mostly in Uzbekistan, likely would continue to shrivel. Kazakh officials hope to preserve the northern brackish lake by diking it off from the main water body to the south and allowing the Syr Darya to gradually refill it. They hope this will allow native fish to return to the north lake and revive its fisheries. There's a "real possibility" the Kazakhs will succeed, says Micklin.

A similar project, now gearing up, seeks to save an important wetland in the 28,000-square-kilometer Amu Darya delta, just south of the Aral Sea in Uzbekistan. Half of the delta's wetlands have already dried up. The project focuses on Lake Sudoche, a roughly 500-square-kilometer lake southwest of Muynak that, by international convention, has been designated a critical habitat for waterfowl. Together with the surrounding marshlands, Sudoche is home to several endangered species, including the Bukhara deer, the Dalmatian pelican, the Siberian crane, and the bastard sturgeon.

The $3.9 million project will include the construction of earthen dams between the dry Aral Sea bed and Sudoche, which is becoming saltier and more oxygen-poor every year. Once completed, the dams should corral as much as 600 million cubic meters of rainwater during the fall and winter. The fresh water is expected to flush the wetlands and raise oxygen levels, improving conditions for wildlife. If the project succeeds in saving Lake Sudoche, GEF managers hope it will stimulate the local economy through increased fishing and hunting.

Project managers acknowledge, however, that the first big flush could have unintended ecological consequences, such as water temperature changes, which could in turn harm native wildlife. "The level of risk is unknown," states a GEF report released last year. It points out, however, that "if nothing is done, Sudoche would become even more saline, the oxygen content of the waters would continue to drop, and the wetlands would lose much of [their] biodiversity and fish life." Adds Micklin, "It's hard to see how the project would make things worse."

The human dimension. As engineers and agronomists try to improve water management and stem the environmental destruction, organizations like DWB are focusing on human health. In one project, DWB staff members are collaborating with Muynak doctors to improve drug therapies at a local tuberculosis (TB) clinic. "We're building a brand-new dispensary," says DWB doctor Darin Portnoy. "They just didn't have any money to do something like this." Karakalpak officials welcome the foreign intervention. "We might not be able to save the Aral Sea," says health minister Babanazarov. "But we may be able to save the people living around it."

Karakalpakstan has dire health problems besides TB—rampant anemia and high infant mortality rates, for example—that also beg for resources. DWB epidemiologist Joost van der Meer is trying to ascertain the causes. "I'd bet on the toxic dust storms," he says. In Nukus, the frequency of major dust storms has increased from about one storm every 5 years in the 1950s to about five a year, says Kamalov. Toxic dust storms, van der Meer says, "are the one thing you can't find anywhere else." But few data exist on the dust's constituents. "I'm not sure of any reliable chemical analysis," says Ross Upshur of McMaster University in Ontario, who has analyzed the scant Aral health data. "This is one of the key areas for initial research."

Lifeline. The sea may be a lost cause, but saving the region's people, including this TB patient in Muynak, is not.

CREDIT: MUTSUMI STONE

Van der Meer acknowledges that it will take a lot of outside help to get to the bottom of the region's health woes. "We have no capacity to do this ourselves," in either labor or lab facilities, he says. Local experts are also appealing for foreign partners. Thus van der Meer hopes to become a matchmaker of sorts, hooking up Western and Uzbek scientists for projects on everything from tracking disease rates to probing the dust's toxicity. What the Karakalpak researchers lack in data or equipment, however, they compensate for in access to a unique research site. As Kabulov points out, "There's no experience for science around the world in which a whole sea has disappeared." **–RICHARD STONE**

PHYSIOLOGY

Heart Failure Simulated

New computer models suggest why failing hearts show diminished contractility and an increased susceptibility to fatal rhythm disturbances

Heart attacks may be the most feared heart ailment. But the most common is a slower but potentially equally deadly disorder, a steady weakening of the heart muscle known as chronic heart failure. Every year in the United States alone, more than 400,000 people develop the condition, which often causes fatal disturbances in heart rhythms. New results, some from computer simulations of the heart, are now helping clarify what causes heart failure and makes it so dangerous.

