mal compressibility) change with temperature in a power-law fashion (proportional to negative powers of $(T - T_s)$) and, by extrapolation, would become infinitely large (or diverge) at the 'singular' temperature T_s. Regardless of a genuine phase transition at T_s, these trends may signal dramatic qualitative changes in water's properties in this temperature range. On general theoretical grounds[6], and also on the basis of constraints imposed by available measurements[7], one expects the entropy to fall rapidly in this temperature region, and to stabilize at the smaller rate of change observed near the glass-transition temperature, $T_g = 136$ K (Fig. 3).

There is gathering evidence from computer simulations that the apparent divergences in the dynamic properties of supercooled water discussed by Speedy and Angell[5] (and analogues at different pressures) are to be understood as realizations of behaviour predicted by mode-coupling theory[8]. In its simplified form[9], mode-coupling theory predicts a dynamical transition temperature near which relaxation times change in a power-law fashion and at which they become infinite (that is, relaxation ceases to occur). A more detailed analysis reveals that the relaxation times do not in fact become infinite at the predicted temperature, so instead of describing the glass transition as originally thought, mode-coupling theory defines a 'crossover' temperature (which would be T_s for water at atmospheric pressure) that marks a change in the character of the liquid's dynamics.

At lower temperatures, significant energy barriers are expected to separate distinct arrangements of particles in the liquid, as originally discussed by Goldstein[10], and impede structural rearrangements. The agents of structural relaxation in water nearing room temperature and atmospheric pressure are 'bifurcated bonds'[11] — defects in the hydrogen bond network — that provide a means of structural rearrangement at low energy cost. Computer simulations seem to indicate that the density of such defects approaches zero near T_s. At lower temperatures, the structure of the liquid would be that of a disordered tetrahedral network of hydrogen bonds, whose restructuring requires substantial expenditure of energy.

Many pieces of the puzzle are now in place, but gaps remain. The entropy of water near T_g appears to be too low compared with theoretical estimates of the entropy of a disordered tetrahedral network[12]. Conversely, recent diffusivity measurements[13] of water near T_g appear too high to be compatible with Adam–Gibbs theory, which relates the relaxation times of liquids to their entropy. The drastic changes in the behaviour of water near T_s raises the question of whether such changes are to be expected in other liquids as well. There is also evidence[14] of deviations from Adam–Gibbs predictions above T_s for a variety of liquids, that need to be explained. The biggest gap is perhaps a satisfactory theoretical justification of the Adam–Gibbs relationship, which has so far remained elusive. Exceptions are expected to illuminate, if not prove, the rule. Making sense of water's behaviour, it appears, will sharpen our understanding of supercooled liquids in general. □

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Cell biology

Boa constrictor or rattlesnake?

Tom Kirchhausen

During nervous transmission, neurotransmitter-filled vesicles fuse with the presynaptic membrane. Endocytosis — an uptake mechanism involving invagination of the cell membrane — then follows, returning the fused membrane to the interior of the cell to be recycled. The protein dynamin is found at the neck of each endocytic invagination, or pit, and is essential not only for recycling of synaptic vesicles, but for clathrin-dependent endocytosis from the plasma membrane of all cells.

The accepted role for dynamin is that it acts as a 'pinchase'[1,2] — that is, it self-assembles into a ring around the neck of a budding pit, then changes shape in response to binding or hydrolysis of GTP. It was assumed that this coordinated change in the conformation of the dynamin ring leads to constriction of the neck, and scission. On page 481 of this issue, however, Sever *et al.*[3] propose that dynamin is not a mechanochemical transducer or 'boa constrictor', but that, like all other known GTPases, it acts as a switch, or 'rattlesnake', to regulate the endocytic step.

Dynamin is a relatively large protein made up of four subunits, each of which contains a GTPase module. It is unusual among GTPases because it has a low affinity for GTP compared with the small and the heterotrimeric GTPases, and because its intrinsic rate of GTP hydrolysis is high and dramatically increased by polymerization. Pure dynamin can spontaneously form rings and spirals, and it decorates microtubules and lipid vesicles with helices of similar dimensions. Any condition that leads to ring formation also stimulates dynamin's GTPase activity.

