physics of earthquake generation. Although Roselend lake is free of earthquakes, the apparent stimulation of geophysical anomalies by changes in its filling or emptying rate is reminiscent of peculiar seismic features evident at other large reservoirs. Earthquakes larger than magnitude five at Koyna reservoir (India) are induced when the lake level rises faster than 12.2 m per week[10] and, at Nurek reservoir (Tadjikistan), the largest local earthquakes occurred during abrupt decreases in the reservoir filling rate[11]. So the Roselend observations might provide clues as to how, at Koyna and Nurek, loading rate or fluid-flow rate influence the behaviour of brittle, inelastic rock.

How do crustal rocks respond inelastically to loading by a surface reservoir? Although induced stresses and pore pressures vary spatially around a reservoir, they are unlikely to be much greater than 0.1 MPa for each 10 m of water depth. Nonlinear behaviour of rock mass seems to occur at low stress, and must therefore be dominated by deformation of fluid-filled void space, including cracks and faults. One question is whether stress concentration at crack tips allows the creation of new crack surfaces under loads such as those imposed by lakes, which could increase permeability, facilitate radon dissipation and locally weaken the rock mass. Another issue is whether the loading-rate dependence of rock-mass deformation reflects the frictional character of fractures or time delays due to pore-fluid diffusion. Trique and colleagues[1] attribute radon and electric-field anomalies to changing rates of fluid flow in the rock, a hypothesis that could be tested by monitoring groundwater flow near Roselend lake.

More than 20 years ago, earthquake scientists demonstrated that raising and lowering subsurface fluid pressure could turn microearthquakes on and off in Colorado's Rangely Oil Field[12]. Laboratory experiments had already shown that increased pore-fluid pressure counteracts the compressive stress on fault planes in rock, reducing the shear stress required for slip, but it was the Rangely results that really caught seismologists' attention. Large-scale field experiments, such as those carried out by Trique *et al.*, are orders of magnitude closer in size to that of earthquake-producing faults, and they encompass the natural fractures that concentrate deformation and conduct fluid. Work at this scale can determine how radon emission and electric fields are affected by crustal deformation, fluid flow and specific geological structures. And that might clarify their relevance to earthquake prediction. □

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Cell signalling

Calmodulin at the channel gate

Michael D. Ehlers and George J. Augustine

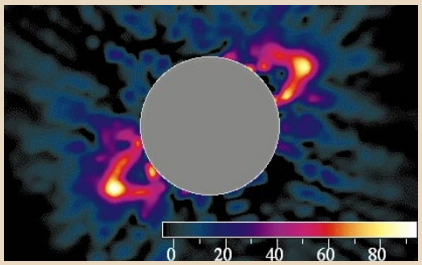
Of all the channels that conduct ions in response to voltage changes across cell membranes, those that carry calcium merit special attention. The Ca^{2+} that enters through these channels acts as a messenger for a host of intracellular signalling events, including feedback processes that regulate activity of the channel itself. Such feedback includes inactivation[1], which closes the channel, and facilitation[2], which enhances channel opening. A number of studies[3–6], including reports by Lee *et al.*[3] and Zühlke *et al.*[4] (pages 155 and 159 of this issue), have now reached the surprising conclusion that calmodulin, which is the classical Ca^{2+} receptor protein inside cells[7], mediates *both* inactivation[3–6] and facilitation[3,4].

Most of the new studies focused on the L-type Ca^{2+} channel, which is involved in contraction of heart muscle, gene expression in neurons, and hormone secretion. The first hint that calmodulin might be involved in Ca^{2+}-dependent regulation of these channels was the observation that deleting part of the channel's cytoplasmic tail prevents inactivation[8]. This deleted region includes a sequence of amino acids that resembles an isoleucine–glutamine (IQ) motif, a domain which, in many other proteins, binds calmodulin.

Four new findings support the idea that calmodulin regulates the properties of Ca^{2+} channels, and that it does so by binding to the IQ-like motif. First, Zühlke *et al.*[4] and Peterson *et al.*[6] show that mutant forms of calmodulin, which cannot bind Ca^{2+}, act as dominant-negative inhibitors of Ca^{2+}-channel inactivation. Although this finding establishes that calmodulin helps to inactivate Ca^{2+} channels, it does not indicate where calmodulin acts. Calmodulin could, for example, bind directly to the channel, or it may have other targets, such as protein

Astrophysics

The planet factory



The first near-infrared image of a dust ring around a young, nearby star has been taken by the Near Infrared Camera and Multi-Object Spectrometer (NICMOS) on board the Hubble Space Telescope. The image may give astronomer Glenn Schneider and his colleagues a new look at early planet formation (*Astrophys. J.* 513, L127– L130; 1999).

