ing chimeras, transported in liposomes, to introduce a mutation into the animals' gene for a factor needed for normal blood clotting. In preliminary experiments, the group also did the reverse; they used DNA/RNA chimeras to reverse the hemophilia-like state in dog liver cells with a clotting-factor mutation.

And at the gene therapy meeting, Li-Wen Lai, a geneticist and molecular biologist at the University of Arizona Health Sciences Center in Tucson, reported that she and her husband, nephrologist Yeong-Hau H. Lien, have used DNA/RNA chimeras to correct a metabolic disease in mice. The mutation disables a kidney enzyme called carbonic anhydrase II and results in dangerously high acid levels in the bloodstream. Lai and her colleagues designed a chimera to reverse it, bound the molecules in liposomes, and then injected them into the ureters of the mice. The gene was corrected in 1% to 15% of the animals' kidney cells. Lai says she and Lien are now working with the animals to see if their blood acidity decreases and if the change lasts over time.

But even though evidence is building that chimeraplasty can work, the success rate can vary from cell type to cell type, and even from experiment to experiment. For example, Yoon repeated her melanocyte experiment 30 times and found cells turned black anywhere from 0.01% to 15% of the time. Such variations convince Capecchi that "it's a little early to talk about human trials," although he now says that chimeraplasty "certainly has potential."

Researchers also worry about safety, although that's a concern with standard gene therapy, too. Perhaps the chimeras will start "fixing" other parts of the genome that aren't broken, in essence creating mutations like those that lead to cancer. "Just how much less frequent is a nonspecific change than a specific change?" Blaese questions. "Those are the issues we are trying to address."

Even so, the first human trial of chimeraplasty may be on the horizon. At the gene-therapy meeting, Steer's group reported results from their recent work on Gunn rats, which carry a single-base deletion in the gene for a liver enzyme that detoxifies the yellow pigment bilirubin. The rats accurately model a rare human hereditary condition called Crigler-Najjar disease, in which patients can't metabolize bilirubin, which builds up to toxic levels. The patients end up severely jaundiced and have to spend 12 to 16 hours a day under blue light, which promotes bilirubin breakdown. If untreated, the disease is lethal, and the only cure is a liver transplant.

Steer and his colleagues have now found that an appropriate chimera corrects the gene defect in a substantial proportion of the Gunn rats' liver cells. Up to 40% of the cells revert to normal, Steer says, as indicated by tests for the genomic DNA, messenger RNA, and protein sequences. Even more encouraging, the bile of the treated rats contains telltale liver metabolites that signify normal enzyme activity.

Light therapy. Crigler-Najjar patients need to endure hours in blue light to break down their toxic bilirubin levels.

CREDIT: SAL DIMARCO JR./NYT PICTURES

Steer attributes the success of the therapy to the system he used to shuttle the chimeras into the rats' liver cells. The molecules are encapsulated in liposomes carrying surface molecules that specifically target them to receptors on the liver cells. "I've had people get up at meetings and say, 'I don't believe your data,'" Steer recalls. "But as more labs are becoming successful, people are beginning to accept this."

Indeed, Blaese is gearing up with Steer to try the technique in three patients with Crigler-Najjar syndrome. The two groups are now doing safety studies in order to obtain Food and Drug Administration approval to go on into humans. If those studies show that the chimeras aren't targeting other DNA sequences and are safe in humans, then researchers could move on to target a very long list of human genetic diseases of the liver. "I wouldn't have to go back to drug discovery," Blaese notes. "I could just go to the human genome project, read off what the gene is, and change the spelling of our molecule."

–TRISHA GURA

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ASTRONOMY

Holes in the Sky Provide Cosmic Measuring Rod

The shadows cast by distant galaxy clusters against the microwave glow of the sky are offering a new gauge of the universe's expansion rate and makeup

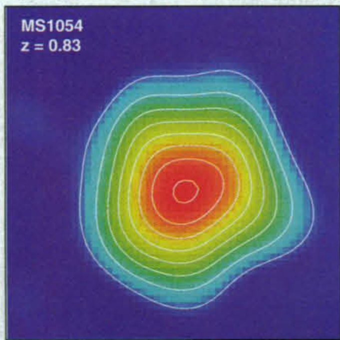
CHICAGO—Most astronomers measuring the universe on the largest scales chase bright lights. They look for beacons called standard candles—flickering stars, supernovae, or certain galaxies—and turn their observed brightnesses into cosmic distances, clues to the universe's expansion rate, its age, and whether it is permeated by a strange energy called the cosmological constant. But one group of observers is chasing shadows instead: the dark silhouettes cast by distant clusters of galaxies against what John Carlstrom, a radio astronomer at the University of Chicago, calls "an amazing backlight": the glow known as the cosmic microwave background radiation (CMBR). The size of the shadows in the CMBR provides a cosmic measuring stick independent of any now in use.

