authors set the scattering length to zero — they 'turn off' the interactions — using a magnetic field[4]. Second, they quench the scattering length to infinity, again using the magnetic field. If we consider increasing the density of the gas by, for example, a factor of eight, the spacing between the atoms decreases by a factor of two. Zooming in (rescaling) by this factor of two, the atomic system looks exactly the same as it did before the density was increased, because the scattering lengths of zero and infinity are unchanged.

Eigen and colleagues vary the density of the gas by a factor of about ten, and observe that the experimental dynamics are independent of the density after rescaling both space and time. They also adjust the temperature of the gas and show that universality holds when one more variable is considered — namely, the length scale on which the gas exhibits quantum-mechanical behaviour.

Prüfer *et al.* and Erne *et al.* uncover a different form of universality. On the face of it, the experiments of these two groups are wildly different. Erne and colleagues start with a three-dimensional gas, quench to one dimension, and observe the density of the gas as a function of position and time. Prüfer and colleagues work in one dimension throughout, explore the internal states (spins) of the atoms and carry out a quench that allows these spins to fluctuate. But, after a short time, both groups observe universality, which they argue results from a phenomenon called a non-thermal fixed point.

For systems in equilibrium, the concept of a fixed point comes from one of the great discoveries of twentieth-century physics, known as the renormalization group. This framework studies how a system evolves as we zoom out from the microscopic to the macroscopic scale, and successfully describes the emergence of key phases of matter such as magnetism. Fixed points are states of a system that remain unchanged on zooming out. Non-thermal fixed points occur when non-equilibrium systems approach such a state, with the role of zooming out played by the passage of time[5].

A classic example of a non-thermal fixed point is wave turbulence, in which the energy of waves is transferred from large to small scales. Prüfer *et al.* and Erne *et al.* demonstrate the first examples of universality caused by non-thermal fixed points in systems dominated by quantum mechanics. Like Eigen and colleagues, the groups show that their results are robust by widely varying the initial conditions of their experiments and observing that the dynamics are effectively unchanged.

Although Prüfer *et al.* and Erne *et al.* use different quenches and measure different properties, their results are remarkably similar. This resemblance provides perhaps the best evidence for the existence of universality in these atomic systems. At a technical level, the experiments do differ in their critical exponents (numbers that describe the properties of fixed points), which indicates that the two fixed points are different.

Together, these three studies provide a substantial step forward in our understanding of quantum systems far from equilibrium. However, a complete picture of the underlying universality remains to be determined. A notable concern for all of the experiments is that the universality occurs over limited time and length scales. Longer times, in particular, would probably be required to realize non-equilibrium steady states that are useful for practical applications. By analogy with wave turbulence, one possibility for extending the reach of the universality could involve continuously pumping energy into the systems; it is well documented that universality is, at best, transient in the absence of an external drive.

From a fundamental perspective, these experiments pave the way for exploring a wide range of theoretical and experimental questions regarding non-equilibrium universality. For example, what are the possible classes of non-thermal fixed points? What happens at extremely high or low energy scales, at which the universality breaks down? And under what conditions does universality arise in generic quenched systems? These are challenging questions to answer, but I, for one, hope that these experiments open the door to placing non-equilibrium quantum systems alongside equilibrium ones in the lexicon of modern physics. ■

Michael Kolodrubetz *is in the Department of Physics, University of Texas at Dallas, Texas 75080, USA.*
e-mail: mkolodru@utdallas.edu

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BIOPHYSICS

Cellular stretch reveals superelastic powers

External forces can make cells undergo large, irreversible deformations. It emerges that stretched mammalian cells grown *in vitro* can enter a state called superelasticity, in which large, reversible deformations occur. SEE ARTICLE P.203

MANUEL THÉRY & ATEF ASNACIOS

In Rudyard Kipling's classic children's bedtime story[1], the elephant's elongated trunk arose because a crocodile grabbed "and pulled, and pulled, and pulled" on the nose of an elephant's child. The elephant's child escaped, but waited in vain for its nose to shrink back to normal. This scenario of an irreversible extension mirrors what happens in the laboratory when cells that are subject to external tension undergo major deformation. However, *Nature*, Latorre *et al.*[2] report on page 203 that mammalian epithelial cells grown *in vitro* can, unexpectedly, demonstrate a mode of reversible, large-scale shape changes — a property termed superelasticity.

