of the superficial layers. If, instead, the inward reflux of auxin is increased, the slope of the QC-directed auxin gradient increases, and the total auxin content of the root increases. Instead of causing indigestion, reflux enables the root to behave like a capacitor, able to take up and maintain a graded charge of auxin without exogenous inputs.

Does this computerized auxin avatar have a real-life counterpart and, if so, what is it like? Grieneinsen *et al.*[2] use fluorescence-imaging methods on roots under a variety of conditions to show that auxin distributions correlate well with those predicted by cellular distributions of PIN proteins. Recognizing the morphogenic potential of a steep auxin gradient, the authors go on to link cellular behaviours observed in the root — including division, differentiation and expansion — to auxin concentration thresholds.

It is unclear exactly how an auxin gradient determines a range of distinct cellular behaviours. But the companion paper by Galinha *et al.*[3] highlights a role for transcription factors of the PLETHORA (PLT) group of proteins. In the model plant *Arabidopsis*, four genes that encode these proteins act to establish and maintain root pattern, and are expressed at both the messenger RNA and protein level in a gradient that closely parallels that of auxin. Based on changes in cellular behaviours that follow genetic perturbation of PLT levels, the authors propose that distinct cellular behaviours are evoked by the different concentration thresholds of PLT proteins, with PLT levels somehow being coupled to the PIN-mediated auxin gradient.

Many questions remain. Although auxin and PIN activities seem to reinforce each other, how are the geometrically precise PIN distributions across the root initially established? At a cellular level, asymmetric PIN localization can be understood in terms of polarized patterns of vesicle trafficking[10], but how are these patterns regulated? It is unlikely that they simply reflect intracellular auxin gradients, because the polarity of PINs can be dramatically reversed during early embryo formation[11]. Also unclear is whether, during these early stages, auxin gradients might depend more on other classes of transporter, or on mechanisms of auxin synthesis and turnover[12]. With respect to PLT levels providing a graded readout of auxin levels, how are these two coupled? The transcriptional induction of PLTs depends on derepression mediated through a particular class of auxin receptor, the F-box type of receptor, but it is unclear how direct this link is or whether other classes of receptor are also involved. Finally, what are the targets of PLT regulation, and how would their regulation by graded PLT levels determine distinct cellular behaviours?

Taken together, these two papers[2,3] provide a fresh look at patterning, reinforcing the potential role for auxin as a morphogen and providing a robust transport-dependent model for its graded distribution. They also illustrate the value of combining biologically grounded modelling with molecular analyses — an approach that is proving increasingly powerful for explaining biological complexity. ■

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NUCLEAR PHYSICS

Neutrons cross the line

Paul-Henri Heenen

For most atomic nuclei, the maximum number of neutrons that can be bound is unknown. The discovery of two neutron-rich nuclei — and the confirmed absence of others — might help solve this conundrum.

Stars are element factories. Every atom in the Universe is a product of stellar nuclear reactions, but many of the stable isotopes that predominate today have formed from nuclei that existed only fleetingly. To understand the isotopic make-up of the Universe, we must first discover which of these ephemeral nuclei can form. In other words, what are the limits of nuclear composition? Reporting in this issue, Baumann *et al.*[1] describe their discovery of two new nuclei, one of which was thought to be impossible to make (see page 1022). This paves the way for a reassessment of nuclear models.

Atomic nuclei are composed of protons and neutrons, bound together by the strong nuclear force. Because this strong attraction is greater between a neutron and a proton than between two like particles, the most stable isotopes for light nuclei have equal numbers of neutrons and protons. But in larger nuclei — those with more than 20 protons — repulsion between the positively charged protons reduces the binding energy of the nucleus, so that the most stable isotopes have more neutrons than protons. In other words, the attraction between the extra neutrons counterbalances the electric repulsion between the protons.

There are about 300 stable nuclei, but these are only a small fraction of those that have a lifetime long enough to have a role in the formation of elements in stars. A chart of nuclei can be drawn that plots the number of protons against the number of neutrons (Fig. 1). Two lines — known as drip lines — can be plotted on the chart to indicate the limits of possible nuclei. On the proton-rich side of the chart, the proton drip line corresponds to the smallest number of neutrons that can be bound for a given number of protons. If a neutron were removed from a nucleus on the proton drip line, then a proton would be spontaneously emitted. Similarly, the neutron drip line indicates the largest number of neutrons that can accompany a given number of protons; extra neutrons will not bind to nuclei on this line.

