including cell-cycle regulation, and, along with hTERT, can immortalize human cells[6]. So it is possible that a central effect of these two proteins is to activate the cell-division machinery and enable the four transcription factors to access chromatin (the complex of DNA and histone proteins in chromosomes), thereby facilitating reprogramming.

Are the iPS cells that Park *et al*. generated, or indeed those obtained in the related studies[3–5], truly pluripotent — that is, do they have the potential to develop into various cell types? The best available assay for the developmental potential of human iPS cells is to test whether they can form teratomas (benign tumours containing cells from various differentiated tissues). Park and colleagues[2] do not report on teratoma formation by iPS-cell lines derived from neonatal or adult tissue, and their characterization of the differentiation of these cells *in vitro* is not extensive.

Similarly, the *in vitro* and *in vivo* data reported in the *Science* paper[4] raise some questions about the developmental potential of the reprogrammed cells derived from neonatal fibroblasts. The authors of the study[3] published in *Cell* used the teratoma test to establish pluripotency of the iPS-cell lines they derived from adult tissues, although, compared with embryonic stem cells, these lines showed some differences in their global patterns of gene expression. Finally, the related study[5] in *Nature Biotechnology* did not include extensive data on the developmental potential of the generated iPS cells. Further comparison of the iPS-cell lines generated in these studies with those derived from embryos is clearly warranted.

Several questions about the mechanism of the reprogramming process arise from these exciting observations[2–5]. So far, all successful direct reprogramming of differentiated mouse and human cells has relied for gene delivery on viral vectors that integrate into the cell's genome. It is therefore possible that the reprogramming in part depends on the effects of integration, or worse still, on other undetected genetic changes.

A crucial point that remains to be established is which genes are sufficient and necessary for reprogramming per se, and which are required for the induction of proliferation in the target cells. So far, the data implicate *OCT4* and *SOX2*, which lie at the heart of the transcriptional network that regulates pluripotency[7], in the reprogramming. Other factors studied seem to facilitate the reprogramming process, and so there might be many different combinations of these genes capable of achieving the same end.

Other questions remain. How do the differentiated state of the target cell, its cell-cycle status and its genetic background influence the efficiency of its reprogramming? And are human iPS cells truly equivalent to embryonic stem cells? Many of the same questions initially arose in the context of cloning by the technique of somatic cell nuclear transfer, which involves replacing an egg-cell nucleus with that of a differentiated adult cell. But the technique of direct reprogramming used in these four studies[2–5] is clearly far more amenable to addressing these questions.

The work of Park and colleagues[2], together with the related studies[3–5], proves beyond doubt that direct reprogramming is an efficient way of generating human pluripotent stem cells from adult cells. The results raise the hope that, one day, iPS cells might fulfil much of the promise of human embryonic stem cells in research and medicine. The generation of iPS cells through direct reprogramming avoids the difficult ethical controversies surrounding the use of embryos for deriving stem cells. The added advantage of direct reprogramming is that it enables patient-specific stem cells to be obtained for studying human disease and for tissue matching in transplantation. What is more, virtually any laboratory capable of carrying out the required cell-culture techniques can now perform direct reprogramming of adult cells. So the year 2008 promises to be very exciting for researchers interested in pluripotent stem-cell biology. ■

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PHYSICS

The force of fluctuations

Sébastien Balibar

Strange forces and effects dominate the world at the microscopic level. One such force, rooted in the random fluctuations of matter, has only now been accurately measured — 30 years after it was first predicted.