Cosmic measuring sticks based on standard candles generally rely on a "distance ladder" in which short-range beacons are used to calibrate others that can reach deeper into the cosmos. But the shadows created by the so-called Sunyaev-Zeldovich (SZ) effect can be seen out almost to the edge of the universe, and they can be converted into distances without any intermediate steps. "This method goes straight out to very large distances in one go," says Mike Jones, an astronomer at Cambridge University in the United Kingdom.

Conceived decades ago by two Russian scientists, the technique is only now showing its potential, thanks to more sensitive instruments for measuring the microwave background and satellite x-ray images of clusters. At a recent American Astronomical Society (AAS) meeting here, Erik Reese of the University of Chicago and Brian Mason of the University of Pennsylvania each presented new results on distances to a half-dozen clusters, based on work by multi-institutional teams. Combined with separate observations of how fast those clusters are rushing away, the distances give the expansion rate, called the Hubble constant, which can be combined with other cosmic measurements to give an age. Uncertainties in the technique are still large, but results so far provide a comfortable fit with a recently announced value for the Hubble constant. And, as more and more SZ observations roll in, they could help determine not only the expansion rate but also how it has changed over billions of years of cosmic history.

That, in turn, could provide a crucial check on observations of distant supernovae suggesting that a cosmological constant is causing the expansion to accelerate (*Science*, 18 December 1998, p. 2156).

Everything in the visible universe lies in front of the CMBR, because it dates from when the cosmos was a mere 100,000 to 300,000 years old. The radiation started out with energies corresponding to the temperatures of the hot young universe but cooled as it expanded. Arriving at Earth 14 billion years or so later, the CMBR photons carry energies equivalent to just 2.7 kelvin, which implies radio and microwave wavelengths.

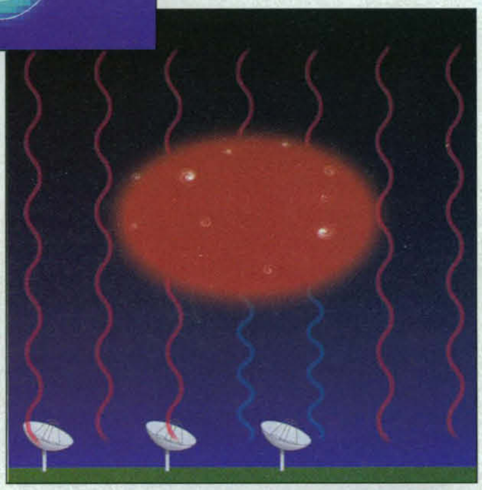


In the early 1970s, astronomer Rashid Sunyaev and physicist Yakov Zeldovich realized that galaxy clusters, collections of thousands of galaxies sprawling across millions of light-years, would make dents in the CMBR—cool spots measuring arc minutes across. (An arc minute is a thirtieth of the width of the full moon.) "These are one of the few things that produce holes in the sky" rather than bright points of emission, says Reese.

The holes, in which the CMBR's temperature drops by thousandths of a kelvin, are caused not by the galaxies themselves but by gas that collects in the gravitational "well" of the clusters. Heated to temperatures of 100 million kelvin as it plummets into the clusters, the gas—several times the mass of the galaxies—is an ionized soup of nuclei and free electrons, which interact with passing microwaves. "About 1% of the time, a photon will scatter off one of these free electrons," says Carlstrom, and will generally be knocked up to a higher energy. That means the photon will be undetected by ground-based instruments, producing the SZ deficit. Just how many photons are scattered—and how deep a hole gets punched in the CMBR—depends on the density of the gas, its temperature, and the diameter of the gas blob along the line of sight to Earth.

Astronomers quickly realized that an absolute measure of cosmic distances was hidden in those shadows. The first step in determining it is to call upon observations of the same clusters by x-ray satellites such as the German Roentgen Satellite and the Japanese ASCA satellite to measure the spectrum of the x-rays, which indicates the gas's temperature, and the x-ray brightness. Combined with the depth of the SZ hole, that gives astronomers enough information to determine both the gas's density and its diameter in light-years. By simple geometry, that length can be combined with the angle the gas blob subtends on the sky to give the cluster's distance. Finally, straightforward optical measurements of how fast the cluster is hurtling away—called the redshift—are thrown into the mix, and the Hubble constant pops out.

