physiological stressors; and reward-driven appetite pathways. Modulation of any of these pathways could be consistent with the reported data. The fact that Lac-Phe reduces appetite selectively in mice fed a high-fat diet could reflect an influence on pleasure-driven eating, although this remains to be examined.

Lac-Phe is not the only appetite-suppressing molecule produced by exercise. Growth differentiation factor 15, peptide tyrosine–tyrosine and glucagon-like peptide-1 also inhibit food intake and are increased in humans after exertion[4–6]. These molecules also have other metabolic functions, influencing energy expenditure, insulin sensitivity and blood glucose levels. Chronic Lac-Phe administration improved the uptake of glucose from blood into tissues in DIO mice, although Li *et al.* posited that this was an indirect consequence of weight loss. Going forward, it will be interesting to assess whether Lac-Phe has a direct effect on glucose uptake by tissues — this would indicate roles for the metabolite beyond appetite suppression, such as potential involvement in nutrient use during exercise.

Some clinical studies have shown post-exercise appetite suppression in men, but there is less evidence to support this phenomenon in women[6–9]. Li *et al.* examined only male mice, so future studies should investigate Lac-Phe in females. More generally, it will also be important to examine the relationship between Lac-Phe levels in blood plasma during exercise and both appetite suppression and weight loss. Might Lac-Phe levels in plasma affect how well exercise can promote weight loss?

The evolutionary adaptive role of exercise-induced appetite suppression is intriguing. One possibility is that the type of strenuous exertion studied by Li and colleagues is indicative of a stressor that threatens immediate survival: energy intake is deprioritized because it is necessary only for longer-term survival. For example, it is better not to be distracted by hunger when trying to escape predators.

Li and colleagues' discovery marks a starting point from which to investigate molecular pathways for exercise-induced weight loss in overweight mice. In addition, the exercise-induced increase in plasma Lac-Phe levels in men points to possibilities for improving weight management in people, if the role of Lac-Phe signalling in appetite and body-weight regulation is shown to translate to humans. It should be noted, though, that many factors, such as social eating and easy access to high-calorie palatable food, can circumvent the effectiveness of any stand-alone intervention. Ultimately, multi-pronged strategies used together are likely to be the best way of combating obesity, regardless of whether the current findings are applicable to humans.

Tahnbee Kim and **Scott M. Sternson** are at the Howard Hughes Medical Institute, Department of Neurosciences, University of California, San Diego, La Jolla, California 92093, USA.
e-mail: ssternson@health.ucsd.edu

1. Li, V. L. *et al. Nature* **606**, 785–790 (2022).
2. Jansen, R. S. *et al. Proc. Natl Acad. Sci. USA* **112**, 6601–6606 (2015).
3. Sternson, S. M. & Eiselt, A. K. *Annu. Rev. Physiol.* **79**, 401–423 (2017).
4. Kleinert, M. *et al. Mol. Metab.* **9**, 187–191 (2018).
5. Stensel, D. *Ann. Nutr. Metab.* **57** (Suppl. 2), 36–42 (2010).
6. Howe, S. M., Hand, T. M. & Manore, M. *Nutrients* **6**, 4935–4960 (2014).
7. Pomerleau, M., Imbeault, P., Parker, T. & Doucet, E. *Am. J. Clin. Nutr.* **80**, 1230–1236 (2004).
8. Hagobian, T. A. *et al. Exerc. Sport Sci. Rev.* **38**, 25–30 (2010).
9. Douglas, J. A. *et al. Int. J. Obes.* **41**, 1737–1744 (2017).

The authors declare no competing interests.
This article was published online on 15 June 2022.

Nuclear physics

Four neutrons might form a transient isolated entity

Lee G. Sobotka & Maria Piarulli

An experiment firing helium-8 nuclei at a proton target has generated evidence that four neutrons can exist transiently without any other matter. But doubts remain, because the existence of such systems is at odds with theory. **See p.678**

To understand the nature of cohesion in any system, you have to push the system until it breaks. In the case of atomic nuclei, this means knowing when the short-range attractive nuclear force that acts between nucleons (protons and neutrons) surrenders to the repulsive long-range Coulomb force between protons, and the extent to which extreme proton-to-neutron ratios can exist in nature. Neutron stars are proof that huge gravitational forces can bind almost purely neutron matter, but whether the nuclear force can do so alone has been a long-standing question. On page 678, Duer *et al.*[1] 'break' a helium-8 nucleus in search of an answer to this question, and find evidence hinting at the existence of a transient system comprising only four neutrons.