The accepted model for how dynamin works arose after a variety of experiments showed that, if dynamin function is inhibited, there is no vesicle scission. When GTP hydrolysis was blocked (using a non-hydrolysable analogue[4] or mutations in the GTPase domain[5]), or when dynamin's ability to self-assemble on membranes was

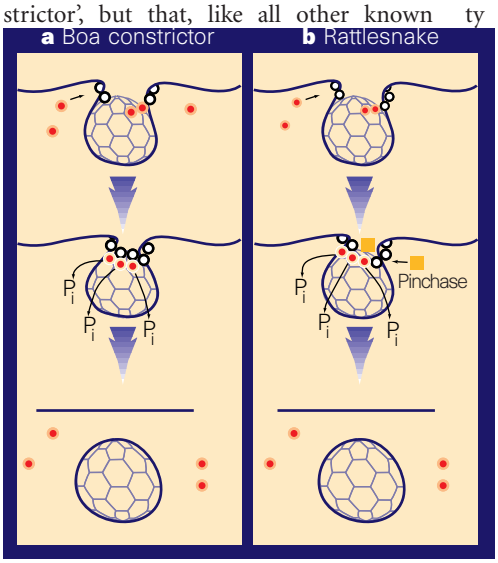

Figure 1 **Two models for the action of dynamin. On clathrin assembly, the membrane deforms into buds. Dynamin tetramers (in the GDP-bound state; red) are recruited to the neck, which acts as a template for formation of the dynamin spiral. Bound GDP is exchanged for GTP, and on completion of a spiral around the neck of a bud — when dynamin tetramers at one end of the spiral stack on tetramers from the other — GTP hydrolysis is accelerated.** a, **The previous model suggested that dynamin acts like a 'boa constrictor' — GTP hydrolysis sends the conformational signal to proceed with scission.** b, **The results of Sever *et al.*[3] indicate that dynamin could recruit 'pinchase', which carries out scission, to the neck.**

inhibited[6–8], endocytosis no longer occurred. Furthermore, if GTP was added to dynamin rings assembled around lipids, these lipid tubes fragmented into small vesicles[9].

Sever and colleagues[3] now show that inhibition of GTP hydrolysis can, in fact, *increase* the rate of endocytosis, raising significant questions about the original model. But what did these authors do that was different? From their earlier work, they knew that dynamin's carboxy-terminal region contains a GTPase effector domain (GED), which is distinct from the GTPase domain (located at the amino terminus). The GED is required to stimulate dynamin's GTPase activity when it forms rings — an effect that could be due either to an increase in the rate at which GDP is exchanged for GTP, or to activation of GTP hydrolysis.

Sever *et al.* first show that the GED acts as a GTPase activating protein (GAP), both when the GTPase domain is isolated in solution and in polymerized rings of intact dynamin. Then, guided by known mutants of rasGAP (a GAP for another GTPase, Ras), they created two dynamin mutants, dyn(K694A) and dyn(R725A). These mutant proteins turned out to have defects in the assembly-dependent GAP activity. Whereas dyn(R725A) directly affects the catalytic GAP function, dyn(K694A) partially interferes with the self-assembly of dynamin.

Because mutations in the GED impair dynamin assembly — and because GEDs associate with each other — we can assume that the GED domain forms part of the contact between stacked dynamin rings (forming the spirals that wind round on themselves). Presumably, dyn(K694A) allows the dynamin spirals to form, but with impaired communication between the rings, reducing stimulation of the GTPase activity. So these new dynamin mutants should be functionally equivalent to mild GTPase mutants, and would be expected to show impaired endocytosis. It was a surprise, then, that Sever *et al.*[3] obtained exactly the opposite result. Overexpression of dyn(K694A) or dyn(R725A) leads to accelerated endocytosis of a probe molecule, transferrin, indicating that GTP hydrolysis, although required to complete the fission cycle, is not rate limiting for endocytosis.