Planets are thought to condense out of the disks of dust and gas surrounding newborn stars by a process of accretion—in which small particles collide and stick together. Such circumstellar disks are hard to see, because the glare from the central star outshines the weaker, reflected light from the disk. This particular image was captured using a coronagraphic camera on NICMOS to block out the glare of the star (grey circle on the image).

This disk is unusual as it is only 1.6 billion miles wide (the ring diameter is 13 billion miles), leaving a large dust-free area inside the ring. The much smaller rings found around planets such as Saturn are held in place by the gravitational force of moons orbiting nearby. The narrowness of this stellar ring implies that it may be confined by one or more unseen bodies — probably new planets. Without some mechanism to keep them intact, dust rings around stars would spread outwards, reducing their ability to form planets.

The colour of the ring is somewhat reddish (scale bar gives flux density in μJy per pixel), showing that it is made up of grains several μm in size, which is larger than typical interstellar dust. This stellar ring is surprisingly young, indicating that planets may have formed in less than ten million years. **Sarah Tomlin**

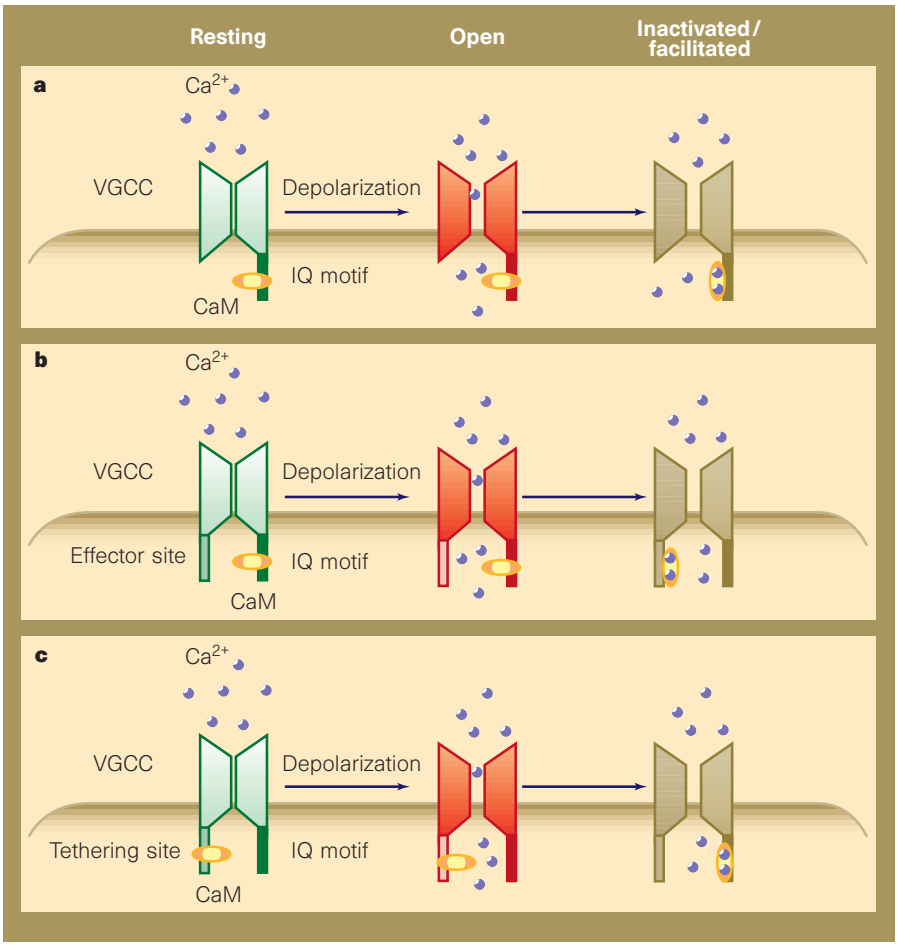


Figure 1 **Three models for calmodulin-dependent regulation of voltage-gated calcium channels (VGCCs), based on the results of Lee *et al.*[3], Zühlke *et al.*[4] and others[5,6]. In each model there is a tethering site, where calmodulin is constitutively bound under resting conditions, and a calmodulin-effector site through which Ca^{2+}-associated calmodulin modulates channel gating. Once the channel is activated by membrane depolarization, tethered calmodulin is activated by incoming Ca^{2+}. The calmodulin then binds to an effector site, which closes (inactivates) or further opens (facilitates) the channel. The calmodulin-binding isoleucine–glutamine (IQ) motif on the cytoplasmic tail of the channel may act:** a, **as both the tether and the effector;** b, **as the tethering site only; or** c, **as the effector site only.**

kinases or phosphatases, that regulate Ca^{2+} channels[9].