Heart failure occurs when the cardiac muscle cells contract less effectively, with individual beats becoming longer and less forceful. It often sets in after a heart attack damages the muscle, but exactly what causes the altered contractility has been hard to pin down. The new work, described in the 19 March issue of *Circulation Research* by a team led by Eduardo Marbán, Raimond Winslow, and Brian O'Rourke of The Johns Hopkins University School of Medicine, suggests that it's largely due to the altered production of two proteins that help control the concentrations of calcium ions in cells.

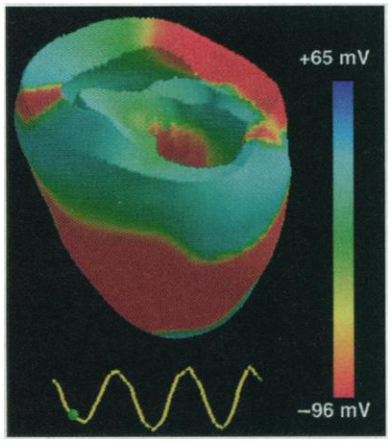
The simulations, which mimic the interplay of many different proteins controlling heart muscle contraction, testify to the power of studying cells as systems (see the special section on Complex Systems beginning on p. 79). They may also have important medical implications, because they show how the biochemical changes might trigger the fatal arrhythmias. "If that turns out to be true, that's important, because half of the people with heart failure die from arrhythmias," says Steven Houser, a cardiac cell specialist at Temple University School of Medicine in Philadelphia. It suggests, he says, that drugs capable of restoring the proper balance of calcium in cardiac cells could be used to treat heart failure and prevent the arrhythmias.

Researchers have known for some time that in heart failure, cardiac muscle cells produce abnormal amounts of key proteins, although they don't know why. For example, two of the proteins that form the membrane channels that funnel potassium ions in and out of cells drop by as much as 70%. Because potassium ions flowing out of muscle cells help reverse the electrical change, or action potential, that triggers muscle contraction, this discovery led to widespread speculation that reduced potassium outflow is what leads to the prolonged action potential and weaker heart muscle contraction in heart failure.

But the malfunctioning heart cells also contain higher than normal amounts of a shuttle protein for calcium, another ion that is important for muscle contractility, and less of a protein that helps store calcium within cardiac cells. "So many things are different in [these cells] that it's impossible to sort out the relative importance of one

thing versus another," says Marbán.

So Winslow and colleagues constructed a computer model of a cardiac cell, incorporating everything known about the various proteins involved in ion movements and their interactions. Then, as they altered the concentrations of the various components to match what's seen in heart failure, they tracked the effect on the cardiac cell's action potential and subsequent muscle contraction. Contrary to expectations, they found that decreased potassium currents "had a minor effect on the action potential duration," says Winslow. But changes in the calcium-handling proteins dramatically lengthened the action potentials and the contractions.



Heart trouble. Misfiring of cardiac cells in one region of a computer model of a failing heart disrupts electrical activity throughout.

That makes sense in light of calcium's role in muscle contraction, says O'Rourke. Its release from an internal storage site known as the sarcoplasmic reticulum in response to an action potential first sets off a contraction, then helps shut off the action potential, resetting the system. What apparently happens in heart failure is that the decline of the calcium storage protein reduces the amount of calcium available for muscle contraction and for the negative feedback on the action potential. As a result, the cell's contraction is weaker and the action potential is prolonged. The cell partly compensates by turning up production of the shuttle protein, which moves calcium into and out of the cell. But this effort fails because less calcium can flow through the cell membrane than into and out of the inner storehouse.

