Auger recombination inefficient, while also enabling interplay between the positive charge on the nanoparticle and the photo-generated electron–hole pairs. This interplay gives rise to luminescent signals unhindered by any competing heat-generation processes. The proposed mechanism also helps to explain some unusual features of the nanoparticles' emission spectra, such as the fact that they are broad and contain several peaks.

This work is a milestone in the rapidly growing field of colloidal nanomaterials, and raises several questions. Are the nanocrystals constantly charged, or do they switch back and forth between uncharged and charged states without causing any change in signal intensity[9]? The nanocrystals' broad, multi-peaked spectra will limit potential biological applications that require multicolour imaging[10], so is it possible to develop non-blinking nanocrystals that retain the narrow emission spectra of other quantum dots? And finally, can Wang and colleagues' nanocrystals be adapted for biological imaging? This would require the nanocrystals to be further engineered to make them water soluble, and so that they can be attached to biological molecules without sacrificing their non-blinking properties. On the basis of experience with other quantum dots, the desirable optical properties of the alloyed nanocrystals are likely to be maintained even after further processing.

The discovery of fluorescent blinking has been one of the most striking discoveries of single-molecule spectroscopy. Nanocrystals do it. Green fluorescent proteins do it[11]. Even certain polymers[12] and organic dyes do it[13]. Blinking seemed to be intrinsic and unavoidable for all single emitters exposed to the elements — until now. Wang and colleagues' discovery[3] is therefore cause for a small celebration, before researchers delve further into the underlying cause and seek possible applications. ■

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COSMOLOGY

# Climbing up the cosmic ladder

Ofer Lahav

**Study of an under-appreciated subclass of stars that brighten and dim periodically brings to light their potential use as cosmic yardsticks — out to distances of a few hundred million light years.**

What is the expansion rate of the Universe? And how old is the Universe? The answers to these and other fundamental cosmological questions depend on a number of factors, among them the measurement of the Hubble constant ($H_0$). This is defined as the ratio of a galaxy's recession velocity — that is, the speed at which it is moving away from Earth — to its distance. Writing in *The Astrophysical Journal*, Bird *et al.*[1] set out to study a class of stars that may well assist in measuring $H_0$ and so help to answer these questions.

Although it is relatively easy to measure a galaxy's recession velocity from the amount by which emission and absorption lines in the galaxy's spectrum are shifted towards redder wavelengths, determining its distance from Earth is much more challenging. But nature has been kind enough to provide astronomers with stars that act as 'standard candles': if they know how bright the candles are, and how bright they look from Earth, they can calculate how far away they are. The apparent flux of a candle is simply proportional to its intrinsic luminosity divided by the square of its distance. Therefore, provided that the intrinsic luminosity of the standard candle is well calibrated, researchers can measure the distance to its host galaxy.

Heroic efforts have been made to identify standard candles. One class of stars, the Cepheids, has become particularly popular. Named after their prototype, Delta Cephei, Cepheids are variable stars marked by a tight correlation between their period of variability and their intrinsic luminosity: the greater the period of the star, the greater its maximum brightness. This period–luminosity (P–L) correlation, discovered about 100 years ago by Henrietta Leavitt, makes Cepheids very useful standard candles.

But using Cepheids as cosmic-distance indicators requires their intrinsic luminosities to be calibrated through distance measurements to their nearby counterparts on the basis of methods other than the P–L correlation. Hence the term 'cosmic ladder': each distance measurement relies on calibration by nearer objects. In their study, Bird *et al.*[1] propose a way of measuring Cepheid distances out to 100 megaparsecs (1 Mpc = 3.26 million light years) and beyond, greatly improving the reliability of the cosmic ladder.

The value of the Hubble constant has been a subject of debate for decades, most notably between Allan Sandage and Gérard de Vaucouleurs, who argued for values of 50 and 100 km $s^{-1}$ $Mpc^{-1}$, respectively. By analysing Cepheids observed with the Hubble Space Telescope, Wendy Freedman and colleagues[2] have derived a value of $H_0 = 72 \pm 8$ km $s^{-1}$ $Mpc^{-1}$, and a very recent study of 240 Cepheids observed with an improved camera onboard the Hubble Space Telescope has yielded an even more accurate figure, $74.2 \pm 3.6$ km $s^{-1}$ $Mpc^{-1}$ (ref. 3). What is remarkable is that these values agree so well with those deduced from studies that combine observations of the cosmic microwave background radiation (relic radiation from the Big Bang) carried out with the Wilkinson Microwave Anisotropy Probe with other cosmological data: $70.5 \pm 1.3$ km $s^{-1}$ $Mpc^{-1}$ (the age of the Universe inferred from such studies is $13.72 \pm 0.12$ billion years)[4].