The locations of the drip lines on the chart of nuclei are still an open question. Experiments performed in particle accelerators have proved the existence of about 3,000 isotopes[2]. Up to three times as many are thought to be awaiting discovery[3], but the short lifetimes of these bashful nuclei and the difficulty involved in making them makes this a formidable task. Nevertheless, some progress has been made. The location of the proton drip line is known for atoms with up to 90 protons — that is, up to thorium. This has been easier to establish than has the location of the neutron drip line, because electric repulsion between protons restricts the number that can be added to a nucleus with a given number of neutrons.

The situation is very different for neutron-rich nuclei, because no electric repulsion exists to limit the number of neutrons that can be added. The neutron drip line is therefore distant from the stable elements on the chart of nuclei, and so is much harder to reach experimentally. Furthermore, the number of neutrons that can theoretically be added to a nucleus increases as the number of protons increases.

The neutron drip line is therefore firmly established only up to oxygen, which has eight protons and can have a maximum of 16 neutrons. Beyond oxygen, the drip line has been tentatively assigned for elements up to sodium, which has 11 protons and a possible maximum of 26 neutrons. Baumann *et al.*[1] now report the discovery of two more neutron-rich isotopes: a magnesium isotope (^{40}Mg, which has 12 protons and 28 neutrons) and an aluminium isotope (^{42}Al, which has 13 protons and 29 neutrons).

The authors prepared these nuclei by firing the most neutron-rich calcium nuclei (^{48}Ca)

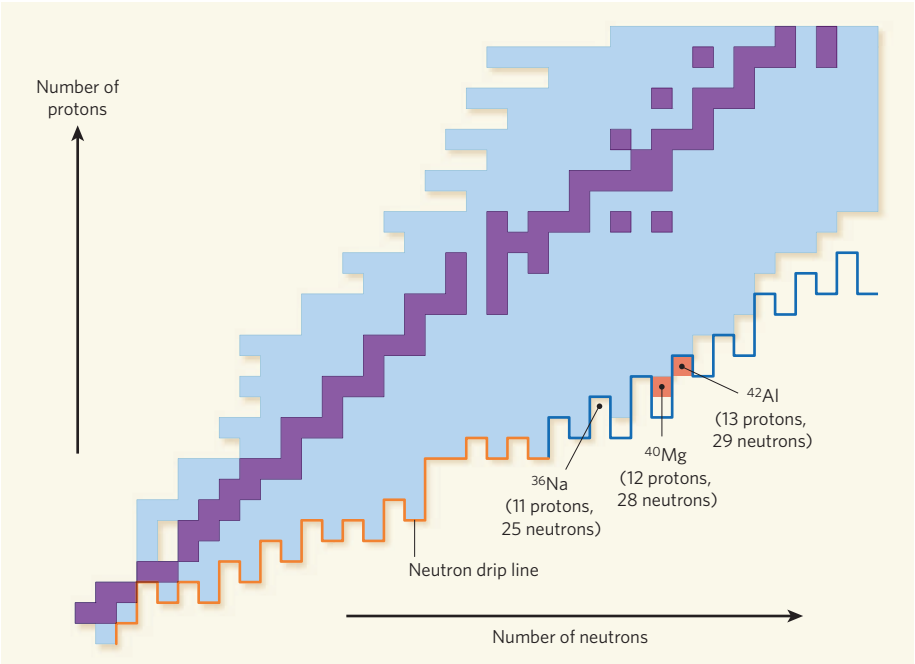

Figure 1 | Partial view of the nuclear landscape. This chart plots the number of protons against the number of neutrons for isotopes of the lightest elements. Purple squares represent stable isotopes, and pale blue squares represent those that have been observed only in particle accelerators. The orange line shows the experimentally determined 'neutron drip line', which indicates the largest number of neutrons that can be bound for a given number of protons. The blue line indicates the best predictions[6,7] of the neutron drip line for heavier elements. Baumann *et al.*[1] have now detected ^{40}Mg and ^{42}Al, but could not find evidence of ^{36}Na. These results suggest that the neutron drip line may extend further into the neutron-rich area than was expected.