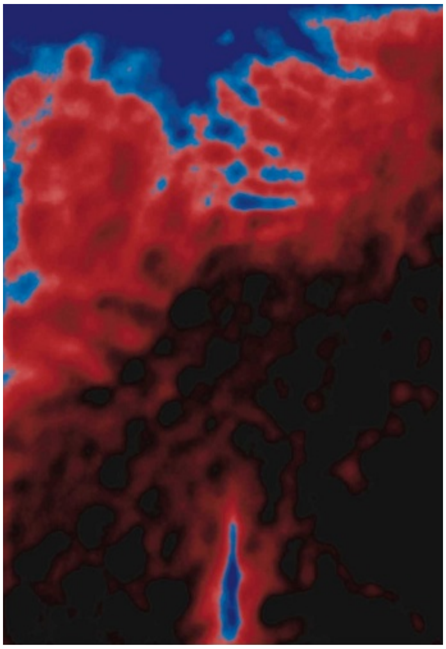
On page 172 of this issue, Hertlein *et al.*[1] present the first direct evidence for a force, known as the 'critical Casimir force', that is caused by the continual fluctuations of matter. The discovery is not a surprise: Michael Fisher and Pierre-Gilles de Gennes had predicted[2] the existence of the force in 1978, and indirect evidence for it had already been found[3–5]. Yet this new, strong evidence is extremely impressive — not least because of the weakness of the force that the authors have uncovered.

Forces are not just what you feel when, say, you push a door to open it. Many forces act without contact: gravitational or electrostatic forces are examples. Physicists have been studying these kinds of forces for more than a century to try to understand why things move, or sometimes don't. Mysteries remain not only at the largest of scales — the nature of the 'dark energy' that seems to be speeding up the expansion of the Universe is still unclear — but also at very small scales. It is this minute realm, inhabited by objects a micrometre or less across, that Hertlein and colleagues set out to explore.

Why bother? To answer that, and to explain how remarkable the tiny forces under investigation are, let us start with the ancestor of the authors' critical Casimir force, the plain old Casimir force. Imagine two metal plates placed a few micrometres apart. Sixty years ago, Hendrik Casimir proposed that two such plates should attract each other, even in a vacuum and in the absence of an electric charge[6]. Casimir forces are the best illustration of something both paradoxical and fundamental: the vacuum is not empty. Electromagnetic waves, such as light or radio waves, propagate in a vacuum, and bodies radiate electromagnetic waves with a temperature-dependent wavelength. Quantum physics predicts that, even at zero temperature, there are electromagnetic waves fluctuating in any vacuum.

Between Casimir's two plates, the only waves that can exist are those with a node (a zero of amplitude) at each plate. For the periodic waves that make up electromagnetic radiation, the distance between the plates must be a multiple of half the wavelength for this condition to be fulfilled. (A violin string works according to the same principle: it resonates when there is an integer number of half-wavelengths in the length of the string between its end and where it is held down.) The presence of the two plates eliminates many modes of electromagnetic fluctuation, and the energy of the system depends on the plate separation. If the energy depends on the separation, there must be a force that moves the plates to minimize that energy. These are Casimir forces, a consequence of quantum fluctuations of electromagnetic fields in confined geometries that is still under study[7].

Fisher and de Gennes's contribution[2] was to realize that Casimir forces can pop up in some situations where the fluctuations are of a classical rather than a quantum nature.



C. HERTLEIN *ET AL.*

Figure 1 | Critical fluctuations. The demixing of water and the solvent 2,6-lutidine (seen here in false colours), is Hertlein and colleagues' laboratory[1] for measuring the critical Casimir force.

Specifically, they occur when a physical system changes state continuously, for example in a liquid–gas transition, or during the phase separation of a liquid mixture near its 'critical' temperature. Above this critical temperature, the liquid–gas transition does not exist. Close to it, there are large density fluctuations, as if the system were hesitating between two very similar states. Fisher and de Gennes predicted that these fluctuations should also be affected by a confining geometry, just as in the original Casimir effect. If two plates are immersed in a fluid system close to its critical point, a critical Casimir force should arise.

This new force should differ significantly from the original Casimir force in two respects. First, it should depend strongly on temperature, because it is highly sensitive to the distance from the critical temperature. Second, it should be either attractive or repulsive, according to the nature of the two surfaces: if they attract the same component of the liquid mixture, the force should be attractive; if each attracts a different component, the force should be repulsive.