Second, several biochemical strategies[4–6] have shown that calmodulin binds to the IQ motif of the L-type Ca^{2+} channel. Binding requires sub-micromolar concentrations of Ca^{2+} — similar to those needed to inactivate Ca^{2+} channels[10] — making the IQ motif a good candidate for the site at which calmodulin acts on the channel. Third, mutations that decrease calmodulin binding to the IQ motif reduce or eliminate the Ca^{2+}-dependent inactivation of L-type channels[4,5]. In the most dramatic case, Zühlke *et al.* found that inactivation was greatly slowed when they replaced the isoleucine (I) of the IQ motif with glutamate, a substitution that markedly reduces calmodulin binding.

Finally, when Zühlke *et al.* replaced the same isoleucine residue with alanine, they found that the L-type channels were facilitated upon repeated activation. Similar alanine substitutions reportedly have little effect on calmodulin binding[5], but, as with calmodulin-dependent channel inactivation, these authors found that facilitation is blocked by Ca^{2+}-insensitive calmodulin mutants and abolished by replacing the isoleucine in the IQ motif with glutamate. These results indicate that the action of calmodulin on the IQ motif can also facilitate L-type Ca^{2+} channels.

The exciting picture to emerge, then, is that Ca^{2+} both inactivates and facilitates Ca^{2+} channels by binding to calmodulin, and that both processes involve binding of Ca^{2+}–calmodulin to the IQ motif. Because Ca^{2+}-insensitive calmodulin mutants prevent incoming Ca^{2+} from inactivating or facilitating the channel[4,6], calmodulin is probably tethered to (or near) the channel before Ca^{2+} enters. This agrees with earlier studies[11], showing the Ca^{2+}-dependent inactivation of Ca^{2+} channels reconstituted in artificial membranes (which lack cytoplasmic proteins)[11]. The close spatial proximity of calmodulin and the channel could also explain why inactivation is resistant to treatments that act only on freely diffusible Ca^{2+} (ref. 12) or on unbound calmodulin[13].

Because L-type Ca^{2+} channels are neither inactivated nor facilitated under resting conditions, they must have both a tethering site, which anchors the calmodulin, and a calmodulin-effector site, which gates the channel (Fig. 1). The IQ motif could serve as tethering site, effector site, or both. Zühlke *et al.*[4] show that some calmodulin can bind to this motif at the concentrations of Ca^{2+} found in resting cells, so perhaps calmodulin is pre-bound to the IQ motif. For the IQ motif to function as both the tethering and effector sites, an influx of Ca^{2+} must cause the calmodulin to undergo a conformational change yet remain bound to the IQ motif (Fig. 1a). Alternatively, the Ca^{2+} influx might cause calmodulin to bind, or bridge, a separate effector site (Fig. 1b). Finally, calmodulin might be tethered to another site near the channel pore and, on binding Ca^{2+}, rapidly translocate to the IQ motif (Fig. 1c)[6].

Calmodulin's sphere of influence even extends to the P/Q-type channels — neuronal Ca^{2+} channels that are not thought to be regulated by Ca^{2+}. Lee *et al.*[3] and Peterson *et al.*[6] show that calmodulin binds, in a Ca^{2+}-dependent manner, to two different sites in the cytoplasmic tail of the P/Q-type channel. One site, which is homologous to the IQ motif found in L-type Ca^{2+} channels[6], has also been detected in yet another Ca^{2+} channel, the R-type channel[6]. The second site is not an IQ motif, and is found downstream of the first[3]. These results indicate that P/Q-type channels — and, perhaps, even other Ca^{2+} channels — may have not one but two calmodulin-binding sites. If so, it will be important to find out whether the different calmodulin-binding domains have different functions. Much like the case for L-type channels, Lee *et al.* show that binding of calmodulin to the second domain imparts a modest Ca^{2+}-dependence to inactivation, and is required for long-lasting Ca^{2+}-dependent facilitation. As yet, the function of the first, IQ-like, motif of P/Q-type channels is not known.

The new observations mean that voltage-gated Ca^{2+} channels enter the company of other ion channels — ranging from Ca^{2+}-activated potassium channels[14] to NMDA (*N*-methyl-D-aspartate) receptor channels[15] — whose activity is regulated by calmodulin binding. By illuminating the molecular events that regulate the function of Ca^{2+} channels, these papers bring us one step closer to understanding how cells encode Ca^{2+} signals. Future studies must determine whether the IQ motif alone acts as both a tethering and an effector site, or whether additional calmodulin-binding sites are involved. We will then be in a better position to comprehend how just one molecule,

100 YEARS AGO

The possessors of certain hereditary characters are unquestionably *sub-prolific*; that is, they eventually contribute less than their average share to the stock of the future population. It may be that they die before the age of marriage, or that they are sexually unattractive or unattracted, or that if married they are comparatively infertile, or that if married and fertile the children are too weakly to live and become parents. It is very probable, though I have no trustworthy facts to confirm the belief, that persons affected with hereditary insanity are sub-prolific because their families, if they have any, are apt to contain members who are afflicted in various ways that render them less likely than others to live and to marry. But I do not propose to go into the details of this or of any other malady, but merely mention it as an illustration of what is meant, when I assume that the possessors of some particular characteristic, not necessarily a morbid one, and which may be called A, are sub-prolific on the average.
From *Nature* 11 May 1899.

