

structure are readily unfolded by CYT-19. So it is possible that the reason for the slower unfolding rate of correctly folded RNAs is that crucial helices are sequestered in the higher-order structure and are thus protected from unwinding by CYT-19. This possibility is supported by an earlier study⁷ showing that CYT-19 cannot easily unwind duplexes hidden within an RNA structure. If this is true for other nonspecific DEAD-box chaperones, this would be an elegant and unexpectedly simple way by which these proteins might preferentially unravel misfolded RNA structures.

Bhaskaran and Russell also make another intriguing observation. Under certain conditions — for example, at reduced magnesium concentrations, a consequence of which is the weakening of higher-order RNA structures — CYT-19 increases the ratio of misfolded RNAs to correctly folded structures. This is remarkable, because misfolded group-I RNAs are thermodynamically less stable than the correct structures and, at equilibrium, the most stable species dominates in a mixture of possible structures.

The authors find that CYT-19 achieves the redistribution of RNA species against their thermodynamic equilibrium by establishing a 'kinetically controlled steady state' (Fig. 1b). In this state, CYT-19 constantly unwinds RNA structures in an ATP-dependent manner, so that the distribution of these structures is no longer dictated by their thermodynamic stabilities but, instead, by the rate at which they are actively unravelled by CYT-19, as well as by the rate of their refolding. Under these conditions, CYT-19 readily unravels both misfolded and correct structures. But when the RNA subsequently misfolds it does so faster than correctly refolding RNA, and therefore accumulates.

Similar ATP-driven redistribution of model RNA complexes by another DEAD-box protein has been reported⁸. So it seems that DEAD-box proteins can establish kinetically controlled steady states for various RNAs. The ability of these proteins to favour the accumulation of thermodynamically less stable RNA species seems particularly beneficial for processes in which RNAs must undergo extensive structural changes, such as during ribosome assembly and pre-messenger-RNA splicing. Both of these processes involve numerous DEAD-box proteins⁴.

The work of Bhaskaran and Russell³ implies that sequence nonspecificity of DEAD-box proteins is more of an asset than a disadvantage, at least for their function as RNA chaperones. Nonspecific chaperone proteins can work on many misfolded RNAs and at different positions within them, which obviates the need for a large number of highly specific proteins that would exclusively aid the folding of each of the many cellular RNAs. The potency of unfolding by the omnipresent and nonspecific DEAD-box proteins also offers one possible explanation

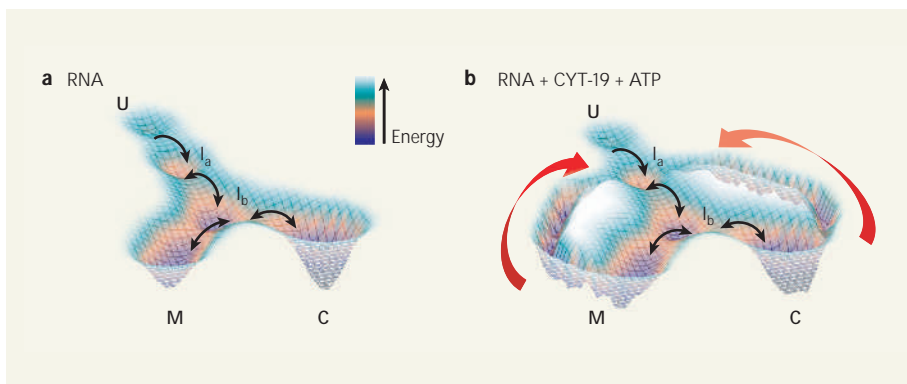


Figure 1 | Schematic folding landscape of group-I intron RNAs. In this representation, valleys indicate structures of varying stability — the deeper a valley, the lower the energy of the structure and the more stable it is. The ridges between valleys correspond to rates of inter-conversion between neighbouring structures; high ridges indicate slow rates. U represents an unfolded RNA, I_a and I_b are intermediate structures, M is a misfolded and C a correctly folded RNA. **a**, Left to their own devices, most group-I intron RNAs first form M, which is less stable than C but forms more quickly. However, M converts back into I_b and I_a at an appreciable rate, allowing further rounds of folding into both C and M. Although C can also convert back to I_b , this process is slow. So with time, C accumulates. **b**, Bhaskaran and Russell³ show that CYT-19 alters the RNA-folding landscape in an ATP-dependent manner. By unfolding both M and C, new pathways for structural conversions are opened that presumably lead to I_a/I_b (red arrows). The formation of the RNA species depends on the rates at which they can interconvert. This represents a kinetically controlled steady state, in which less stable structures can accumulate. The levels of ATP determine and maintain the topology of the folding landscape, and in the absence of ATP the landscape changes back to that seen in **a**.

tion for why some RNAs tolerate misfolding into fairly stable structures. This is because they can rely on DEAD-box proteins to rescue them. But an increased awareness of the versatility of nonspecific DEAD-box proteins highlights the next question: why does the cell use so many of these enzymes?

