previous work, providing support for their conclusion that diet and the microbiome have larger and more pervasive influences on serum composition than do genetic factors.

Diet and the microbiome could predict the data for some molecules with similar levels of accuracy, as would be expected, given that diet can affect microbiome composition. But Bar and colleagues showed that these data types provide non-overlapping information, too. For example, dietary information uniquely predicted particular metabolites associated with the consumption of citrus fruit, whereas the presence of a type of microbe belonging to the Lachnospiraceae family strongly predicted the presence of indoxyl sulfate – a bacterial breakdown product of the amino acid tryptophan, previously linked to diseases of the kidney and vasculature[5].

To make predictions about the concentrations of molecules present in blood samples, Bar *et al.* used a machine-learning method called gradient-boosted decision trees, which can capture complex interactions. Decision trees learn simple 'if–then' rules to make predictions (Fig. 1). This method layers individual decision trees, successively improving them by training new models that focus specifically on reducing the prediction errors of the older ones.

Bar and colleagues interpreted these models using an approach called feature-attribution analysis. This yields specific hypotheses about how individual factors, such as microbes, foods and genetic variants, influence a particular prediction, here, the molecular composition of blood. More-complex models can be prone to 'overfitting' – making erroneous predictions that are based on noise or irrelevant details. The authors therefore fitted and evaluated their models conservatively, but, even more importantly, they confirmed many of their predicted microbe-to-metabolite links in two large, independent study groups. Finally, Bar *et al.* tested one set of their predictions in a smaller study, identifying molecules (cytosine and betaine) associated with the consumption of wholewheat bread, and then showing that individuals randomly assigned to eat the bread had the expected changes in these metabolites.

This study is comprehensive, but plenty of room remains for future exploration. The authors used the well-validated and standardized Metabolon platform to measure serum metabolites, but no such metabolomic analysis method can cover the full range of blood-borne compounds. Certain types of molecule, such as blood lipids, might therefore be under-sampled compared with others. This might explain why the authors mostly detected metabolite associations with only one of the two most abundant lineages of gut bacteria[6,7]. Metabolomics can detect molecules whose identity is unknown beyond their molecular weight, and, indeed, the authors report several associations with such unknown metabolites. Although these might point to previously unknown aspects of biology (interestingly, for example, one such association was linked to the age of the participant), without metabolite identification, only limited conclusions can be drawn.

The authors' microbiome data provide DNA information for all the genomes present in stool extracts. However, Bar *et al.* distil these data down to the level of abundances of bacterial species, excluding non-bacteria such as yeasts or protozoan organisms. Limiting analyses to the species level also obscures the fact that strains of the same bacterial species can differ in gene content. For example, the metabolism of the drug digoxin *in vivo* by the bacterium *Eggerthella lenta* requires a gene that is present in only certain strains of *E. lenta*[8]. Finally, the authors were unable to link serum metabolites to specific bacterial enzymes responsible for their generation, which would have helped to connect the associated links to the underlying molecular mechanisms.

These limitations should not detract from the most useful aspect of this paper. By making the full data set available to the research community, Bar and colleagues could help enable the development of future computational methods, potentially resolving some of these limitations, or even providing ways to answer new questions. Their data are likely to be a rich and valuable resource for scientists interested in the mechanisms by which diet, the microbiome and genetics affect our biochemistry and physiology.

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Precision measurement

Fine-structure constant tests standard model

Holger Müller

A highly precise measurement of a physical constant known as the fine-structure constant provides a stringent test of the standard model of particle physics, and sets strong limits on the existence of speculative particles. **See p.61**

Every physicist knows the approximate value (1/137) of a fundamental constant called the fine-structure constant, α. This constant describes the strength of the electromagnetic force between elementary particles in the standard model of particle physics and is therefore central to the foundations of physics. For example, the binding energy of a hydrogen atom – the energy required to break apart the atom's electron and proton – is about $\alpha^2/2$ times the energy associated with an electron's mass. Moreover, the magnetic moment of an electron is subtly larger than that expected for a charged, point-like particle by a factor of roughly $1 + \alpha/(2\pi)$. This 'anomaly' of the magnetic moment has been verified to ever-increasing accuracy, becoming "the standard model's greatest triumph"[1]. On page 61, Morel *et al.*[2] report a measurement of α with an accuracy of 81 parts per trillion (p.p.t.), a 2.5-fold improvement over the previous best determination[3].

The measurement of α involves three steps. First, a laser beam makes an atom absorb and emit multiple photons and, in doing so, recoil (Fig. 1a). The mass of the atom is deduced by measuring the kinetic energy of this recoil. Second, the electron's mass is calculated using the precisely known ratio of the atom's mass to the mass of an electron[4,5] (Fig. 1b). Third, α is determined from the electron's mass and the binding energy of a hydrogen atom, which is known from spectroscopy[6] (Fig. 1c).

