metastatic site. The authors report that, on average, more than about 93% of mutations detected in a given sample were present in every cell of that sample. This is in stark contrast to previous studies[10], which have reported much higher levels of variation. The extreme homogeneity observed by Priestley *et al.* could, in principle, reflect the fact that only a few founding cancer cells colonized each metastasis, but might instead reflect the limited regional sampling achieved by the fine-needle biopsy method.

Future clinical studies of metastasis are likely to consider liquid biopsies as an alternative collection method. Liquid biopsies involve collecting samples of a person's blood and applying specialized laboratory techniques to isolate cancer-derived components, such as circulating tumour cells, circulating tumour DNA and released subcellular vesicles. This approach is less invasive than fine-needle or surgical biopsies. It also offers other advantages, including the ability to collect cells simultaneously from all metastatic cancer sites in the body (instead of just one), and to repeat sampling at multiple times during treatment, thereby providing dynamic temporal information about a cancer and its response to therapy. Liquid biopsies also enable researchers to document metastatic evolution at the DNA, RNA and protein levels in parallel[11,12].

Ultimately, the true value of any research comes from improvements to treatment. To maximize the potential for clinical impact, Priestley and colleagues' data set is open-access. The authors have already accumulated more than 80 collaborative requests to investigate topics ranging from the possible presence of viral genetic material in the samples to the relationship between the sequences and patient drug responses (go.nature.com/2ommmn2). The data set is also being used to investigate whether any mutational variants involved in driving metastasis lie in regulatory DNA regions, and to enable efforts to deduce the anatomical origin of metastatic cancers diagnosed without a known primary-tumour site. Indeed, it is already powering exploration of these questions. The publicly available repositories are also being used in a Drug Rediscovery protocol[13], in which patients with metastases who have exhausted standard therapies are matched with promising off-label treatments (anticancer medicines that have not been specifically approved for use against the person's type of cancer) on the basis of results from WGS.

Obtaining metastatic biopsies is not without risks to the patient, such as bleeding and infection. This is partly why sample collection has been so limited until now. Those who donated samples to this study have provided researchers with a valuable gift. It is hoped that the database will, in turn, provide the new insights and therapeutic strategies that are so urgently needed.

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1. Lambert, A. W., Pattabiraman, D. R. & Weinberg, R. A. *Cell* **168**, 670–691 (2017).
2. Priestley, P. *et al. Nature* **575**, 210–216 (2019).
3. Robinson, D. R. *et al. Nature* **548**, 297–303 (2017).
4. Zehir, A. *et al. Nature Med.* **23**, 703–713 (2017).
5. Marusiak, A. A. *et al. Oncogene* **38**, 2860–2875 (2019).
6. Bielski, C. M. *et al. Nature Genet.* **50**, 1189–1195 (2018).
7. Dewhurst, S. M. *et al. Cancer Discov.* **4**, 175–185 (2014).
8. Campbell, P. J., Getz, G., Stuart, J. M., Korbel, J. O. & Stein, L. D. Preprint at https://doi.org/10.1101/162784 (2019).
9. Reiter, J. G. *et al. Science* **361**, 1033–1037 (2018).
10. Granahan, N. & Swanton, C. *Cell* **168**, 613–628 (2017).
11. Yu, M. *et al. Science* **345**, 216–220 (2014).
12. Medford, A. J. *et al. NPJ Precis. Oncol.* **3**, 18 (2019).
13. van der Velden, D. L. *et al. Nature* **574**, 127–131 (2019).

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Experimental physics

Progress on the proton-radius puzzle

Jean-Philippe Karr & Dominique Marchand

Atomic physicists and nuclear physicists have each made a refined measurement of the radius of the proton. Both values agree with a hotly debated result obtained by spectroscopy of an exotic form of hydrogen called muonic hydrogen. **See p.147**

The proton, discovered 100 years ago[1], is an essential building block of visible matter. The nucleus of a hydrogen atom consists of a single proton, making this atom a suitable platform for determining the proton's intrinsic properties. One such property is the proton charge radius, which corresponds to the spatial extent of the distribution of the proton's charge. In 2010, a highly accurate measurement of the proton radius was made using spectroscopy of muonic hydrogen — an exotic form of hydrogen in which the electron is replaced by a heavier version called a muon[2]. However, the value obtained was almost 4% smaller than the previously accepted one[3]. Bezginov *et al.*[4], writing in *Science*, and Xiong *et al.*[5], on page 147, report experiments that could represent a decisive step towards solving this proton-radius puzzle.

