begins with a protein sample that has been applied to a special sample grid. Plunging it into liquid ethane flash-freezes and traps the protein particles in a thin film of amorphous ice. Two-dimensional images of the individual particles in the sample grid, obtained by applying a beam of electrons, are averaged computationally to yield a 3D structure. The 2D images are incredibly 'noisy' because a low dose of electrons must be used to avoid damaging the radiation-sensitive biological sample. As such, these images have historically been unsuitable for determining structures at an atomic level of detail. However, the advances reported since 2013 have allowed single-particle cryo-EM data to be collected that rival those obtained using X-ray crystallography.

The resolution revolution of cryo-EM has continued to advance[6]. Yip *et al.* and Nakane *et al.* harnessed technological improvements to determine the structures of a stable iron-storing protein called ferritin (termed apoferritin in the absence of metals) to a resolution of approximately 1.2 ångströms. These structures are the highest-resolution single-particle cryo-EM reconstructions so far determined, and the data are of sufficiently high quality to resolve the individual atoms in apoferritin (Fig. 1). This unprecedented feat would not have been thought feasible merely a decade ago.

Yip and colleagues' success relied on hardware advances, including components such as a spherical-aberration corrector plus a monochromator device that applies a series of filters to ensure that only electrons with a narrow spread of energies interact with the specimen, thereby enhancing the resolution of the final image. Nakane and co-workers applied a different technology, a cold field-emission gun that also generates electrons with a narrow energy spread, together with a technology that reduces noise in each image by filtering out those electrons that interact non-productively with the specimen. Moreover, Nakane *et al.* captured data with a next-generation, highly sensitive electron-detecting camera.

In addition to analysing apoferritin, Nakane and colleagues obtained a structure at 1.7 Å resolution of a form of the receptor for γ-aminobutyric acid type-A ($GABA_A$) that was engineered to be more stable than the common form found in humans. This receptor is a protein complex that resides in the cell membrane of neurons and is a target for numerous therapeutics. Obtaining such a high resolution by single-particle cryo-EM had been deemed near impossible for a biological specimen such as this, one that exhibits a high level of flexibility in terms of its structural mobility compared with structurally rigid molecules such as apoferritin. The structure reveals details of the $GABA_A$ receptor that have never been seen before, providing insights, for example, into the binding of a molecule called histamine in the core of the protein.

The developments in cryo-EM hardware described by Yip, Nakane and their respective colleagues have driven a major advance in the resolution of single-particle cryo-EM. Each team used hardware that tackled distinct aspects of cryo-EM imaging that had previously limited the resolution attainable. With these technologies, the increased signal-to-noise ratio of cryo-EM images will expand the technique's applicability. For example, this might include using the technique to determine high-resolution structures of heterogeneous samples such as those formed of membrane proteins, or macromolecular complexes that vary in conformation or composition. Perhaps the melding of these technologies will enable the determination of cryo-EM structures at a resolution beyond even 1 Å. This once might have seemed a near impossible quest to embark upon.

However, these technologies represent the elite echelon of cryo-EM instrumentation and are currently out of reach for most institutes because of the cost of purchase and operation. Moving forward, these types of advance will help us learn more about what is limiting the attainable resolution and might therefore enable the design of better instrumentation. Although such high-resolution structures are not necessary to answer every biological question, the extra detail such hardware can provide would limit inaccuracies in 3D structures and provide a better platform for understanding biological functions. Nevertheless, for most macromolecules, the inherent structural flexibility and structural heterogeneity will instead probably be the resolution-limiting factor, regardless of the capabilities of the instrumentation available. For such less-stable specimens, the application of new sample-preparation technologies, together with improvements in data-collection throughput and algorithm advances, will offer fresh ways to probe the conformational landscapes of these complexes. Thus, although cryo-EM's resolution revolution might be nearing its end, more revolutions await in the years to come that will make this technique even more powerful and applicable to the investigation of diverse biological questions.

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Nuclear physics

Why neutrons drip off nuclei

Calvin W. Johnson

The neutron drip line refers to the maximum number of neutrons that can be packed into the atomic nuclei of each chemical element. A mechanism has been proposed that could explain the long-debated origin of this drip line. **See p.66**

Whereas some people play extreme sports, many nuclear physicists seek the thrill of extreme isotopes, by finding, for each chemical element, the largest possible number of neutrons that can be held by an atom. This boundary of nuclear existence, called the neutron drip line, has not been fully mapped – although the construction of rare-isotope facilities[1] will bring the goal closer. Moreover, even the theoretical location of the drip line is uncertain[2,3]. On page 66, Tsunoda *et al.*[4] argue that the mechanism responsible for the drip line is more subtle than previously understood and is related to deformation, a hallmark of much of ordinary nuclear physics.

The strong nuclear force that binds protons and neutrons together favours equal numbers of each particle. By contrast, weaker but longer-range electrostatic repulsion discourages the accumulation of protons in atoms. Competition between these two forces produces the valley of stability – the V-shaped