Several groups have tried either to obtain experimental evidence for these astonishing forces or to calculate their effects. Both proved extremely difficult. The first indirect evidence came in 1999, with studies of films of liquid helium on copper plates[3]. Liquid helium has a critical point at very low temperature, where it becomes a superfluid (it starts to flow without friction). Close to this point, the liquid film became thinner, and this phenomenon was successfully analysed by assuming the existence of critical Casimir forces.

Hertlein and colleagues' direct proof[1] comes from measuring the force between two solid objects: a silica plate and, about 0.1 micrometres away, a polystyrene sphere about 3 μm in diameter. Both plate and sphere could be treated such that the expected forces would be either attractive or repulsive. The authors immersed everything in a mixture of water and the organic compound 2,6-lutidine near the mixture's critical point at 307 kelvin (34 °C) (Fig. 1). Their extremely sensitive apparatus used the technique of total internal reflection microscopy to measure the force between the plate and the sphere to an accuracy of 1 femtonewton (10^{-15} N). The size of the Casimir force they found was less than 600 femtonewtons, and its sign could be changed by treating the surfaces differently. A neighbouring group of theorists at the University of Stuttgart in Germany calculated[8] the variation of the effect with temperature and distance; their result is almost exactly the same as that from the experiments.

Is this discovery of any practical importance? As is so often the case, it's too early to tell. But the authors suggest that, as their force can easily be tuned by changing the temperature or by a surface chemical treatment, it could be used to control the aggregation of colloids, a central problem in many areas of materials science. They also note that the original Casimir force turns out to be a problem for attempts to actuate microscale devices: for instance, it makes microcantilevers stick to neighbouring walls. By plunging such devices in a tailored liquid mixture, this mechanical problem could be suppressed by creating repulsive forces. They might well be right in their predictions. Even better, these new forces might find applications that no one has even thought of yet. ■

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QUANTUM MECHANICS

Evolution stopped in its tracks

Lev Vaidman

How do you watch the evolution of something that doesn't evolve? In the classical world, even posing this question would provoke raised eyebrows. But where quantum physics is involved, no question is too silly.

"A watched pot never boils," the saying goes, although the laws of physics tell us that this can't be true. More precisely, the cosy intuitions of classical physics tell us this can't be true. But enter the topsy-turvy realm of quantum physics, and the saying and the science converge. Specifically, a phenomenon known as the quantum Zeno effect states that if we find a system in a particular quantum state, and repeatedly and frequently check whether it is still in that state, it will remain in that state. It does this even if, without constant checking, it would evolve to another state. The watched quantum pot never boils.

Bizarre and abstruse as the whole thing might sound, it could have practical applications, in particular to the field of quantum information[1]. Hence the interest in theoretical studies such as that of De Liberato[2], which appears in *Physical Review A*. De Liberato looks more closely at systems that are subject to the quantum Zeno effect, and finds a procedure that allows us to observe how such systems try to evolve, even though they do not do so. Although Zeno measurements are part of this procedure, they do not stop the evolution. De Liberato instead finds a new, and in this case more powerful, method to hold a quantum system in a given state so that its evolution can still be measured.

But first, some background. The Zeno of the quantum Zeno effect is Zeno of Elea, a Greek philosopher of the fifth century BC from the colonies of southern Italy. In his arrow paradox, he postulated that an instant is indivisible; an arrow, therefore, cannot be in different places at the beginning and the end of an instant. Because, within any instant, the arrow cannot change its place, it can't in fact move at all. Somewhat surprisingly, and despite the development of mathematical tools such as calculus to deal with continuous motion, philosophers are still not sure that classical physics can provide a good answer to Zeno's paradox. What is the nature of the impetus that provides an instantaneous velocity[3]?

Quantum mechanics, oddly enough, has an answer. Its impetus is quantum-mechanical momentum, which is a property of a quantum state at any instant. The velocity of a moving quantum arrow, as represented by its associated quantum wave, can be estimated at any