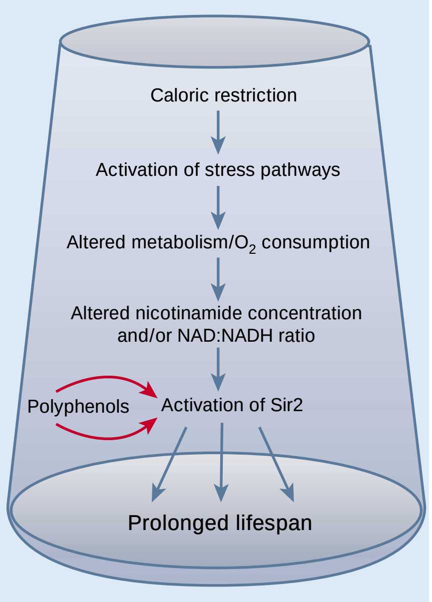

Figure 2 **The pathway to long life. When yeast cells are deprived of food (caloric restriction), stress pathways are activated and the cells are forced to derive energy from alternative substrates. This produces alterations in oxygen consumption, which in turn affects the ratio of oxidized to reduced forms of nicotinamide adenine dinucleotide (NAD:NADH) or the concentration of its derivative nicotinamide. NAD stimulates the activity of Sir2, which in turn chemically modifies several proteins that are involved in cellular processes affecting longevity. Howitz *et al.*[1] have found that plant polyphenols directly activate Sir2 and seem to mimic the beneficial effects of food restriction. Related pathways may exist in higher organisms.**

societies, eating less for the sake of longevity is not likely to gain widespread compliance. More palatable would be a drug that could mimic the effects of caloric restriction — a chemical that would allow the individual to eat normally, while tricking the body to respond as though food were in short supply. Such mimetics might be thought of as the pharmaceutical equivalent of 'eating your cake *without* having it'.

Studies of longevity in simple organisms have greatly expanded our understanding of how caloric restriction might increase lifespan. In the budding yeast *Saccharomyces cerevisiae*, nutrient withdrawal extends longevity through a pathway that requires the enzyme Sir2 (ref. 3). Overproducing this enzyme can prolong the life of yeast grown under normal nutrient conditions[4]. Similarly, in the evolutionarily more advanced worm *Caenorhabditis elegans*, increased expression of the worm's version of Sir2 has also been shown to extend lifespan[5].

The Sir2 enzyme belongs to a large family of evolutionarily conserved molecules termed sirtuins. In lower organisms, such as yeast and worms, these enzymes regulate a wide range of cellular activities that affect lifespan, including modulating how tightly DNA is packaged inside cells. In mammalian cells, sirtuins act as regulators of programmed cell death and differentiation (cell maturation)[6]. Sirtuins exert their effects on these cellular processes by removing acetyl groups from specific target proteins. Interestingly, this 'deacetylase' function depends on the intracellular concentration of a molecule involved in metabolism — nicotinamide adenine dinucleotide (NAD). This molecule can exist in two states, oxidized and reduced, and it is the oxidized form that greatly enhances Sir2 activity. It seems that in yeast, caloric restriction may regulate Sir2 activity, and hence prolong life, by subtly shifting the ratio of oxidized to reduced NAD or by altering the level of the NAD derivative nicotinamide[7,8]. Together, these findings suggest a potential mechanism by which metabolic activity and lifespan might converge (Fig. 2).

Building on the knowledge that caloric restriction prolongs longevity through Sir2, Howitz *et al.*[1] searched for a small molecule that could activate this enzyme directly. Using several chemical 'libraries', these investigators discovered two related compounds that each stimulated Sir2 activity. Both compounds belong to a family of molecules called polyphenols — products of metabolism in plants. One of the most widely studied of these compounds is resveratrol, a plant polyphenol that is abundant in red wine and is reputed to underlie many of wine's health-related benefits. Interestingly, resveratrol seemed to be the most potent Sir2 activator of all of the plant polyphenols tested. The authors showed that this chemical prolonged the lifespan of yeast by approximately 70%. The extension of longevity was entirely dependent on Sir2 — yeast strains deficient in this enzyme did not benefit from resveratrol treatment.

