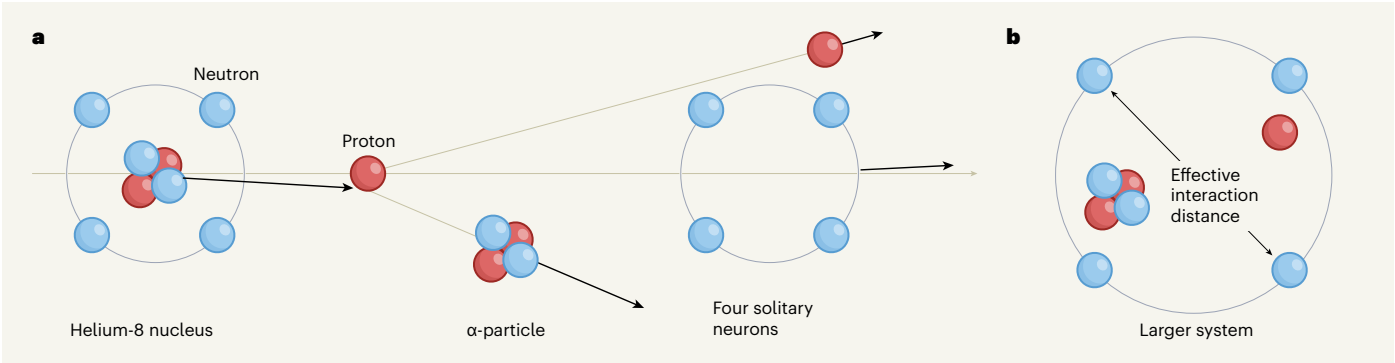

Figure 1 | A collision experiment for detecting purely neutron matter. **a**, Duer *et al.*[1] performed an experiment in which helium-8 nuclei (comprising two protons and six neutrons) were fired towards stationary protons. On collision, the helium-8 nucleus ejected an α-particle (containing two protons 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

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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

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From the archive

An appreciation of reptiles, and the President's address on the occasion of an astronomical centenary.

50 years ago

The Temperature and Water Relations of Reptiles. By J. L. Cloudsley-Thompson — I think it is fair to say that reptiles have a fascination for most people but especially to biologists, most of whom work in an academic system that is largely organized about ... mammals. There is a strong imaginative interest in the lives of creatures that may eat enough food in four days to keep them for the next 6–9 months, live through all their lives without drinking, that may withstand loss of 40 per cent of their body water, but may die when exposed continuously to "optimal" temperatures. Added to this is a particular sympathy for animals that have to go and sit in the Sun after meals to get warm enough to digest them, while we only have to find the heat to cook them. Reptiles have to achieve by ingenuity what their more sophisticated mammalian and avian colleagues are naturally equipped to do with their internal temperature-controlling systems.

From *Nature* 23 June 1972

100 years ago

The foundation of [the Royal Astronomical Society] on January 12, 1820, caused a ripple in the aether which has spread out ever since in widening circles. To-day that ripple embraces about 5000 of the fixed stars. The remaining thousand million or so are still outside. Though a good many of the best-known stars must by this time have received the tidings, 90 per cent. of the naked-eye stars are still in ignorance. We should like to think that the stars of the morning sing together with joy on this our Centenary; but the cold truth must be faced that not 1 in 100,000 can yet have heard of our birth. But we shall look out on the heavens again to-night with renewed enthusiasm and joy; and if from the majority of the stars we can expect no more than an unrecognising stare, there are half-a-dozen old favourites which—we may fairly be persuaded—will give us an answering twinkle. — A. S. Eddington