at a natural tungsten target. Neutrons transfer from the tungsten to the ^{48}Ca nuclei, which can then break up to form ^{40}Mg or ^{42}Al. Although the number of nuclear interactions that could lead to the desired isotopes was extremely small (approximately 1 in 10^{15} reactions), Baumann *et al.* were able to identify them efficiently using state-of-the-art particle accelerator and detection technology. Just three collision events corresponded to the formation of ^{40}Mg, whereas 23 others led to that of ^{42}Al. The authors' results also seem to confirm that several other nuclei (^{30}F, ^{33}Ne and ^{36}Na) do not exist, as they were not observed during the experiment. This is curious, because isotopes of these three elements have been detected[4,5] that each contain a further neutron (that is, ^{31}F, ^{34}Ne and ^{37}Na).

The discovery of ^{42}Al and the non-appearance of ^{36}Na are telling results. These isotopes have odd numbers of both neutrons and protons. This means that they lack a stabilizing effect seen in other nuclei: superconductivity. In superconductors, electrons form pairs that differ only by the orientation of their spins. Protons and neutrons share the same tendency to pair up, with the nucleus receiving a boost of stability for each proton or neutron pair formed. An 'odd–odd' situation is a worst-case scenario for nuclei, because they have an unpaired proton and an unpaired neutron that do not contribute to superconductivity.

The idea of proton and neutron pairs helps explain irregularities in the neutron drip line. For example, ^{35}Na nuclei exist, but Baumann and colleagues' results suggest that it isn't possible to add one neutron to make ^{36}Na. But it is possible to add two neutrons to produce ^{37}Na, an isotope with an even number of neutrons — presumably because the additional neutrons form a nucleus-stabilizing pair. Similarly, one can conclude from the stability of the odd–odd nucleus ^{42}Al that it should be possible to add an extra neutron to reach ^{43}Al, because the formation of a neutron pair will stabilize the heavier isotope. In fact, the authors did observe a single collision event that is consistent with the existence of ^{43}Al, but this result requires further confirmation.

So why does ^{42}Al form at all, if it has an odd–odd nucleus? This isotope breaks the established staggered pattern of the neutron drip line, and was predicted not to exist. The answer could be that aluminium nuclei have reached a threshold of stability that minimizes the negative effect of extra neutrons, as has been suggested by some quantum-mechanical calculations. With the existence of ^{42}Al confirmed, there are now good arguments to suggest that the neutron drip line could extend as far as ^{47}Al.

Baumann and colleagues' results stretch the limits of current particle accelerators, so exploration of the neutron drip line at higher proton numbers will have to wait for the next generation of facilities. In the meantime, we must rely on models to predict where the neutron drip line falls — models that currently provide contradictory results. The authors' findings will certainly help to improve the accuracy of these models, so allowing a more confident assessment of the nuclear terra incognita. ■

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CANCER

Mixing cocktails

Charles L. Sawyers

A major hurdle in treating cancer is that tumour cells acquire drug resistance. To overcome this problem, one strategy might be to fine-tune the right mixture of drugs that target specific molecules.

Certain cancers are caused by oncogenic primary or 'driver' mutations in specific kinases — enzymes that regulate the activity of other proteins. Consequently, kinase inhibitors have been used in the clinic as effective single-agent drugs to shrink tumours. Kinase 'addiction' persists in advanced cancer, and patients who relapse after initially responding to kinase-inhibitor therapy often develop secondary mutations in the target kinase that confer drug resistance without impairing the kinase's oncogenicity[1]. Two reports[2,3] in *Science* now show that lung cancers and glioblastoma — a malignant tumour of the central nervous system — use another option to escape drug treatment. Rather than mutate the drug target further, these cancers recruit other kinases that are not affected by the inhibitor to substitute for the pharmacologically impaired kinase and to restore downstream molecular signalling cascades that contribute to tumour growth.

Engelman and colleagues[2] stumbled across this new resistance mechanism by isolating cells from a lung-cancer cell line in which the driver