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Sunday, Dec 14, 2003

News

Posted on Sun, Oct. 12, 2003

Newest imaging methods begin 'golden age' of seeing inside body

BY RACHEL EHRENBERG
The Dallas Morning News

DALLAS - (KRT) - For the latest in surveillance technology, you wouldn't always want to call the CIA. To spy on the body's innards, for example, you might try OCI or SHG. They are among a wave of newcomers joining veterans like MRI and PET in the alphabetic arsenal of imaging technology.

While agents of the old guard have helped scientists gather intelligence about the body's inner workings, new technologies are taking reconnaissance to ever-greater depths. X-rays, once used mainly to picture broken bones, now capture cartilage, collagen and fat. Joystick in hand, researchers can "fly through" a holographic image of a tumor. And with the neural equivalent of a traffic helicopter, scientists are tracking information flowing along the brain's superhighways.

Some of the methods, particularly those exploiting lasers, have stimulated scientists to herald a new era of imaging. "It is probably the beginning of a golden age of microscopy," says physicist David Kleinfeld.

Modern imaging methods date back to 1895, when German physicist Wilhelm Rontgen pointed the rays from a gas discharge tube at his hand and saw his bones projected on a screen. The rays he called "X," for unknown, are still used widely. But today's techniques show a lot more than bones. From nerve cells to fat pads to tiny tumors, scientists are spying on the body from the outside to better understand what goes on within.

Kleinfeld and his colleagues use ultra-fast lasers to precisely slice and image sections of brain tissue, a method that will be an important tool for mapping the brain. Called two-photon laser scanning microscopy, or TPLSM, the technique requires a special laser that produces light pulses lasting a millionth of a billionth of a second.

"These pulses are very energetic," said Kleinfeld. "They aren't around for very long, but when they are there, they do a lot."

The short pulses don't produce damaging heat, but they rip the atoms in the samples of brain tissue apart, removing layers that are thinner than a human hair. When each new layer is uncovered, a lower-intensity laser takes an image of the freshly exposed surface, the scientists reported recently in the journal Neuron.

Previously, getting microscopic images of the brain was a laborious task. For one thing, tissue was hand-sliced, and the slivers of brain had to be kept frozen, making them prone to warping and damage. The new technique destroys tissue as it is imaged, so samples can't be saved for later examination. But TPLSM's impact could be broad, says Kleinfeld, who works at the University of California, San Diego. It allows precise mapping of structures like blood vessels, and by marking proteins with a dye beforehand, scientists can use the laser slicing technique to see where in the brain the molecules do their stuff.

Another new version of laser I-spy allows Cornell University researchers to watch nerve cells as they develop. The technique, called second-harmonic generation microscopy, or SHG, takes advantage of the way stiff, slender structures called microtubules grow within nerve cells. Microtubules are the I-beams and railroad tracks in many types of cells, helping to transport goods and provide scaffolding. Depending on which part of a nerve cell they are supporting, these microtubules grow differently, and that difference can be detected by laser beams.

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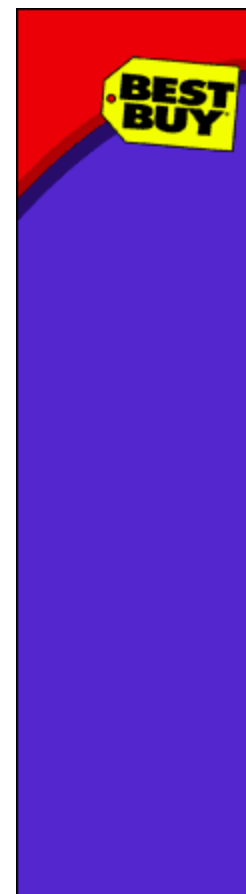


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In addition to shedding light on how the brain is wired, the technique may help scientists understand which cells are sick in the early stages of Alzheimer's disease, or how nerves regrow following spinal cord injuries. The scientists and their colleagues at Harvard Medical School and Massachusetts General Hospital reported the work recently in the Proceedings of the National Academy of Sciences.

Scientists can study cells live and "in action" with SHG, said Daniel Dombeck, a physics graduate student at Cornell University and lead author of the study. "In the past you had to kill the sample and fix it in place," explained Dombeck. "You couldn't look at one cell over time."

Other researchers are happy to see scientists tackling new questions with SHG. Previously the method was used to study things like the distances between molecules, said Kleinfeld. "This is the first application to real biology."

The lasers used with SHG shine "coherent light." When you hold a flashlight up to your hand, your skin glows red, but you can't see any defined structures. This is because the light is scattered into jumbled separate paths. With coherent light, all these individual light paths are in lockstep.

