up to 16 nanometres in kinesin[9]. Detailed modelling[12] of F_1 indicates that ATP binding might trigger elastic bending in the catalytic β-subunit, which then applies torque to the γ-subunit in the rotor. In kinesin, a rigid helical structure may act as a mechanical relay between a phosphate-sensing loop at the ATP/ADP-binding site and a linker region that is usually mobile but which becomes immobilized upon ATP binding[9]. Energy flow in GroEL is poorly understood. Indeed, questions about all three enzymes remain; for example, do mechanical signals generally occur as elastic strain, as in F_1, or can some protein domains become thermally activated upon ATP binding? Temperature-dependent kinetic studies and efficiency considerations may help to separate entropic and enthalpic contributions, but energy flow will probably remain murky until investigated further. The hope is that new experimental approaches, such as those relying on protein databases to enable statistical comparisons of closely related proteins[13], will speed our understanding. ■

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Fundamental physics

Newton rules (for now)

Frank Wilczek

Three hundred years after Newton explained the falling of an apple and the motion of the planets, physicists are beginning to test his universal law of gravity down to micrometre distances — with interesting results.

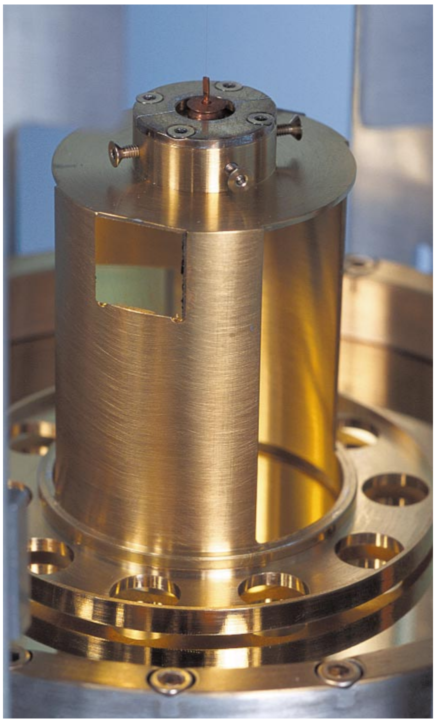

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Figure 1 **Apparatus used at the University of Washington[1] to test Newton's inverse square law. They measured the motion of a metal ring suspended above a rotating disk to show that Newton is correct down to ring–disk separations of at least 200 μm. The photograph shows the metal ring, which has ten holes bored in it, suspended from a torsion pendulum. The rotating disk below the metal ring is hidden from view by a sheet of metal foil that minimizes electrical forces on the pendulum. As the disk rotates, the gravitational force causes the ring to twist back and forth ten times for each revolution of the disk. The twisting of the pendulum is measured by reflecting a laser beam from a small mirror attached to the upper part of the pendulum. The entire apparatus is coated in gold to prevent electrical forces interfering with the weak gravitational signal.**

Newton's formula for the force of gravitational attraction is the oldest, and perhaps the most revered, universal law of physics. Yet it is not sacred. The experimental support for Newton's force law at sub-centimetre distances is surprisingly weak. There are theoretical suggestions about why and how deviations from Newton's law might arise at these distances. A group of experimentalists at the University of Washington, Seattle, has tackled the question, using ingenious but surprisingly low-tech, small-science techniques to test newtonian gravity down to 200 μm. As they report in *Physical Review Letters*[1], Newton's law still rules, which puts some theoretical speculation about large 'extra dimensions' on the ropes.

In modern physics, the precise form of Newton's formula for the gravitational force — proportional to mass, inversely proportional to distance squared — is rooted in profound principles. Force proportional to mass means acceleration independent of mass. Thus Newton's law implies that the motion induced by gravity is independent of the material properties of the body it acts upon. This idea is deeply engrained in Einstein's theory of general relativity, in which gravitational fields (produced by matter) change the geometry of space-time, causing it to become curved. It is the curvature of space-time that controls the natural acceleration of bodies. The inverse square form of Newton's law is a consequence of the field equations for gravity. The form of these equations, in turn, is dictated by the general principles of quantum field theory (specifically, the requirement that they derive from a local lagrangian function).