However, the case is by no means closed: there are persistent claims for lower values, such as $62.3 \pm 1.3$ km $s^{-1}$ $Mpc^{-1}$ (ref. 5). Only time will tell whether the currently endorsed value of about 70 km $s^{-1}$ $Mpc^{-1}$ will survive further scrutiny. Future research, using better and bigger Cepheid samples, is necessary to reassess its value and increase Cepheids' reliability as cosmic-distance indicators.

The downside of conventional (short-period) Cepheids is that they only 'climb' the cosmic ladder out to distances of about 20 Mpc. More distant Cepheids would be helpful both in extending the ladder and in calibrating studies that rely on another class of more distant standard candles — type Ia supernovae — to determine the expansion rate of the Universe.

Enter Bird and colleagues[1]. They draw attention, by re-analysing data from the literature, to a somewhat neglected class of objects called ultra-long-period (ULP) Cepheids. They re-examine 18 Cepheids that have periods ranging from 80 to 210 days. As the P–L relationship dictates, if their periods are longer, they are brighter and so can be observed over greater distances — 100 Mpc and beyond. As such, these Cepheids offer the potential to improve the accuracy of connecting the steps — or even skipping unnecessary steps — of the cosmic ladder.

The authors[1] also note that these ULP Cepheids have a relatively 'shallow' P–L relationship — the luminosity changes modestly with the period. They conclude that ULP Cepheids are more standard-candle-like than classical Cepheids, in particular when observed at wavelengths for which extinction due to dust

is smaller. They also claim that the uncertainty in the derived cosmic distances is as good as that obtained with classical Cepheids or type Ia supernovae.

But as the authors themselves acknowledge, ULP Cepheids' use as distance indicators also comes with limitations. First, they are relatively rare. Second, they require more observations to cover their long variability periods. Future observations, ideally undertaken with telescopes in space, would both help to overcome this limitation and offer insight into the evolution of these stars.

What Bird *et al.* did not attempt to do was test the implications of the observed ULP Cepheids for the value of $H_0$. In the wider picture, a more accurate determination of Cepheid and supernovae distances will have profound implications for understanding the basic properties of our Universe. The Hubble constant is just the value of the Hubble function $H(z)$ at the present epoch (or redshift $z=0$). Cosmologists would like to measure $H(z)$ accurately out to high redshifts, because this function depends on the contents of the Universe.

The current measurements imply that only about 4% of the Universe is made up of normal (baryonic) matter, whereas the rest of it is made up of cold dark matter (21%) and the even more mysterious dark energy (75%), which seems to be causing the expansion of the Universe to speed up. But other scenarios, such as an epoch-dependent dark energy or modifications to Einstein's theory of general relativity, are not excluded by the observations.

There are also indirect methods of estimating $H(z)$, such as those based on the large-scale distribution of galaxies, clusters of galaxies and gravitational lensing (the deflection of light from distant sources by foreground objects). And indeed, there are plans for several dark-energy surveys of billions of galaxies that will lead to a more refined estimation of $H(z)$ and other cosmological functions. Better calibrated samples of type Ia supernovae will also be crucial for pinning down $H(z)$, and the proposed class of ULP Cepheids may well play an important part in this effort. ■

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MEMBRANE-PROTEIN STRUCTURE

# Piercing insights

Hagan Bayley

**Pore-forming proteins are deadly biological weapons that punch holes in target-cell membranes. The structure of the pore formed by a bacterial toxin suggests that diverse pore formers have similar assembly pathways.**

Nature's pore-forming proteins are primitive but lethal weapons[1]. Bacteria use them to wage war against rival bacteria and to attack human cells. Not to be outdone, our immune defences use pore formers too, such as the complement component C9, which attacks bacteria and protozoa, and perforin, a protein that kills virus-infected cells. But despite their ubiquity, very little is known about the detailed structures of the pores formed by these proteins, as their elucidation presents substantial technical challenges. Fortunately, on page 726 of this issue, Mueller and colleagues[2] now describe a striking X-ray structure of the pore formed by a bacterial toxin, which differs markedly from the sole previous example[3]. Nevertheless, they propose an assembly mechanism that has features in common with many other pore formers.

