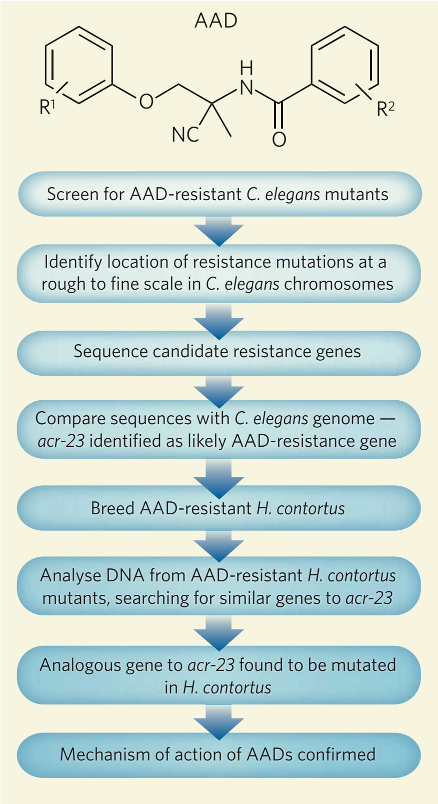

Figure 2 | Determining the biological target of antiparasitic drugs. Kaminsky *et al.*[4] report a class of compounds known as amino-acetonitrile derivatives (AADs) that kill parasitic worms such as *H. contortus* in livestock. R^1 and R^2 represent general chemical groups, and may be attached to the aromatic rings at any vacant position. AADs also kill the non-parasitic worm *C. elegans*, the genome of which has been sequenced. The authors were therefore able to determine the biological target of AADs by studying AAD-resistant *C. elegans*, as shown in the flow chart. The gene responsible for AAD resistance must produce the protein targeted by the compounds.

found in mammals. The mutant worms were susceptible to other classes of anthelmintics, providing further credence to the idea that AADs have a new biological target.

The authors then looked to see whether AADs attack the same target in parasitic nematodes. They selected for AAD-resistant *H. contortus* larvae *in vitro*, and for adult worms *in vivo*, by giving sheep doses of the new anthelmintic that were too low to get rid of the parasite completely. They then used nAChR-specific DNA probes on both AAD-resistant and AAD-susceptible parasites to find nAChR genes likely to be responsible for the resistance. They found that part of a nematode-specific nAChR gene (named *Hcdes-2H* by the authors) was missing in the AAD-resistant worms, and that this gene was closely related to *acr-23*. This suggests that the mode of action of AADs is similar in both *C. elegans* and *H. contortus*. It also suggests that the presence of evolutionarily related nAChRs in other species of parasitic nematode can be used to predict the effectiveness of AADs against those species, which could be useful when deciding on a course of treatment for worm-infected animals.

Kaminsky and colleagues' compounds[4] show considerable promise as a new class of anthelmintics, although further development will be necessary before a drug reaches the market. Of course, as with any class of drugs against infective pathogens, there is a risk that resistance to AADs may develop; indeed, the authors have already shown that this is possible. But knowing the likely mode of action of AADs will help in devising strategies to slow the development of resistance, and will also enable sensitive molecular tools to be made for detecting AAD resistance if and when it appears. ■

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COSMOLOGY

Patchy solutions

George Ellis

The Universe seems to be expanding ever faster — a phenomenon generally ascribed to the influence of 'dark energy'. But might the observed acceleration be a trick of the light in an inhomogeneous Universe?

Ten years ago, observations of distant supernovae brought a startling realization: the Universe's expansion is apparently accelerating. This observation required a quick patch-up of the dynamics of cosmologists' standard 'concordance' model of the Universe. The sticking plaster was dark energy — a mysterious substance contrived to counteract the attractive tendencies of cosmology's dominant force, gravity.

Unfortunately, the physical origin of dark energy is almost as problematic as the problem it solves. A favoured explanation is a 'cosmological constant' with a small positive value that arises from a non-zero energy density of the cosmic vacuum. But when particle theory is used to tot up the energy of the quantum vacuum, the answer greatly exceeds the size of cosmological constant required to explain acceleration. So might dark energy instead be some kind of anti-gravity field — a 'quintessence'? But even less is known of the essence of quintessence than of the cosmological constant. Given this situation, a quite different explanation for the acceleration observations — one that does not invoke any new physics — would be welcome. A clutch of recent papers[1–8] rehearses and refines one such idea: that the observed cosmic acceleration might be caused by an inhomogeneous Universe.