Atomic physicists determine the proton radius by measuring the energy difference between two electronic states of a hydrogen atom using spectroscopy. According to quantum mechanics, there is a non-zero probability that the electron will be found inside the proton if the electron is in a rotationless state (an *S* state). When inside, the electron is less strongly influenced by the proton's electric charge than it would otherwise be. This effect slightly weakens the binding of the electron and proton, and causes a tiny shift in the energy of the *S* state with respect to other states. The high precision achieved both by experiments and by the theory of quantum electrodynamics allows this energy shift and, in turn, the proton radius, to be extracted from measurements.

A muon is about 200 times heavier than an electron. As a result, there is a much higher probability that the muon in a muonic-hydrogen atom will be found inside the proton than would the electron in an ordinary hydrogen atom. Consequently, the associated energy shift is about 8 million (200^3) times larger for muonic hydrogen than for regular hydrogen[6]. Muonic hydrogen is therefore a highly sensitive probe of the proton radius.

Bezginov and colleagues' work concerns the Lamb shift of ordinary hydrogen — the energy difference between the 2*S* and 2*P* excited states. This shift was investigated previously in muonic hydrogen[2,7]. To measure the Lamb shift, the authors developed an experimental method[8] that derives from a technique known as Ramsey interferometry, which is used in atomic clocks.

This experimental method has many technical advantages over other approaches with regard to eliminating systematic uncertainties, filtering environmental noise, and simplicity in the shape of the spectral signal. A key feature of the set-up is the ability to measure a full spectrum in only a few hours. This allowed Bezginov *et al.* to carry out a meticulous study of systematic uncertainties and to extract a precise value for the proton radius: 0.833 ± 0.010 femtometres (1 fm is 10^{-15} metres).

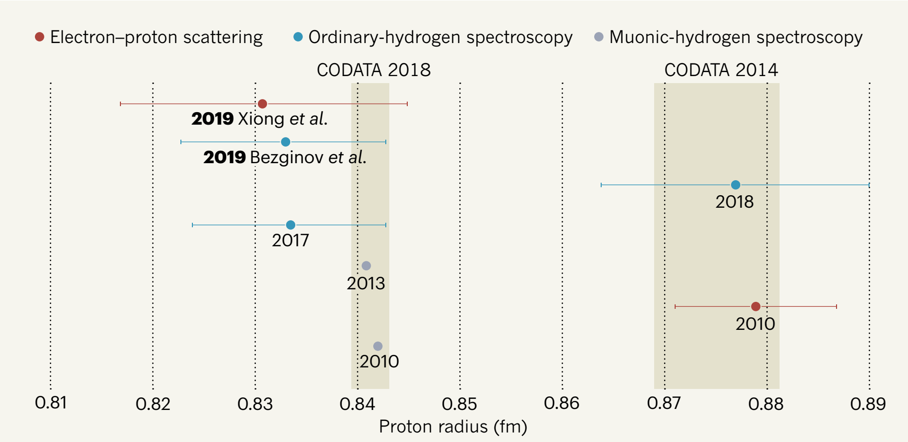

Figure 1 | Values for the proton radius. A key property of the proton is its charge radius — the spatial extent of its charge distribution. This quantity is expressed in femtometres (1 fm is 10^{-15} metres). The data points are values for the proton radius obtained over the past decade, including the latest results, from Bezginov *et al.*[4] and Xiong *et al.*[5], with uncertainties indicated by the error bars. The data were obtained using three different measurement techniques: electron–proton scattering[5,10], spectroscopy of ordinary hydrogen[4,9,13] and spectroscopy of an exotic type of hydrogen called muonic hydrogen[2,7]. The error bars for the two data points associated with muonic-hydrogen spectroscopy are too small to be depicted in this figure. The bands denote the values adopted by the Committee on Data for Science and Technology (CODATA) in 2014 (ref. 11) and in 2018 (see go.nature.com/2bwkrqz).