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1. Herschlag, D. *J. Biol. Chem.* **270**, 20871–20874 (1995).
2. Schroeder, R., Barta, A. & Semrad, K. *Nature Rev. Mol. Cell Biol.* **5**, 908–919 (2004).
3. Bhaskaran, H. & Russell, R. *Nature* **449**, 1014–1018 (2007).
4. Linder, P. *Nucleic Acids Res.* **34**, 4168–4180 (2006).
5. Yang, Q. & Jankowsky, E. *Nature Struct. Mol. Biol.* **13**, 981–986 (2006).
6. Mohr, S., Stryker, J. M. & Lambowitz, A. M. *Cell* **109**, 769–779 (2002).
7. Tijerina, P., Bhaskaran, H. & Russell, R. *Proc. Natl Acad. Sci. USA* **103**, 16698–16703 (2006).
8. Yang, Q., Fairman, M. E. & Jankowsky, E. *J. Mol. Biol.* **368**, 1087–1100 (2007).

ENVIRONMENTAL SCIENCE

Nutrients in synergy

Eric A. Davidson and Robert W. Howarth

A literature meta-analysis of the effects of nitrogen and phosphorus on plant growth prompts a thought-provoking inference — that the supply of, and demand for, these nutrients are usually in close balance.

The nutritional needs of plants start with carbon, hydrogen and oxygen, which they obtain from atmospheric gases and from water. They also require nitrogen (a constituent of all proteins) and phosphorus (not least as a component of nucleotides, including those in DNA and RNA). Writing in *Ecology Letters*, Elser and colleagues¹ provide a timely contribution to our understanding of how nitrogen and phosphorus, both individually and in combination, affect primary producers such as crops, trees and algae.

This is a topic with a long history. In the nineteenth century, Justus von Liebig proposed his 'law of the minimum', which describes crop production as being limited by the nutrient in shortest supply. According to this law, once the nitrogen (N) need of a crop is met by fertilization, another element such as phosphorus (P) becomes limiting (Fig. 1a), and there is no further response to additional N.

Since Liebig's day, the use of N and P fertilizers has revolutionized agriculture. The consequences have been both desirable and

undesirable. Synthetic fertilizers have fuelled the Green Revolution and greatly lessened world hunger and malnutrition. But they have also led to severe air and water pollution and other adverse effects on the environment and human health^{2,3}. The widespread distribution of excess N and P within natural ecosystems has caused degradation of coastal waters globally, and an increase in hypoxic areas ('dead zones') on nearly every continent^{3,4}. Excess N and/or P lead to algal blooms and so consumption of the oxygen required for productive fisheries and for healthy marine habitats. In the United States, two-thirds of coastal rivers and bays are degraded through the consequences of excess nutrients⁵. Similar problems occur in fresh waters, and excess fertilization of forests can lead to decline and loss of biodiversity. Management strategies for mitigating the two pollutants can differ². So the long-standing debate over the relative importance of N and P as agents of excess production in different ecosystems is of immense practical significance.

This is the context in which Elser and colleagues' study¹ is set. It is a meta-analysis of more than 300 publications reporting results of nutrient-amendment experiments in marine, freshwater and terrestrial ecosystems, with the effects of the two elements being assessed in terms of increased biomass or production. The study supports some well-established rules of thumb in biogeochemistry. Examples are the greater limitation on P than N in mature forests growing on highly weathered lowland soils in the tropics; the greater responses to P than N addition in freshwater ecosystems; and the greater responses to N addition in marine ecosystems.

More importantly, the analysis demonstrates a surprisingly consistent pattern of a synergistic effect of N and P addition on net primary productivity across all ecosystem types. Adding N and P together seems to give photosynthesis by algae and higher plants more of a boost than adding either one separately. The authors infer from this that the stoichiometry of N and P supply and demand must generally be in close balance in most ecosystems. According to this interpretation, P is rarely available in great excess relative to N, so a modest addition of N quickly provokes a limitation on P. When N and P are added together, N and P limitation may alternate in numerous small incremental steps, ultimately producing a synergistic effect (Fig. 1b).