50 YEARS AGO

Reports of tumours in insects are relatively rare. Paillot mentions proliferation in the fat cells of *Euxoa segetum* Schiff., following infection by virus diseases (pseudo-grasseries I and II). Tumours have been described in the fruit-fly, *Drosophila melanogaster* Meigen, by Stark and Russell: in larvae of the Pygaera group of butterflies, by Federley; and in the stick insect, *Dixippus morosus* Br., by Pflugfelder. They have been found in a large Orthopteran insect, *Leucophaea maderae* F., by Scharrer. All the tumours so far discovered in insects are apparently non-malignant, although malignancy has been claimed by Stark and Federley. Russell found that those in *Drosophila* reported by Stark as malignant were similar in structure to benign tumours occurring in the same insect, and that the so-called malignant tumours could be successively transplanted without hampering the development of the host. The tumour strains discovered by Federley apparently have been lost. Various stimuli will provoke tumour proliferations in insects. Spontaneous tumours occur in several genetic tumour strains in the fruit-fly, but the stimulus is not known.
From *Nature* 14 May 1949.

calmodulin, can both inactivate and facilitate Ca^{2+} channels. □

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Materials science

The hard problem of carbonitrides

Barry M. Klein

'Materials by design' is the goal of theorists who are developing a fundamental understanding of the macroscopic properties of materials from a microscopic, atomistic point of view. In a paper on page 132 of this issue, Jhi *et al.*[1] move us towards this goal by relating the hardness properties of carbonitrides — compounds containing carbon or nitrogen, together with a transition metal[2] — to fundamental aspects of the material's electronic structure such as the electronic energy bands, or the charge density and chemical bonding. They show that the elastic properties of the carbonitrides, which relate to their hardness, can be explained by the filling of electron states depending on whether the underlying lattice is occupied by transition-metal or carbon and nitrogen atoms, or by vacancies. The authors have used state-of-the-art theoretical and computational methods to reach this conclusion from first principles, without recourse to tweaking the theoretical parameters with experimental data. An understanding of the hardness of the carbonitrides does not seem so hard any longer.

Carbonitrides (such as TiC or NbN) often form in the simple NaCl crystal-lattice structure of ordinary table salt. The valence electron concentration, or number of electrons that are active in the bonding of these materials (there are eight such electrons in TiC, and ten in NbN) can be changed by forming alloy compounds with varying amounts of transition metal(s), carbon and nitrogen atoms, or vacancies. Such materials often have interesting properties ranging from superconductivity at relatively high temperatures[3,4] (for example, $T_c > 17$ K for NbN), to high melting temperatures, and to the extreme hardness (such as TiC, which has a relative hardness somewhere between that of aluminium oxide and diamond) that makes them important materials for cutting tools and related applications.

Hardness is defined empirically as resistance of a material to denting or scratching. Relative hardness may be determined by a material's response to an 'indenter' pressed into, or moved along, its surface. The hardness and related mechanical properties of materials often involve complicated phenomena such as the motion or pinning of dislocations (mismatched lattice planes), or other 'large defect' properties of solids that, ultimately, should relate back to the fundamental microscopic properties of the perfect lattice. Theoreticians have long nibbled away at the problem of relating the hardness of carbonitrides to the underlying chemical bonding that is governed by the electron distribution in these materials. But unravelling the underlying properties of carbonitrides in terms of quantifiable physical and chemical quantities such as 'bonding' has been limited to qualitative descriptions of these materials, such as describing them as 'covalent metals', in analogy to hard semiconductor materials such as diamond.

It is only in the past decade that theoreticians have been able to study electronic structures with enough accuracy to be able to determine fundamental properties such as elastic behaviour and lattice-vibrational properties of solids from first principles. Using the formalism developed by Walter Kohn and colleagues (see for example, ref. 5) that led to his share of the 1998 Nobel Prize in Chemistry, an elaborate but computationally workable machinery for doing quantitative studies of the electronic structure of materials has become possible (see ref. 6 and references therein). In essence, the resulting so-called Kohn–Sham equations reduce the solid-state many-body problem (roughly 10^{23} electrons and nuclei for each cubic centimetre of a solid) to a set of one-particle Schrödinger equations that need only be solved in a single unit cell of a perfect, periodically repeating solid. The results for properties of solids in the ground state