Nuclear physicists measure the proton radius using the 'elastic' scattering of electrons from protons. In this interaction, the incident electron transfers energy to the targeted proton through the exchange of a virtual (transient) photon. In a similar way to microscopy, short-wavelength photons (which transfer a lot of energy) reveal details at small scales. To determine the full extent of the proton's charge distribution, one should, in principle, use photons of infinite wavelength (that transfer zero energy), but no scattering at all would occur in this situation. Experiments therefore aim to achieve the lowest-possible energy transfer and then to extrapolate down to zero. This extrapolation, which relies on a parameterization of experimental data, is one of the main challenges in precisely determining the proton radius.

Xiong and colleagues implemented several key improvements over previous studies in their experiment, the Proton Radius experiment at Jefferson Laboratory in Virginia. Crucially, this investigation explores extremely low energy transfers (ten times closer to zero than previous data) while also probing larger energy transfers, to ensure consistency with existing data. The scattered electrons were detected through their energy loss in a detector called an electromagnetic calorimeter. This set-up avoided the need to use a magnetic spectrometer, the multiple settings of which induce systematic errors.

Furthermore, rather than making absolute measurements, Xiong *et al.* advantageously relied on relative measurements. Specifically, they determined the ratio between the number of events corresponding to elastic electron–proton scattering and the number related to Møller scattering — a well-understood and calculable quantum-electrodynamics process in which electrons are scattered from atomic electrons. This strategy led to the cancellation of many systematic effects that are associated with absolute measurements.

In addition, the protons were in a hydrogen gas that was kept inside a chamber that did not have entrance and exit windows as used in previous similar experiments.

"These independent measurements tip the scales in favour of a small proton radius."

This arrangement avoided background noise that would have been produced by the interaction of particles with window materials. Overall, Xiong and colleagues' chosen set-up, careful systematic-uncertainty checks at each step and exhaustive study of several parameterizations to extrapolate the data to zero energy transfer lend support to their value for the proton radius: 0.831 ± 0.014 fm.

The independent measurements of the proton radius made by Bezginov *et al.* and Xiong *et al.* are precise and consistent (Fig. 1). They tip the scales in favour of a small proton radius, in agreement with the highly accurate results from muonic-hydrogen experiments[2,7].

But to conclusively solve the proton-radius puzzle, one still needs to understand why there are discrepancies between the latest results and the data from previous hydrogen-spectroscopy[9] and electron–proton scattering[10] experiments. For instance, the value of the proton radius[11] adopted by the Committee on Data for Science and Technology in 2014 was 0.8751 ± 0.0061 fm. Because no convincing explanation for these discrepancies has been proposed, worldwide efforts must be pursued to validate the latest results and to critically assess the different measurement techniques.

Next-generation experiments will provide innovative approaches to this task. For example, the Muon Scattering Experiment[12] at the Paul Scherrer Institute in Switzerland is simultaneously investigating muon–proton and electron–proton scattering. This experiment is testing for possible differences in the behaviour of electrons and muons — an observation that would imply the existence of physics beyond that of the standard model of particle physics. On the spectroscopy side, high-precision measurements will be extended to other nuclei such as helium, and to molecules. It is highly probable that the harvest of results from future experiments will not only definitely solve, but might also explain, the proton-radius puzzle.

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1. Rutherford, E. *Phil. Mag. Ser. 6* **37**, 581–587 (1919).
2. Pohl, R. *et al. Nature* **466**, 213–216 (2010).
3. Bernauer, J. C. & Pohl, R. *Sci. Am.* **310**(2), 32–39 (2014).
4. Bezginov, N. *et al. Science* **365**, 1007–1012 (2019).
5. Xiong, W. *et al. Nature* **575**, 147–150 (2019).
6. Pohl, R., Gilman, R., Miller, G. A. & Pachucki, K. *Annu. Rev. Nucl. Part. Sci.* **63**, 175–204 (2013).
7. Antognini, A. *et al. Science* **339**, 417–420 (2013).
8. Vutha, A. C. & Hessels, E. A. *Phys. Rev. A* **92**, 052504 (2015).
9. Fleurbaey, H. *et al. Phys. Rev. Lett.* **120**, 183001 (2018).
10. Bernauer, J. C. *et al. Phys. Rev. Lett.* **105**, 242001 (2010).
11. Mohr, P. J., Newell, D. B. & Taylor, B. N. *Rev. Mod. Phys.* **88**, 035009 (2016).
12. Gilman, R. *et al.* Preprint at https://arxiv.org/abs/1709.09753 (2017).
13. Beyer, A. *et al. Science* **358**, 79–85 (2017).