How, then, might deviations arise? One way is through the existence of extra, non-gravitational forces. Indeed, we know that there are other forces in physics, even at macroscopic distances. For example, there are $1/r^2$ electric forces between charged bodies, and $1/r^4$ magnetic forces (with complicated angular dependence) between magnetic bodies, where r is the separation. Even between unscreened neutral, non-magnetic bodies there are attractive short-range $1/r^7$ van der Waals forces. If our goal is to test the foundations of physics, however, our focus must be on non-electric, non-magnetic bodies, and forces beyond van der Waals.

Within the framework of quantum field theory, forces are associated with the exchange of virtual particles. Thus new forces are associated with new particles. The range of the force depends inversely on the mass of the particle. If the particle mass is m, then the range of the corresponding force is $\hbar/mc$, where $\hbar$ is Planck's constant and c is the speed of light. Numerically, a particle of mass 2×10^{-5} electron volts (25 billion times lighter than the electron) yields a force with a range of 1 centimetre. Thus in looking for deviations from Newton's force law — specifically new forces operating at supermolecular but sub-centimetre distances — we are probing for the existence of extremely light, extremely weakly interacting particles[2,3].

Many examples of such particles have been suggested, with various motivations. So-called axions[4] arise in attempts to explain the accurate time-reversal symmetry of the 'strong force' — the short-range interaction that holds protons and neutrons together in nuclei. Dilatons arise in superstring theory (a fundamental theory of elementary particles that requires extra dimensions). Familons and modulons arise in attempts to understand the origin of the subtle differences between particles in different families — for example the difference between the electron and its heavier cousins, the muon and tau leptons[5].

None of these exotic particles has yet been detected. Physicists have seen only the effects of exchanging massless 'gravitons', which are the particles thought to be responsible for transmitting gravity — a force they already know exists. In 1998, Arkani-Hamed and colleagues predicted[6] new effects involving extra dimensions and gravity, which captured the imagination of many physicists, and heightened interest in the search for deviations from Newton's force law.

Arkani-Hamed *et al.*[6] proposed that gravitons sense not only the four (three of space and one of time) macroscopic dimensions available to other particles, but also one or more additional spatial dimensions. Although these extra microscopic dimensions were once assumed to be too small to see, in some models they might be as big as a millimetre. If the size of the extra dimensions is d, strong deviations from Newton's force law are predicted for separations less than d. In the language of particle physics, when gravity spreads to the extra dimensions it produces a whole tower of new particles — so-called Kaluza–Klein gravitons — that modify the inverse square law.

In their experiment at the University of Washington, Hoyle *et al.*[1] suspended a metal ring containing ten equally spaced holes from a torsion (twisting) pendulum (Fig. 1). The pendulum was placed over a cleverly shaped rotating disk that contained two layers of holes (ten in each layer). They measured the torque on the pendulum produced by rotating the disk at different frequencies. The torque was created by the tendency of gravity to align the holes in the ring and disk. The measurements were repeated at different ring–disk separations, going from 10 mm down to 200 μm. All the components had to be precisely machined and electrically inert.

Hoyle *et al.*'s results show no deviations from newtonian physics, although the experiments were sensitive to forces of finite range and strength comparable to gravity down to 2 mm, and had significant sensitivity to stronger forces that kick in below this distance. The coupling strength of new force-transmitting particles with masses less than 10^{-3} electron volts is therefore severely constrained by this result. It indicates that if the extra dimensions proposed by Arkani-Hamed *et al.*[6] exist, then they must be smaller than 200 μm.

