cleavage requires presenilin and is sensitive to neuronal stimulation — cleavage is induced by treatments that cause ion influx into neurons and trigger the release of neurotransmitters, the chemical messengers that propagate electrical signals from one neuron to the next. The result of N-cadherin cleavage is also intriguing. Part of this cell-surface protein protrudes through the cell membrane into the cytoplasm (the intracellular space), and cleavage releases this biologically active intracellular domain. Marambaud *et al.* found that this portion, N-Cad/CTF2, represses the activity of another protein termed CBP, a 'transcriptional coactivator' that helps another protein, CREB, do its job of turning on sets of target genes.

This is an exciting finding, as CBP and CREB are widely expressed proteins that directly or indirectly regulate many genes during normal cell growth and disease. CBP has also been linked to human neurodegenerative disorders and mental retardation[8]. And CREB-regulated gene expression has an enduring, albeit elusive, connection to the molecular basis of learning and memory[9].

How does N-Cad/CTF2 influence CBP and CREB, and what are the consequences for neuronal gene regulation? The authors[2] present a series of experiments indicating that N-Cad/CTF2 binds to CBP in the cytoplasm, marking it for degradation and thus reducing the total cellular pool of CBP. An odd feature of this mechanism is that CBP is normally detected only in the nucleus, so N-Cad/CTF2 must either target newly synthesized CBP, or it must somehow 'pull' nuclear CBP into the cytoplasm to destroy it. CREB is not directly affected by N-Cad/CTF2, but without its partner, CBP, it is a less potent gene activator.

The notion that γ-secretase cleaves N-cadherin, generating a cytoplasmic protein fragment that influences the activity of many genes, including those potentially involved in memory formation, has far-reaching implications. At the very least, these findings will reinvigorate the debate about the relative importance of extracellular amyloid-related processes and intracellular signalling and gene regulation in Alzheimer's disease. Marambaud *et al.* report that several different presenilin mutations that are associated with the disease impart two characteristics to cells — the failure to produce N-Cad/CTF2 and the concomitant inability to suppress CREB-mediated gene activation (Fig. 1b).

So according to the new model, the presenilin mutations provoke a gain-of-activity change in numerous genes, which might possibly impair memory and other aspects of neuronal function, without necessarily killing neurons through toxic amyloid overload. Tantalizing evidence in support of this idea is that certain rare presenilin mutations are linked to a form of dementia that is not associated with pronounced amyloid-plaque formation[10]. Furthermore, CBP- and CREB-regulated gene expression is often perturbed in other human neurodegenerative diseases[11].

Many details of this model, such as which CREB-responsive genes are most susceptible to regulation by N-Cad/CTF2 and whether this protein also affects other gene-activation pathways that do not use CREB, have yet to be addressed. Whether N-Cad/CTF2 induces CBP destruction in animals also awaits confirmation, as Marambaud *et al.* deduced this effect from studies in cultured cells. But as a promising first step in this direction, the authors examined neurons from genetically engineered mouse embryos that harbour an Alzheimer's disease-associated presenilin mutation. These mouse cells contained reduced amounts of N-Cad/CTF2 and increased levels of both nuclear CBP and the protein c-Fos (which is encoded by a gene that is activated by CREB) (Fig. 1b).

The new findings[2] also raise the question of whether presenilin mutations contribute to Alzheimer's disease by influencing gene-regulatory pathways other than those affected by N-cadherin cleavage. Indeed, several other γ-secretase substrates (including APP, the Notch receptor protein, and the Deleted in Colon Cancer protein) are known to modulate various aspects of neuronal form and function. Could the cumulative effect of interfering with several such pathways trigger early neuron damage, before detectable amyloid plaques form and kill neurons? If so, are these pathways relevant to sporadic Alzheimer's disease, which is not associated with presenilin mutations? Future research might provide the answers to these questions. But as the new study illustrates, after almost a century of investigation, Alzheimer's disease has been slow to reveal its secrets. ■

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Cosmology

The shape of the Universe

George F. R. Ellis

An analysis of astronomical data suggests not only that the Universe is finite, but also that it has a specific, rather rigid topology. If confirmed, this is a major discovery about the nature of the Universe.

