

silicon carbide and a mere 0.38° for iridium. The catch is that a single-crystal iridium layer has never been grown as a free-standing wafer: it requires its own single-crystal substrate. Diamond has been grown successfully on iridium that was itself grown on substrates of MgO (refs 5, 6) or SrTiO₃ (refs 4, 7, 8). But once again there is a size limitation, as MgO and SrTiO₃ wafers can be made only 2–3 inches in diameter.

The first stage of single-crystal growth is the nucleation of myriads of tiny diamond crystallites across the substrate (up to 10¹² diamond nuclei per square centimetre). If the individual crystallites are well aligned on the substrate, the 'grain boundaries' between growing crystallites eventually merge to form a film of single-crystal diamond with relatively few defects. Schreck *et al.*^{7,8} showed that a 34- μm -thick film developed into a single-crystal diamond with a dislocation (or defect) density of about 10⁹ cm⁻², which is comparable to that of high-quality single-crystal films of electronic materials such as gallium nitride.

But the deposition of diamond on iridium/SrTiO₃ is plagued with problems. For instance, there is some roughening of the iridium substrate during the nucleation process, and lateral inhomogeneities often develop in the diamond film^{7,8}. And when the diamond is cooled to room temperature (from the growth temperature of 800 °C), the very different thermal-expansion coefficients of iridium and diamond create thermal stress that leads to delamination of the diamond film from the substrate¹.

Using sapphire as the substrate for iridium growth could solve some of these problems. Sapphire has many desirable properties, such as mechanical and chemical stability, and high crystalline quality. Moreover, large-diameter samples are available and relatively inexpensive. Golding and co-workers^{1,2} have taken the first step by growing high-quality iridium on sapphire wafers (Fig. 1), and they are in the early stages of studying diamond heteroepitaxy on these improved substrates. Following on from this, the optimal growth conditions and the quality of thick diamond films deposited on the new substrate should be explored. Such further experiments may well confirm sapphire as a feasible large-diameter substrate, of relatively low cost, and more stable than MgO and SrTiO₃.

In parallel with experiments on diamond growth, researchers are also busy with the fabrication of diamond-based devices. High-performance devices have been built based on synthetic diamond crystals that were produced by high-pressure high-temperature (HPHT) techniques or by homoepitaxy of diamond on HPHT diamond crystals³; a high-quality field-effect transistor has been fabricated on heteroepitaxial diamond grown on iridium/SrTiO₃

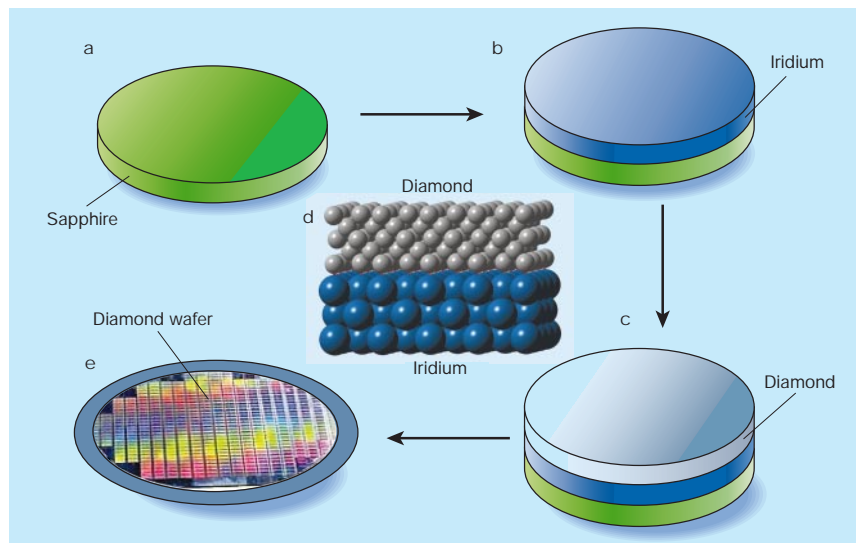


Figure 1 Heteroepitaxy for diamond wafers. Iridium is a good substrate on which to grow single-crystal diamond wafers, but an iridium layer must itself be grown on another substrate. **a**, Golding and co-workers^{1,2} propose a new substance for this substrate — sapphire. **b**, The crystal structure of sapphire directs the ordered growth of iridium on its surface, and then **c**, diamond is deposited on top. **d**, It is because the atomic spacing of the iridium crystal closely matches that of diamond that a high-quality diamond wafer can be grown. **e**, Just as is done currently with silicon wafers, electronic components could be cut from the large-diameter, high-quality diamond wafers made according to Golding and colleagues' prescription.