The fundamental dynamics of the Universe are embodied in Albert Einstein's general-relativistic field equations, which describe how gravity arises through the distortion of spacetime by mass and energy. The simplest class of solution to those equations, that on which the concordance model is based, assumes that matter is distributed both homogeneously (everything is similar in all regions of space) and isotropically (everything looks the same in all directions). That assumption is consistent with observations, but it is not a direct consequence of them. It is the favoured solution both because it is the simplest and because it rests on a cherished cosmological assumption. This is the 'copernican principle': that the characteristics of the Universe in our neighbourhood are not special in any way, but are typical of the whole.

A cherished assumption this might be, but it is also fundamentally untested. It is consistent with the supernova observations, but only provided that some form of dark energy is present. The central plank of the new research is the claim that, by jettisoning the copernican principle and our assumptions about the distribution of matter in the Universe, we can also abandon the troublesome chimaera of dark energy.

The first type of inhomogeneity considered is local inhomogeneity[1–5]. Local inhomogeneities in the Universe's matter distribution certainly exist — we live in one, a galaxy — but there is always an averaging scale implicit in the representation of any physical variable (Fig. 1), which might hide such inhomogeneities. The essential question[9] is in what way the dynamics of the Universe is altered when the bumpy local representation is averaged out to the homogeneous, isotropic global model assumed by standard cosmology. In a recent status review, Thomas Buchert shows[1] how averaging Einstein's equations on a small scale leads to a repulsive 'backreaction' term in the equations representing the large-scale, smoothed-out Universe that mimics the effect of dark energy.

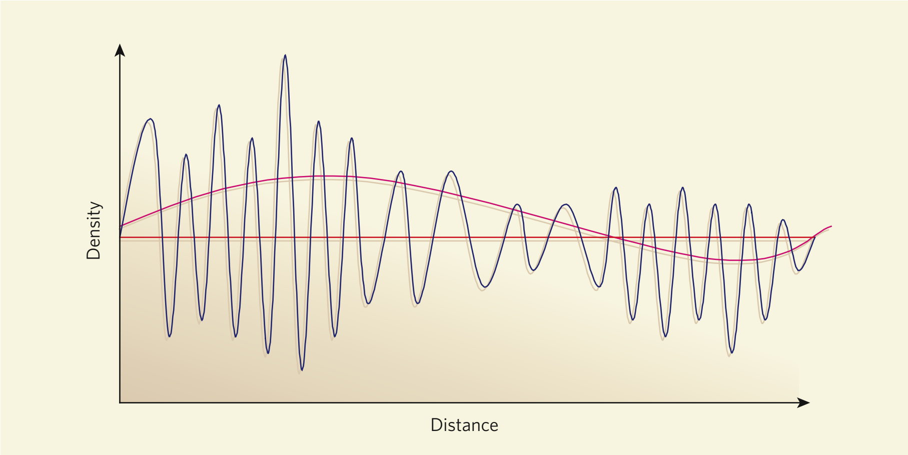

Figure 1 | Averaging the Universe. **These three curves represent the same distribution of matter on three different averaging scales. The blue curve shows considerable detail; the pink one is averaged on a medium scale to show the overall inhomogeneity; and the red one is averaged on a very large scale to show the uniform cosmological average. The effective general-relativistic field equations describing the behaviour of the Universe will be different at each of these scales; the essential question in assessing the role of inhomogeneities is how the averaging of the small-scale terms adds up to affect the dynamics of the large-scale averaged depiction.**

But local inhomogeneities also affect cosmological observations of distant sources, which are sensitive to focusing effects on the emitted light caused by changes to the local gravitational field[10]. Averaged over all sources, the focusing of null geodesics — the paths followed through space-time by massless particles such as photons — agrees when a lumpy, small-scale model is averaged to attain a smooth, large-scale model. But for individual sources, a correction will be required depending on whether the light rays from the observed object traverse mainly voids or matter before reaching us. The observational effects of lumps should be determined using an averaging process based on the paths taken by light[11], rather than just by averaging over space. This might significantly change the apparent luminosity of distant objects, but the result will depend on the details of how matter is distributed — which is not well enough known to give a definite answer.