It's not quite that simple in practice, because space is curved on very large scales and the gas blob doesn't have a sharp edge. What's more, not every blob will be spherical, with the same dimensions along and across the line of sight. So astronomers have to combine the values from a number of clusters—assumed to be spherical on average—to get a true value. Various other subtleties, such as "cooling flows" within the gases that can throw off the temperature measurements, led to some Hubble constants that were unrealistically small when astronomers began exploiting the SZ effect in the 1980s and early 1990s, says Steven Myers, a radio astronomer at the University of Pennsylvania.



Chasing shadows. Radio telescopes like BIMA (*bottom*) see a hole in the microwave background (*top*) where a galaxy cluster scatters photons.

The latest measurements take that "cautionary tale" into account, says Myers. At the AAS meeting, he, Mason, and Anthony Readhead of the California Institute of Technology (Caltech) in Pasadena presented results for five relatively nearby clusters observed with a 5.5-meter dish at the Owens Valley Radio Observatory (OVRO) in California. "These clusters are all well-studied in the x-ray," says Myers. The result was a Hubble constant of about 71 kilometers per second per megaparsec (3.26 million light-years). Although the uncertainty is about 20%, the central value meshes nicely with the figure of 70 recently announced by the so-called Hubble Key Project, which combined measurements of several different standard candles (*Science*, 28 May, p. 1438).

Carlstrom, Reese, Chicago's Joseph Mohr, Marshall Joy of the NASA Marshall Space Flight Center in Huntsville, Alabama, and several other collaborators looked at much more distant clusters, some of them nearly halfway to the edge of the visible universe. To discern the much smaller shadows cast by such remote clusters, they used arrays of radio dishes at OVRO and the Berkeley-Illinois-Maryland Association (BIMA) facility at Hat Creek, California, rather than single dishes. Each array is an "interferometer," in which signals from the various dishes are combined for a sharper picture of the radio sky. Although BIMA was designed for millimeter waves, the team adapted it to measure the centimeter waves of the CMBR by jamming the dishes together and outfitting them with special receivers (see illustration).

Using the millimeter array has another advantage, adds Carlstrom: The team can get "lots and lots of observing time in the summer," when the atmosphere becomes too humid for observations of millimeter waves, which are absorbed by water vapor. Carlstrom's team has now measured the SZ effect in 27 very distant clusters, Reese reported at the meeting, and has derived Hubble constants for six of them. Their central values range from 60 to 67, depending on what the team assumes about the curvature of space, with about 20% to 25% uncertainty.

So far, such measurements aren't precise enough to strongly confirm or challenge the results of other techniques. But Barry Madore of Caltech, a member of the Key Project, welcomes the prospect of having an independent measure of the Hubble constant. "I think it's wonderful work," he says. "What they're doing now is the right thing to do, increasing the sample size … so that they get a better representation of what their objects really are doing." Half a dozen other groups around the world are attempting the same thing, as SZ pioneer Mark Birkinshaw of the University of Bristol in the United Kingdom described recently in *Physics Reports*. "The potential of this method for measuring the Hubble constant is only starting to be realized," he wrote.

CREDITS: ERIK REESE *ET AL.*

The SZ technique could also reveal other vital statistics of the cosmos. Besides galaxies and glowing gas, clusters must contain even larger amounts of invisible "dark matter" to generate the gravity that holds the gas in place. "These clusters are kind of a garbage can which should contain the universal mix," says Carlstrom. If so, comparing a cluster's SZ shadow, which reveals how much ordinary matter it contains, with its total mass should reveal the cosmic ratio of ordinary to dark matter. Because cosmologists can use other measurements to calculate how much ordinary matter must have been forged in the big bang, they can parlay that ratio into the grand total of all matter in the cosmos.

But perhaps the field's greatest ambition is to use the SZ effect to measure not just the expansion rate, but how it has changed over billions of years. Observations based on exploding stars called type Ia supernovae have suggested that the expansion is actually speeding up, an indication that the common gravitational attraction of all matter in the universe is being overwhelmed by a mysterious repulsion. Distant clusters like those found by the Chicago group could eventually check the supernova results. Astronomers need better x-ray pictures of those far-off clusters, however, to extract precise Hubble constants from them.