When our skin gets cut, it breaks apart at the wound site. This is because the surface of skin, like that of most organs, is subjected to tension. This tension helps to limit the size and sculpt the shape of organs. Moreover, a cell can both generate and resist tension. In the cytoplasm, there are fibre-like elements of the cell's structural 'skeleton', called cytoskeletal filaments, that can transmit force. The type of cytoskeletal filaments that form from the protein actin can be moved by myosin proteins to generate the contractile forces that regulate cell shape. Adhesion sites that join cells together can relay this force between cells and cause tension to build up throughout an entire tissue[3]. However, cells under tension do not usually tear apart, because their material properties enable them to resist this tension[4,5].

If cells under tension undergo small-scale deformations, the resulting changes are mainly elastic[6], and a linear relationship exists between an increase in tension and an increase in deformation[7,8]. But in large-scale deformations, cells can enter a state termed plasticity, in which the breakage of bonds between cytoskeletal filaments leads to irreversible deformations that prevent full cellular recovery, even if the associated stress is released[9]. Latorre and colleagues describe a mechanism whereby cells under tension that undergo large-scale deformations change from being in an elastic state to enter a regime in which the cells elongate without requiring an increase in tension. Moreover, these deformations are reversible, indicating that cells can shift from an elastic state to what is called a superelastic state, and

thus avoid entering a state of irreversible deformation.

Why has superelasticity not been previously detected in living cells, despite decades of investigations into cellular properties? One explanation could be that the timescale matters[10]. In previous experiments, external forces have usually been applied for seconds or minutes[8,11], whereas Latorre and colleagues studied changes that occurred over several hours. Cells subjected to rapidly increasing tension often rupture, even at low tension levels, in just a few minutes[8], whereas even if the tension is 100 times higher, it can be resisted if cells stretch at their own rate, such as if they slowly spread out over a surface[12].

Latorre and colleagues grew monolayers of mammalian epithelial cells *in vitro* on a deformable substrate surface that enabled them to estimate the forces acting on the system. The authors exploited the ability of cells to pump water from the upper to the lower side of the cell (Fig. 1). This induced a build-up of water underneath the cells, generating pressure that caused a dome-like bulging of the cell layer under tension. Using microscopy and physical-modelling techniques, Latorre and co-workers precisely measured the tension in these cellular domes.

The regularity of the curvature of the structures indicated constant tension, in which all of the cells experienced the same level of force. However, the uniformity of deformation was lost above a certain deformation threshold, and some cells in the domes became more stretched than others. The reason this occurred in only some cells was probably due to variability in cellular mechanical properties[6,8], wherein some cells were more sensitive than others to external tension. The highly stretched cells had entered a state of superelasticity: they were no longer resistant to the tension and instead elongated under this constant force. It is as if the cells had transitioned towards 'fluidization' of their cytoskeletal filaments[13]; in other words, instead of behaving like a coiled spring that resists force, these cells entered a distinct mechanical state akin to the way in which a liquid flows.