The only bound system that contains two nucleons is the deuteron, a system with one proton and one neutron. This system is stabilized by the alignment of the intrinsic angular momenta of the proton and the neutron — something that is not possible for systems containing just two neutrons or two protons. Even more than not being bound, the two-neutron system also falls short of being a 'resonance', which is the term used to describe a peak in the relative energy of the system's constituents. Such peaks can be attributed to transient aggregates, in which the lifetime is inversely proportional to the width of the peak. If energies could be measured that are suggestive of a resonance associated with matter comprising only neutrons, this would be one of the most noteworthy results in the past century of nuclear physics. Duer and colleagues' work indicates that the four-neutron system (a tetraneutron) has an energy spectrum with a 'resonance-like' feature.

The authors undertook an experiment in which helium-8 nuclei (comprising two protons and six neutrons) were fired in a fast beam towards a stationary target of protons (Fig. 1a). The collision resulted in each helium-8 nucleus ejecting an α-particle, which contains both protons but only two of the six neutrons, thus leaving behind four neutrons. The experiment did not detect these residual neutrons — instead, it detected the α-particle and a proton emerging with equal and opposite momenta. The neutrons remained in the moving frame of the beam without recoiling from the collision. By measuring the energy of the α-particle and proton, the team could attribute the missing energy to the four undetected neutrons. This energy provided a statistically unambiguous peak of the four missing neutrons that had a positive mean value, the classic signature of a resonance.

Duer *et al.* performed simulations suggesting that this peak was consistent with a resonance at 2.37 megaelectronvolts with a width of 1.75 megaelectronvolts, where both values have uncertainties of around 15%. This result is consistent with some previous work, but, statistically, it is far superior to other reported values (see, for example, ref. 2). The possibility that the observed peak could have resulted from processes other than α-particle knockout (leaving an isolated tetraneutron) — for example, the ejection of two neutrons, followed by two more — was considered by the authors, and dismissed. However, the measured resonance was relatively wide, which can make it

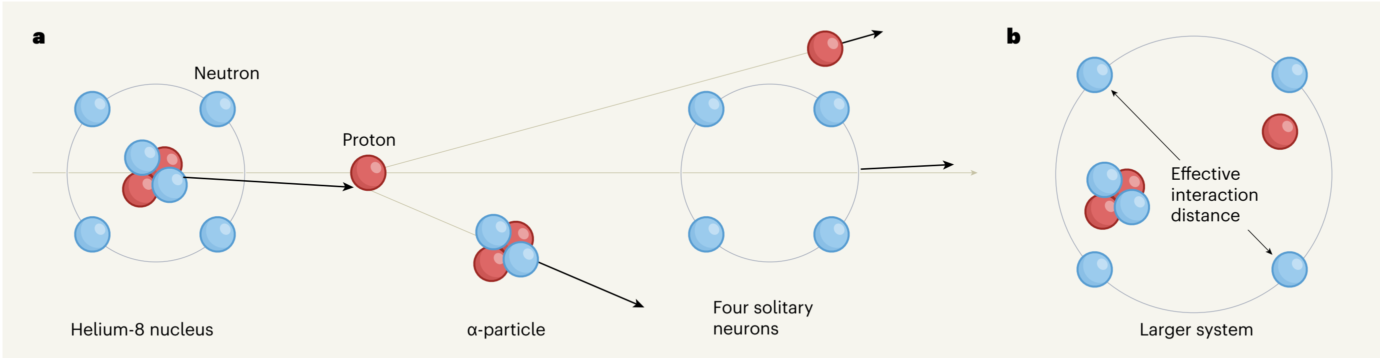

Figure 1 | A collision experiment for detecting purely neutron matter. **a**, Duer *et al.*[1] performed an experiment in which helium-8 nuclei (comprising two protons and six neutrons) were fired towards stationary protons. On collision, the helium-8 nucleus ejected an α-particle (containing two protons and two neutrons), leaving behind four neutrons. The authors measured the energy of the α-particle and proton emerging from an exit channel, and attributed the 'missing' energy to the four neutrons. Many such measurements by the authors resulted in a peak in the energy probability distribution that is consistent with the system forming a transient state of four neutrons. This would be the first statistically significant measurement of purely neutron matter bound without gravitational force. (Adapted from Fig. 1 of ref. 1.) **b**, However, because the distance over which neutrons effectively interact is very large, the observed peak in the energy spectrum could represent a larger system, rather than evidence of four solitary neutrons.

challenging to extract the relevant information, and the ultrashort lifetime associated with the resonance implies that it might not be possible to fully decouple the effects of other particles entering and exiting the reaction.