So a new concept for dynamin function emerges (Fig. 1). GDP–dynamin is recruited to the forming bud, where it assembles into rings. Dynamin's intrinsic GAP is activated on completion of a spiral around the neck of the bud, when dynamin tetramers from one end of the spiral stack onto tetramers at the other end (rather than by lateral interactions along the dynamin ring). GTP hydrolysis then sends a signal to as-yet-unidentified effectors to proceed with fission. So the GTPase domain has to do a balancing act: too rapid GTP hydrolysis would prevent ring formation or block recruitment of the pinchase machinery to the GTP-bound ring; but a complete failure of GTP hydrolysis would not activate fission.

Presumably, if the neck of the vesicle is too large this will preclude efficient lateral dynamin associations (dynamin rings do not form on templates larger than 30 nm across). One end of the spiral cannot connect up with the other, and the GTPase will not be activated. By sensing the dimensions of neck constriction dynamin acts as a checkpoint, in effect coordinating the last step of budding. Sever *et al.* predict that if dynamin forms an incomplete ring it should have low GTPase activity (to allow recruitment of the fission machinery), and that only after the rings stack should there be a dramatic increase of GTPase activity.

But the new model is not without problems. We must assume that the GTPase mutants studied previously did not just affect the rate of GTP hydrolysis, but that they also inhibited the interaction with unknown downstream effectors. We must also explain why Sever *et al.* find that endocytosis is increased. Perhaps the delay in GTP hydrolysis allows a deeper dynamin spiral to form, increasing the number of binding sites for downstream effectors or prolonging their activation. And we must find out why dynamin changes shape on binding GTP — does this change allow the fission machinery to bind, or does it allow the dynamin spirals to interact, leading to rapid GTP hydrolysis?

Although one possible conclusion is that dynamin is not the true pinchase, the system could, in theory, work with dynamin alone. The pinching would have to happen after the conformational change that occurs on binding GTP, which has been assumed to cause vesicle scission. But there could be a second, more elusive, conformational change after GTP hydrolysis, before the dynamin spiral falls apart. And perhaps the GTPase defect in Sever and colleagues' mutants allows a longer spiral to assemble, which is why the fission reaction is faster. □

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Daedalus

New eyes

The human eye, as the spectacles industry shows, is astonishingly imperfect. We cannot blame evolution; our primitive ancestors must have had perfect vision for their spacious world. But then civilization invented craft-work, reading and other close-up activities. Young eyes had to adapt to very short distances. Daedalus surmises that such repeated stresses on the lens of a growing eye give rise to short-sightedness, and possibly astigmatism too.

Now almost every organ of the body is flexible enough to adapt to the demands made on it. Why does the eye alone persist in useless errors such as astigmatism? One theory blames the invention of spectacles. Once an optometrist has prescribed corrective lenses for your eyes, they are fixed in their imperfection. Any changes they might make will make your vision worse; so they have no 'motive' for improvement. Daedalus now has a remedy.

These days, he points out, children (and indeed many adults) spend most of their waking hours in front of TV, computer or games-machine video screens. So he is devising a screen which appears at optical infinity, like the 'head-up' display in a fighter cockpit. For the dwindling numbers of young book-readers, a similar infinity book-viewer should also be possible. Users of these devices should reach adult life in much better ophthalmic shape.

To correct remaining errors, Daedalus recalls a flexible spectacle lens he once invented, made of the piezoelectric polymer PVDF. It was deformed into the desired shape by a pattern of voltages applied through transparent electrodes and maintained by a small battery-powered circuit. As the wearer's eyes altered, his optometrist simply updated the voltages. Daedalus now reckons that these cunning spectacles should be set so as to under-correct the wearer's vision slightly. His eyes will therefore have an incentive to 'learn' the slight adjustment needed for sharp vision. When they have done so, the 'training glasses' will be under-corrected again, provoking further adaptation. In due course the glasses will be reduced to plane lenses. They can then be discarded, for the wearer will have perfect vision.

Thus the optimization mechanism, which our eyes must possess, will be put to good use at last. We will recover the keen vision of our distant ancestors, at least until middle age when our lenses start to harden. Even then, Daedalus's training glasses may be able to encourage a valuable extra degree of optical flexibility.

David Jones