

behaves—information needed to serve as a reference point for diagnosing damaged hearts. Over the next 5 years, he will be collecting such data from 100 human volunteers of all ages.

The tagging technique is already proving itself in clinical research. Cardiologist Shapiro, for instance, has recently demonstrated that the left ventricle—the main pumping cavity of the heart—twists as it contracts. Before the advent of heart tagging, no one had seen this twisting explicitly in the human heart, although it had been predicted on theoretical grounds. Now Shapiro is trying to understand the function of this twisting and subsequent untwisting and whether it is connected with certain forms of heart disease.

“We think the untwisting provides suction that helps the heart fill [with blood] very fast,” he says. “This is very important because the filling of the heart is known to be the limiting step in heart function in many cases, and many diseases interfere with filling.” Shapiro is now using Zerhouni’s magnetic resonance tagging method to study this untwisting motion in human subjects, both normal and those whose hearts don’t fill well, in order to determine if it is a faulty untwisting motion that causes the poor filling function.

In a second study, Shapiro is studying the effects of angioplasty—the medical technique in which a balloon is placed in a clogged coronary artery and then blown up to open the blood vessel—on the function of the part of a heart damaged by a heart attack. An earlier clinical study by other doctors could detect no effect of such angioplasties on damaged heart tissue, a surprising finding that called into question the way angioplasties are being used. With Zerhouni’s tagging technique, Shapiro says he can perform a much more sensitive measure of heart function, and he hopes to see whether the earlier studies missed something.

Even though Shapiro and the other team members are enthusiastic about what they are learning, taking part in such a collaboration does have costs, they concede. “The obvious pitfall,” Douglas notes, “is that you have to wait for a time when several of you can meet [before making decisions on how to proceed]. You have to put in some ‘overhead’ and spend time talking to others.”

Fortunately, the Johns Hopkins team has managed to avoid one common plight of collaborative efforts, Douglas adds. “As an engineer, I’ve been warned about working with M.D.’s” because of their “big egos,” he says. But in this case, those egos never materialized. “No one’s acting like a prima donna.”

■ ROBERT POOL

Cosmologists Begin to Fill in the Blanks

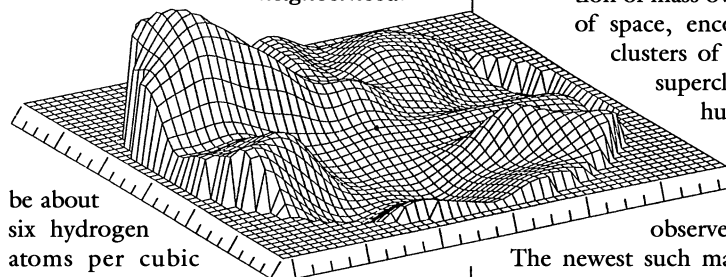
They are mapping out more Dark Matter than ever before—but is there enough to reach “critical” density?

Brighton, England—COSMOLOGY, WHICH has spent generations being a playground for theoretical abstractions and little else, is fast becoming an observational science. Witness an international conference* held here last month, where several independent groups reported intriguing, if preliminary, evidence that apparently confirms a long-standing conjecture: that the universe is poised in a state of “critical density,” balanced precisely between an endless expansion and an ultimate recollapse into a “Big Crunch.”

“It’s one of the revolutions in the subject,” said University of Sussex astronomer Bernard Jones in his summary talk at the symposium. “Certainly it is the thing that has impressed me the most at this conference.”

Jones had good reason to be excited. Many cosmologists believe that the average density of the universe ought to be precisely equal to the critical density, which has been estimated to

Mountainous mass. A new plot of cosmic mass density shows the Great Attractor looming over everything in the neighborhood.



be about six hydrogen atoms per cubic meter for the present

epoch of the universe. If the density had started out even slightly less than critical at the Big Bang, they argue, then the superheated cosmic plasma would have expanded so fast that neither stars nor galaxies would have had a chance to form. Conversely, if the average density had started out even slightly higher than critical, then the universe would have expanded and recollapsed in less than a microsecond—more of a Big Burp than a Big Bang. Since the universe is billions of years old, and since there are stars

and galaxies all around us, the density must have somehow been just right.

However, anyone who accepts this argument also has to live with a serious embarrassment: Astronomers can’t find anywhere near that much matter in the universe. The mass in all the visible stars and galaxies, averaged over the immense distances between them, adds up to only about 1% of the critical density. To make up the difference, researchers are forced to assume the remaining 99% of the mass consists of invisible “Dark Matter”—presumably a haze of some kind of massive but weakly interacting elementary particles left over from the Big Bang.

That assumption is not quite as ad hoc as it sounds. Astronomers have found ample evidence for Dark Matter by observing its gravitational influence on the internal motions of galaxies and clusters of galaxies. Yet even in the largest clusters, the Dark Matter never seems to account for more than about

10% of the critical density. That missing 90% has thus become a major cosmological conundrum. If it exists at all, then it can only be found by mapping out the distribution of mass over truly vast regions of space, encompassing not just clusters of galaxies, but whole superclusters on a scale of hundreds of millions of light-years.

And that is precisely what the observers are starting to do.

The newest such maps come from two complementary survey techniques. One technique, discussed at Brighton by Avishai Dekel of the Hebrew University in Israel, is based on measurements of galaxies’ “peculiar” velocities: their motions relative to the overall expansion of the universe. Since these motions are presumably caused by gravitational forces, explained Dekel, they can in principle reveal the existence of lumps and gaps in the cosmic mass distribution.