From *Nature* 24 June 1922

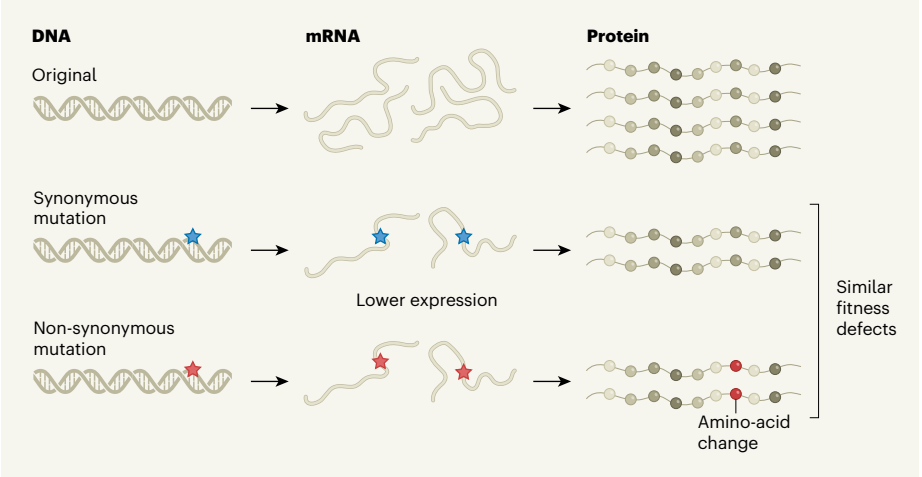

Figure 1 | Mutations can lower fitness without affecting protein sequences. DNA is transcribed into messenger RNA, which is translated into protein. DNA mutations can be synonymous (blue star), meaning that they have no effect on the sequence of the encoded protein, or non-synonymous (red star), meaning that they alter at least one amino acid. Shen *et al.*[1] compared the effects of these two types of mutation in yeast. They find that, on average, both types of mutation reduce the amount of mRNA produced from a gene compared with the amount produced from the original DNA sequence. Both also reduce the fitness of yeast cells.

synonymous mutations don't always have selectively neutral, or 'silent', effects[2,3]. For instance, the sequence of a gene can influence its expression level, meaning that synonymous mutations can affect protein abundance[4,5]. The sequence of the messenger RNA transcribed by a gene can affect its shape and stability[6,7]. Some species have evolved to use certain codons more than others throughout their genomes, which might be an adaptation to optimize the rate and accuracy of gene expression[4,8]. These phenomena all suggest that synonymous changes can have small but fundamental effects on cellular function and organismal fitness.

However, evidence to the contrary can be found by comparing species. Closely related species typically have very similar protein sequences — this indicates that evolution occurs in gradual steps, with natural selection disfavouring most non-synonymous mutations. Synonymous changes are more common between closely related species[9,10], suggesting that these variants are mostly selectively neutral, or nearly so.

Shen *et al.* set out to systematically explore the effects of synonymous changes in the budding yeast *Saccharomyces cerevisiae*. The authors used the genome-editing technology CRISPR–Cas9 to create thousands of synonymous and non-synonymous mutations in 21 yeast genes that are known to have diverse functions and expression levels. They cultured strains carrying each of these mutations alongside non-mutant cells, tracking whether each mutant sequence became more or less frequent in the population over time — an indicator of their effect on cell fitness. As expected, mutations that altered proteins tended to be harmful, slowing growth of the mutant population by 1.5% on average, and beneficial changes were rare. Surprisingly, synonymous mutations were only slightly less harmful, on average, and showed a similar overall pattern of effects, suggesting that synonymous mutations are often strongly non-neutral (Fig. 1).

For most of the genes they studied, Shen and colleagues were able to measure the expression level of each mutant version by sequencing mRNA. They found that synonymous and non-synonymous mutations were about equally likely to affect gene-expression levels. Expression was correlated with fitness, especially when mutations caused reduced expression. The effects of both synonymous and non-synonymous mutations could be predicted on the basis of the codons involved — mutations that maintained or created a codon that is uncommon across the yeast genome were more likely to be deleterious than were those involving common codons. These results imply that a change in protein sequence might not be the biggest reason non-synonymous changes are so often harmful. Instead, a mutation's effect on mRNA expression and stability might be more relevant.

If synonymous and non-synonymous mutations have similar effects on fitness, why is there a difference in how often they are retained in populations? One possibility is that the two mutation types actually have different — but very subtle — effects on fitness. Such a difference would be detectable by long-term natural selection, but not measurable in the laboratory. However, the authors suggest an alternative explanation: selection acts over long timescales, across which a species might find itself in diverse environments. It follows, then, that the average effect of a mutation in different environments influences its evolutionary fate. Perhaps, Shen *et al.* propose, non-synonymous changes have variable effects depending on

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the environment, and so are often harmful in at least one environment encountered by a species. By contrast, synonymous changes might consistently be either bad or neutral. This would mean that non-synonymous mutations are rarely retained in the long run, but synonymous changes that are always neutral can persist.

To test this idea, Shen and colleagues measured the fitness of their yeast mutants in several kinds of environment, created using different culture media. As predicted, non-synonymous changes were more variable in their effects and were more likely to be non-neutral in at least one environment. These findings, along with results of computer simulations, led the authors to conclude that their hypothesis can explain the observed paucity of non-synonymous differences between species, even in a scenario in which synonymous variants are just as likely as non-synonymous variants to be deleterious in any particular environment.