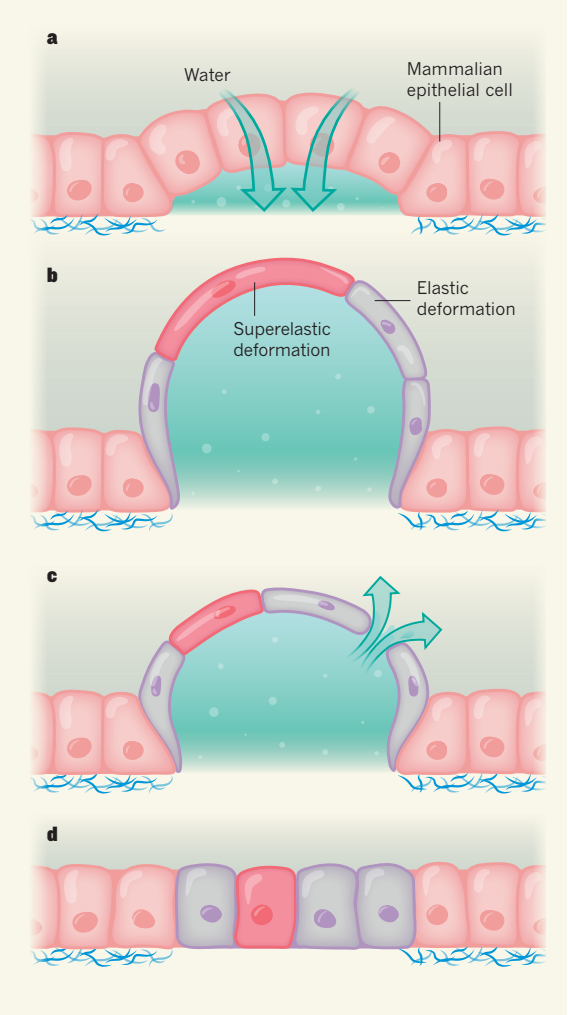

Figure 1 | Cells can exist in a state of superelasticity. **a**, Latorre *et al.*[2] analysed the stretching of monolayers of mammalian epithelial cells grown *in vitro* on top of a layer of fibronectin protein (blue). These cells can pump water from the upper to the lower side of the cell (green arrows). This resulted in a build-up of water beneath a dome-like layer of cells. The water build-up generates pressure and puts the cells under tension. **b**, The tension caused some stretched cells to undergo small-scale elastic deformations in which there is a linear relationship between the increase in tension and the extent of cellular deformation. The authors unexpectedly discovered that some cells underwent large-scale deformations and entered a state of superelasticity, in which cellular deformation increases without requiring a corresponding increase in tension. **c**, As pressure inside the dome-like layer of cells rose, rupture eventually occurred as a result of the breakage of an adhesive junction between cells; water escaped through this breakage point. **d**, The cellular deformations were fully reversible, and the cells returned to their initial small size.

How do cells resist the application of force solely until a certain level of deformation is reached, yet after that point, transition to a state of superelasticity? One explanation could be the availability of actin. The pool of cellular actin is limited[14], and each actin-based structure assembles itself at the expense of other potential such structures. When all cellular pools of actin are exhausted, actin-based structures can't form any more.

Latorre *et al.* focused on the cell cortex, a meshwork of actin filaments and myosin that forms a thin layer beneath the cell membrane. The authors measured cortex thickness, which is tightly coupled to the tension that the cortex is under[15]. Cortex thickness decreased with cellular stretching, suggesting that a sufficiently thick cortex might be required to enable cellular elasticity, and raising the possibility that, below a certain thickness, the cortex stops resisting tension and starts to 'flow'. However, the authors could not identify a clear transition in the structure of the cortex between that found in an elastic or in a superelastic state.

Perhaps finer details of the actin-network architecture are crucial for understanding the transition to superelasticity. The protein-mediated crosslinking of actin filaments ensures that components of the actin network are connected successfully, and that they function as a whole, rather than as numerous independent units[16]. It's possible that, as the cortex thins during cell stretching, a point is reached when this network connectivity is lost, and disconnected parts of the network start separating, or 'flowing apart', under tension. If this is true, the density of actin-filament crosslinking proteins might be a key factor in the transition towards superelasticity. Moreover, the investigation of actin-network density and crosslinking during specific developmental stages might reveal whether superelastic deformations occur as tissues are being shaped during development.

A cellular elongation process that does not require an increase in force for increased deformation will end when rupture occurs. Latorre and colleagues note that when the layer of cells ruptured, holes appeared between adjacent cells. Pressurized water inside the dome escaped through the rupture point, the dome collapsed and the superelastically stretched cells returned to their initial unstretched size. That the adhesive junctions joining cells, rather than the cells themselves, are the points of weakness, is consistent with observations of tissue rupture made using externally stretched cellular monolayers[11].

If the adhesive junctions had not ruptured in Latorre and colleagues' experiments, would the individual cells have kept on elongating? Probably not. A type of cytoskeletal structure called an intermediate filament might have an effect in this type of scenario. Intermediate filaments have been under-studied in comparison with actin filaments because of their slow turnover dynamics and the absence of convenient experimental tools, such as drugs, that can disassemble them. However, their importance in cellular mechanics is gaining recognition[17].

Intermediate filaments make a substantial contribution to the elasticity of stretched cells[18] and can support extensive levels of stretching[19]. These filaments typically form in a wheel-spoke-like architecture that connects the nucleus to junctions between epithelial cells[20]. This raised another question: might these filaments have a role in the resistance to tension at high strain that would allow cells to limit their deformation?

Evidence directly supporting this possibility has been lacking. Latorre *et al.* used a laser to cut bundles of intermediate filaments in stretched cells in a state of superelasticity, and found that this induced cellular relaxation — a release

of stress and an elongation that increased the cellular area. This suggests that intermediate filaments might protect superelastic cells from undergoing an unlimited deformation by acting like springs that resist tension at high levels of deformation. In such circumstances, the ability of intermediate filaments to return to their usual length after being stretched might even enable such cells to recover their initial shape when tension is released.