Could plant polyphenols be the long-sought elixir of youth? Previous studies have hinted that these compounds have several potential health benefits, especially in protecting against age-related maladies such as cancer, neurodegeneration and atherosclerosis[9]. Interestingly, caloric restriction is also thought to protect against these diseases. But caution is warranted before endorsing a strict Cabernet Sauvignon-based regimen. First, the concentration-dependent effects of resveratrol as observed by Howitz *et al.* were complicated. At relatively low doses these molecules stimulated sirtuin activity, but, at least in certain assays, higher doses had the opposite effect. This is not an ideal characteristic for a pharmaceutical drug. Second, and more importantly, life extension in yeast is a long way from life extension in higher organisms. Indeed, how sirtuins function in mammalian ageing is not yet known.

Further unravelling of the molecular signalling pathways that accompany caloric restriction should provide clues to other potential targets for drug development. In a strange way, however, the study by Howitz *et al.* suggests that Ponce de León's misbegotten quest for a fountain of youth surrounded by flowering plants was not so delusional after all. The explorer's only mistake was that he kept sampling the waters, when he should have been testing the plants. ■

Toren Finkel is at the Cardiovascular Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892-1622, USA.
e-mail: finkelt@nih.gov

1. Howitz, K. T. *et al. Nature* **425,** 191–196 (2003).
2. Masoro, E. J. *Exp. Gerontol.* **35,** 299–305 (2000).
3. Lin, S. J., Defossez, P. A. & Guarente, L. *Science* **289,** 2126–2128 (2000).
4. Kaeberlein, M., McVey, M. & Guarente, L. *Genes Dev.* **13,** 2570–2580 (1999).
5. Tissenbaum, H. A. & Guarente, L. *Nature* **410,** 227–230 (2001).
6. Denu, J. M. *Trends Biochem. Sci.* **28,** 41–48 (2003).
7. Anderson, R. M. *et al. Nature* **423,** 181–185 (2003).
8. Lin, S.-J. *et al. Nature* **418,** 344–348 (2002).
9. Tapiero, H., Tew, K. D. & Matthe, G. *Biomed. Pharmacother.* **56,** 200–207 (2002).

Condensed-matter physics

Vortices and hearts

John Clarke

A single vortex of flux, formed inside a superconducting Josephson junction, has been detected undergoing quantum tunnelling — a feature that could be developed into a quantum bit.

Vortices are ubiquitous — from the mythical whirlpool of Charybdis in the Strait of Messina, to the putative cosmic strings that were frozen into space-time shortly after the Big Bang. In superconductors, too, swirling currents generate vortices of flux. On page 155 of this issue, Wallraff *et al.*[1] show that a single flux vortex can undergo macroscopic quantum tunnelling[2] to escape from a potential well inside a long Josephson junction; they also show that the vortex's energy in the controllable well is quantized. These observations of uniquely quantum phenomena mean that this system becomes another entrant on the growing slate of candidates to make superconducting 'qubits' for quantum computing.

