ancestor, after which the two copies of the duplicated gene diverged in sequence in different offspring, and different copies were ultimately lost[6]. The result is two present-day species with so-called microsyntenic genomic differences, which are detectable only by sequencing. When these species hybridize, the differences act in a similar way to translocations to reduce spore viability[7] (Fig. 1b). So, the chromosomal model of speciation might prove to be generally true in yeasts, but only when smaller genomic differences, as well as translocations, are taken into account.

There is another intriguing point to the study by Delneri and colleagues. Mating yeasts generally have one copy of each chromosome; the zygotes produced by mating have two copies, one from each parent; and during gamete production (meiosis) the chromosomes are duplicated and segregated at random to produce four spores, each with again just one copy of each chromosome (Fig. 1). But Delneri *et al.* found that, for many of the spores produced by interspecies hybrids, there is a clear tendency to retain the complete set of chromosomes from one parent, plus (as usual) about half the chromosomes from the other. The authors suggest that the chromosome numbers might have been unbalanced in the hybrid zygotes, before they underwent meiosis. This fits with previous findings that hybrid zygotes formed between *Saccharomyces sensu stricto* and the more distantly related *sensu lato* species tend to kick out most of the chromosomes from one of the parents[8]. Making spores that include the complete genome of one parent could provide an elegant way for a hybrid to overcome the meiotic problems caused by translocations or microsyntenic differences[4].

Yeasts are proving to be an exciting system for the study of speciation and chromosome evolution, both in nature[1,4,5] and in artificial culture[9]. The *S. cerevisiae* genome sequence, which represented the mother of all eukaryotic genome projects, will soon be joined by a brood of new genome sequences from closely related yeast species[10–13]. Because most of these species are amenable to genetic manipulation, the opportunities for experimental dissection of species barriers will be almost limitless. ■

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1. Delneri, D. *et al. Nature* **422,** 68–72 (2003).
2. White, M. J. D. *Modes of Speciation* (Freeman, San Francisco, 1978).
3. Fischer, G., James, S. A., Roberts, I. N., Oliver, S. G. & Louis, E. J. *Nature* **405,** 451–454 (2000).
4. Greig, D., Borts, R. H., Louis, E. J. & Travisano, M. *Proc. R. Soc. Lond. B* **269,** 1167–1171 (2002).
5. Greig, D., Louis, E. J., Borts, R. H. & Travisano, M. *Science* **298,** 1773–1775 (2002).
6. Fischer, G., Neuveglise, C., Durrens, P., Gaillardin, C. & Dujon, B. *Genome Res.* **11,** 2009–2019 (2001).
7. Lynch, M., O'Hely, M., Walsh, B. & Force, A. *Genetics* **159,** 1789–1804 (2001).
8. Marinoni, G. *et al. J. Bacteriol.* **181,** 6488–6496 (1999).
9. Dunham, M. J. *et al. Proc. Natl Acad. Sci. USA* **99,** 16144–16149 (2002).
10. Cliften, P. F. *et al. Genome Res.* **11,** 1175–1186 (2001).
11. Kamvysselis, M., Patterson, N., Birren, B., Berger, B. & Lander, E. S. in *Proceedings of the Seventh Annual International Conference on Computational Biology (RECOMB '03)* (eds Waterman, M. *et al.*) (ACM, New York, in the press).
12. Dietrich, F. S. *et al. Curr. Genet.* **35,** 233 (1999).
13. Koszul, R. *et al. FEBS Lett.* **534,** 39–48 (2003).

Cosmology

Filling in the background

Sean Carroll

Data from NASA's Wilkinson Microwave Anisotropy Probe reveal the cosmic microwave background in more detail than ever before. But will cosmology become a victim of its own success?

Not so long ago, cosmology was, half-jokingly, thought of as "a search for two numbers". The numbers in question were the Hubble constant, which measures the rate at which the Universe is expanding, and the energy density, measured in terms of the critical density for which the Universe is flat (that is, when space has zero curvature). What was worse, many of the field's own practitioners despaired of determining these numbers with any real precision. The difficulty of controlling systematic errors in conventional observations of objects at cosmological distances presented a daunting obstacle.