(ref. 9); and advances are being made in diamond doping, in which the electronic properties of the material are manipulated by adding small amounts of impurity atoms¹⁰.

An attractive, rival approach has been proposed that uses silicon as the substrate for iridium growth, with a CaF₂ interlayer¹¹, to take advantage of the ready availability of large, low-cost silicon wafers. Nevertheless, the development of diamond–iridium–sapphire heteroepitaxy by Golding and co-workers^{1,2} and the progress made in device fabrication raise unprecedented hope for the future of large-scale diamond electronics. ■

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Theoretical biology

Safeguards and spurs

Stephen C. Stearns

Biological traits are buffered against genetic and environmental upset by a process called canalization. New work suggests this may be a general feature of regulatory gene networks, selected to survive gene loss.

One of the biggest challenges facing twenty-first-century biologists is understanding how genes are connected to the traits seen in whole organisms. At a basic level, we know that the overall appearance and behaviour of an organism are determined by the interaction between its genes and the environment. Yet this interaction is incredibly complicated.

For instance, some kind of developmental buffering seems to ensure that similar traits are produced despite genetic changes (mutations) and environmental perturbation. A better understanding of this buffering effect, known as canalization, could change how we think about evolution and development.

Theoretical insights^{1–3} and experimental

Neurobiology

Motor proteins branch out

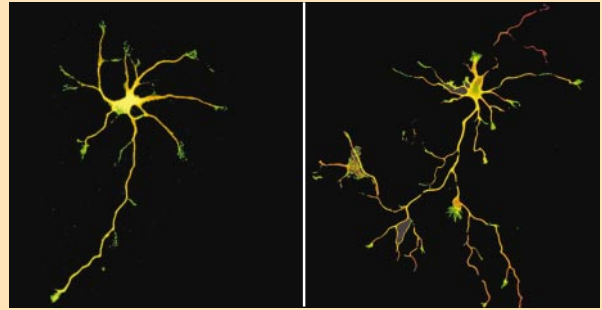
Molecular motors are perhaps best known for their ability to transport cargo around inside cells. To do so, these tiny vehicles move along defined intracellular 'tracks'; motor proteins of the kinesin family, for instance, move on microtubule filaments. But some kinesins have a quite separate function, at least in cultured cells: they can break down microtubules into their constituent parts. Writing in *Cell* (114, 229–239; 2003), Noriko Homma *et al.* show that the kinesin KIF2A has this activity *in vitro* — and they propose that this function is essential *in vivo* for the brain to develop normally.

The authors started by generating mice that lack KIF2A, and found that the animals died within a day of birth with severe brain abnormalities. Delving deeper, Homma *et al.* discovered defects in the collateral branches of neurons. During development, nerve cells extend projections — axons — to form appropriate connections in the

brain. Sometimes, branches also extend outwards from the axons to form further connections. These collateral branches generally remain short until the primary axon has found its way.

But that doesn't appear to happen in KIF2A-deficient mice. The authors took neurons from the hippocampus of normal and mutant mice and cultured the cells for two days. The normal neurons (left-hand image) extended a single primary axon, with some short collateral branches. The mutant nerves, by contrast, developed abnormally long collateral branches, which rebranched several times (right-hand image).

Video analysis showed that, in wild-type neurons, any collateral branches that formed actively shrank back. But in the mutant cells the branches continued growing. So KIF2A seems to be necessary to stop the branches lengthening. How does it do this? Homma *et al.* found



that the protein can depolymerize microtubules within extending neuronal protrusions, and that this activity is reduced in KIF2A-deficient cells. Moreover, when the authors studied the polymerization and depolymerization of microtubules in another type of cultured brain cell (it's difficult to do this in neurons), they found that, if KIF2A was missing, microtubules carried on growing when they reached the edge of the cell. But in the presence of KIF2A, microtubules either stopped growing or showed

cycles of growth and shrinkage.

