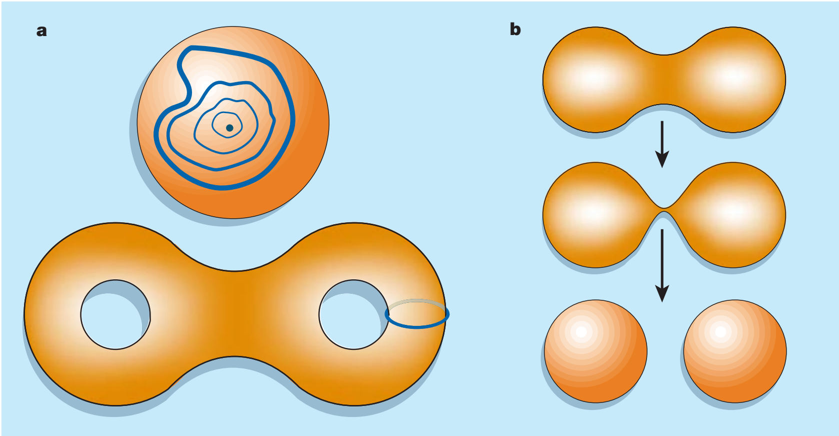


Figure 1 **Testing topology.** a, **On the surface of a sphere, every loop can be deformed to a single point. But on any other surface, such as the two-holed torus shown here, some loops cannot be deformed to a point. Topologically, these are two-dimensional objects, but in three dimensions the 'shrinkability' of loops becomes the basis of Poincaré's conjecture.** b, **Perelman's solution[2,3] to the Poincaré conjecture starts with 'Ricci flow': to achieve constant curvature of its surface, an object such as this dumbbell-shaped bubble splits into two round ones.**

identified is flat, and topologically that is a torus. Finally, tori with two or more holes can be realized as surfaces of constant negative curvature.

Thurston suggested that something similar should happen in three dimensions. He proved that exactly eight different 'geometries' can occur. It turned out to be too much to expect every three-dimensional space to have a single canonical geometry, but Thurston's 'geometrization conjecture' asserted the next best thing: every three-dimensional space can be cut up, in a systematic way, so that each piece has precisely one of those eight geometries. This new conjecture was much more ambitious than Poincaré's: it aimed at understanding all three-dimensional spaces, not just the three-sphere. In particular, the Poincaré conjecture was an easy consequence of the geometrization conjecture: the condition on loops meant that only one piece would be needed, and the associated geometry must be that of the three-sphere.

Perelman's work[2,3] is a new approach to the geometrization conjecture. If it pans out, it will constitute a huge leap forward in three-dimensional topology and mathematical physics. It is based on the Ricci flow, an idea of Richard Hamilton's[5]: if a soap bubble is deformed away from its normal round shape, surface tension will pull it back to a perfect sphere. The Ricci flow is an analogous way to deform any surface so that its curvature 'tries' to become constant. Along the way, though, it may have to split into separate pieces; for example, a dumbbell-shaped bubble must break up into two round ones (Fig. 1b).

Hamilton defined the Ricci flow in three dimensions, and developed a programme to prove that when a three-dimensional 'bubble' follows the flow, the pieces it breaks into are essentially those predicted by the geometrization conjecture. Perelman's papers do not carry out the entire Hamilton programme, but it looks as though they might establish enough of it to prove the geometrization conjecture. That in turn will prove the Poincaré conjecture.

If everything hangs together, a 99-year search is at an end. If not, Perelman's papers will still shed a huge amount of light on the Ricci flow, which is important in quantum field theory and pure mathematics, and may well pave the way to an eventual proof of the two conjectures. Either way, the spin-off is

Molecular physiology

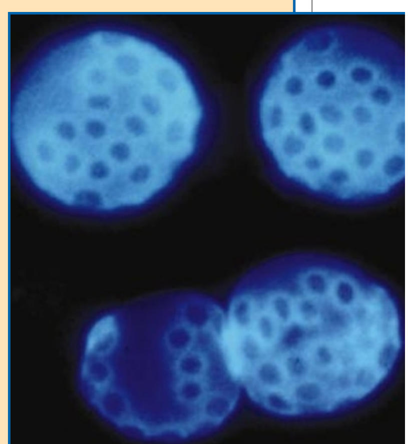
Tuned for longer life

Sometime early in the sixteenth century, 40-year-old Luigi Cornaro decided to cut his food intake dramatically for health reasons — he then lived on to the age of 102, writing treatises on the merits of his abstemious lifestyle. Five centuries later it is not clear whether severely limiting food consumption can, in general, extend human life, although calorie restriction does indeed extend the lifespan of commonly studied organisms such as yeast, nematode worms and mice. The latest turn of events is described by David A. Sinclair and colleagues elsewhere in this issue (R. M. Anderson *et al. Nature* **423,** 181–185; 2003). In studies of the yeast *Saccharomyces cerevisiae*, the researchers have pinpointed an enzyme, Pnc1, that seems to be a key link between environmental stress, metabolic energy and lifespan.

Sinclair and colleagues explore the control of an intriguing protein named Sir2 (silent information regulator 2), which has been shown to extend the lifespan of various laboratory organisms. Sir2 is a histone deacetylase, found in cell nuclei, where it is thought to turn genes on and off by influencing the packing of chromosomal DNA. Sir2 action requires the ubiquitous energy cofactor NAD^+, generating nicotinamide in the reaction, and nicotinamide also turns out to be a potent inhibitor of Sir2. But how exactly does metabolic energy affect Sir2 activity and lifespan?

The involvement of nicotinamide led Sinclair and co-workers to Pnc1, an enzyme that breaks nicotinamide down to nicotinic acid. They find that increasing the levels of Pnc1 in yeast leads to a dramatic lengthening of lifespan, as nicotinamide depletion results in Sir2 activation (yeast lifespan is usually measured by the number of buds, or daughters, produced by a given cell, individual bud scars showing up as darker circles on the blue-stained yeast cells shown here). Various types of stress are known to extend yeast life, including glucose restriction, high temperatures and elevated salt concentrations, and Pnc1 levels are raised in all of these circumstances. This suggests that Pnc1 is a key regulator of Sir2, and is responsible for tuning a yeast's lifespan and reproductive capacity to the quality of its environment.

Whether these ideas apply to multicellular organisms will have to be tested in worms and mice. On the one hand, one might imagine that mechanisms designed to protect single yeast cells from the vicissitudes of their environment would not be needed in more complex organisms, which possess homeostatic systems designed to protect and nourish individual cells.



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On the other, lifespan is likely to be controlled by evolutionarily ancient mechanisms. So understanding Sir2 regulation in multicellular organisms, and identifying the genes that are controlled by Sir2 and its relatives, should prove generally rewarding.

Richard Turner