What shape is space? On page 593 of this issue, Luminet *et al.*[1] suggest that the topology of the Universe may be a 'Poincaré dodecahedral space' — as illustrated on this week's cover. And this is no idle abstraction: Luminet *et al.* show that this topology, unlike many others, is supported by data from NASA's Wilkinson Microwave Anisotropy Probe (WMAP), published earlier this year[2].

In thinking about the large-scale shape of the Universe, three interlinked questions must be confronted. First, what is its spatial curvature? There are three possible answers. Three-dimensional sections of space-time may be 'flat' — in such space sections, parallel lines stay the same distance apart and never meet (as in Euclidean space). Or the space sections may be 'negatively curved', such that parallel lines diverge from one another and never meet (the three-dimensional analogue of a Lobachevsky space). Finally, they may be 'positively curved', such that parallel lines converge and eventually intersect (the three-dimensional analogue of the surface of a sphere). The particular case that exists depends on how well the amount of matter in the Universe, coupled with the driving force of dark energy, balances the Universe's kinetic energy of expansion. This is usually expressed in terms of the normalized density parameter Ω_0, which is unity for flat space sections; for positive spatial curvature, Ω_0 is greater than one.

The second question is whether the Universe is 'open' or 'closed' — that is, is it spatially infinite, containing an infinite amount of matter, or is it spatially finite, containing a finite amount of matter? Positively curved space sections are necessarily closed, but the converse does not necessarily follow: both flat and negatively curved space sections can be finite if their connectivity is more complicated than in Euclidean space, meaning that their topology is quite unusual[3,4] (for example, in a flat toroidal space, as you exit right you enter left, and space is finite). So the third issue is, what is the large-scale topology of the Universe?

It is worth noting that none of these

features is determined by the Einstein gravitational field equations, which are differential equations that govern local, rather than global, properties of space-time[5]. Topology and curvature seem to be fixed by the initial conditions at the start of the Universe that have since determined its dynamical evolution. To investigate the topology and curvature of the Universe, we must use astronomical observations; from observed values of the energy densities and the expansion rate in the Universe, the curvature can be deduced using Einstein's field equations.

If the Universe is closed, and has a small enough diameter, we may be able to see right round it because photons can traverse the whole Universe — Luminet *et al.*[1] illustrate this point well with the image of an insect crawling around the surface of a cylinder (Fig. 2 on page 593). If this is so, we may be able to identify multiple images of the same structure but in different directions in the sky[4,6], or see an effect on the statistics of clustering of galaxies[4]. Furthermore, the existence of such a 'small universe' should be detectable through its influence on that Rosetta Stone of present-day cosmology, the cosmic microwave background (CMB) radiation[7,8].