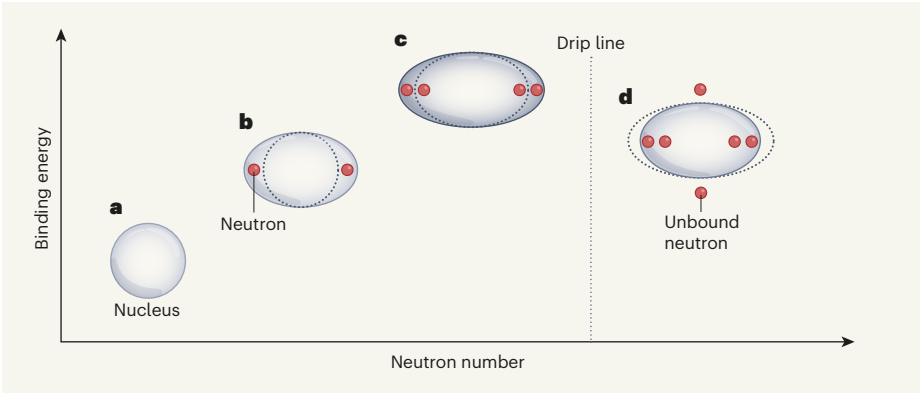

Figure 1 | A mechanism for the neutron drip line. The maximum number of neutrons that can be added to an atomic nucleus corresponds to a boundary called the neutron drip line. Tsunoda *et al.*[4] suggest that the mechanism responsible for the drip line is linked to nuclear deformation. **a**, They consider a spherical nucleus that has a particular binding energy — the difference between the total energy of the nucleus and the energy of its components. **b**, If neutrons are added, the nucleus deforms to the shape of an ellipsoid, and the binding energy rises. **c**, If more neutrons are packed in, the nucleus becomes even more deformed, and the binding energy increases further. **d**, As the drip line is approached, the nucleus becomes less deformed. If even more neutrons are added, the binding energy falls, and the neutrons do not bind to the nucleus.

surface that corresponds to stable nuclei when the energy per nucleus is plotted as a function of the number of protons and neutrons. The bottom of this valley is associated with the most stable isotopes, which have just the right mix of protons and neutrons. Add neutrons to these isotopes, and you move up the valley walls.

However, neutrons cannot be added forever. It takes energy to pull atomic nuclei apart, because their total energy is less than that of their components. This deficit is called the binding energy (shown as negative energies in Figure 4 of the paper[4]). If adding a neutron increases the binding energy, the neutron sticks. Otherwise, the energetically disfavoured neutron 'drips off'. Note that there is also a proton drip line, driven by increasing electrostatic repulsion.

Nuclear physicists have long assumed that the neutron drip line is governed by the preference of the strong nuclear force for proton–neutron symmetry. In the nuclear-shell model, protons and neutrons occupy quantum shells, much like electrons in an atom, and each shell has a particular potential energy. The thinking was that if the proton–neutron symmetry decreases, the potential energy also falls, to the point at which adding a neutron lowers the binding energy.

But protons and neutrons do not stay in a single shell. Instead, driven by the strong nuclear force, they jump from shell to shell, forming different configurations (see Figure 1 of the paper[4]). Like a flock of birds wheeling in the sky, protons and neutrons move collectively. For example, they can pair up with dance partners, such as electrons in a superconductor, and they can produce deformed (ellipsoid) nuclei that rotate, throwing off γ-rays. It turns out that nuclei are easily deformed — especially when the energy gap between shells is small. With 'magic' numbers of protons or neutrons, akin to the filled electron shells that drive the chemical inertness of noble gases, this energy gap is large, and deformation is suppressed.

Aware of this picture, Tsunoda *et al.* calculated the various contributions to the binding energy, such as the mean (monopole) energy generated from adding a neutron to a shell, the energy from deformation and the energy from protons and neutrons pairing up. They discovered that, as neutrons are added to nuclei of elements ranging from fluorine to magnesium, the monopole contribution rises steadily. At the same time, the nuclei initially become increasingly deformed, magnifying the rise in the binding energy. But, as even more neutrons are added, the nuclei become difficult to deform, and the deformation contribution falls more quickly than does the increase in the monopole contribution. When that happens, the binding energy falls, giving rise to the drip line (Fig. 1). Intriguingly, although the pairing contribution is non-negligible, it is approximately constant and so does not drive the drip line.

"The mechanism responsible for the drip line is more subtle than previously understood."

The rise and fall of deformation for these neutron-rich nuclei touches on another topic: magic numbers far from nuclear stability. At the bottom of the valley of stability, 20 is a magic number. For example, calcium (with 20 protons) has many stable isotopes that are difficult to deform, and calcium-40 (with 20 protons and 20 neutrons) is 'doubly magic'. But, moving away from stability, as the balance between protons and neutrons shifts, previous magic numbers can be replaced with new ones[5], for example at 16 neutrons. Both theory[4,5] and experiment[6] show that, as neon and magnesium isotopes collect more than 16 neutrons, the energies of the lowest-energy states that have 2 and 4 units of angular momentum become markedly lower (see Figure 3 of the paper[4]), which is a typical sign of increased deformation.

Tsunoda and colleagues' proposed mechanism draws on concepts familiar to nuclear physicists — in particular, the competition between deformation and mean shell structure. But some questions remain. For example, although the authors' calculations were highly detailed, requiring supercomputers, they largely ignored the unbound (continuum) single-particle states that have an essential role in defining the drip line for lighter nuclei than those considered here. Moreover, although the authors drew on *ab initio* interactions between protons and neutrons, they made empirical tweaks to the single-particle energies, which are part of the potential energies of the shells. Such 'by-hand' adjustments leave the robustness of the proposed mechanism unclear.

But the biggest question concerns the drip-line mechanism for even heavier elements than those considered here. This mechanism could be driven either by the mean shell structure and leaking of neutrons into the continuum, or by the competition between deformation and the mean potential-energy profiles that define magic numbers — or some combination of the two. For these heavier elements, the drip line is associated with rapid neutron-capture nucleosynthesis[7] — a process that forges many heavy elements, such as iodine, gold and the rare-earth metals. To fully understand this process, we have to go to nuclear extremes.

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