Alongside their experimental results, the authors present the rather disparate theoretical findings that have previously been made for the tetraneutron. In our view, there are only two clear statements that can be made from theory on this issue. First, a bound tetraneutron is incompatible with physicists understanding of the nuclear interaction[3]. Second, calculations that fully account for the plethora of possible unbound states indicate that a tetraneutron resonance cannot exist[4,5]. The more recent of these studies[5] suggests that the density of states of the four-neutron system (the proportion of states available to a system at a given energy) increases as the energy decreases to zero. The study also reports a timescale associated with the four-neutron system that is not linked to the width of a resonance.

One ingredient in this story is conspicuous by its absence: the modelling of reactions that could feasibly generate a four-neutron system with the rigorous treatment used in the above-mentioned theoretical studies[4,5]. Of course, it is possible that a system containing four isolated neutrons simply cannot be realized by removing nucleons using a neutron-rich beam. The distance over which neutrons interact is very large, which means that the α-particle and proton might 'feel' them through quantum-mechanical entanglement, effecting a resonance-like feature for the whole system, rather than for an isolated four-neutron system (Fig. 1b).

Duer and colleagues' work is part of a new generation of experiments that use particle-accelerator facilities to produce intense neutron-rich beams as a means of studying multi-neutron systems. Some of these experiments aim to detect such systems directly, and so, if successful, these investigations will be able to extract correlations in the momenta of the four neutrons. Even with this information, such projects are still plagued by an inability to model realizable tetraneutron-producing reactions.

So, is the peak observed by Duer *et al.* a resonance? Our honest answer is that we are not convinced that it is — at least, not a resonance of an isolated four-neutron system. However, the work has generated data of high statistical significance on pure, or nearly pure, neutron systems that researchers must now try to understand using theory that models the full many-body problem.

Lee G. Sobotka and **Maria Piarulli** are in the Department of Physics and the McDonnell Center for the Space Sciences, Washington University in St. Louis, St Louis, Missouri 63130, USA. **L.G.S.** is also in the Department of Chemistry, Washington University in St. Louis.
e-mails: lgs@wustl.edu; mpiarulli22@wustl.edu

1. Duer, M. *et al. Nature* **606**, 678–682 (2022).
2. Kisamori, K. *et al. Phys. Rev. Lett.* **116**, 052501 (2016).
3. Pieper, S. C. *Phys. Rev. Lett.* **90**, 252501 (2003).
4. Deltuva, A. *Phys. Lett. B* **782**, 238–241 (2018).
5. Higgins, M. D., Greene, C. H., Kievsky, A. & Viviani, M. *Phys. Rev. Lett.* **125**, 052501 (2020).

The authors declare no competing interests.

Molecular evolution

Mutations matter even if proteins stay the same

Nathaniel Sharp

Systematic editing of yeast genes to generate thousands of mutations indicates that, overall, the mutations have similar effects on yeast fitness regardless of whether they change the protein sequences encoded by the mutated genes. **See p.725**

Although some mutations in a gene alter the amino-acid sequence of the protein that the gene encodes, others — known as synonymous mutations — have no effect on protein sequence. Does it follow, then, that synonymous mutations are unimportant? On page 725, Shen *et al.*[1] present evidence that synonymous mutations are frequently just as harmful as the non-synonymous mutations that alter proteins, upending a common assumption about molecular evolution.

Synonymous mutations are possible because of the way in which DNA encodes proteins. In a gene, each set of three DNA bases forms a block called a codon, which encodes one amino acid or a stop signal. There are about three times as many codons as amino acids, so there is redundancy in the genetic code — most amino acids are encoded by more than one codon. Synonymous mutations change a codon into another one that encodes the same amino acid.

It has long been understood that