

levels are much lower because of rapid diffusion of drug out of the tumour, then the calculated number of interactions possible in the ^{59}Fe for sufficient Mössbauer toxicity becomes too few. Finally, there is a big question as to the potential development of the technique for clinical use, and Mills *et al.* provide no indication of their views on this subject. The half-value layer of 14.4-keV photons is only 4.4 mm in tissue. An envisaged therapy could therefore be applied only to superficial lesions, for which there already exist many

other simpler irradiation procedures, for example, electron-beam, ion-beam, soft X-ray and photodynamic therapies. If the main challenge of cancer is its deep-seated and metastatic nature, then the role of photoactivation by these methods has severe limitations. □

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Quantum cosmology

Baby universes and making the cosmological constant zero

L. F. Abbott

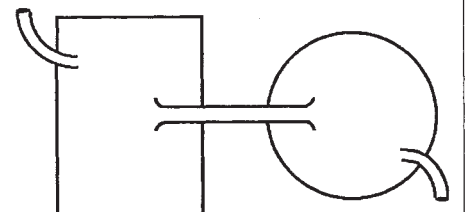
CAN quantum-mechanical processes in our Universe create and destroy other universes, and if so what effects would this have on us? This intriguing question has been the subject of much recent speculation¹⁻³ culminating in the suggestion by Sidney Coleman⁴ that the creation and destruction of baby universes and the coupling of our Universe to other universes through wormholes may resolve one of particle physics' most puzzling problems, the mystery of the cosmological constant. Although this work is extremely speculative it does provide an interesting and imaginative new approach to an old and vexing problem.

The cosmological constant can be defined most simply as the energy density of the vacuum, that is, the amount of energy in a unit volume of empty space. Intuition may suggest that this quantity must be zero, but this is incorrect. In principle, the vacuum energy density can assume any value positive or negative and current ideas about particle physics and gravity suggest that it should be quite large^{5,6}. The cosmological constant can be measured by looking for the characteristic effects that a non-zero vacuum energy density would have on the geometric structure of space-time as predicted by Einstein's general relativity. No such effects have been seen and present observational limits imply that the cosmological constant is smaller than theoretical expectations by a staggering factor of about 10^{-120} . The only way to account for this enormous discrepancy between theoretical expectation and experimental reality is to assume that the parameters of nature are involved in an extraordinarily accurate and utterly mysterious conspiracy resulting in cancellations between various contributions to the vacuum energy density.

The new proposal to account for this conspiracy relies on combining the principles of quantum mechanics with general

relativity, a notoriously problematic union. In fact we have no satisfactory theory of quantum gravity and even the simplest application of quantum mechanics to the geometric structure of space-time faces serious conceptual difficulties. Work on the cosmological constant is based on procedures developed by Stephen Hawking and his collaborators^{7,8} for calculating a quantum-mechanical wavefunction describing the spatial geometry of the Universe. In fact,

A representation of various processes involving wormholes. Our Universe is represented by the large rectangular sheet, whose horizontal direction is one spatial dimension (the other two having been ignored to simplify the diagram) and, with the qualification that is to follow, whose vertical direction can be thought of as time. The thin tubes are the wormholes. At the upper left, a wormhole appears in our Universe and creates a baby universe whose birth is represented by the circle at the top of the wormhole. In the centre, a wormhole connects our Universe to another universe depicted as a sphere. In the other spherical universe, a baby universe is being destroyed. Now for the qualification. If such processes can occur at all (and nobody knows if they can) they must be quantum-mechanical, so a simple classical space-time diagram as shown here is not applicable. But such figures are useful visual aids and if the time variable is taken to be imaginary rather than real, they provide a semi-classical approximation for the corresponding quantum process.



Hawking noted several years ago that his 'wavefunction of the universe' seemed to imply that zero is the most likely value for the cosmological constant⁹.

Coleman's new work extends Hawking's result by assuming the existence and importance of quantum fluctuations which change the topological structure of space-time (see figure). It should be stressed that we really have no idea whether such fluctuations can occur, but if they do and if their effects are relevant we can proceed to analyse what those effects might be. The first thing we know is that the connecting wormholes, filaments of distorted space-time, would have to be very tiny — about 10^{-33} cm, the natural size for gravitational quantum-mechanical

fluctuations. Thus they would not be directly observable. Rather, as has been shown, their effect would be transmitted indirectly through the values of the constants of nature.