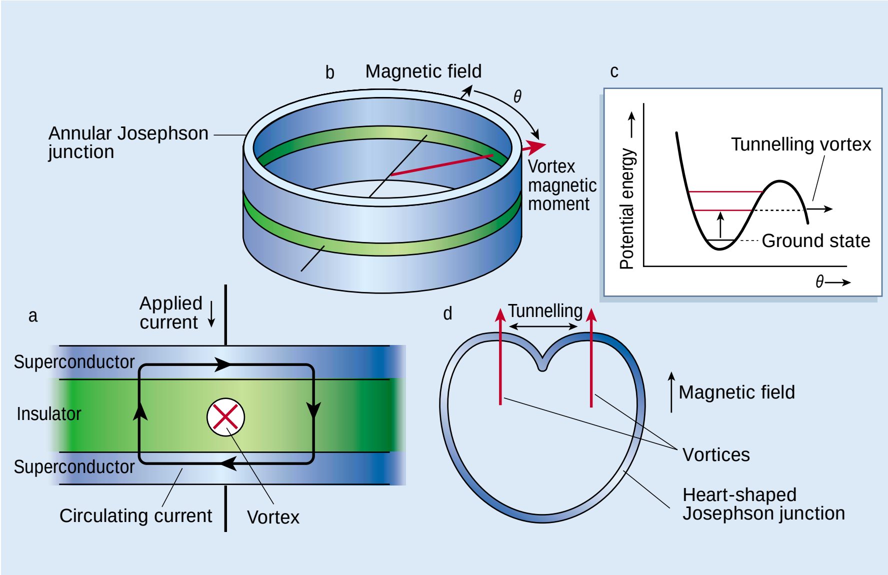

Figure 1 **Quantum tunnelling and the single vortex.** a, **The long Josephson junction (shown here in cross-section) consists of two superconducting films separated by an insulating layer through which Cooper pairs of electrons can tunnel. The circulating supercurrent creates a vortex.** b, **In the annular version of the junction[1], the magnetic moment of the vortex is at an angle θ to the direction of an applied magnetic field.** c, **As θ changes, the potential energy of the vortex varies periodically (with cos θ), reaching a minimum when the magnetic field and moment are aligned. A current applied across the junction tilts the potential well, and microwave radiation excites the vortex from its ground state to a higher energy level from which it is more likely to escape the potential well through tunnelling.** d, **If the annular Josephson junction were instead a heart-shaped junction, with two minima of potential energy, the system could make a useful quantum bit: a single vortex could tunnel between states in the two wells, at any instant being in a superposition of both states.**

Two kinds of vortex can develop in a superconductor. The first, the Abrikosov vortex, penetrates certain (type II) superconductors above a critical value of applied magnetic field. It can hop between pinning sites under thermal activation, causing dissipation in current-carrying wires and generating noise in sensors such as superconducting quantum interference devices (SQUIDs). Quantum tunnelling of Abrikosov vortices remains controversial. Wallraff and colleagues' work[1], however, is concerned with the second kind of vortex, the Josephson vortex. This exists in a Josephson junction, formed by a sandwich of two superconducting layers and a thin insulating layer, through which electrons in the form of Cooper pairs can tunnel coherently (Fig. 1a).

In an elegant twist on the conventional linear junction, Wallraff *et al.* made an annular junction between two narrow rings of the superconductor niobium, stacked one on top of the other (Fig. 1b). The flux in each ring is quantized in units of $h/2e$ (where h is Planck's constant and e is the charge on an electron); when this flux quantum number differs between the two rings by one unit, the difference is manifested as a single vortex in the junction. If a magnetic field is applied in the plane of the annulus, at an angle θ to the magnetic moment of the vortex, the potential energy of the system is proportional to the cosine of θ (Fig. 1b) — so the energy of the vortex is periodic in θ, with a minimum when the applied field and the vortex moment are parallel.

If an external current is then applied to the junction, across the two superconducting layers, the resulting imbalance in the tunnelling currents produces a force on the vortex, tilting its potential well and lowering — but not removing — the barrier to escape. At high temperature, in the classical regime, the vortex can escape from this well, lifted by thermal energy over the barrier it forms. At low temperature in the quantum regime, however, the vortex escapes by macroscopic quantum tunnelling through the barrier (Fig. 1c).

Wallraff *et al.*[1] investigate the escape process by ramping up the current that is flowing through the annular junction until they see a jump in the voltage across the junction, which corresponds to the vortex beginning to rotate rapidly around the annulus (the voltage is proportional to the vortex's velocity). This 'depinning' of the vortex, and its subsequent escape from the well, is a stochastic process, so repeated measurements yield a distribution of switching currents at which depinning occurs. As the temperature is lowered, the width of this distribution shrinks, indicating a crossover from the classical regime to macroscopic quantum tunnelling in the quantum regime.