It seems, then, that microtubule growth drives the protrusion of collateral branches — possibly by pushing out the edge of the cell — and that KIF2A normally keeps this process under control by depolymerizing microtubules when they reach the edge. It remains possible that KIF2A has an indirect role: perhaps it carries microtubule-depolymerizing molecules to the edge. But the protein's *in vitro* activity would seem to argue against this. **Amanda Tromans**

results^{4,5} alike are enlivening discussion of canalization. Theoretically, it seems that canalization can be a by-product of the existence of genetic regulatory networks that maintain their function when any given gene is knocked out⁵. On the experimental side, the protein and molecular chaperone Hsp90 has properties that suggest it could be a central player in a general canalizing mechanism^{4,5}. On page 549 of this issue, Bergman and Siegal⁶ advance the discussion by showing — with both a simulation model and new analysis of data on the effects of gene knockouts in yeast — that most genes in regulatory networks have canalizing properties.

The authors first set up computer simulations of gene networks, in which each virtual gene regulates the expression of itself and every other gene. A matrix showing the regulatory relationships is the 'genotype' — the representation in the model of the set of genes relevant to the issue at hand. The traits that might be buffered (the 'phenotype') are represented by the equilibrium profile of gene expression that results from the regulatory relationships. The starting point is arbitrary, and not yet at equilibrium. A gene is then knocked out at random by setting its value in the matrix to zero, and the population is allowed to evolve.

The results were striking: the knockout populations showed, in general, much more phenotypic variation between individuals

than did populations in which genes were not deleted. And simulated populations with a supply of knockout mutations evolved more rapidly to an equilibrium (optimum) phenotype than did simulated populations without such a supply. The authors propose that the knocked-out regulatory genes usually have canalizing effects on phenotypic variation that are lost when the genes are knocked out — releasing previously hidden variation. In my view, however, this in itself does not provide evidence of canalization, for an increased supply of mutations with diverse effects would be expected to accelerate evolution whether or not a regulatory network with canalizing effects existed.

On the other hand, Bergman and Siegal also analysed experimental data from a large-scale project with the yeast *Saccharomyces cerevisiae*; this project aims to delete each yeast gene in turn, and to study the effects. The genetic background of the yeasts is identical, save for the gene knockout, so here the authors were studying the effects of environmental variation on phenotype. They found that deleting a gene at random increased environmentally induced variation in the expression of other genes — again suggesting that such phenotypic variation is usually canalized.

Bergman and Siegal interpret these findings as providing support for the notion of 'evolutionary capacitance'. By this they mean

that evolution is accelerated when genetic or environmental stress disturbs canalizing mechanisms. The disturbance reveals genetic and phenotypic variation that had previously been hidden, and which now becomes available to fuel an evolutionary response that would not have been possible had the canalizing mechanism not been functionally compromised.

How do these results fit with previous work? From experiments on fruitflies and thale cress^{4,5} we know that trait variation increases when Hsp90 is functionally compromised, and that the function of Hsp90 can be compromised by environmental stress. From theory we know that knockout mutations in genetic regulatory networks reveal hidden genetic and phenotypic variation, and speed the approach to a new optimum. And Bergman and Siegal's analysis of yeast knockouts suggests that knocking a gene out at random in a genetically uniform background increases environmentally induced variation in the expression of other genes.

So far so good. But a crucial element in the theory is missing from the data: we do not yet have an experimental demonstration that compromising a canalizing mechanism accelerates evolution to a new optimal phenotype. We only know that the amount of genetic variation that is expressed as phenotypic variation is increased. That such

experiments are hard to do is only a temporary excuse; it does not scratch the logical itch. Bergman and Siegal's work makes it more plausible that capacitance effects will be found. Yet there are at least three reasons why their results are not yet sufficient to convince a sceptic that capacitance is real.

First, in their simulations the authors looked only at gene expression (the 'transcriptome'), rather than at anything approaching the complexity of whole-organism phenotype. So their results leave us uncertain about what might happen in between. Variation in gene expression might in fact lead to canalization at the whole-organism level, if appropriately regulated transcriptome variation is part of the mechanism that canalizes whole-organism traits.

Second, variation released in the transcriptome could also produce changes in reproduction and mortality rates, which determine the strength of natural selection. If increased genetic variation were accompanied by reduced variation in reproductive success, or by reductions in the correlation between variation in traits and variation in reproductive success, the rate of evolution would not necessarily change. In fact, if the effects were strong enough, the rate of evolution might even decrease.