But that's not all the Johns Hopkins group found. Another, as yet unpublished, computer model—this time of the whole heart—showed that elongated action potentials in a small number of cardiac cells could have grave consequences for the heart as a whole. Previous work has shown that elongated action potentials can lead to an altered electrical rhythm of cardiac cells, known as early after depolarization, or EAD, which in turn has been linked to arrhythmias. In their global heart model, the Johns Hopkins team found that EADs in a small region of the failing heart could have a ripple effect, triggering global abnormal electrical activity typical of arrhythmias.

"This is really valuable, high-quality work along the way to coming up with new treatments for heart failure," says Donald Bers, a physiologist and cardiac cell specialist at Loyola University in Chicago. The models, he says, suggest that if researchers can boost the amount of calcium available to cardiac cells, they should see changes in the duration of action potentials. Winslow says they've already begun such studies—in one case by adding a hormone that increases the activity of the storage protein—and that "the preliminary results are looking very promising." –ROBERT F. SERVICE

MEETING AMERICAN PHYSICAL SOCIETY

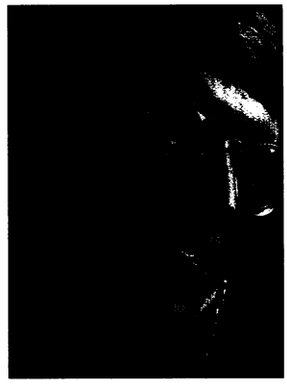
Celebrating a Century of Physics, en Masse

ATLANTA—The American Physical Society celebrated its 100th anniversary in grand style here from 20 to 26 March, producing a meeting whose list of abstracts alone filled two phone book–sized volumes. About 11,400 physicists participated in what was billed as the largest such gathering ever.

Hawking Blesses the Accelerating Universe

Stephen Hawking clearly wished to say a word about the cosmological constant, or lambda, the mysterious energy that seems to be permeating space and counteracting gravity on cosmic distance scales. In an overflowing third-floor room at the Ritz-Carlton Hotel here on 23 March, the celebrated cosmologist painstakingly answered a list of written queries from the press, generally with good humor, sometimes with impatience ("That is a ridiculous question," he responded at one point), and always with a razor-edged wit. But after apparently noticing a short discussion between his assistant, Chris Burgoyne, and the *Science* reporter about whether a question about Hawking's views on lambda could be added to the list, Hawking interjected with his synthesized voice: "The question about the cosmological constant."

It was a question he had answered a year ago, shortly after observations of exploding stars called supernovae began suggesting that lambda was causing cosmic expansion to accelerate (*Science*, 30 January 1998, p. 651, and 27 February 1998, p. 1298). At that point, Hawking had expressed doubts, calling the results preliminary and apparently regarding lambda as unnecessary in light of his own views of cosmic origins. But the staying power of the results seems to have impressed him along with the rest of the cosmology community. "I have now had more time to consider the observations, and they look quite good," he said. "This led me to reconsider my theoretical prejudices. I now think it is very reasonable that there should be a cosmological constant."



Hawking's new public stance comes a few months after similar statements by Alan Guth of the Massachusetts Institute of Technology, who originally devised the theory of inflation, the most influential explanation for how the big bang expansion got started. The simplest versions of inflation predict a universe filled with far more matter than it appears to hold, so Guth had been exploring alternative, low-density versions of inflation. But the supernova results now have Guth favoring a universe fleshed out, or "flattened," by a combination of matter and lambda (whose energy is equivalent to matter). "With these observations, I am comfortable with an inflationary universe that is flat," he told *Science* during a January meeting of the American Astronomical Society in Austin, Texas.

No one yet knows just what might produce a cosmological constant of the size indicated by the supernova results. Some theories, in fact, predict that it should be as much as 10^{123} times larger than that. But such a powerful cosmic repulsion would presumably keep galaxies, stars, and intelligent life from forming. Uncomfortable with the idea that physical parameters like lambda are simply lucky accidents, some cosmologists, including Hawking, have suggested that there have been an infinity of big

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