

explanation for the mechanisms by which root permeability to water is downregulated in response to anoxia.

What is still unclear, though, is why a plant — flooded or otherwise — would ever choose to restrict water flow through its roots. Roots acclimate to waterlogged soils primarily by forming large gas-filled spaces in the root cortex that provide a low-resistance path for oxygen diffusion⁹. So the physiological significance of Tournaire-Roux and colleagues' findings may lie in the possibility that reductions in root permeability can enhance this morphological acclimation of flooded roots.

This may not be as far-fetched as it seems. Air spaces in the root are formed when specific cells in the root cortex undergo programmed cell death; the cue for this is a build-up of the gaseous hormone ethylene⁹. Flooding leads to an increase in ethylene concentrations in roots, both because anoxia activates an enzyme called ACC synthase, the key biosynthetic enzyme for ethylene, and because waterlogged soils retard the diffusion of the gaseous hormone away from the root. But ethylene accumulation is also affected by the rate at which ACC, the precursor to ethylene, is transported away from the roots in the transpiration stream¹⁰. So downregulation of root permeability could theoretically provide a mechanism that, by reducing the flow of water through roots, accelerates the build-up of ethylene and the transformation of the root into a form that is appropriate for dealing with flooding.

Whether or not this indeed occurs requires further experiments using the sort of genetically modified plants made possible by Tournaire-Roux and colleagues' findings. Plants with pH-insensitive aquaporins could now be engineered, allowing researchers to test whether a decrease in root permeability is required to signal the need for the formation of air spaces. But for now, it is satisfying to see that the paradoxical thirstiness of flooded plants has been placed on firmer ground. ■

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