This is an impressive synthesis¹, but several caveats are in order. First, we lack a mechanistic understanding of how the availability of one resource affects the supply of and demand for another resource. At the cellular level, regulation of the relative dynamics of the demand for N for the synthesis of enzymes, and the demand for P for the synthesis of nucleic acids and also of ATP, is poorly known. At the organismal level, some species have adaptations for obtaining a nutrient that would otherwise be difficult to acquire (for example, diverting carbon and

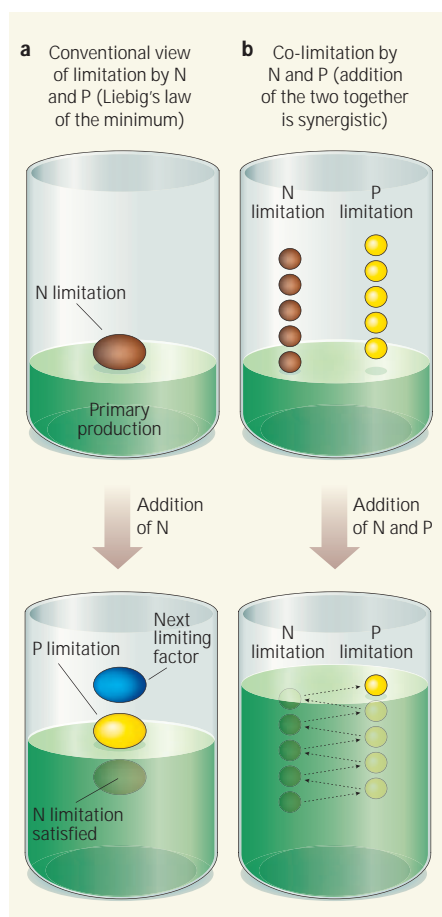


Figure 1 | Nutrients and primary production. a, The conventional view of Liebig's law of the minimum. Here, after the need for nitrogen (N) is met, N is not limiting, and increased production successively depends on satisfying limitation by phosphorus (P) and then any other limiting factors. b, A modification of the law of the minimum, based on one interpretation of the synthesis by Elser *et al.*¹. From their meta-analysis, they infer that supply and demand of N and P are usually in close balance, so that an incremental addition of one causes a modest limitation by the other. Alleviation of each incremental limitation in turn produces a synergistic effect when both nutrients are added together.

nitrogen to the fungal mycorrhizae that form symbioses with plant roots to improve access to P in nutrient-poor soils). But our knowledge of such trade-offs is only qualitative. And at the ecosystem level, the factors that may influence the relative importance of N fixation from the atmosphere, such as the availability of N, P and molybdenum (an essential component of N-fixing enzymes), and competition for light and water, are not well understood⁶.

Second, the doses of N and P addition — either through natural pulses or in bioassay experiments — may be very important, but were not specifically addressed by Elser and colleagues. If the doses are large enough, adding both nutrients may simply alleviate first one nutrient limitation and then the other,

as per Liebig's classic law, and this could look like a synergistic effect. The assertion that the stoichiometric supply of N and P in natural systems is generally close to balanced could be further tested by quantitative dose-response experiments.

Third, there is the issue of the timescale of nutrient-amendment experiments. Experiments that are short in duration relative to the life cycles of the organisms being studied measure only the response of the organisms that are dominant in the ecosystem at the time of the assay^{5,7}. Longer-term ecosystem-scale responses to nutrients can be different, as the dominant species change with changes in biogeochemical processes. A short-term assay in a freshwater lake, for example, would probably indicate P limitation, followed by an apparent synergistic effect with N limitation once enough P were added. But in one experiment⁸, years of P fertilization led to a predominance of N-fixing cyanobacteria that produced enough reactive nitrogen to keep the lake P limited.

Finally, resource limitation may simultaneously involve several nutritional elements, along with light, water and carbon dioxide. If responses to the addition of N and P are synergistic, we would expect complex synergies among other potential limiting resources as well.

