to determine the redshift from this star's spectrum than it is from that of a strong-field neutron star.

Cottam *et al.* observed EXO0748−676 during a series of 28 X-ray bursts — the flashes from thermonuclear fusion that occur when sufficient hydrogen and helium has piled up on the star's surface. They found three strong spectral lines, which they identify as the signatures of 25-times-ionized iron (Fe XXVI in astronomical nomenclature), Fe XXV and O VIII. The inferred redshift for all three is 0.35, which defines a range of possible values for the mass and radius of this star (Fig. 1). Such identifications should always be handled with care, because there are in principle many atomic species and many transitions to check. But Cottam *et al.* make a good case that these are the most probable sources of these lines. If the identifications are correct, the redshift is exactly in the range expected for a star made of normal neutron matter, and doesn't fit the models for the most compact strange-matter stars[8], although there is still room for exotic components (Fig. 1).

The importance of these results inspires caution. It would be good to see lines measured with self-consistent redshifts from more neutron stars, to guard against the possibility that the lines have been misidentified in these two sources. Moreover, constraints on models for high-density matter would be strengthened considerably if both the mass and gravitational redshift were measured for other neutron stars. In any case, high-resolution instruments such as Chandra and XMM–Newton are dramatically fulfilling their promise as sensitive probes of matter in extreme environments. ■

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Protein folding

With a little help…

Charles L. Brooks III

Experiments and computer simulations are converging in their exploration of the timescales on which protein folding occurs. Such developments are a promising way forward in molecular biophysics.

From a cast of thousands, and the experiments of a few, a new combination of computer simulation and experiment to investigate protein folding has emerged. This work, described by Snow *et al.* on page 102 of this issue[1], shows that the key events in the folding of a small artificial protein can be directly examined by atomic-level computer simulation. Moreover, the results are in general agreement with experiments performed under analogous conditions.

Snow *et al.* have brought the distributed computing machinery embodied in the Folding@home project[2,3] to bear on the direct simulation of folding of small, though conformationally rich, polypeptides. The polypeptides are based on a specially designed mini-protein named BBA5 — which, for all its small size, nonetheless adopts a canonical native fold, the α-helix and β-hairpin. The authors look at the folding of BBA5 mutants (that is, proteins with sequences that differ from BBA5 by substitutions of one or two residues), and show that the folding occurs on a timescale of 1–10 μs at temperatures near 300 K. The general agreement between experiment and simulation for this system suggests that current methods for describing atomic interactions by computer simulation (with 'force fields' and molecular-dynamics methods) are adequate for exploring the timescales and energies of folding.

Folding is a highly complex, structure-organizing process, in which a chain of amino acids passes through several stages before the protein concerned — say, an enzyme — reaches its final folded and active form. Many small proteins adopt their folded state from a diverse set of less structured conformations by crossing a single barrier (transition state) in a nearly all-or-none, two-state fashion on timescales ranging from a few microseconds to milliseconds and longer. Progress in experimental methods during the past few years provides the tools to explore folding processes on the fastest of these timescales[4]. On the other hand, even the fastest timescales are very long compared with routine times accessed in molecular-dynamics simulations of proteins.

The problem, then, in computer simula-

100 YEARS AGO

The Health Department of the City of London has had a number of samples of ice-creams bacteriologically examined. A large proportion of the samples were found to be unsatisfactory; in several micro-organisms were very numerous, while in some virulent organisms of the *Bacillus coli* type were present; one contained pyogenic organisms and produced abscesses in guinea-pigs, and another contained an anaërobic organism, perhaps the bacillus of malignant oedema. Many of the ice-creams from which samples were examined had set up gastro-enteritis in boys employed by the Post Office.

ALSO…

New fields for research are continually opening up; the last illustration of this is the discovery by Prof. G. Elliot Smith that it is possible to map the convolutions of the brains of non-mummified ancient Egyptians. The brain is naturally preserved in the vast majority of the bodies in Egyptian cemeteries from predynastic to recent Coptic, the favourable conditions being burial in dry soil and removal from all direct access to the air... In a memoir, which will be published in a short time, he intends to give a full account of the structure of the brain in the predynastic and protodynastic Egyptians.

From *Nature* 6 November 1902.

50 YEARS AGO

The Nobel Prize for Physiology and Medicine for 1952 has been awarded to Prof. Selman Abraham Waksman… for his discovery of streptomycin, the first effective antibiotic against tuberculosis. Prof. Waksman was born in 1888 in Priluka, a small town in the Ukraine, emigrated to the United States in 1910 and became a naturalized citizen there in 1915. The whole of his scientific life since 1911 has been spent at Rutgers University and has been devoted to the study of microbiology, and particularly to that group of soil micro-organisms which are frequently spoken of as ray fungi and belong to the genus *Actinomyces* or *Streptothrix*. Following the discovery of penicillin, which is fully effective only against Gram-positive bacteria, Waksman and his collaborators began, in 1939, a systematic search for an antibiotic active against Gram-negative bacteria and found it, in 1944, in streptomycin, a metabolic product of *Streptomyces griseus*… They also showed that streptomycin is highly active *in vitro* against *Mycobacterium tuberculosis*.

