potassium[8]; and chronic seizures induce vessel formation (angiogenesis), increasing vascular surface area and producing a crop of porous, newly formed vascular elements that have poor barrier function[9]. The blood–brain barrier therefore seems to be involved in the initiation, progression and perpetuation of seizures.

These exciting findings[2,3] document two routes to the development of seizures and epilepsy. Kim *et al.* show that meningeal inflammation can signal 'inwards' to the brain parenchyma, activating the vasculature there and compromising the blood–brain barrier. Fabene and colleagues confirm that, in the presence of an epilepsy-inducing factor, even mild systemic inflammation leading to minimal disruption of the blood–brain barrier can produce seizures. These authors' results[3] are

convincing and of potential significance for treatment, as they studied some molecules that could be used to inhibit the adherence of white blood cells to endothelial cells in humans.

But as far as therapeutic application is concerned, these findings are fraught with concerns about how well the animal models reflect epilepsy in humans. What's more, long-term administration of adhesion-molecule blockers would pose some risk[10], as they would alter immune function and increase vulnerability to infection. However, short courses of such treatment after brain trauma, for example, which is known to increase liability to seizures, might offer the opportunity both to enhance patients' chances of recovery and to generate a proof-of-principle for the validity in humans of observations derived from animal models. ■

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QUANTUM PHYSICS

Quantum force turns repulsive

Steve K. Lamoreaux

The experimental verification that a bizarre quantum effect — the Casimir force — can manifest itself in its repulsive form is pivotal not only for fundamental physics but also for nanotechnology.

In 1948, Hendrik Casimir predicted[1] that two uncharged, perfectly conducting plates in a vacuum would be attracted to each other because of quantum fluctuations in the vacuum's electromagnetic field between the plates. Generalized for real materials by Evgeny Lifshitz[2] in 1956, Casimir's prediction has been verified many times and is now known as the Casimir–Lifshitz (C–L) force. But for all systems studied experimentally so far, the C–L force is attractive. Writing in this issue (page 170), Munday *et al.*[3] report the first experimental measurement of a repulsive C–L force.

The attractive C–L force has been measured with great precision, and has been taken into account in the design of nanoscale mechanical devices. But in many instances, the attractive nature of the force has led to more problems than solutions. One such problem is that the components in a nanodevice can stick together irreversibly. The desirability of a repulsive C–L force stems from its potential to fix this problem and also to enable objects to be levitated in fluids, which could find applications in nanotechnology. Proposals for the design of 'metamaterials' capable of producing such a repulsive force have been put forward, but attempts to achieve this have been unsuccessful[4].

Munday and colleagues' experiment[3] is based on a further generalization[5] of Lifshitz's formulation of the force, which allows the vacuum to be replaced by a material — here, a liquid. One of the most precise tests of Lifshitz's theory was performed[6] by Edward Sabisky

and Charles Anderson in 1973, when they measured the binding energy of a superfluid helium film to a crystal surface.

But Lifshitz's theory also asserts that if the properties of the liquid and plates are appropriately chosen, the C–L force can be repulsive. A repulsive C–L force can be generated by judicious choice of the dielectric permittivities of the plates and the liquid, which describe their ability to store electric-field energy. If the dielectric permittivities of the plates are ε_1 and ε_2, respectively, and that of the liquid in the gap is ε_3, the force will be repulsive when $\varepsilon_1 > \varepsilon_3 > \varepsilon_2$. And because these permittivities depend on the frequency of the electromagnetic field, this relationship must hold over the broad range of frequencies that contribute to the C–L force.

If this relationship is met, the C–L force will cause the liquid to wet the material's surface. For example, if one plate is replaced by air or a vacuum ($\varepsilon_2 = 1$), and if the liquid's permittivity is less than that of the other plate, the liquid will spread out in a thin film, rather than forming droplets as is the case with water on an oily glass surface. For instance, liquid helium, which has a very small permittivity, readily forms a thin film on almost all surfaces (except caesium films) because it is 'repelled' by the vacuum ($\varepsilon_1 > \varepsilon_3 > \varepsilon_2 = 1$), or highly attracted to the surface, and so wets the surface. In contrast, liquid mercury, which has a high permittivity, does not wet glass ($\varepsilon_1 < \varepsilon_3 > \varepsilon_2 = 1$).