A second demonstration of the quantum nature of the vortex is the quantization of its energy in the potential well[3]. The applied magnetic field and current can be adjusted so that the well contains (say) three energy levels; absorbing radiation of specific frequencies will induce the vortex to make a transition between them. Typically, the transition frequency from the ground (lowest) state to the next energy level up is about 10 GHz, so that at a temperature of, say, 25 mK — corresponding to a frequency of about 0.5 GHz — the vortex is virtually certain to be in its ground state. The probability that the vortex will tunnel from the ground state is low, because the barrier is relatively high and wide (Fig. 1c). But irradiating the system with 10-GHz microwaves causes the vortex to make a transition to its excited state, from which the tunnelling escape rate is much higher. By observing a peak in the escape rate as a function of microwave frequency, Wallraff *et al.* demonstrate that the energy of the vortex in the well is quantized, and depends on the magnetic field and current exactly as predicted.

These observations of macroscopic quantum tunnelling and quantized energy levels in a Josephson junction are in themselves not new. In fact, they were first demonstrated in a small, current-biased junction[3], and then in an 'rf SQUID' — a Josephson junction shorted by a superconducting loop[4]. But the experiment performed by Wallraff *et al.*[1] is unique in that it clearly addresses the behaviour of a single vortex. Consequently, an exciting direction to explore with this annular junction is its potential as a qubit in a quantum computer.

There have been rapid developments in superconducting qubits, in which two states of a variable must exist in a quantum superposition. This superposition has been demonstrated in a single, current-biased Josephson junction, where it involves two neighbouring energy levels in the well[5]; in a SQUID, where it involves the up and down flux states[6,7]; and in the charge of a tiny superconducting island, where it involves two states differing by a single Cooper pair[8,9]. Evidence for the entanglement of two superconducting qubits has also been reported[10,11].

How would one make a Josephson-vortex qubit? One possibility is to base it on two of its quantized energy levels, analogous to the single-junction qubit[5]. A more intriguing idea, already suggested by Wallraff *et al.*[12], is to make a heart-shaped qubit (Fig. 1d). The two lobes, combined with the applied field, create a double-well potential between which the vortex tunnels, in analogy with the SQUID qubit. Superposition of the two states resolves their degeneracy, forming two distinct energy levels. To evaluate the usefulness of the vortex qubit, its relaxation time and decoherence time should be measured — that is, how long it remains in the excited state and how long the coherent quantum superposition lasts. As with other superconducting qubits, the enemies are noise, dissipation and resonances in the environment and in the structure itself. Beating these down remains a great challenge for the field. ■

John Clarke is in the Department of Physics, University of California, Berkeley, and the Materials Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720, USA.
e-mail: jclarke@physics.berkeley.edu

1. Wallraff, A. *et al. Nature* **425,** 155–158 (2003).
2. Caldeira, A. O. & Leggett, A. J. *Ann. Phys.* **149,** 374–456 (1983).
3. Martinis, J. M., Devoret, M. H. & Clarke, J. *Phys. Rev. Lett.* **55,** 1543–1546 (1985).
4. Rouse, R., Han, S. & Lukens, J. E. *Phys. Rev. Lett.* **75,** 1614–1617 (1995).
5. Martinis, J. M., Nam, S., Aumentado, J. & Urbina, C. *Phys. Rev. Lett.* **89,** 117901 (2002).
6. Friedman, J. R., Patel, V., Chen, W., Tolpygo, S. K. & Lukens, J. E. *Nature* **406,** 43–46 (2000).
7. Chiorescu, I., Nakamura, Y., Harmans, C. J. P. M. & Mooij, J. E. *Science* **299,** 1869–1871 (2003).
8. Nakamura, Y., Pashkin, Yu. A. & Tsai, J. S. *Nature* **398,** 786–789 (1999).
9. Vion, D. *et al. Science* **296,** 886–889 (2002).
10. Pashkin, Yu. A. *et al. Nature* **421,** 823–826 (2003).
11. Berkley, A. J. *et al. Science* **300,** 1548–1550 (2003).
12. Wallraff, A., Koval, Yu., Levitchev, M., Fistul, M. V. & Ustinov, A. V. *J. Low Temp. Phys.* **118,** 543–553 (2000).