Latorre and colleagues' work has revealed a more complex relationship between cell size and the forces that cells experience than was previously appreciated. Future studies should attempt to unravel the mechanisms that enable cells to enter a state of superelasticity and to recover from high levels of deformation. Now that we know cell shape is not an appropriate proxy for assessing cellular tension, it will be crucial to develop ways to accurately monitor tension levels in tissues, so as to better understand the factors that influence tissue shape. ■

Manuel Théry *is at UMR 1160, Paris Diderot University, Saint-Louis Hospital, CEA, INSERM, AP-HP, 75010 Paris, France, and at UMR5168, University Grenoble-Alpes, BIG/LPCV, CEA, CNRS, INRA, Grenoble, France.* **Atef Asnacios** *is at UMR7057 CNRS, Paris Diderot University, MSC, 75205 Paris Cedex 13, France.*
e-mails: manuel.thery@cea.fr; atef.asnacios@univ-paris-diderot.fr

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MEDICAL RESEARCH

Immune–cell crosstalk in multiple sclerosis

Interactions between the B and T cells of the human immune system are implicated in the brain disease multiple sclerosis. It emerges that B cells make a protein that is also made in the brain, and that T cells recognize this protein.

RICHARD M. RANSOHOFF

A hallmark of the disease multiple sclerosis is an inflammatory autoimmune attack[1] on the proteins of the myelin sheath, a structure that wraps around the nerve fibres that project from neurons. The myelin sheath provides protection and nourishment to nerve fibres and enables efficient transmission of nerve impulses. Myelin-sheath injury causes a range of symptoms, depending on the neurons that are affected. Which immune-system cells and protein targets have key roles in the initiation and progression of multiple sclerosis is not fully understood, and such information might aid the development of new treatments. Writing in *Cell*, Jelcic *et al.*[2] present an analysis of immune-system cells found in people with multiple sclerosis that deepens our understanding of how immune cells might contribute to this disease.

One factor linked[3,4] to the risk of developing multiple sclerosis is the possession of a particular version of a protein called HLA. HLA proteins enable cells to display antigens — fragments of proteins — on their surfaces. If the receptor for an antigen (the T-cell receptor; TCR) on a T cell recognizes an antigen presented by an HLA protein, the T cell is activated to trigger an immune response against cells that express the antigen. Variations in the antigen-binding capacity of different HLA proteins and in the antigen-recognition capacity of TCRs enable the body to respond to a wide range of antigens associated with disease-causing microorganisms. However, there is a danger that if an HLA protein efficiently binds an antigen that is normally part of the body, and if a T cell that recognizes the HLA–antigen complex is activated, autoimmunity could develop. Such a mechanism might underlie the fact that the version of HLA called HLA-DR15 is a risk factor for multiple sclerosis[3], and is estimated[4] to contribute 60% of the total genetic risk for developing the condition.

T cells from people with multiple sclerosis are more prone to divide *in vitro* than are T cells from people without the condition[3]. Such cell division is reminiscent of the division that occurs as the result of normal immune-cell activation by an antigen stimulus, but in this case it does not seem to require the addition of an antigen stimulus to the sample of immune cells[3]. This suggests either that the normal requirement for antigen recognition is being bypassed, or that these T cells recognize an antigen that is present on other immune cells in the blood sample. Jelcic *et al.* investigated further, analysing in more detail the behaviour of immune cells in blood samples of people with multiple sclerosis. They convincingly demonstrate that both T cells and another type of immune cell called a B cell from these samples could proliferate when grown *in vitro*. The authors term this type of division autoproliferation, because it occurs spontaneously *in vitro* without the addition of an antigen.

Jelcic *et al.* found that signalling through a TCR-initiated T-cell proliferation, and that cell proliferation was associated with the production by T cells of a signalling protein called IFN-γ (Fig. 1), which is associated with multiple sclerosis[5]. IFN-γ is a potent activator of a category of immune cells called macrophages, which directly damage the myelin sheath[6,7] in multiple sclerosis.

The authors implicate B-cell proliferation in driving T-cell autoproliferation, because neither T cells nor B cells divided if the cultured cells were exposed to a drug called ibrutinib. Ibrutinib inhibits the protein BTK, which is essential for signalling downstream of the B-cell antigen receptor that leads to B-cell proliferation[8]. Interestingly, a phase IIb clinical trial (see go.nature.com/2yhfphu) has reported preliminary evidence that the BTK inhibitor evobrutinib could potentially provide benefit for people with multiple sclerosis (see go.nature.com/2qtqby9).

Each of the multiple-sclerosis treatments currently in use suppresses disease-associated brain inflammation, but in different ways. Jelcic *et al.* took advantage of this to test whether interactions between B cells and T cells are needed for T-cell autoproliferation, and whether this phenomenon might be involved in processes that lead to the symptoms of multiple sclerosis.

The authors analysed blood samples from people with the disease who were receiving different anti-inflammatory treatments, and compared these results with control samples from people with the disease who were not receiving treatment. For those receiving an antibody called natalizumab, which causes an increase in the numbers of T cells and