However, the recoil energy is tiny and

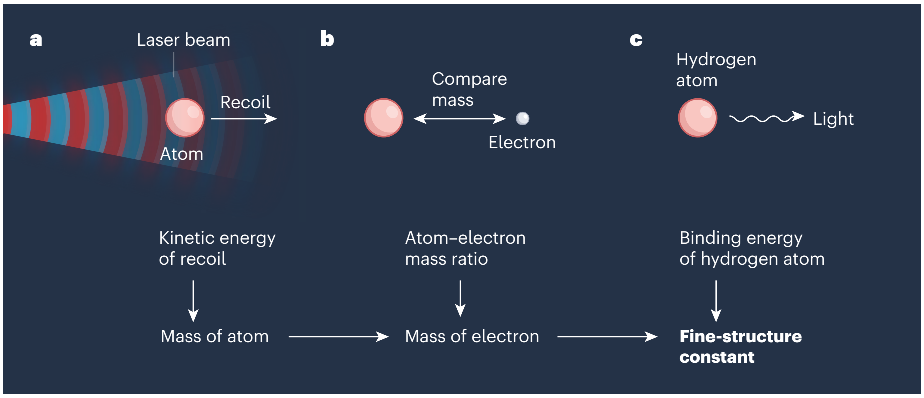

Figure 1 | Process for measuring the fine-structure constant. Morel *et al.*[2] report a highly precise determination of the fine-structure constant – the physical constant that defines the strength of the electromagnetic force between elementary particles. **a**, In the measurement of this constant, a beam of light from a laser causes an atom to recoil. The red and blue colours correspond to the light wave's peaks and troughs, respectively. The kinetic energy of the recoil is used to deduce the atom's mass. **b**, The value of the atom's mass is then combined with the precisely known ratio of the atom's mass to the electron's mass[4,5] to infer the mass of an electron. **c**, Finally, the electron's mass and the binding energy of a hydrogen atom are used to determine the fine-structure constant. The binding energy is known from spectroscopy[6], whereby light emitted from a hydrogen atom is analysed.

therefore hard to measure. Laser-based cooling of atoms has enabled physicists to carry out atom interferometry – a measurement technique that uses the interference of matter waves associated with the atoms. In an atom interferometer, atoms have a 50% probability of interacting with photons from laser pulses. Consequently, such atoms exist in two quantum states simultaneously: one in which they are at rest and the other in which they move, having absorbed the momentum of the photons.

This situation is equivalent to the production of two partial matter waves that move away from each other. These matter waves are recombined by firing more laser pulses, generating constructive or destructive interference (whereby the waves reinforce or cancel each other) and therefore a high or low probability of observing the atoms. The phase shift between the interfering waves – the displacement of one wave with respect to the other – is proportional to their travel time and the recoil energy.

Subsequent improvements to this approach have realized long travel times and interactions with many photons. In 2011, the research group behind the current breakthrough, at the Kastler–Brossel Laboratory in Paris, used the technique to determine α with an accuracy[7] of 660 p.p.t. In the following year, scientists carried out a measurement of the electron's anomalous magnetic moment to derive a standard-model prediction for α with an accuracy[8] of 250 p.p.t. And in 2018, my team at the University of California, Berkeley, published an atom-interferometry determination of α that agreed with the previous one but pushed the accuracy[3] to 200 p.p.t.

Now, Morel *et al.* have improved the accuracy to 81 p.p.t. In another triumph for the standard model, the measured value of α agrees with the standard-model prediction from the anomalous magnetic moment, even at such precision. This result confirms, for example, that the electron has no substructure and is truly an elementary particle. If it were made of smaller constituents, it would have a different magnetic moment, contrary to observation.

The measurement also places strong bounds on the existence of certain dark-sector particles, a speculative family of particles, some of which might constitute dark matter – the unseen matter component of the Universe. In quantum field theory, empty space is a sea of 'virtual' particles that spring into a brief existence. Virtual dark-sector particles would shift the electron's magnetic moment in subtle, yet measurable ways.

"This result confirms that the electron has no substructure and is truly an elementary particle."

However, there is a remaining puzzle. Although there is only a slight tension between each of the determinations of α and the standard-model prediction from the anomalous magnetic moment, there is a strong tension between Morel and colleagues' latest measurement and its two predecessors. As shown in Figure 1 of their paper[2], this situation is possible because the latest measurement and its predecessors deviate from the standard-model prediction in opposite directions.

The authors suggest that the difference between their research group's own measurements could be caused by speckle – small-scale spatial variations of the laser intensity – or by a phase shift arising in electronic-signal processing. However, it is no longer possible to evaluate such a shift in the group's earlier experiment, and speckle should produce a variation between the measurements in the opposite direction to that needed to explain the discrepancy.

Morel and colleagues also leave open the reason for the disparity with the 2018 measurement. The two experiments differ in the use of rubidium versus caesium atoms, in the types of atom–light interaction used and in how the laser beams are prepared and aligned. These choices imply different influences of the environment on the atoms.

For example, the largest corrections applied to data taken in both experiments arise from the laser beams. Both the speckle mentioned earlier and the overall beam profiles affect the magnitude and direction of the atom recoil. The discrepancy between the results could be explained if my team had over-corrected for these effects or Morel *et al.* had under-corrected. Most probably, it will take further experimental work to tell.

Experimenters are therefore gearing up to clarify the origin of this discrepancy and to challenge the standard model yet again. For example, my team is aiming to further improve the precision in the measured value of α by building an atom interferometer that enables unprecedented control over the laser-beam shape. Moreover, necessary improved measurements of atomic masses are already under way[5]. And finally, a refined determination of the electron's anomalous magnetic moment is being prepared at Northwestern University in Illinois[9]. Together, these improvements will allow physicists to approach an accuracy of 10 p.p.t. At that point, the effects of the tau lepton – a heavier cousin of the electron – will be observed in the experiments and many hypothesized dark-sector theories could be probed.

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