Although many liquids can wet surfaces such as glass or silica, only a few sets of materials (plate–liquid–plate) will satisfy the

requirement for a repulsive force between the plates. The set used by Munday *et al.* consisted of silica and gold, with bromobenzene as the liquid separating them. The authors' experimental set-up (see Fig. 2 on page 171) used an atomic force microscope that was modified to detect average surface forces rather than atomic-scale point forces. A typical atomic force microscope consists of a microcantilever with a sharp tip at its end that is moved above the specimen's surface. As the tip scans the surface, the cantilever bends in response to the surface force felt by the tip. This bending is monitored by measuring the angular displacement of laser light reflected from the top surface of the cantilever, and allows the force's topography to be mapped out.

To measure the C–L force, Munday and colleagues replaced the sharp tip by a microsphere (of diameter about 40 micrometres) coated with gold. This served as the gold plate. Using a spherical surface for one plate simplifies the geometry of the system, which is completely defined by the radius of the sphere and the distance of closest approach to the flat silica plate. Although this leads to a significant — but easily calculated — modification of the force, it eliminates the need for angular alignment of the plates.

A problem associated with all C–L force measurements is the calibration of the system. Munday and colleagues have come up with a clever technique to overcome this problem. When the separation between the gold sphere and the silica plate is changed, the fluid produces a hydrodynamic force that changes linearly with the velocity at which the separation is altered. By measuring the total force at two different velocities, the hydrodynamic force can be isolated with high accuracy from the C–L force. Scaled to the appropriate velocity, the hydrodynamic force can then be subtracted from the total force at a given sphere–plate separation, yielding a clean measurement of the C–L force. The measurements spanned a range in separation from 20 nm to several hundred nanometres, with the minimum distance being

limited by the roughness of the gold and silica surfaces, and the maximum distance limited by the system's sensitivity.

Munday and colleagues' demonstration of a repulsive C–L force is pivotal for both fundamental physics and nanodevice engineering. For example, it might be possible to 'tune' the liquid (possibly by mixing two or more liquids) so that the force becomes attractive at large separations, but remains repulsive at short range. This would provide the means for quantum levitation of an object in a fluid at a fixed distance above another object, and so could lead to the design of ultra-low-friction devices. The applications of the C–L force to nanodevices remain to be investigated, but the prospects look exciting. ■

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PROTEIN SYNTHESIS

Errors rectified in retrospect

Kurt Fredrick and Michael Ibba

During protein synthesis, mistakes in adding amino acids to the growing polypeptide chain are usually prevented. If they are not, a quality-control mechanism ensures premature termination of erroneous sequences.

For cells to flourish, the genetic code must be translated with great accuracy into the amino acids that proteins are made from. During translation, the cell's protein-synthesis factory — the ribosome — carefully monitors the process by which new amino acids are added to a growing polypeptide chain. For each one, a specific trinucleotide (a codon) on messenger RNA is paired with a complementary anticodon on a transfer RNA, which at its other end carries the corresponding amino acid. Once codon–anticodon pairs have formed, the amino acid is chemically linked to the polypeptide chain by a peptide bond. At this point, it was thought that the quality-control duties of the ribosome were more or less complete. But Zaher and Green[1] present evidence in this issue (page 161) that, even after peptide-bond formation, the ribosome can detect codon–anticodon mismatches and reacts by bringing the protein's synthesis to a premature end.

The matching of codons and anticodons by the ribosome is a tricky process, involving a certain amount of leeway (Watson–Crick wobble) to allow the reading of all 64 codons that make up the genetic code. So it is not surprising that, despite careful matchmaking, mistakes are sometimes made, resulting in misfolded or non-functional proteins that must be refolded or destroyed after translation is finished. During protein synthesis, mistakes are generally thought to occur at a rate of about 1 in every 20,000 amino acids, although levels can be higher or lower depending on the conditions[2,3]. Studies in different living systems support this estimated rate of error, whereas experiments with individual components of the protein-synthesis machinery in vitro have yielded less clear-cut results.