In the past decade, all this has changed: our description of the Universe is now considerably more detailed, and the most important cosmological parameters are being determined with precision. The change can be traced back to 1992, when NASA's Cosmic Background Explorer (COBE) satellite first observed[1] small temperature fluctuations, or anisotropies, in the cosmic microwave background (CMB), the relic radiation from the Big Bang. Since then, we have obtained improved measurements of distances to galaxies and supernovae, large-scale structure, light-element abundances, clusters of galaxies, cosmological dynamics and even of the CMB itself. Such measurements have pinned down a precise picture of the state of our Universe that was beyond the hopes of most cosmologists just a short time ago. Now another NASA satellite, the Wilkinson Microwave Anisotropy Probe (WMAP), has returned much higher-resolution images[2,3] of CMB fluctuations, confirming and extending this remarkable achievement (Fig. 1). These new results provide a worthy book-end to a decade of startling discoveries.

Our Universe is expanding — distant galaxies are moving further away from each other. Using the laws of general relativity and some knowledge of the Universe's constituents, we can trace the evolution of the Universe backwards in time to an era when the density of matter and radiation was significantly higher and a plasma of photons, electrons and nuclei existed in thermal equilibrium. At a temperature of approximately 3,000 K (when the Universe was about 400,000 years old), atomic hydrogen formed and the Universe became transparent. The CMB that we observe has (mostly) streamed freely to us from that moment, cooling as the Universe expanded to a black-body temperature of 2.73 K.

Although the CMB is remarkably uniform from place to place in the sky, small anisotropies in its temperature indicate perturbations in density that are thought to have grown into galaxies and large-scale structure in the contemporary Universe. By assuming that the perturbations originated at very early times, and have roughly equal amplitude at all length scales, we can obtain a good fit to observations of the anisotropies as a function of angular scale. Perturbations of different wavelengths evolve differently as the Universe expands, but they do so in a calculable way that depends on cosmological parameters such as the Hubble constant and the energy density, as well as on the amplitude of the initial fluctuation. Observations of these anisotropies therefore reveal a great deal about the characteristics of our Universe[4].

Perhaps the most significant aspect of the WMAP results is not the discovery of an unexpected feature of the Universe, but the confirmation of the generally accepted cosmological model that has been constructed over the past several years. In this model, the Universe is spatially flat and 14 billion years old, with an energy density consisting of 30% matter and 70% dark energy (a smoothly distributed component that varies slowly, if at all, as the Universe expands). The matter comes mostly in the form of dark matter, which is believed to be made of a type of particle that is as yet undetected; only 4% of the total energy density of the Universe is ordinary matter (such as stars, planets, gas and dust). Although this model is consistent with a wide variety of observations, it is clearly problematic from various points of view. As ordinary matter and dark matter presumably originate through very different mechanisms, why is their abundance so similar (within an order of magnitude)? Worse still, why is the total abundance of matter comparable to that of dark energy if they are changing rapidly with respect to each other as the Universe expands? Furthermore, the leading candidate for dark energy is vacuum energy, or the cosmological constant, for which theoretical estimates disagree with observations by 120 orders of magnitude.

But, as ungainly as this model appears, the WMAP results confirm it spectacularly. Previous CMB observations had reached similar conclusions, but it was necessary to stitch together results from many different experiments to cover a wide range of angular scales, and there always lurked the possibility of unknown systematic biases between different data sets. For the first time, WMAP has provided images of CMB anisotropies that cover the entire sky and yet resolve features as small as 0.3 degrees. One obstacle to the construction of all-sky CMB maps is the need to distinguish the sought-after CMB signal from foreground emission from sources both inside and outside our Galaxy. WMAP (like other experiments) achieves this by producing maps in five different frequency bands, and using differences in frequency dependence to separate foreground emission from signal. Fits to the resulting spectrum of anisotropies provide constraints on cosmological parameters that are in excellent agreement with previous data.

But WMAP has done more than simply confirm other experiments. A crucial finding was the measurement of a polarization signal in the CMB, which was first detected by the DASI telescope last year[5,6]. WMAP has detected polarization at large angular scales, correlated with the temperature fluctuations themselves. This effect, which developed long after the CMB formed, is due to the reionization of the Universe by high-energy radiation from the first generation of stars. The WMAP findings indicate that these first stars formed when the Universe was only 200 million years old, earlier than previously believed.