Other scientists are using coherent light to create holographic movies of tumors. At Purdue University, scientists have developed technology that allows visual "fly-throughs" of the cellular galaxy. Steering with a joystick, the researchers can swoop through a rat tumor, backing up in real time when they see a structure they want to stop and examine. The technology, called Optical Coherence Imaging, or OCI, could allow scientists to study a tumor's inner cells, from the outside.

A key to OCI's success is specially designed holographic film. Unlike the human eye, the film is sensitive to coherent light and the film rejects incoherent, scattered light. Shining two laser beams onto the film, the researchers created a video of the interior of a tiny tumor. The team reported the work recently in Applied Physics Letters.

"The benefit is this film is dynamic, it is just like a movie," said physicist Ping Yu, now at the University of Missouri-Columbia. "It has a very fast response time; if you find something interesting, you can just move back."

OCI can only image shallow structures, because light penetrates to a maximum of about 2 millimeters below the skin. But the technology may be used to monitor how well a tumor's inner cells respond to drugs by allowing scientists to study growth without cutting the tumors up.

Other scientists are developing new ways of tweaking older technologies. Brookhaven National Laboratory's Zhong Zhong is using high-intensity X-rays to image soft tissues such as tendons and skin. The technique, called Diffraction Enhanced Imaging, or DEI, may help detect diseases such as lung and breast cancers, or cartilage damage in osteoarthritic patients, Zhong and his colleagues reported recently in the journal Anatomy.

Conventional X-rays are absorbed by the large atoms that make up dense tissue, like the calcium in bones and teeth, but such X-rays mostly pass through softer tissues such as skin or fat. Higher-intensity X-rays are absorbed even less, so the team used a high powered X-ray machine called a synchrotron.

"The higher the energy, the less it is absorbed," says Zhong. "We just upped the energy."

The scientists calibrate the synchrotron's beams, which are a thousand times brighter than those made by conventional machines, by aiming them at a silicon crystal. When directed at the body part of choice, the beams bend and scatter, hitting the film on the other side at different intensities and creating an image. DEI scans on cadavers show a variety of tissues; there are fat pads, blood vessels, tendons and skin. And the radiation exposure is significantly less than that of conventional X-rays, says Zhong.

Another old imaging technique that's being tweaked into doing new tricks is MRI, or magnetic resonance imaging. Conventional MRI uses a combination of radio waves and a strong magnetic field to spur the hydrogen atoms in your body to send out signals that are collected and transformed into an image. Today, one of the most popular versions of MRI is functional magnetic resonance imaging, or fMRI. The technique detects blood flow, and scientists are using it to learn about what parts of the brain go to work when a person smells or thinks or feel certain things. "fMRI is the 600-pound gorilla of imaging," says Michael Moseley, a professor of radiology at Stanford University's School of Medicine and president of the International Society for Magnetic Resonance in Medicine.

Today there are still other variations on MRI that scientists are using to understand the brain's structure and function. In the early 1990s, Moseley did pioneering work using diffusion or dMRI, a method that detects water flowing out of brain cells. He was one of the



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first to show that in the minutes following a stroke, water flowing across damaged brain tissue slows considerably.

Usually water moves across brain cells at about 1 millimeter per minute, but when cells die or are stressed, the water movement slows down, and the sluggish flow can be detected with dMRI. A recent study led by doctors at Massachusetts General Hospital found dMRI to be 90 percent accurate at detecting strokes.

A newer variation on dMRI is diffusion tensor, or DT-MRI. Using this technique, scientists are building elaborate road maps of the brain's white matter, the pathways that bring information from one area of the brain to another. DT-MRI is helping scientists understand a multitude of ills, from Alzheimer's to dyslexia. Diffusion tensor MRI also tracks water movement, but from many more directions than regular dMRI. Like people moving about in a city, water diffuses randomly in the brain's gray matter. But on the white matter tracks, the highways taking information to and from the cities, water movement is very directed. Scientists track this flow with DT-MRI.

Moseley says a combination of techniques will probably yield the most intriguing information. "fMRI combined with tensor will show you the road map underneath all that activation - people with dyslexia or schizophrenics might have altered road maps," he said.

In 10 years scientists will probably "be imaging the actual processes that occur when cells are active," said Moseley. "It is stunning to see what is going on right now in molecular imaging right now. Everyone is in an absolute frenzy."

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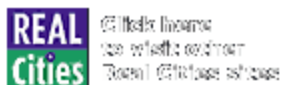
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