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level, allowing each dimension to evolve independently.

However, these results do not establish the precise nature of the genetic changes responsible for the differences in morphology. Are the changes in CaM levels between species due to one or more differences in the CaM gene itself — for example in the flanking regulatory regions of the genome that control where and at what rate the gene is transcribed? Or are they due to changes in one or possibly many genes scattered throughout the genome that act upstream of CaM to cause it to be expressed at higher levels in the developing beaks of cactus finches?

Genetic mapping studies in other animals and plants, such as maize (corn) and teosinte (from which maize was domesticated)[5], suggest that mutations directly affecting the expression level of a single gene have been responsible for some profound evolutionary changes. The application of mapping techniques could answer this question in Darwin's finches. Such information would add to the debate over whether evolution proceeds through the accumulation of many mutations of small effect in many genes, or through one or a few mutations of large effect in a single gene. Although it is difficult to generalize from a few examples, Darwin's finches still have much to tell us about the evolutionary process. ■

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PARTICLE PHYSICS

A finer constant

Andrzej Czarnecki

For the first time in a decade, the precision of the fine-structure constant — central to understanding the electromagnetic force — has improved. But even greater accuracy is required to test new physics.

How does the colour of a rose relate to the hardness of oak? To physicists, both result from electromagnetism, an interaction whose strength is encoded in one pure number — the fine-structure constant. Appropriately for something introduced at the dawn of quantum mechanics, the fine-structure constant is denoted by the Greek letter alpha (α). It was once believed to be a simple fraction, 1/137, a circumstance that provoked theorists to search for some deeper meaning to it. Studied closer, the denominator turned out not to be an integer. Writing in *Physical Review Letters,* Gabrielse and colleagues[1] use a measurement of the electron's magnetic moment reported in a companion paper[2] to find that $\alpha = 1/137.035999710(96)$, the most accurate value yet. But why is this important — and why is even this accuracy not enough?

Electromagnetism dominates most phenomena at scales larger than the subatomic (which is ruled by nuclear forces) but shorter than the astronomical (the realm of gravity). Thus, α can be measured in many ways, using any system of well-understood electromagnetic nature. When Arnold Sommerfeld first used α in 1915, he named it the fine-structure constant because it described subtle features of the radiation spectrum of the hydrogen atom. Its value was initially best determined by measuring atomic transitions. In the 1970s, more precise values came from solid-state systems, through the discovery of electrical phenomena such as the Josephson and the quantum Hall effects (Fig. 1).

For the past quarter-century, the world record for the most accurate value of α has been held by amazing experiments performed on a single electron trapped in a vacuum permeated by electric and magnetic fields[3]. The electron, as a charged and rotating particle, is a tiny magnet with a strength — its magnetic moment — given by $\mu = g\,(e/2m)s$, where e, s and m are the electron's charge, spin and mass. The proportionality coefficient g would be 1 for a classical spinning ball. For the point-like electron, relativity theory demands that $g = 2$.

This is not yet the whole story. The physical vacuum, far from being 'nothing', vibrates with activity. Elementary particles borrow energy from the vacuum to pop up and disappear again through quantum fluctuations. The electron interacts with such 'virtual' particles, mainly photons, and its g-factor is increased slightly by an amount that depends on α. This deviation, known as 'g minus two' ($g-2$) is among the most precisely calculated quantities in physics. In fact, quantum electrodynamics, the theory of electron interactions with light, was born through efforts to understand its value.

The dream of the theorist is an exact expression for $g-2$ in terms of α, but that seems as

50 & 100 YEARS AGO

50 YEARS AGO

"Nuclear magnetic resonance and electron spin resonance" — It is no new idea that most of the advances in the techniques of chemistry have come from the use of apparatus and methods originally devised by physicists. This is particularly true of spectroscopy, where the main applications associated with the different frequency bands have moved over, one after another, from the pure physicist to the chemist... It would appear that during the past eighteen months a similar move has been taking place with the two new techniques of nuclear magnetic resonance and electron spin resonance... As with all techniques which study the interaction of atoms with external forces, it soon became clear that these new methods also had very great potentialities as tools for chemical investigation, and during the past few years these applications have been brought to light in a very striking way. **D. J. E. Ingram**
From *Nature* 4 August 1956.

100 YEARS AGO

"Strength of a Beetle" — Last night a small beetle (*Aphodius fossor*), the length of which is ½ inch, flew in at my window and alighted on a table next to me. As it buzzed about I put a lid of a tin box over it, but to my surprise the beetle walked about bearing the lid on its back. I then put the tin box on top of the lid, and was absolutely amazed to find that the insect tilted up a corner of the combined box and lid, and nearly escaped. The weight of the beetle when dead was ½ grain, alive I suppose it was a little more; but the box and lid weighed 1758 grains! Assuming that the living insect weighed 1 grain, it must have tilted up 1758 times its own weight! Of course, the strength required to tilt up a box on edge is nothing like so great as that required to actually lift the weight, but nevertheless the feat seems to me sufficiently astounding. The dimensions of the box are 3⅛ x 2⅛ x 1½ inches.
From *Nature* 2 August 1906.

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elusive as deriving α itself. For now, only the first four terms of the Taylor expansion of $g-2$ are known (this is a mathematical expression consisting of a series of terms that, added together, come closer and closer to the true value of a quantity). Getting that far took six decades and spawned a rich tool-box of mathematical methods and tricks that has benefited other branches of science. Not least among these is the field of symbolic computation, which aims to harness the power and patience of computers to tackle huge algebraic equations.