It was one such experiment that piqued Zaher and Green's interest. When looking at the formation of simple two-amino-acid peptides, they sometimes saw error rates as high as 1 in 2,000 — an order of magnitude higher than they had expected. To further explore these high error rates, they turned to an occasional mistake that is well documented in living systems: the erroneous translation of the AAU codon into the amino acid lysine, rather than asparagine. They also began to look at the formation of longer peptides of up to four amino acids. Much to their surprise, they found that, once a mistake has been made, the ribosome becomes much less efficient at adding amino acids. So rather than continuing to grow, the nascent peptide chain was released from the translational machinery prematurely.

Ribosomes contain three binding sites for their tRNA substrates: the aminoacyl (A) site, the peptidyl (P) site and the exit (E) site. During each round of amino-acid chain elongation, codon–anticodon pairing allows entry of the correct tRNA into the A site (Fig. 1a). The nascent polypeptide chain bound to the tRNA at the P site is then transferred to the tRNA bearing a new amino acid at the A site, thereby lengthening the chain by one residue. This cycle of amino-acid addition is completed when the tRNA originally at the P site moves to the E site and the tRNA at the A site shifts to the P site, freeing up the A site for the next tRNA (Fig. 1a). The tRNA translocations are accompanied by mRNA movement by three
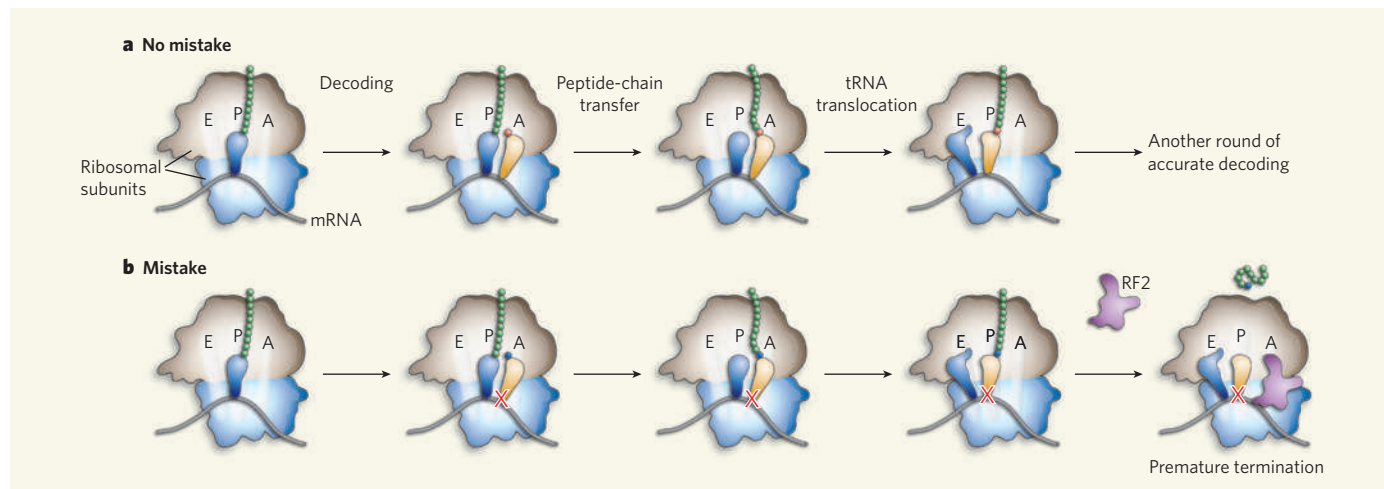

Figure 1 | Ribosomal matchmaking. a, Normally, the correct tRNA (yellow) enters the A site of the ribosome and the appropriate amino acid (red) is incorporated into the growing peptide chain, which transfers from tRNA in the P site to the tRNA at the A site. Both tRNAs, as well as the mRNA, then shift towards the E site. **b,** When mistakes are made and the mismatched codon–anticodon helix (indicated by a red cross) translocates to the P site, the ribosomal complex becomes susceptible to premature termination by translation factors such as RF2, and the erroneous sequence is prematurely released.