reading is only now emerging, DNA proofreading had long been characterized. DNA polymerases cleave misincorporated nucleotides from the growing DNA chain, but the cleavage activity resides in a protein domain distinct from the domain for synthesis (*14*). The spatial separation of the two activities probably allowed optimization of two dedicated active sites during evolution, whereas RNA polymerase retained a single tunable active site. This could explain how some DNA polymerases achieve very high fidelity, which is required for efficient error correction during replication of large DNA genomes.

In the future, structural studies will unravel the stereochemical basis for RNA proofreading. Further biochemical and single-molecule studies should clarify how back-stepping and other rearrangements at the tunable polymerase active site are triggered. Techniques must also be developed to probe the in vivo significance of different aspects of the transcription mechanism discovered in vitro.

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PHYSICS

A More Precise Fine Structure Constant

The fine structure constant, a vital quantity in quantum theory, sets the scale for the physical world. Recent measurements have improved its precision by a factor of 10.

Daniel Kleppner

Relativistic quantum electrodynamics (QED)—the theory that describes electromagnetic interactions between all electrically charged particles—is the most precisely tested theory in physics. In studies of the magnetic moment of the electron (a measure of its intrinsic magnetic strength), theory and experiment have been shown to agree within an uncertainty of only 4 parts per trillion. This astounding precision has just been improved. A new measurement by Odom *et al.* (*1*) has increased the experimental precision by a factor close to 6. In a parallel theoretical effort, Gabrielse *et al.* (*2*) have extended the QED calculations of the magnetic moment to a new level of precision. By combining these advances, the precision with which we know the value of the fine structure constant is now 10 times as high as that obtained by any other method. The fine structure constant is a dimensionless number, $~1/137$, which involves the charge of the electron, the speed of light, and Planck's constant. It is usually designated α, and it plays a ubiquitous role in quantum theory, setting the scale for much of the physical world. Thus, α occupies an honored position among the fundamental constants of physics.

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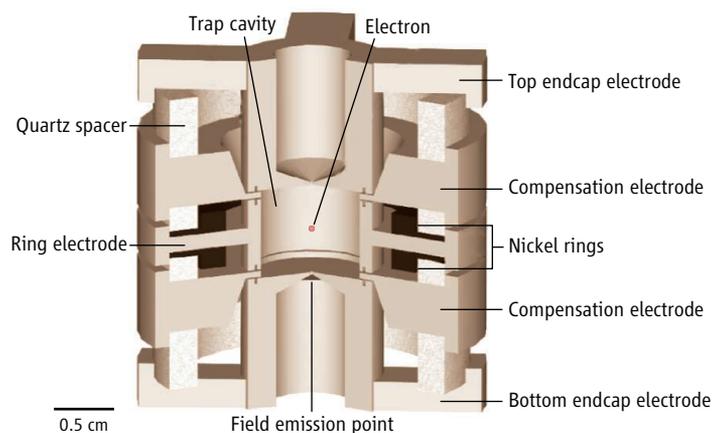
One-electron cyclotron. A magnetic field along the axis confines the electron radially; an oscillating electric field applied to the endcap electrodes confines it longitudinally. Nickel rings slightly perturb the magnetic field so as to couple the radial and longitudinal motions. The electron is trapped in a cavity that inhibits spontaneous emission. Other electrodes are used to control the electric field so as to reduce QED effects of the vacuum.

The quantity that has been measured by these researchers is the ratio of the magnetic moment of the electron to the fundamental atomic unit of magnetism known as the Bohr magneton. This dimensionless ratio is called the *g*-factor of the electron. Because the *g*-factor is a basic property of the simplest of the elementary particles, it has played a prominent role both in motivating and testing QED. According to Dirac's theory of the electron (*3*, *4*), for which he received the Nobel Prize in 1933, the *g*-factor should be exactly 2. In the period immediately following World War II, new data on the spectrum of hydrogen led to the creation of QED by Schwinger, Feynman, Tomonaga, and Dyson (*5*). According to QED, the electron *g*-factor would differ slightly from 2. Kusch and Foley discovered experimentally that the *g*-factor differed from 2 by about 1 part in a thousand (*6*). For this work Kusch received the Nobel Prize in 1955, followed by Schwinger, Feynman, and Tomonaga, who received the Nobel Prize in 1965. In 1987 Dehmelt published the measurement referred to above, accurate to 4 parts per trillion, for which he received the Nobel Prize in 1989 (*7*). The major experimental innovation in Dehmelt's measurement was a technique that allowed him to observe a single electron. The experiment of Gabrielse and colleagues builds on Dehmelt's work but incorporates major innovations that make the isolated electron into a quantum system whose energy levels can be probed.

The experiment compares the two types of motion of an electron in a magnetic field. The first is circular motion around the direction of the field at a frequency known as the cyclotron frequency f_c because the motion is described by the same equation as that for charged particles in a cyclotron accelerator. The second type of motion is spin precession. An electron possesses intrinsic spin, somewhat in analogy to the spin of a flywheel in a gyroscope. If a gyroscope is suspended by one end of its axle, it

experiences a torque due to its weight and precesses about a vertical axis. Similarly, in a magnetic field, an electron experiences a torque due to its magnetic moment, and the electron spin axis precesses about the field at a frequency f_s. The g-factor differs from 2 by the ratio $(f_s - f_c)/f_c$. The quantities actually measured are the cyclotron frequency f_c and the difference frequency $(f_s - f_c)$.

