Photoacoustic tomography can 'see' in color and detail several inches beneath the skin

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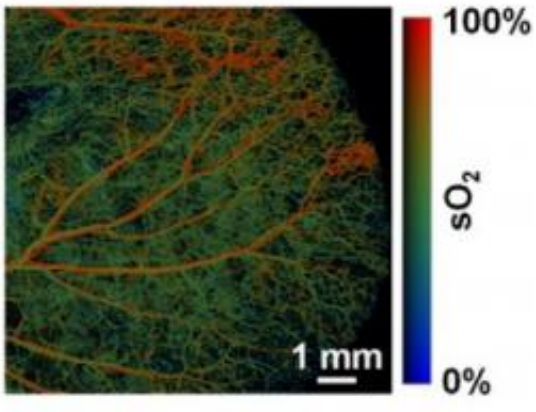


The arteries (red) and veins (green) stand out clearly in a photoacoustic microscope image of a mouse ear. The new imaging technique, which marries sound and light to garner optical quality images of tissues beneath the skin is very sensitive to color changes like those that occur as hemoglobin becomes saturated with oxygen. Credit: Song Hu/Lihong Wang

Every new imaging technology has an aura of magic about it because it suddenly reveals what had been concealed, and makes visible what had been invisible. So, too, with photoacoustic tomography, which is allowing scientists to virtually peel away the top several inches of flesh to see what lies beneath.

The technique achieves this depth vision by an elegant marriage between light and sound, combining the high contrast due to light absorption by

colored molecules such as hemoglobin or melanin with the spatial resolution of ultrasound.

Lihong V. Wang, PhD, the Gene K. Beare Distinguished Professor of Biomedical Engineering in the School of Engineering & Applied Science at Washington University in St. Louis, summarizes the state of the art in photoacoustic imaging in the March 23 issue of *Science*.

He is already working with physicians at the Washington University School of Medicine to move four applications of photoacoustic tomography into clinical trials. One is to visualize the sentinel lymph nodes that are important in breast cancer staging; a second to monitor early response to chemotherapy; a third to image melanomas; and the fourth to image the gastrointestinal tract.

Among the most exciting advances is the ability of photoacoustic tomography to reveal the use of oxygen by tissues, because excessive oxygen-burning (called hypermetabolism) is a hallmark of cancer.

In the early stages of cancer, there isn't much else to go on, Wang says, and so an early warning diagnostic test that does not require a contrast agent is potentially a game changer.

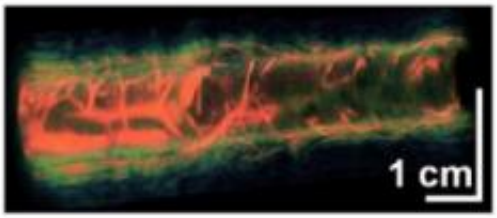
How photoacoustic tomography works

Although we've all come to accept the grayness of X-ray images, where structure appears as lights and shadows, they are a poor substitute for "photographs" of our insides.

No such photographs exist because light photons can penetrate soft tissue only to the depth of about a millimeter before they're so scattered it isn't possible to unsnarl their paths and create an image. But scattering doesn't destroy the photons, which can reach a depth of about 7

centimeters (about 3 inches).

The trick of photoacoustic tomography is to convert light absorbed at depth to sound waves, which scatter a thousand times less than light, for transmission back to the surface. The tissue to be imaged is irradiated by a nanosecond-pulsed laser at an optical wavelength.



Since most animals have body plans that are essentially a tube within a tube, a surprising amount of the body is within the reach of photoacoustic tomography. This image shows a rabbit's esophagus and adjacent internal organs. Photoacoustic colonoscopy would allow physicians to visualize not just superficial polyps but also deeper lesions Credit: Joon Mo Yang/Liihong Wang

Absorption by light by molecules beneath the surface creates a thermally induced pressure jump that launches sound waves that are measured by ultrasound receivers at the surface and reassembled to create what is, in effect, a photograph.

Light, unlike X-rays, which also penetrate deeply, poses no health hazard. Moreover, photoacoustic images have much higher contrast than X-ray images because there are many highly colored molecules in the body that serve as "endogenous" contrast agents. These include hemoglobin, which changes color as it gains or loses oxygen, but also melanin, the pigment that makes moles dark, and DNA, which in its "condensed" form in the cell nucleus is "darker" than the cell cytoplasm.

With a little help from "exogenous" (introduced) contrast agents, such as organic dyes or genes engineered to express colorful products, photoacoustic tomography can also image tissues, such as lymph nodes, that otherwise blend in with their surroundings. Wang also has been experimenting with "reporter genes," genes that encode a colored product, which shows up well in photoacoustic images.