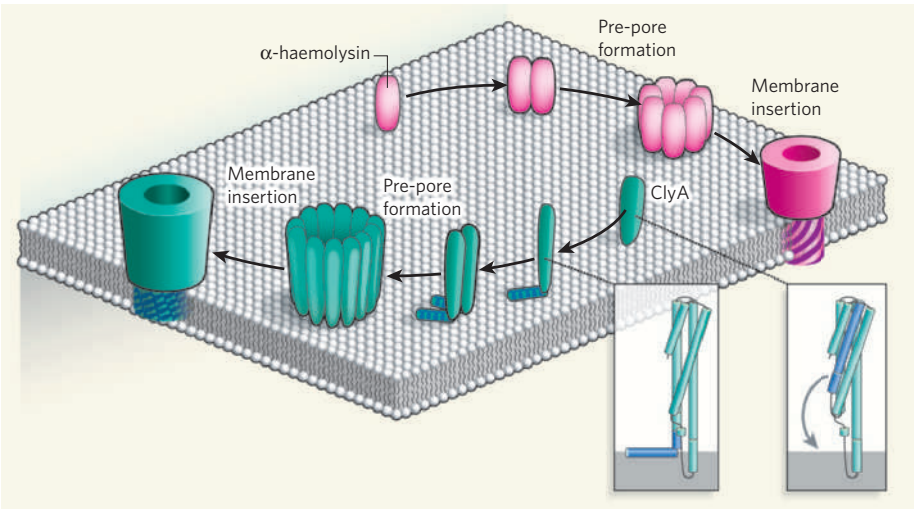


**Figure 1 | Assembly of staphylococcal α-haemolysin and ClyA pores show common principles.** The staphylococcal α-haemolysin pore (pink) is made up of seven subunits, which span the lipid bilayer as a β-barrel, whereas ClyA (green) forms an iris-like barrel of α-helices from its twelve subunits[2]. The conformational changes undertaken by α-haemolysin before insertion are minimal; by contrast, ClyA undergoes radical reorganization before membrane penetration, with extension of one of the three helices in each subunit in an arc towards the membrane surface (as shown in the insets). Even so, crucial aspects of the assembly pathway, including the participation of a non-penetrating pre-pore intermediate, are similar.

Many pore-forming proteins damage their targets simply by forming holes in the targets' outer membranes, whereas others, such as anthrax toxin, transport noxious substances into the victim's cells. Unlike most membrane proteins, which are inserted into membranes within the cell as they are made, pore-forming proteins are usually made in water-soluble, secreted forms, which then assemble in the target-cell membrane.

The pores derived from soluble pore-forming proteins fall into two main classes. The best described are pores with transmembrane β-barrels, in which polypeptide strands weave back and forth across the lipid bilayer, creating a sheet that forms a cylindrical surface. One example is the α-haemolysin of *Staphylococcus aureus*, which spans the lipid bilayer of target cells as a 14-stranded barrel, with two polypeptide strands contributed by each of seven subunits[3]. By contrast, each subunit of the large pores formed by the extensive family of cholesterol-dependent cytolysins (CDCs) contributes four strands to each membrane-spanning β-barrel, which comprises up to 50 subunits[4].

In the second class, there are many pores that are thought to be formed from spiral polypeptide rods, known as α-helices, rather than from extended β-strands[1]. These proteins are often used in bacterial assaults on other bacteria. Despite considerable effort, attempts to obtain three-dimensional structures of α-helical pores, either by X-ray diffraction or at lower resolution by electron microscopy, have failed. Most of these proteins probably resemble antimicrobial peptides, which often form poorly defined or weakly associated oligomers, militating against structure determination. Therefore, the structure of the α-helical toxin pore formed by cytolysin A (ClyA) described by Mueller