A new dimension to this discussion comes from David Wiltshire and others[2,3], and from Teppo Mattsson[4], who argue that in analysing the observations one should take into account the dominance of large-scale voids in the Universe and the way that local pockets of higher density are tied into the expanding Universe. By going back to the roots of general relativity, Wiltshire considers how measurements of space-time in a smoothed model and in a small-scale model that takes voids into account are related. It seems that our interpretation of observations is crucially affected by the differences between the two. The magnitude of the effect may be sufficient to significantly affect the acceleration that the supernova observations seemingly demand; indeed, some claim it can explain it away fully[3,4]. But this point of view is disputed[5], and needs to be evaluated carefully in light of a realistic view of the nature of local inhomogeneities in the real Universe.

An alternative to locally inhomogeneous models that might provide an explanation of the acceleration observations is large-scale inhomogeneity — a breakdown of the copernican assumption on the Hubble scale (the scale of the visible Universe)[6]. The observed acceleration and data from NASA's WMAP satellite, which is probing anisotropies in the cosmic microwave background (the radiation left over from the Big Bang), can be explained by assuming that we are near the centre of a Hubble-scale inhomogeneity of anomalously low density in a Universe that is spherically symmetrical[7]. Testing the existence of the requisite spatial inhomogeneity is difficult with observations of galaxies or other sources, because their evolution over time is unknown, but is in principle possible[12] using the anisotropies or the spectrum of the cosmic microwave background. But such tests are dependent on models of matter–radiation interactions.

Spatial homogeneity is one of the foundations of standard cosmology, so any chance to check those foundations observationally should be welcomed with open arms. Further tests are being proposed[13], but they depend on models of gravity or matter. A potentially substantial step forward is provided by Clarkson *et al.*[8]. They show that a simple observation of the copernican principle that is independent of any theory of gravity or model for dark energy is possible through redshift and area–distance observations of distant galaxies.

As the supernova observations are analysed further, a pivotal question is what physical properties are acceptable for any proposed dark-energy solution. Despite what some adventurous workers propose, we perhaps need to query any violation of energy conditions that implies the existence of negative kinetic-energy terms, as indicated by some analyses[14]. It may be that such observations are trying to tell us that there is something fundamentally wrong in our assumptions; and that the acceleration

50 & 100 YEARS AGO

50 YEARS AGO

In these days when the output of scientific literature challenges the ability of the worker in even the most specialized fields to keep himself informed about current research, news of the publication of yet another scientific journal must sometimes be received with mixed feelings. This will not, however, prevent geologists from wishing success to the Geological Society of Egypt, which in 1957 published the first number of the *Egyptian Journal of Geology*, which is to be produced in the future twice-yearly.

From *Nature* 15 March 1958.

100 YEARS AGO

The Diseases of Animals. By Nelson S. Mayo — This work, which purports to be one of popular advice on the care and common ailments of farm animals, is written entirely from the American point of view, and deals with American methods principally, in most distinctly American orthography. It cannot be doubted that its usefulness to the British rural public, not less than the pleasure of reading it, are considerably lessened thereby. It is decidedly irritating to readers on this side of the Atlantic to see such abominations as "sulfur," "esophagus," "sulfate," "mold," and others of a similar kind. There is, nevertheless, a good deal of useful and practical information on the care of animals and farm stock which the farmer would do well to know, no matter in what part of the world he carries on his occupation ... So far as this country is concerned, there is still room for a good up-to-date popular scientific work which will give the farmer such simple knowledge of the breeding, accidents, and diseases of his animals as will show him the occasion and the wisdom of consulting the skilled veterinarian.

From *Nature* 12 March 1908.

conundrum could have a geometric, rather than a dynamic, solution. ■

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PHYSICAL CHEMISTRY

Did life grind to a start?

J. Michael McBride and John C. Tully

Many solids can adopt two mirror-image crystal forms, and often grow as mixtures of both. A curious mechanism of crystal growth might explain why some mixtures convert into one form when subjected to grinding.

If Alice had been a biochemist, she would have found an even more unfamiliar world on the far side of the looking-glass. In principle, the molecules of life can adopt two mirror-image forms (often described as left- and right-handed), which from a chemical perspective are equally likely to exist. Yet all biological molecules on Earth adopt a single handedness, even though their reflections in Alice's looking-glass world should function just as well (Fig. 1). Did the machinery of early life impose the observed bias, or was the development of life favoured by a pre-existing pool of single-handed molecules? And if the latter is true, how could this pool have formed?