The way that wormholes affect our Universe depends on the number of 'baby universes' they lead to (see figure). Rather than using the number of baby universes of type i , Coleman uses a closely related variable α_i . Because the wormholes affect the values of the parameters in physical theories and because wormhole effects are governed by the variables of α_i , all the constants of nature become functions of the α_i . This means that particle masses, the fine-structure constant, the gravitational constant and, of course, the cosmological constant all depend on parameters characterizing the topological structure of space, a remarkable concept.

Furthermore, if we can predict anything about the distribution of α_i values we may learn something about the values of physical parameters like the cosmological constant. Because the α_i s are part of our description of spatial geometry, their probability distribution is determined by the wavefunction of the Universe. Using the techniques of Hawking, Coleman finds that the probability distribution for the α_i contains a factor which is infinitely peaked at values of these parameters which make the cosmological constant vanish (for small positive cosmological

constants, it is proportional to the exponential of the exponential of one over the cosmological constant). Thus, the cosmological constant vanishes because it is infinitely more likely that the constants of nature assume values which make it vanish, than that they do not.

One of the most positive aspects of the Coleman-Hawking programme is that it avoids a major obstacle which has derailed most other attempts to adjust the cosmological constant to zero (an interesting exception is in ref. 10). Our Universe is filled with matter and radiation which throughout most of its history (presumably up to the present) have completely obscured any effects of a small but non-vanishing cosmological constant. So how

can any mechanism determine the constant's value and adjust it to zero? The answer in Coleman's approach is that the Universe peeks through a wormhole into a large empty universe thus escaping the problem of the obscuring matter and radiation in our Universe (see figure).

On the negative side, the approach relies on a shaky formalism and on many untested assumptions. It nevertheless comes up with the desired result, a zero cosmological constant. Of course, much would be forgiven if the theory could provide a correct value for another fundamental parameter, especially one that is non-zero. In principle, because Coleman's scheme is a method for predicting the values of the α_s and as all the parameters

of nature are functions of these, it is a theory of parameters. Unfortunately, early results have been disappointing so it remains to be seen whether the Coleman-Hawking approach, if it is indeed correct, will prove revolutionary or merely comforting. □

1. Hawking, S.W. *Phys. Rev. D* **37**, 904-910 (1988).
2. Lavrelashvili, G.V., Rubakov, V.A. & Tinyakov, P.-G. *JETP Lett.* **46**, 167-169 (1987).
3. Giddings, S. & Strominger, A. *Nucl. Phys. B* (in the press).
4. Coleman, S. *Nucl. Phys. B* **310**, 643-668 (1988).
5. Abbott, L.F. *Sci. Am.* **256**, 106-113 (1988).
6. Weinberg, S. *Rev. mod. Phys.* (in the press).
7. Hawking, S.W. in *Relativity, Groups and Topology II* (eds De Witt, B. & Stora, R.) 314-349 (North-Holland, 1983).
8. Hartle, J.B. & Hawking, S.W. *Phys. Rev. D* **28**, 2960 (1983).
9. Hawking, S.W. *Phys. Lett. B* **134**, 403-404 (1984).
10. Linde, A. *Phys. Lett. B* **200**, 272-274 (1988).

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Sex determination

Right gene, wrong chromosome

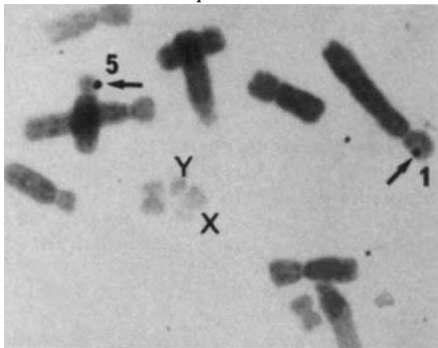
Jonathan Hodgkin

IN December last year, David Page and colleagues reported¹ on the human Y chromosome a 'zinc-finger' gene which is likely to be identical with TDF, the Y-linked testis-determining factor responsible for initiating male development. The identification of this gene, now called *ZFY*, touched off a predictable hunt for corresponding genes in other animals. In their original paper, Page *et al.* showed that *ZFY* is strongly conserved on the Y chromosome of various different placental mammals (eutherians), and also found that there is a closely related gene, *ZFX*, on the X chromosome of all these species. Now the hunt for *ZFY* cognates has extended to other vertebrate groups, with disquieting results. Exactly a year after identifying the zinc-finger gene, Sinclair, Page *et al.* report on page 780 of this issue² that the marsupial sequences most closely related to *ZFY* are on autosomes, not on the Y chromosome. This observation is based only on hybridization data, but it is unlikely to be wholly artefactual.