So we are left with plenty of questions. Nonetheless, Elser and colleagues' meta-analysis¹ provides the most thorough examination of short- and medium-term nutrient-amendment experiments to date. Their synthesis adds to a growing body of evidence that addressing the 'off-farm' environmental consequences of food production will require efforts to reduce losses of both N and P from agricultural systems^{2,5,7}. It also provides an improved basis for formulating testable hypotheses to describe nutrient interactions in other ecosystems. ■

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rwh2@cornell.edu

1. Elser, J. J. *et al. Ecol. Lett.* doi:10.1111/j.1461-0248.2007.01113.x (2007).
2. Howarth, R. W. *et al. in Millennium Ecosystem Assessment. Ecosystems and Human Well-being Vol. 3: Policy Responses* 295–311 (Island, Washington DC, 2005).
3. UNEP/WHRC. *Reactive Nitrogen in the Environment: Too Much or Too Little of a Good Thing* (United Nations Environment Programme, Paris, 2007). www.whrc.org/policy/Reactive_nitrogen.htm
4. Diaz, R. J., Nestlerode, J. & Diaz, M. L. *Proc. 7th Int. Symp. Fish Physiology, Toxicology, and Water Quality* EPA-600-R-04-049, 1–33 (US Environmental Protection Agency, 2003).
5. National Research Council. *Clean Coastal Waters: Understanding and Reducing the Effects of Nutrient Pollution* (National Academies Press, Washington DC, 2000).
6. Vitousek, P. M. *et al. Biogeochemistry* **57/58**, 1–45 (2002).
7. Howarth, R. W. & Marino, R. *Limnol. Oceanogr.* **51**, 364–376 (2006).
8. Schindler, D. W. *Science* **195**, 260–262 (1977).

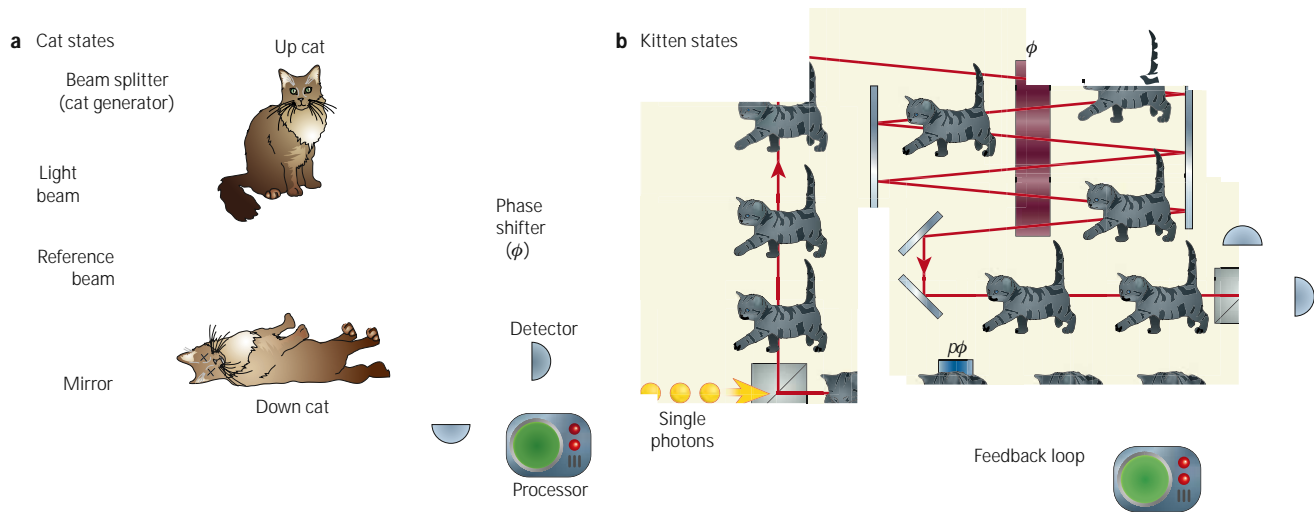


Figure 1 | Towards the Heisenberg limit. According to quantum theory, the accuracy possible in an interferometric measurement of a phase shift, ϕ , reaches a fundamental 'Heisenberg' limit that scales as the inverse of the number of photons involved in the measurement. But attempts to reach this gold standard experimentally have fallen short. **a**, A promising approach previously investigated⁷ sent single Schrödinger's cat 'High-NOON' states consisting of large numbers of photons through the interferometer — all the photons went down one of two arms, but it was impossible to tell which (up cat indicates all photons in the upper path; down cat, all in the lower path).

This approach effectively divided the wavelength of the light (and so its resolving power) by the number of photons in each state, but failed to deliver the hoped-for accuracy, owing to the difficulty of producing and caring for the large cat states. **b**, Higgins and colleagues¹ reach the Heisenberg limit by exploiting a series of smaller, 'kitten' states each involving just one photon. These states are easier to prepare, and are more robust against noise and loss; but the lower flux must be compensated by cycling the states through the interferometer many times and using a complex quantum feedback loop to adjust the phase shift, $p\phi$, of the reference beam.

rule is therefore called the Heisenberg limit.