To carry out the measurement, Gabrielse and co-workers designed a one-electron cyclotron in which the underlying quantum nature of the electron's motion is both exploited and controlled (see the figure). In the theory of QED, the vacuum plays an important dynamical role. The radiation field of the vacuum (a fluctuating field in totally empty space) is a principal source of the electron moment anomaly. The vacuum field is slightly affected by conducting surfaces, such as the electrodes in the one-electron cyclotron. By carefully controlling the geometry of the cyclotron, Gabrielse and his colleagues essentially eliminated perturbation of the g-factor by the vacuum. Using principles of cavity QED, the researchers arranged the geometry so as to substantially prevent the orbiting electron from radiating its energy, thereby lengthening the observation time of each measurement.

Because cyclotron motion is inherently quantized, the energy of a circulating charged particle can change only in steps of hf_c, where h is Planck's constant. Normally these energy steps are so small compared to the particle's energy that the underlying quantum nature of the motion is unimportant. In the quantum one-electron cyclotron, however, the energy is so finely controlled that each discrete step can be observed. To accomplish this, the research team had to eliminate effects of thermal radiation by carrying out the experiment at a temperature of 0.1 K. Under these conditions, and using a technique called quantum jump spectroscopy, they could clearly see whether the electron was in the ground cyclotron energy state, or had taken one, two, or more energy steps.

An intriguing feature of the one-electron cyclotron is that the energy steps are not exactly equal due to the relativistic shift of the electron's mass with energy. One would hardly expect relativity to play a role at the ultralow energy of the one-electron cyclotron, but at the scale of precision of the experiment, relativistic effects are important. Odom et al. measured $g/2 = 1.00115965218085$, with an uncertainty of only 7.6 parts in 10^{13}, or 0.76 parts per trillion (1).

Calculation of the electron moment anomaly with the theory of QED presents a formidable challenge. The calculation involves evaluating the coefficients of terms in a power series, with each new term much more complex than the previous one. The third-order term was calculated in the mid-1990s (8). The fourth-order term, needed to interpret the new experimental results, required evaluating 891 Feynman diagrams (9). This task involved numerical integrations on supercomputers over a period of more than 10 years, augmented by delicate analytical calculations that were required to deal with the infinities that underlie QED.

If the fine structure constant were known to a precision of 0.7 parts per billion, it could be inserted in the theoretical formula to provide a true test of QED. A discrepancy would be of major importance because it would be an indication of new physics. A number of different experiments have yielded values of α, but none with the precision required for this test. Consequently, the theoretical results are most usefully applied to extract a new value of α from the experiment. The new value is approximately 10 times as accurate as previous values. For the record, the value (expressed as an inverse value) found by Gabrielse and Kinoshita and their colleagues is $α^{-1} = 137.035999710$, with an uncertainty of 0.7 parts per billion.

Although theories in physics all have boundaries to their areas of validity, nobody knows where that boundary is for QED. It is hoped that other measurements of α will continue to improve so that they can be combined with these new measurements to extend QED's area of validity or, better yet, find its boundary. Furthermore, there are a number of avenues for improving the measurements made by Gabrielse and his colleagues. The electron's magnetic moment is now known to better than a part per trillion, but the ultimate precision is not yet in sight.

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CELL SIGNALING

Protein Kinases Seek Close Encounters with Active Genes

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Signaling kinases may form integral components of transcription complexes, influencing gene expression in an unexpected way.

Upon exposure to changes in the environment or to developmental cues during differentiation, a cell reprograms transcription in its nucleus through a circuitry of signals that ultimately alters gene expression. Many of the steps of such signal-transducing cascades are executed by kinases, enzymes that transfer phosphate molecules onto target substrates. Often, kinases at the end of such cascades (terminal kinases) trigger the necessary response by directly phosphorylating transcription factors, coregulatory proteins, or the proteins that, with DNA, make up chromatin. Until recently, the prevailing view has been that terminal kinases operate enzymatically, without stable association with the chromatin that harbors target genes of a signaling pathway. But an alternative model whereby such kinases also play a structural role by binding to factors within transcription complexes at target genes has been slowly gathering support (1). On page 533 of this issue, Pokholok et al. (2) report a global analysis in yeast of the association of kinases with genes that they regulate, further supporting this model. Their findings suggest that such interactions can be observed not only with sequence-specific transcription factors positioned at regulatory (promoter) regions lying upstream of target genes, but also with the coding region of genes in some cases.

The yeast HOG mitogen-activated protein kinase (MAPK) pathway responds to changes in external osmolarity by activating the Hog1p MAPK, which then regulates expression of osmoresponsive genes (3, 4). The necessity of its transcription factor substrate to retain Hog1p in the nucleus after cellular exposure to osmotic stress suggested that Hog1p might form stable interactions with its substrates, and experiments that identified potential binding partners for Hog1p indicated the same (5, 6). A breakthrough came when chromatin immunoprecipitation (ChIP) experiments showed that in response to osmotic stress, Hog1p is

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