The result is disquieting because in marsupials, much as in eutherians, the Y chromosome is male-determining, and it is therefore expected to carry the equivalent of TDF. So if *ZFY* is autosomal in marsupials, it cannot be the primary Y-linked male determinant as it appears to be in other mammals. There are two possible conclusions: either *ZFY* is not TDF after all; or *ZFY* is testis-determining in eutherians, but something else plays the primary role in marsupials.

Several pieces of evidence favour the second possibility. The circumstantial evidence identifying *ZFY* as the human TDF is strong: for this not to be the case, it would be necessary to assume that the real TDF is an elusive, poorly conserved gene in the same small genetic interval (less

than 300 kilobases) as *ZFY*. On the other hand, *ZFY* itself is strongly conserved (at least as measured by DNA hybridization) and it also has a primary structure consistent with a regulatory role. Second, it is misleading to regard the marsupial gene or genes as corresponding to *ZFY per se*; instead they could equally or better correspond to *ZFX*. The marsupial X chromosome (see figure) is smaller than the eutherian X, and does not carry an obvious *ZFX* sequence. Several of the



Chromosomes of the kangaroo *Macropus eugenii*. (Courtesy of A.H. Sinclair.)

genes conserved on the X chromosome in all eutherians are located on autosomes in marsupials, suggesting that a translocation has taken place. Consistent with this, Sinclair *et al.*² find that a probe for the Duchenne muscular dystrophy gene, which is near *ZFX* in humans, hybridizes to chromosome 5 in wallabies, in the same interval as the apparent *ZFY* cognate.

In humans, both *ZFX* and *ZFY* could be required for testis formation. Some human XY female embryos have chromosomal defects in the Xp21 region where *ZFX* is located³, and might have a non-functional *ZFX*. Therefore, one possible explanation of the results would be that in eutherians *ZFY* potentiates the expression

or action of *ZFX*, which by itself (in XX or XO individuals) cannot trigger testis formation; whereas in marsupials some other Y-linked gene would potentiate the autosomal gene, which can be called '*ZFA*'.

Genes hybridizing to a *ZFY* probe have also been detected in other vertebrate groups, but in these as well the most conserved sequences seem to be autosomal⁴. This is true of reptiles with a chromosomal sex-determination mechanism; reptiles with environmental (temperature-controlled) sex determination, such as turtles; and finally of birds, which have ZW female/ZZ male sex determination. So again, it could be that *ZFA* is consistently testis-determining, but under different primary regulation in each of these groups. Bull and co-workers have found that the turtle *ZFA* is transcribed during the critical temperature-dependent period for this species, which is consistent (but no more than that) with a role in sex determination.

Evolutionary differences in the primary sex determining signal should come as no surprise⁵. Even within a single taxonomic group such as Diptera there can be a bewildering variety of different sex-determination mechanisms, which may nevertheless turn out to have common underlying elements. Radical changes in mechanism can also be made artificially. For example, primary sex determination in the nematode *Caenorhabditis elegans* is normally achieved by the X chromosome-to-autosome ratio, as in the fruitfly *Drosophila*, yet it is possible to alter the system in various ways by mutating major autosomal sex-determining genes^{6,7}, so that the primary role is transferred to either autosome III (carrying the switch gene *tra-1*) or autosome II (carrying the switch gene *tra-2*). Many of the different vertebrate and dipteran schemes can be imitated by appropriate manipulation of nematode genes, although there seems to be little in common at the molecular level in the sex-determining genes of these three groups.

Seen from this perspective, the results obtained with *ZFY* probes are not discouraging, but they tend to focus more attention on *ZFX* as a possible major player in the process of sex determination. It remains essential to discover more about the functions of *ZFY* and *ZFX*, and what is involved in testis determination in biochemical terms: what do these zinc fingers regulate? □

1. Page, D.C. *et al. Cell* **51**, 1091-1104 (1987).
2. Sinclair, A.H. *et al. Nature* **336**, 780-783 (1988).
3. Bernstein, R. *et al. Science* **207**, 768-769 (1980).
4. Bull, J. J. *et al. Science* **242**, 567-569 (1988).
5. Bull, J. J. *Evolution of Sex-Determining Mechanisms* (Benjamin/Cummings, Menlo Park, 1983).
6. Hodgkin, J. *Nature* **304**, 267-268 (1983).
7. Miller, L.M. *et al. Cell* **55**, 167-183 (1988).

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