From *Nature* 8 November 1952.

tions of protein folding, is to 'beat Boltzmann' — that is, beat the odds of arriving at the transition state for folding and unfolding while retaining some information about the timescales of reaching this point. One answer to this problem biases the energies of protein conformations, using methods called umbrella sampling, to restrain the regions of conformational space the system explores, and then reconstructs the unbiased energy landscape using theoretical techniques from statistical mechanics. This approach has been successfully applied to several different protein structures, lending insights into protein-folding characteristics such as the manner in which protein topology dictates the folding mechanism, the direct role that the solvent (water) can play in mediating the later stages of protein folding, and a host of other processes[5].

Beating Boltzmann can also be accomplished by looking at the reverse process and increasing the probability of arriving at the unfolding transition state through the use of high temperature. By coupling the protein–solvent system to a high-temperature bath (typically well above the standard boiling point of water), molecular-dynamics simulations can be performed over timescales of many nanoseconds to observe the protein denaturing. Information about the mechanism and timescale for protein unfolding can be directly gleaned from such simulations, although experimental unfolding rates must be extrapolated to the temperatures of the simulations to make direct comparison[6]. Both of these approaches are yielding insights into the problems of protein folding and unfolding. But neither permits the direct observation of folding dynamics under folding conditions.

To explore folding directly, as Snow *et al.*[1] have done, one must overcome the 'Boltzmann waiting time' required by individual molecular trajectories to sample transition-state conformations and proceed into the energetic 'basin' of native folds. A clever way of doing this, employed by Snow *et al.*, is to use the statistical nature of the distribution of these waiting times. By considering (tens of) thousands of trajectories, some protein chains will be in conformations near the transition region, and will proceed rapidly to the native fold. Monitoring the fraction of such trajectories and the timescale required, on average, for these protein molecules to reach the native fold leads to an estimate of the mean folding time. This is simply constructed as the ratio of the length of an individual trajectory to the fraction of trajectories that folded in that time. Snow *et al.* examined 7,500–9,000 trajectories for durations of 20 nanoseconds for each of two mutants of BBA5, and observed some 100 folding events. The resulting estimates of the folding time were in good agreement with their experimental findings.

To achieve the amount of sampling of individual trajectories needed for Snow and colleagues' studies, a highly distributed and loosely coupled network of volunteer computers, exploiting the tremendous resources of personal computers connected to the Internet, was used. Because each folding trajectory is independent of the others, work to compute the molecular dynamics of folding can be parcelled out to the volunteers' home computers using the web. The software developed by Snow *et al.* manages this task and assembles the computed properties for analysis of folding. Distributed computing systems such as Folding@home are an enormous resource for exploring scientific questions such as protein folding, and provide a new way of simulating complex biological processes. They also represent unique social experiments, permitting the public at large to be directly involved in investigations ranging from a search for drugs to combat AIDS[7] to the quest for intelligent life beyond the Earth[8,9].

The future will see a continuing expansion of the worldwide resources exploited by Folding@home as personal computers and networks become faster. New problems will be examined and new questions answered. As for protein folding, larger and more realistic systems will be required to truly advance our understanding of this complex process. Whether this is possible with current models remains to be demonstrated — with a little help from our friends. ■

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Plant ecology

Express delivery by bat

Peter D. Moore

The seeds of plants need to be dispersed to locations where they can survive and grow. In the deserts of Mexico, it seems that a species of bat is the dispersal agent of choice for a giant cactus.

Eating fruit is a means of making a living for many mammals and birds. And from the plant's point of view, frugivores may provide an answer to the vexed problem of seed dispersal. But some fruit-eaters are more effective at the job than others, in terms of distance covered, quantity consumed and the quality of the locations in which seeds are eventually deposited. Some frugivores, in other words, are worthy of more encouragement than others. Writing in the current issue of *Ecology*[1], Godínez-Alvarez, Valiente-Banuet and Rojas-Martínez come to the conclusion that a species of bat is the best option for dispersing the seeds of the giant columnar cactus *Neobuxbaumia tetetzo*, found in the Tehuacan Valley of Mexico. The authors' work reveals a fine example of coevolution in action.

It is in the evolutionary interests of an individual plant to leave as many copies of its genes in the next generation as possible. This involves adequate seed production, but it is even more important to ensure that seeds are transported to sites where their survival and success is assured[2]. The most efficient frugivorous dispersal agent will consume the fruit readily, will have a gut in which the seed is not damaged (and where its germination potential might even be enhanced), will travel away from the parent plant after fruit consumption, and will defecate in a location that is suitable for seed germination, establishment and survival. The evolution of such dispersal systems therefore involves the selection of the most appropriate agent and the modification of the fruit to suit the needs of that agent.

In the Tehuacan Valley of central-southern Mexico, the desert vegetation is dominated by a giant columnar cactus, *Neobuxbaumia tetetzo* (Fig. 1). However, the vegetation is heterogeneous, areas of cactus being interspersed with patches of scrub consisting largely of *Mimosa luisana*[3]. The vegetation forms a dynamic system in which the cactus seedlings survive only in the shade of the *Mimosa* bushes, but as the cacti grow, so the bushes die and the mature cacti form pure stands. The eventual death of an ageing cactus is then followed by invasion of shrubs, and the cycle continues.

The cycle is maintained because of the germination and establishment requirements of the young cacti. The seedling stage is the most vulnerable phase of the plant's life, and studies have shown[4] that giant cacti may need the shade of other plants in their very early stages of growth to protect them