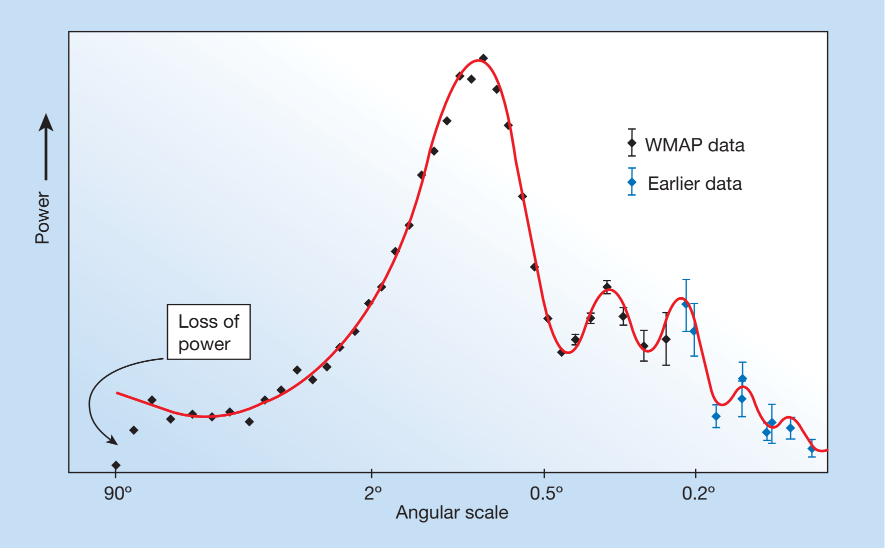

Figure 1 **Power spectrum of the cosmic microwave background (CMB) radiation. Data[2] from the Wilkinson Microwave Anisotropy Probe (WMAP) have extended the accuracy of the spectrum far beyond what was known from earlier measurements. This plot reflects the small differences in the temperature of the CMB across the sky. There are a series of peaks in the spectrum at small angular separations, but at large scales that structure disappears, and the data were expected to follow the 'Sachs–Wolfe plateau'. The WMAP measurements, however, fall below this plateau at the largest angular scales. Standard cosmological models cannot explain this, but Luminet and colleagues' topological model[1] for a finite universe can.**

The CMB is the relic radiation of the Big Bang, and the very slight changes in its temperature across the sky record the density fluctuations that existed at a certain point in the early history of the Universe. Data on these anisotropies[2,9] from WMAP and other sources suggest that the density parameter Ω_0 has the value 1.02 ± 0.02. This is compatible with flat space sections. Further data might move the value of Ω_0 towards or even below unity. But taking the present data at their face value, the conclusion is that the Universe is spatially closed and hence has finite space sections. This tentatively answers two of the three questions mentioned above.

But there is a further intriguing feature in the data. The so-called power spectrum of anisotropies (Fig. 1) shows a distinctive set of peaks when the anisotropy is compared between regions of sky separated by small angles. But on large angular scales (for regions typically more than 60° apart), there is a strange loss of power that does not fit with the expectations of standard cosmological models (in particular, there is less power in the quadrupole than expected). Some have proposed that this can be attributed to as yet undiscovered laws of physics at work in the early Universe[10].

Luminet *et al.*[1], however, suggest it is because we live in a universe with positively curved space sections and non-standard topology. The smaller-than-usual diameter of the Universe means that there is a maximum length scale that fits into it — and consequently there is a loss of power in the CMB spectrum on scales that are larger than this maximum[7]. The authors propose that the spatial sections of the Universe are dodecahedral sections of a space of positive curvature, fitted together to make finite three-dimensional spaces. This topology accounts for the WMAP data better than do standard models[1].

Can this proposal be confirmed? Yes indeed. First, Luminet and colleagues' model suggests that $\Omega_0 = 1.013$, and future observations will produce data that should pin down the value of Ω_0 to this level of accuracy (the current value from WMAP is accurate only to 2%). Second, a remarkable paper by Cornish *et al.*[11] showed that, however complex the spatial topology, in a small universe there will be circles of identical temperature fluctuations in the CMB sky that could be identified from data on the CMB anisotropies. Luminet *et al.* determine what those circles would be in their model. Future analyses of WMAP data — and of data from its successor, the Planck satellite, to be launched in 2007 — should be able to verify whether the circles are there or not.

In many models of the Universe, it is assumed that spatial homogeneity extends outside our visual horizon for ever. However, in the case of chaotic inflation[12,13] — a variant of the inflationary model for an exponential expansion that occurred in the wake of the Big Bang — the Universe is very inhomogeneous on scales much larger than we can observe, and we are in one expanding bubble in the middle of innumerable other, similar ones. But if Luminet *et al.* are correct, chaotic inflation is ruled out: there is only one expanding universe bubble, and we can see almost all the way round it.

In 1917, Einstein[14] proposed that spatially closed universes are advantageous because that would remove the problem of boundary conditions at infinity[15]. A small universe in which we have seen most of what exists is even more advantageous[6]; indeed, strictly speaking, they are the only universes in which we can predict the astronomical future — the return of Halley's comet, for example — because only in them do we have access to all the data needed to make such predictions. The WMAP data, as interpreted by Luminet *et al.*[1], suggest that we might indeed live in such a small closed universe. ■

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