This theoretical progress has gone hand in hand with experimental breakthroughs. Whereas particle physicists have consistently strived to build higher-energy accelerators, Gabrielse and Peil at Harvard University succeeded in constructing a cyclotron with the lowest energy so far[4]. In this cavity, cooled to 100 millikelvin, a single electron can be trapped and screened even from some of the vacuum fluctuations. Such is the tranquillity of its setting that individual quantum levels of the electron motion and spin can be discerned. Transitions among the lowest-lying states have now allowed Gabrielse and colleagues to determine the g-factor to an accuracy of one part in a trillion (ref. 2) and, when compared with the theoretical expression, improve our knowledge of α (ref. 1).

Can the accuracy of α be improved indefinitely? This is unlikely using the electron $g-2$. Gabrielse and colleagues' measurement[1] is, for the first time, sensitive not only to electromagnetic forces but also to tiny, strong nuclear effects. This is an impressive achievement, but also hints at obstacles ahead: the uncertainty inherent in nuclear forces will eventually limit how well α can be read off from $g-2$.

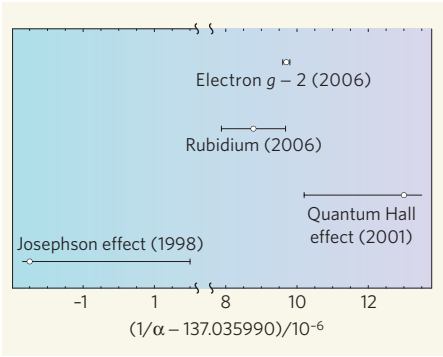

Figure 1 | Approaching alpha. **The fine-structure constant, α, is present wherever there is electromagnetism. The accuracy of its determination reflects our degree of understanding of various phenomena. Gabrielse and colleagues' value[1] using the electron g-factor is the best yet; other sources include photon collisions with rubidium atoms, the Josephson effect and the quantum Hall effect. Neutrons, caesium and several other atomic systems have also been used.**

But this emerging sensitivity to physics beyond electromagnetism is creating new opportunities. The electron has a heavier cousin, the muon, whose $g-2$ has recently been measured. The result disagrees[5] with our understanding of fundamental interactions by a tantalizing 2.8 standard deviations: too much to ignore, but not enough to claim a discovery of something new wiggling in the vacuum. Nevertheless, this could be the first evidence of particles that are too massive to have been seen in our laboratories, but that were perhaps crucial in the design of the Universe.

Could measurements of the electron help clarify what has or hasn't been seen? To probe the putative new force the muon might have sensed, the accuracy of the electron $g-2$ measurements should be improved by a factor of at least a dozen. Of course, an independent value for α would be needed to interpret the result.

Excitingly, atomic studies — the original source of information on α — are currently seeing a renaissance, and could produce sufficiently precise values. The new laser-based tools of optical lattices and frequency combs, recognized with the 2005 Nobel Prize in Physics, have been applied[6] to trap rubidium atoms and thus determine α with an error of seven parts in a billion. This is about nine times cruder than Gabrielse and colleagues' value[1]. But if the expected improvements in the atomic approach materialize, the electron $g-2$ will be freed to check out new physics.

Improving our knowledge of the fine-structure constant by another order of magnitude with an independent method is a daunting task. But the cunning of the α hunters justifies cautious optimism. ■

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CHEMICAL BIOLOGY

Cutting out the middle man

Tom W. Muir

Wouldn't it be nice if you could control the function of any protein with one small molecule? Unlikely as it sounds, this could become possible through a crafty process known as protein splicing.

One of the most exciting things about chemical biology is its potential to develop new tools for probing cellular processes. Small 'drug-like' molecules that can diffuse into cells and quickly elicit a discernible response offer distinct advantages over genetics-based approaches for exploring the highly choreographed inner workings of a cell[1]. In particular, small molecules can allow cellular processes to be rapidly perturbed in a reversible and often tunable fashion, allowing the dynamic features to be teased out. But finding a small-molecule modulator that is specific for one protein is a formidable challenge; finding one molecule that could somehow modulate the function of any desired protein seems impossible. Yet in the *Journal of the American Chemical Society*[2], Yuen *et al.* describe the results of a study, based on the pharmacological regulation of protein splicing, that suggest this might not be a complete pipedream.

Protein splicing is one of the most dramatic protein modifications known[3]. It is a self-catalysed process in which an internal protein domain, known as an intein, removes itself from a host protein with concomitant linking together of the flanking polypeptides, the exteins (Fig. 1, overleaf). Some inteins are remarkably promiscuous with respect to the extein sequences within which they sit. Indeed, inteins have found widespread applications in protein engineering as a way to introduce biochemical and biophysical probes into proteins[4].

Protein splicing results in a new polypeptide sequence being produced at the site of intein excision. Because a protein's function is intimately linked to its sequence, splicing has the potential to regulate the activity of the host protein. With this in mind, conditional inteins have been reported whose splicing activity is triggered by changes in temperature[5] or by the application of small molecules[6–8]. The appeal of these systems is that inducible inteins can be dropped into target proteins with standard molecular-biology techniques.

The work of Yuen *et al.*[2] builds on a previous study[7] from the same group, in which directed protein evolution was used to develop a controllable protein-splicing element that could be activated by the addition of a ligand — a molecule that binds to the protein. The controllable intein was based on a hybrid

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