That possibility was dramatically confirmed in 1986, when a group of seven astronomers published convincing evidence that our galaxy and most of the other galaxies for hundreds of millions of light-years in every direction are streaming toward a cer-

* Texas/ESO-CERN Symposium on Relativistic Astrophysics, Cosmology, and Fundamental Physics, 16-21 December 1990, Brighton, United Kingdom.

tain point in the southern sky at some 600 kilometers per second. The cause of these peculiar motions—presumably a huge concentration of Dark Matter—was quickly dubbed the Great Attractor.

Now, said Dekel, he and his colleagues Edmund Bertschinger of the Massachusetts Institute of Technology and Sandra Faber of the Lick Observatory in California have re-analyzed that same velocity data with a new mathematical algorithm that allows them to map the mass concentrations in our cosmic neighborhood with unprecedented detail. Our galaxy is located at the center of that map (see figure), near the edge of a wide valley of very low density, while off to one side, about 200 million light-years away, rises the mountainous Great Attractor. The dense Virgo cluster, which was long thought to be the dominant concentration of mass in our vicinity, turns out to be nothing more

than a shoulder on the mountain.

The second, complementary mapping technique was discussed in Brighton by members of two independent observing teams. Both have taken carefully selected samples of the galaxies from the most complete survey of the local universe available—the catalog of galaxies identified in 1983 by NASA's Infrared Astronomy Satellite (IRAS)—and then systematically measured the selected galaxies' redshifts due to cosmic expansion. Since each redshift is approximately proportional to the galaxy's distance, the result is a map of the galaxy distributions in three dimensions.

These galaxies represent only a tiny fraction of the mass contained in the invisible Dark Matter, of course. But presumably their distribution is roughly the same as the Dark Matter's. And indeed, the redshift surveys yield density maps that are qualitatively

similar to the one discussed by Dekel. When all these new maps are taken together, moreover, they yield a new estimate of the average mass density—and one that, for the first time, begins to approach the theoretical expectations. Within the uncertainties, the new average density appears to be at least half the critical density—already a fivefold increase over the previous figures—and may very well be equal to the critical density.

As intriguing as the results are, of course, the observers are quick to say that the uncertainties are still very large. But then, as University of California, Berkeley, astronomer Marc Davis pointed out, both mapping approaches are only in their infancy, although they are rapidly improving. "This is so complicated," he says, "we'll be playing this game for years. But we've started to demonstrate the power of the method."

■ M. MITCHELL WALDROP

On the Road to Mandelate...Racemase

The three-dimensional structure of the enzyme mandelate racemase provides a surprising clue to enzyme evolution

EVERY ORGANISM DEPENDS ON ITS ENZYMES to perform the everyday functions of life, obtaining energy from food, for example. A simple bacterial cell has a couple thousand of these essential protein catalysts; a human being has tens of thousands. How did all these enzymes, each with its own specific set of chemical capabilities, evolve?

Now a serendipitous—and surprising—discovery by a team of enzymologists and structural chemists may help answer that question. The researchers have found that two distinct enzymes, known to catalyze different chemical reactions, have essentially the same three-dimensional shape. That kind of structural similarity has never been seen before. And it is more than just a biochemical oddity.

When an enzyme catalyzes a reaction, it must first bind the reacting chemicals, called "substrates" in enzymology jargon. The binding is exquisitely specific, and one theory of enzyme evolution focuses on that specificity, postulating that an enzyme evolves by undergoing mutations that enable it to perform a new reaction on the same old substrates. But the current discovery suggests, says team member Gregory Petsko, an x-ray crystallographer at Rosenstiel Center at Brandeis University, that

in at least some cases the reverse may be true; that evolution may work by selecting a pre-existing enzyme for its chemical capabilities and then altering its specificity so that it can bring about its usual chemical reaction on a new substrate. "It looks to us like it's the chemistry that counts," says Petsko.

That idea is "right on the money," agrees chemist Bruce Erickson of the University of North Carolina at Chapel Hill, who likes the work so much that he recently arranged for Petsko to give a seminar at UNC. "It's more difficult to change chemistry than specificity."

Not only are the findings providing new insights into evolution, but they may also have practical applications for enzyme design. Researchers are very interested these days in using the techniques of genetic engineering to mutate enzyme proteins to improve their efficiency or otherwise alter the reactions they catalyze. But the mutations do not always have predictable effects on enzyme activity, notes another team member, George Kenyon of the University of California, San Francisco. He suggests that a better understanding of natural enzyme evolution might help researchers design their mutations more rationally.

Kenyon, Petsko, and their colleagues did

not set out to trace enzyme evolution, however. Kenyon is a biochemist who for the past 20 years has been studying an enzymatic pathway that enables some strains of the common soil bacterium *Pseudomonas putida* to get their nutrition from a chemical called mandelate, which is produced by decomposing plant matter. The pathway consists of five enzymes that work together to convert mandelate to benzoate. The benzoate is then broken down by another set of enzymes (in the beta-ketoadipate pathway) to compounds that can be used to generate adenosine triphosphate, the cell's major source of chemical energy.

Kenyon knew from earlier work that the five enzymes of the mandelate pathway are physically clustered within the bacterium. He was interested, he recalls, in crystallizing all of the enzymes in the pathway and determining their three-dimensional structures. He wanted to see whether the surfaces of the proteins have affinities for one another that could explain the clustering. So Kenyon joined forces with enzymologists John Gerlt and John Kozarich, both of the University of Maryland, and crystallographer Petsko.

Gerlt was intrigued by the project because of the opportunity to learn more about mandelate racemase, the first enzyme in the pathway. This enzyme rearranges the order of the atoms attached to one of the carbon atoms in mandelate by removing a hydrogen ion from one side and attaching it to the opposite side. "It looked like a very simple model for understanding how enzymes make and break carbon-hydrogen bonds," Gerlt says. "This is a fundamental, but poorly understood, part of enzyme-catalyzed reactions."

Gerlt agreed to clone and sequence the