One explanation could be that a fundamental physical bias exists that generates an excess of a particular molecular handedness. Proposed theories invoke the weak nuclear force, or the action of 'circularly' polarized light somewhere in the Universe. But these influences would be far too weak to explain the existence of a single molecular form. So, if a pool of single-handed molecules existed on prebiotic Earth, it must have developed from a mixture containing almost equal numbers of mirror-image forms where the excess of the major form was amplified dramatically. Reporting in the *Journal of the American Chemical Society*[1], and at a meeting at the Nordic Institute for Theoretical Physics in Stockholm[2], Noorduin *et al.* describe a remarkably simple system for the spontaneous amplification of molecular handedness — stirring a slurry of crystals in the presence of glass beads.

More than 50 years ago, the theoretical physicist Charles Frank addressed the existence of single-handed biomolecules in what became a much-cited paper[3]. He commented: "I have long supposed that this was no problem on the basis of a supposition that the initial production of life is a rare event." He went on to prove mathematically that, in a system containing entities that both copy themselves and destroy their mirror images, an initial random event that provides a tiny excess of one hand would necessarily lead to the exclusive occurrence of that form, even if mirror-image versions could also form randomly. He concluded: "A laboratory demonstration may not be impossible." This seminal paper was Frank's sole contribution to biology — he is better known for his insights concerning the mechanisms of crystal growth. He might have been gratified to learn that his own field is supplying increasingly convincing laboratory demonstrations to support his biological model.

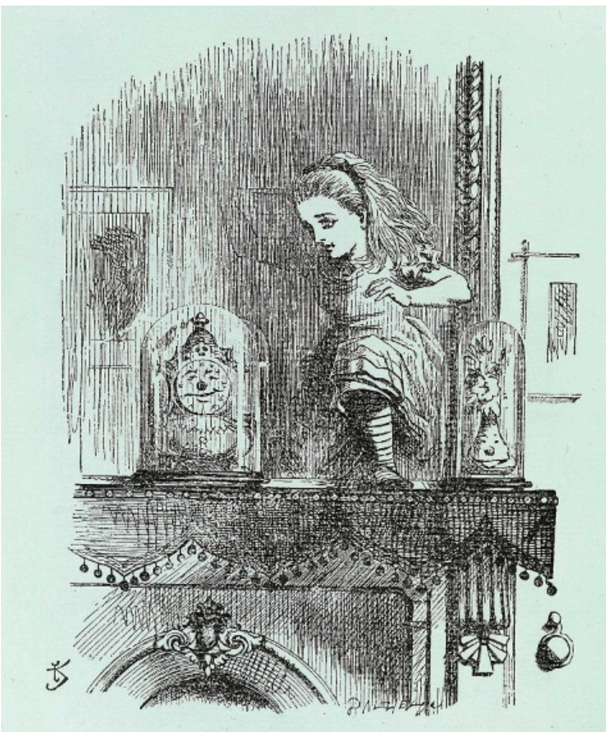

Figure 1 | **Molecules through the looking-glass.** The molecules of life in Alice's looking-glass world would be mirror images of those in ours, and should work just as well. So why don't they exist?

THE ART ARCHIVE

The first such demonstration came in 1990 with the report[4] that a highly concentrated solution of sodium chlorate (whose dissolved molecules have no handedness) deposits crystals of a single mirror-image form on cooling, if stirred. This phenomenon was soon understood to involve the random formation of a single crystal of arbitrary handedness, from which seed crystals of the same handedness were broken off by the stirrer[5,6]. A feature of this 'secondary nucleation' mechanism is that only crystals larger than a certain critical size will grow; smaller crystals dissolve, because a higher proportion of their molecules occupy unstable positions at the crystal surface. The critical size is inversely related to the concentration of the solution. Because the initial fortuitous growth of crystals of one handedness reduces the concentration of the surrounding solution, the formation of mirror-image crystals that are large enough to grow becomes impossible.

To obtain single-handed crystals of sodium chlorate by secondary nucleation, a single seed crystal is required, and the solution must begin in a so-called supersaturated state, which is far from equilibrium. But in 2005, it was discovered that single-handed crystals of sodium chlorate could be obtained from a slurry of mixed mirror-image crystals in a saturated solution[7] (a system near to equilibrium). If there was an excess of one crystal form in the solid material, simply stirring the slurry resulted in complete conversion of the crystals to the dominant form, even if the initial excess was only a few per cent. The secret of this success was to add glass beads, which continually grind the crystals during stirring. As the starting conditions in this system are so different from those required for secondary nucleation, the mechanism must be different.

Noorduin *et al.*[1] now show that the grinding method works for a different compound — an amino-acid derivative. This may not seem like big news, but there is a crucial distinction from the previous work. Unlike sodium chlorate, the amino-acid derivative