This sounds all very well and good, and people continue to talk about putting squeezed light into LIGO some day. But the fact is that infinite squeezing is hard to come by, and the Heisenberg limit had until now never been realized in practice.

Enter, stage left, the weirdness of quantum entanglement, which occurs when the quantum states of remote particles become intertwined. In 1986, a way was proposed to get close to the Heisenberg limit not with squeezed light, but with quantum-entangled neutrons in a matter-wave interferometer⁵. The entanglement idea percolated along for a number of years, but really gained momentum in the past ten, when people realized that the entanglement approach to interferometry could be implemented using ideas from quantum computing such as error correction and quantum feedback⁶.

A quantum computer is, in essence, a big machine filled with quantum-entangled qubits. A quantum interferometer is also a big machine filled with quantum-entangled particles, and these can be treated as qubits. A popular approach to the phase-estimation problem exploits whacky beasts such as the Schrödinger's cat 'High-NOON' state⁷, in which all the photons are either in one arm of the interferometer or the other, but you can't tell which arm is which (Fig. 1a). In this case, a NOON state of n photons, each of wavelength λ , acts like a single high-frequency photon of wavelength λ/n . Hence, if one has ten red photons of 500 nm wavelength in an $n = 10$ NOON state, the result is an entangled red-photon state, but one with the resolving power of an X-ray photon of wavelength 50 nm. The shorter the wavelength, the more accurate the phase

estimation. Much progress was made with such states on both the theoretical and experimental front, and they have got closer to the Heisenberg limit than have squeezed states. But owing to losses in the interferometer and the fragile nature of these states, they have never quite reached the mythical Heisenberg limit⁸.

Until Higgins and colleagues came along¹. In January 2007, in a theoretical talk at the Physics of Quantum Electronics workshop in Snowbird, Utah, Howard Wiseman from Griffith University in Brisbane, a co-author on the paper, made the remarkable claim that you could get to the ultimate uncertainty limit by sending not Schrödinger's cat through the interferometer, but a bunch of Schrödinger's kittens — single photons. You then compensate for the lower flux and apparent lack of quantum entanglement with an elaborate quantum feedback loop (Fig. 1b). Good luck with that, I remember thinking to myself: applying a feedback loop to single photons at light speed would be technologically impossible any time soon. I am now forced to eat my hat. The authors' optical interferometer, operating at the Heisenberg limit, involves no squeezing, minimal entanglement, and no Schrödinger's cat; the quantum weirdness is in the feedback loop.

This loopy demonstration in fact implements an ingenious phase-estimation algorithm based on quantum computing⁹ that uses simple optics to recycle photons through the phase shift to be measured. Although the solution is too low in intensity to be of use in LIGO anytime soon — the largest number of photons the authors used was 378, whereas LIGO has a circulating power of 10^{14} photons per second — the work breaks new ground. It could have other, more immediate applications in areas

such as quantum metrology, quantum imaging and quantum sensing.

So what is the immediate lesson to be learned? That tricks from quantum computing will find their practical near-term implementation in spooky gizmos with scientific and practical importance, but nothing to do with computers at all. Bravo!

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- Higgins, B. L., Berry, D. W., Bartlett, S. D., Wiseman, H. M. & Pryde, G. J. *Nature* **450**, 393–396 (2007).
- Michelson, A. A. & Morley, E. W. *Phil. Mag.* **24**, 449–463 (1887).
- www.ligo-la.caltech.edu
- Caves, C. M. *Phys. Rev. D* **23**, 1693–1708 (1981).
- Yurke, B. *Phys. Rev. Lett.* **56**, 1515–1517 (1986).
- Lee, H., Kok, P. & Dowling, J. P. *J. Mod. Opt.* **49**, 2325–2338 (2002).
- Bouwmeester, D. *Nature* **429**, 139–141 (2004).
- Nagata, T., Okamoto, R., O'Brien, J. L., Sasaki, K. & Takeuchi, S. *Science* **316**, 726–729 (2007).
- Kitaev, A. Y. *Electr. Coll. Comput. Complex.* **3**, article 3 (1996).

Clarification

"Environmental science: Nutrients in synergy" by Eric A. Davidson and Robert W. Howarth (*Nature* **449**, 1000–1001; 2007).

This News & Views article discussed a paper in *Ecology Letters* (doi: 10.1111/j.1461-0248.2007.01113.x; 2007), and included the comment that the results in the paper support the rule-of-thumb that the biological response to phosphorus addition is greater than that to nitrogen addition in freshwater ecosystems. That is true for lake benthos, but not for lake ecosystems as a whole, where the responses to nitrogen and phosphorus are similar.