A pessimist might worry that the field will become a victim of its own success. The provisional cosmological model fits the observations very well, and one could imagine a future of increasingly precise measurements of cosmological parameters without significant improvements in our fundamental understanding. It seems more likely, however, that a future generation of new experimental approaches (searches for gravitational waves, direct detection of dark matter, measurements of the dark-energy equation of state) will yield their own surprises. Many of the deepest cosmological mysteries remain — the origin of the matter–antimatter asymmetry, the nature of dark matter and dark energy, and the smoothness of initial conditions in the Universe (perhaps a result of inflation). It's a good bet that the fun is only beginning. ■

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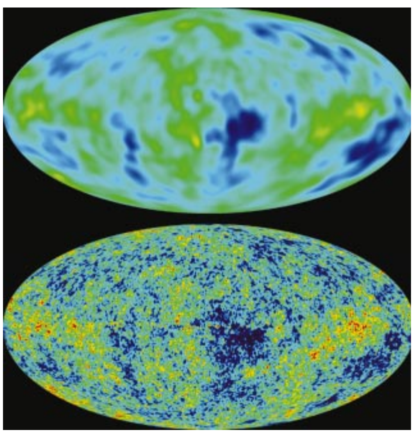
1. Smoot, G. *et al. Astrophys. J.* **396,** L1–L4 (1992).
2. Bennett, C. L. *et al.* Preprint astro-ph/0302207 at <http://arXiv.org> (2003).
3. http://lambda.gsfc.nasa.gov/product/map/map_bibliography.html
4. Hu, W. & Dodelson, S. *Annu. Rev. Astron. Astrophys.* **40,** 171–216 (2002).
5. Leitch, E. M. *et al. Nature* **420,** 763–771 (2002).
6. Kovac, J. M. *et al. Nature* **420,** 772–787 (2002).



NASA/WMAP SCIENCE TEAM

Figure 1 **Temperature fluctuations in the cosmic microwave background. In 1992, the Cosmic Background Explorer[1] (COBE) was the first instrument to detect the tiny variations in the temperature of this radiation across the sky (upper image). The latest data from the Wilkinson Microwave Anisotropy Probe[2,3] resolve the picture in much finer detail (lower image).**

Immunology

Fast and feel good?

Vijay K. Kuchroo and Lindsay B. Nicholson

Claims that fasting eases symptoms of autoimmune disease have been met with scepticism. But the idea receives some support from the finding that leptin, a hormone that controls body weight, also regulates autoimmunity.

Malnourished people present a tempting target for pathogens. Measles, for example, is renowned for being a more serious disease in populations that are starving or close to starving. Yet many people with the autoimmune diseases rheumatoid arthritis or multiple sclerosis, whose immune systems attack their joints or brain, claim that the symptoms of their disease can be reduced by fasting or a change in diet[1]. The idea that food can support a robust immune system and help fight infection, and that starvation can lead to a dampened immune response and alleviate symptoms of autoimmune disease, has mostly been taken as folklore, with little or no scientific basis. But in a paper in the *Journal of Clinical Investigation*, Sanna and colleagues[2] have shown an intimate relationship between autoimmune disease, starvation and leptin — a key regulator of body weight — in mice.

Leptin is a hormone that was shown in 1994 to be mutated in a certain type of obese mouse[3]. It is also produced in humans. Leptin is secreted by adipocytes (fat cells) as well as by other tissues, and the initial studies of its function concentrated on its role in regulating food intake and body weight. Recently, leptin has been implicated more generally in insulin metabolism, nutrient use, reproductive function and the response to stress[4].

Leptin also regulates inflammatory and immune responses and directly affects the immune system, especially T cells[5]. The addition of this hormone to T cells in culture can alter both their growth rate and the pattern of cytokines — soluble proteins that mediate immune function — that they secrete. For instance, leptin has been shown to enhance the activity of T cells that produce pro-inflammatory cytokines; these same T cells orchestrate many organ-specific autoimmune diseases.

Sanna *et al.*[2] have now studied the role of leptin during the course of the mouse autoimmune disease experimental autoimmune encephalomyelitis (EAE), which serves as a model of human multiple sclerosis. The authors used several methods to look at leptin's effects. They found that increases in leptin levels in the circulation of mice were correlated with the period before and at the start of clinical disease. They also used mice in which the gene for leptin is non-functional to confirm previous reports that these mice do not develop EAE. Furthermore, T cells that can induce EAE after being transferred into normal mice did not do so after being transferred into leptin-deficient mice. Sanna *et al.* also found that starvation — which reduces leptin levels — inhibited the development of EAE.

This brings us back to the clinical observations that suggested that starvation can regulate symptoms of autoimmune disease. Many controlled trials in humans have shown that fasting and dietary change can ameliorate the symptoms of rheumatoid arthritis, but the explanation put forth — that this is due to a reduction in the levels of anti-food (allergic) antibodies — is difficult to substantiate[6,7]. In view of Sanna and