Behavioural ecology

Father knows best

Paul W. Sherman and Bryan D. Neff

When females mate with several males, paternity may be uncertain. But male savannah baboons are seldom confused: when intervening in fights between youngsters, they generally support their own offspring.

Behavioural ecology is the study of how natural selection shapes behaviour in relation to ecological and social conditions. A fundamental principle is that individuals should promote the spread of their own genes over those of competitors. For example, adults sacrifice themselves to defend and nourish offspring. But they try to avoid providing assistance to non-relatives (that is, they avoid 'misdirecting' their nepotism), usually by guarding their mate against other sexual liaisons and attempting to distinguish their own offspring from unrelated young[1].

Mistakes in discrimination are most likely for males of internally fertilizing species, especially when the females accept multiple partners. Indeed, in most such species males do not care for young, and it has been suggested that this is because they are uncertain which juveniles are their own. But a new study by Buchan and colleagues[2], described on page 179 of this issue, reveals that when male savannah baboons (*Papio cynocephalus*) intervene in fights between juveniles, they favour offspring over nonkin. This work is important because it reveals that such intervention is a manifestation of nepotism, that paternal care can occur even when females copulate with several different males, and that the kin-recognition mechanisms of a wild primate approach those of humans in precision and sophistication.

In nature, multiple mating is commonplace and widespread, and molecular genetic analyses reveal that it typically results in females bearing the offspring of several males[3,4]. To avoid misdirecting nepotism, males generally rely on indirect cues of their paternity of entire broods[5]. For example, male bluegill sunfish (*Lepomis macrochirus*) are less willing to defend eggs and fry against predators, and more likely to abandon or cannibalize young, if cuckolders had lurked nearby during spawning (a proven threat to paternity) than if they had experienced no cuckolders[6]. However, there has been no evidence that bluegill sunfish, or males in any other wild vertebrate, can distinguish offspring from unrelated juveniles within a given brood[7] — until now.

Buchan and colleagues' study[2] builds upon 30 years of continuous research on the baboons of Kenya's Amboseli Basin, located at the foot of Mount Kilimanjaro. These primates live in multi-male, multi-female troops, in which adult males frequently intervene in fights that break out between juveniles. Such intervention and physical support shields young from injury and stress, and enhances their dominance rank. During 1999–2002, the researchers recorded which youngster was assisted when an adult male baboon intervened in a fight. By analysing DNA from faecal and blood samples the authors established, *post hoc*, whether there was a genetic relationship between each male–juvenile dyad. They report that when males were faced with a choice, they were significantly more likely to support offspring than unrelated juveniles (Fig. 1). Male support of females that are being attacked is a well-known indicator of 'friendship'; it now seems that such behaviour toward youngsters is in fact paternal care.

But how do male baboons avoid misdirecting their nepotism? Two mechanisms are possible. First, males might rely on indirect cues of paternity, as with the male bluegill sunfish that notice cuckolders during spawning. Female baboons are most fertile during the last five days of the follicular phase of their oestrous cycle, which is recognizable by the degree of swelling of their sexual skin. Males might therefore behave according to a simple darwinian algorithm (behavioural rule), such as 'assume that a juvenile is your offspring if you frequently copulated and consorted with (guarded) its mother when her perineum was maximally swollen'. If so, males should distinguish such 'behaviourally predicted' offspring from unrelated juveniles born to females with whom they did not copulate. Moreover, the probability of a male assisting a juvenile should correlate with the proportion of time that the male spent sexually monopolizing its mother during her period of maximum fertility. This is indeed what Buchan *et al.* observed.

A second, complementary recognition mechanism involves a male using direct (phenotypic) cues, such as how a juvenile looks or smells, to assess his likelihood of being its father. This mechanism, known as phenotype matching, is widespread in nature[8], including among primates. In humans, the resemblance of a baby to its mother's husband is a well-known source

J. SILK

Figure 1 **Paternal love: a male baboon intervenes in a squabble between two juveniles on behalf of his own offspring.**