More experiments and theoretical investigations will be necessary to determine how generally this model applies to different species and circumstances. In the meantime, Shen and colleagues' study should push researchers to evaluate long-standing assumptions about molecular evolution. Patterns of synonymous genetic variation have been used as a 'neutral' standard for inferring how selection acts on different genes, estimating current and historical population sizes, and more. For example, the number of synonymous differences between species is used as a 'molecular clock' to estimate how long ago speciation events took place – but these estimates would be inaccurate if selection actually constrains a lot of synonymous variation, effectively slowing the clock. Treating synonymous mutations as though they are neutral might be accurate enough for some approaches, but whether this is always the case should be formally established.

Revising our expectations about synonymous mutations should expand our view of the genetic underpinnings of human health. Synonymous mutations can cause proteins in humans to be inappropriately folded or expressed, just as in yeast – and we know this can influence treatment outcomes and disease risk[3]. There is clearly more to discover about the effects of mutations, especially if we consider them all equally worthy of our attention.

Nathaniel Sharp is in the Department of Genetics, University of Wisconsin–Madison, Madison, Wisconsin 53706, USA.
e-mail: nathaniel.sharp@wisc.edu

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In retrospect

60 years of chemistry of the noble gases

Felice Grandinetti

The landmark synthesis of a xenon compound in the early 1960s dispelled a long-standing myth about the reactivity of the noble gases – and opened the door to the rich chemistry of these elements, studies of which continue today.

In 1962, the chemist Neil Bartlett reported the first preparation of a xenon-containing compound in *Proceedings of the Chemical Society*[1]. Despite being less than half a page in length, this paper soon became a milestone of science[2], marking the true beginning of the field of noble-gas chemistry. The findings stimulated research beyond the synthetic chemistry of these elements, casting light on chemical bonding, reactivity in different phases of matter and the geochemistry of the deep Earth.

The noble gases are natural constituents of air, yet remained unknown until the end of the nineteenth century. Once they were isolated, their strong resistance to forming compounds with other elements quickly became apparent. It is now known that this behaviour is due to the fact that atoms of noble gases have a full outer shell of electrons, a finding that has had major implications for theories of chemical bonding. But at the time, this lack of reactivity was extremely puzzling, and much effort was devoted to finding ways to activate these elements[3]. Encouraged by theoretical predictions, for nearly 40 years chemists remained confident that it would be possible to prepare noble-gas compounds, especially those of krypton (Kr) and xenon (Xe).

An episode in 1933 changed that assumption. In that year, the influential scientist Linus Pauling predicted[4] that three noble-gas compounds could be synthesized: the hexafluorides of xenon and krypton (XeF_6 and KrF_6, respectively) and a xenon-containing acid (H_4XeO_6). This prompted his colleagues Don Yost and Albert Kaye to attempt the preparation of either a chloride or fluoride of xenon. The fluoride should indeed have formed, but the results were essentially negative[5]. A victory seemingly within reach soon became seen as an irremediable defeat, and a myth was born: noble gases are completely inert.

Over the next three decades, the only achievements in noble-gas chemistry concerned clathrates – solids in which atoms of noble gases are trapped in the crystal lattice of a host compound[6]. These solids were reported soon after the discovery of argon (Ar), but were never regarded as genuine noble-gas compounds because the trapped elements do not form true chemical bonds. Similarly, numerous noble-gas ions and charge-neutral species were detected in gas-phase experiments[7], but were not regarded as real compounds. So it was that, in July 1961, Pauling wrote[8]: "Xenon is completely unreactive chemically. It has no ability whatever to form ordinary chemical compounds, involving covalent or ionic bonds. The only chemical property that it has is that of taking part in the formation of clathrate crystals." Chemists were resigned to the invincible inertness of noble gases.

Less than one year later, Bartlett (Fig. 1) finally disproved this myth: he reported the preparation of an ionic xenon compound that he thought was xenon hexafluoroplatinate(v) ($Xe^+[PtF_6]^-$). He had previously prepared[9] another hexafluoroplatinate(v) compound, $O_2^+[PtF_6]^-$, by reacting molecular oxygen (O_2) with platinum hexafluoride (PtF_6). This reaction occurs because the platinum reagent attracts electrons so strongly that it removes an electron from the oxygen molecules. Bartlett then noticed that the first ionization potential – the energy needed to remove an electron from an atom or molecule – of an oxygen molecule is very close to that of a xenon atom, and therefore surmised that PtF_6 could pull an electron away from xenon to form a chemical compound. Sure enough,

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