Third, Bergman and Siegal's analysis of yeast data reveals an increase in phenotypic, not genetic, variation when genes are knocked out at random. Yet capacitance requires that the increased variation be, at least in part, genetic. It has been asserted^{7,8} that increased phenotypic variation implies increased genetic variation in such circumstances. But it might not.

So the existence and importance of evolutionary capacitance remain uncertain. But if canalization does turn out to be a pervasive property of genetic networks — one that evolves rapidly and serves as an evolutionary capacitor — a key feature of the genotype–phenotype connection will have been clarified. And that would stimulate further questions. One is how part of the organism's response to environmental change remains canalized while others become 'plastic', or flexible. Also, how do the genetic networks that might be producing canalization as a by-product interact with the mechanisms that determine plasticity (if they interact at all)? Does evolutionary capacitance explain the periods of stasis and rapid change that are seen in experimental studies of evolution — or perhaps even in the fossil record? The answers to such questions may seem beyond reach, but in fact we can start right now with evolutionary experiments on the functional genomics of microorganisms. ■

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on the atoms. In other words, the conduction electrons have a slight preference energetically to have their spins oriented in the opposite direction to that of the magnetic moments localized on the atomic sites in the lattice. As the temperature falls below the value that characterizes this ordering preference, the local atomic moments become progressively screened and the entropy associated with the local magnetic degeneracy 'dresses' the conduction electrons, dramatically increasing their effective masses and making them into 'heavy fermions'. This reduction of atomic moments drives down the magnetic ordering temperature, and as the local interaction between magnetic moment and conduction electron becomes stronger, the moment and the magnetic ordering temperature simultaneously drop to zero — this is the quantum critical point.

Much of the interest in quantum critical physics stems from its relevance to the physics of phenomena that involve correlated behaviour of electrons — the prime example here being heavy-fermion superconductivity, the resistance-less flow of current at very low temperatures. Discovered³ in 1979, this particular variant of superconductivity demanded a new understanding of the nature of heavy-fermion materials, as their magnetic character had been thought to be hostile to the occurrence of superconductivity. In the 1990s, it became clear that the systematic appearance of superconductivity in some heavy-fermion materials happens in the vicinity of what has since been recognized as a quantum critical point⁴. Although this is not true for all heavy-fermion materials (including YbRh₂Si₂, studied by Custers *et al.*²), the tantalizing link between superconductivity and quantum critical points has driven efforts to understand both phenomena.

Classically, critical phenomena are narrowly confined to the region around a critical point, but, in contrast, the influence of a quantum critical point spreads through the phase diagram, well away from the point itself. The effects are many and can be parametrized through properties that vary with a power of temperature, such as electrical resistivity, magnetic susceptibility and specific heat. In their experiments, Custers *et al.*² have traced the variation of such properties as they tuned their heavy-fermion material, YbRh₂Si₂, into a quantum critical point by applying magnetic fields.

In these experiments, to probe the quantum critical point more deeply, the authors 'doped' their samples of YbRh₂Si₂, replacing some of the silicon atoms with germanium. Germanium atoms are slightly larger than silicon ones, and so increase the pressure in the atomic lattice and drive down the strength of the magnetic field at the critical point to almost zero. Custers *et al.* have now provided the most complete study so far of the heavy-fermion quantum critical point, combining

Condensed-matter physics

Singular behaviour

Zachary Fisk

Quantum fluctuations at absolute zero may push a system into a different phase or state. The 'quantum critical point' at which this happens in certain materials has now been probed in greater detail.

More than a century of probing the physics of magnetism has only served to heighten its interest for physicists. Over the past decade, a new focus has evolved — the behaviour of magnetic materials at a 'quantum critical point'. Critical points are perhaps more familiarly associated with phase transitions such as those between water, steam and ice. But at zero temperature there are quantum phase transitions, fluctuations between different states of a phase diagram that are governed by Heisenberg's uncertainty principle. In certain magnetic materials, the temperature at which the system takes on a magnetically ordered state can be tuned, either chemically

or through some external influence, towards absolute zero, the transition point being a quantum critical point¹. The question is, at a quantum critical point, do we see something new that does not occur in classical systems? On page 524 of this issue, Custers *et al.*² go some way towards an answer, through the closest approach yet to a quantum critical point in a 'heavy-fermion' material.

Heavy-fermion materials, a class of so-called correlated-electron materials, are metallic compounds with a chemically ordered lattice of magnetic ions, in which conduction electrons interact antiferromagnetically with the local magnetic moments