In the near future, the University of Washington group promises still more precise results, extending to even shorter distances. Another direction for this sort of experiment is to test whether the gravitational force is really independent of the type of material. Whereas gravity is strictly dependent on mass, other hypothetical particles will generally have some dependence on a combination of mass and other quantum numbers, such as spin. For example, axion-mediated forces depend primarily on spin[2]. It is important to continue progress at this unusual frontier of fundamental physics experiments, which complements work using gigantic particle accelerators, is relatively cheap and is largely unexplored. ■

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Cell biology

Proteolytic relay comes to an end

Martin Scheffner and Noel J. Whitaker

The cellular protein-degrading machinery detects target proteins by the signals they display. One such signal works for artificial test proteins, but only now has a natural equivalent been found.

The selective degradation of proteins is vital in every cell and organism. It is, for instance, involved in eliminating misfolded proteins and in controlling protein activity. Not surprisingly, then, malfunctions in protein degradation are associated with many human diseases, including neurodegenerative disorders and cancer. Proteins that are doomed to be destroyed exhibit distinct signals that mark them as targets for protein-degrading (proteolytic) systems. One such signal is the nature of the amino acid at the amino-terminal end ('N-end') of a target protein. This 'N-end rule' applies both to bacteria and to higher organisms, yet its physiological relevance has remained unknown, until now.

On page 955 of this issue, Rao *et al.*[1] report that site-specific cleavage of the SCC1 protein — an event that is necessary to allow duplicated chromosomes to segregate during cell division — generates a protein fragment that is targeted for destruction through recognition of its amino terminus. Moreover, failure to destroy this fragment results in chromosomal instability. So, one physiological function of the N-end rule is to rid the cell of the potentially harmful leftovers of site-specific protein cleavage.

The basis of selective protein turnover is the specificity of the interaction between a given proteolytic system and its target proteins. This implies that the targets must feature amino-acid sequences or structures that are specifically recognized as degradation signals by components of the proteolytic system. In a quest to identify such signals, Bachmair *et al.*[2] discovered that the type of amino acid present at the amino terminus of an artificial protein has a marked effect on the protein's turnover rate in budding yeast, *Saccharomyces cerevisiae*. According to the N-end rule, the amino-terminal amino acid can be characterized as having either a stabilizing or a destabilizing effect on a test protein. 'N-end-rule substrates' are those with amino-terminal amino acids that are destabilizing.

Members of the same group[3] went on to show that, in higher organisms, N-end-rule substrates are degraded by the so-called ubiquitin/proteasome pathway[4]. In this proteolytic system, substrates are first tagged with several copies of the small protein ubiquitin. Tagged substrates are then degraded by the 26S proteasome complex. The implication is that substrate recognition in this system is mediated mainly by a component of the ubiquitin-conjugating machinery — the protein UBR1, in the case of N-end-rule substrates[5,6]. Cells from bacteria to humans can process artificial proteins according to the N-end rule, with some variations in the amino-terminal amino acids that are stabilizing or destabilizing (see ref. 7). The actual mode of recognition, however, is probably different, because bacteria do not contain ubiquitin.

This is a fascinating story, but one with a significant caveat. Until now, there were no known cellular substrates — and thus no physiological functions — for the N-end rule. In fact, all known cytosolic and nuclear proteins in yeast have a stabilizing amino acid at their amino terminus. Does this mean that cells have evolved mechanisms to counteract the N-end rule? Or is there nonetheless a definable physiological role for this rule? A first clue to the answers came from studies of pathogenic viruses and microbes. These organisms frequently produce long polypeptide chains that are cleaved by site-specific proteases to generate distinct, active proteins. In some cases, this results in destabilizing amino acids being uncovered at the amino termini of the newly created proteins[8–10]. So, the products of site-specific proteases might be a source of protein targets for the N-end rule. This supposition has now been elegantly proved by Rao and colleagues[1].

During the cell-division cycle, a cell must duplicate its chromosomes; the two copies of each chromosome are called sister chromatids. These must be held together until a later phase in the cell cycle (anaphase), at which