And those pictures should be on the way. The U.S. Chandra satellite and the European XMM satellite, to fly within the next year, should ride to the rescue with much more sensitive x-ray detectors and spectrometers. "It'll be a revolution when the new x-ray satellites are really able to do those SZ images justice," says Myers. –JAMES GLANZ

CONSERVATION BIOLOGY

Lynx and Biologists Try to Recover After Disastrous Start

An effort to bring lynx back to Colorado is mired in controversy after five animals starved to death earlier this year

The distress call grew louder as Tanya Shenk snowshoed across drifts high in the Rocky Mountains last February. Shenk, a wildlife biologist for the state of Colorado, was in no hurry: The signal from the radio collar meant the victim was dead, perhaps killed by a predator. But when Shenk finally found the lynx curled under a spruce in Rio Grande National Forest, she realized to her horror that the emaciated beast, its telltale tufts of black hair shooting from the tips of its ears, had starved to death.

Similar scenes have played out four more times, including once last month, unleashing a torrent of criticism over a $1.4 million program to bring the dwindling Canada lynx back to Colorado. News of the starved animals has outraged critics, some of whom maintain the effort was doomed from the start: Even before the first lynx were flown in from Canada late last year, analyses had suggested that the animal's main winter prey, the snowshoe hare, was in perilously short supply. And some wildlife biologists worry that the furor over the Colorado program will provide ammunition to critics of other wildlife reintroduction programs around the country.

Scientists at the Colorado Division of Wildlife (CDOW) regret the starvation deaths but defend the reintroduction, which they claim may be their best shot at bringing the lynx back to Colorado. CDOW biologists cite a biological imperative to their timetable: Lynx in Canada are booming, so the population—this year, at least—could stand to lose the few dozen individuals shipped stateside. Some observers applaud the effort. Bringing back species like the lynx "is going to take a level of risk that none of us are really comfortable with," says the U.S. Forest Service's Bill Ruediger, endangered species program leader for the Northern Rockies. "I give them credit for doing it."

Other experts disagree, contending that individual animals should not suffer to such a degree for the sake of a species. Death and the struggle for survival in unfamiliar terrain go hand in hand: Managers expect up to half the animals in any given carnivore reintroduction program to die, felled by other predators or hit by cars after ranging far from release points. "We certainly expect them to have a high mortality rate," says Richard Reading, co-chair of Colorado's Lynx and Wolverine Advisory Team (LWAT) and director of conservation biology at the Denver Zoological Foundation. "But what you don't expect is starvation." "Without the right habitat and enough food source," adds Scott Mills, a lynx researcher at the University of Montana, Missoula, "reintroduction just becomes a death sentence."

All systems go? This lynx is one of a few dozen from Canada struggling for survival in Colorado.

The lynx as a species managed to stave off one death sentence a quarter-century ago, when fur trappers hunted the animal nearly to extinction in the lower 48 states. A furtive creature about twice the size of a housecat, the lynx once ranged from northern Canada and Alaska to southern Colorado, but now only about 500 remain south of the Canadian border. Only once before have wildlife biologists attempted to bolster lynx numbers in North America, when 83 cats from the Yukon Territory were released in New York's Adirondack mountains in the late 1980s. The program failed miserably: Most lynx were killed by cars, and few if any survivors or their offspring are believed to be around today, says carnivore biologist John Weaver of the Wildlife Conservation Society.

Since the last confirmed sighting in Colorado in 1973, CDOW biologists have tried everything from baited traps to cameras mounted deep in the woods to spot any lynx lurking in the Rockies, without success. Deeming the effort futile, CDOW director John Mumma and several staff biologists concluded during a rafting trip in 1997 that the lynx deserved a shot at reestablishing itself in the southernmost fringe of its historic range, says Gene Bryne, the recovery team's lead biologist.

In late 1997, CDOW managers decided they had to act fast if they wished to run their own show. The U.S. Fish and Wildlife Service (FWS) at the time had begun considering a petition to list the lynx as threatened with extinction in the lower 48 states; a ruling is expected later this year. If FWS opts for extending federal protection to the lynx, it would call the shots on how and where to do so. "We had a short window of opportunity," says Bryne. "This was the last chance for the state of Colorado to reintroduce lynx."

A biological clock was also ticking. Lynx and snowshoe hare populations go through 10-year cycles of boom and bust. When hares are depleted, lynx begin starving—until hares rebound and the lynx follow suit. Lynx in Canada were cresting, so

CREDIT: CDOW