Putting down the scalpel

Sentinel node biopsy provides a good example of the improvement photoacoustic imaging promises over current imaging practice. Sentinel nodes are the nodes nearest a tumor, such as a breast tumor, to which cancerous cells would first migrate.

In a sentinel node biopsy, a surgeon injects a radioactive substance, a dye, or both near a tumor. The body treats both substances as foreign, so they flow to the first draining node to be filtered and flushed from the body.

"A gamma probe or a Geiger counter is used to locate the radioactive particles," Wang says, "but it gives only a rough idea of the node's location." To find the node, the surgeon must cut open the area and follow the dye visually to the sentinel lymph node.

Roughly 10 percent of the patients who undergo this procedure are found to have cancerous nodes, but 5 percent of the patients suffer a side effect, such as numbness, swelling (lymphedema) or a decreased range of motion. So the diagnostic procedure itself is not without risk.

Wang proposes instead simply to inject an optical dye that shows up so clearly in photoacoustic images that a hollow needle can be guided directly to the sentinel lymph node and a sample of tissue taken through the needle.

In the clinical trial now under way, he says, the surgeon is not taking tissue but instead deploying a tiny metal clip through the needle. The patient then undergoes lymph node dissection, the "standard of care" treatment. The dissected lymph node is X-rayed to see whether it contains the clip.

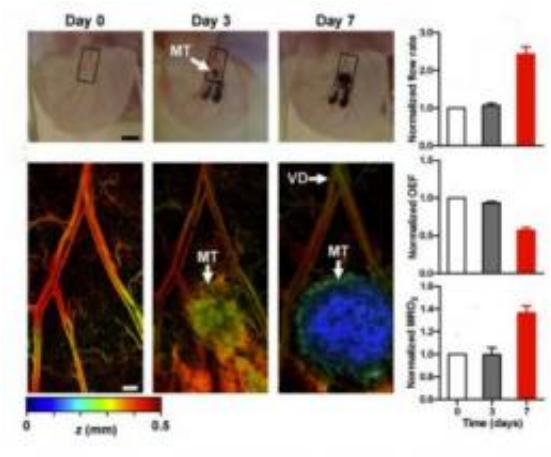
"If this technique proves accurate, we will be converting a surgical procedure into a needle biopsy possible on an outpatient basis," Wang says. "In the U.S. alone, 100,000 of these surgical biopsies are done very year, so the new procedure would spare many patients injury — not to mention expense."

Seeing function

One exciting aspect of photoacoustic tomography is that images contain functional as well as structural information because color reflects the chemical composition and chemistry determines function.

Photoacoustic tomography, for example, can detect the oxygen saturation of hemoglobin, which is bright red when it is carrying oxygen and turns darker red when it releases it.

Almost all diseases, especially cancer and diabetes, cause abnormal oxygen metabolism. So the metabolic rate of oxygen use is an important hallmark of disease.



One of the most exciting uses of photoacoustic tomography is to measure oxygen metabolism, a marker for cancer that may permit much earlier diagnosis than is now possible. In this example, melanoma tumor cells were injected into a mouse ear on day one. By day seven, there were noticeable changes in the blood flow rate (top graph, right), and the metabolic rate of oxygen usage (bottom graph, right). Counterintuitively, the tumor did not increase the oxygen extraction fraction (middle graph). MT stands for melanoma tumor and VD for vasodilation. The colors correspond to depth, with blue being superficial and red deep. Credit: Junjie Yao/Lihong Wang

Together with other parameters that can be measured in the photoacoustic images, such as vessel cross-section, concentration of hemoglobin and blood flow speed, the gradient of oxygen saturation can be used to calculate the oxygen use by a region of tissue.

The imaging technique most widely used to measure oxygen use is positron emission tomography (PET), which requires the injection or inhalation of a radioactively labeled tracer and undesirable radiation exposure.

Last year in the Journal of Biomedical Optics, Wang's team demonstrated that oxygen metabolism betrayed the presence of a

melanoma (a skin cancer) and of a glioblastoma (a brain tumor) within a few days of the injection of tumor cells in an animal model. Oxygen use doubled in a week.

"Because hypermetabolism is a quintessential hallmark of cancer," Wang says, "photoacoustic imaging may allow cancer to be detected at the earliest stage without using a foreign contrast agent."

Wang will be speaking about photoacoustic tomography at the annual meeting of the American Association for Cancer Research (AACR) this spring.

A singular vision

Wang, who has worked on photoacoustic imaging for more than 10 years, sees a subtler but ultimately even more transformative advantage to the technology.

"Every issue of every top journal publishes exciting lab discoveries," he says, "but only a tiny fraction of them are ever translated into clinical practice." Part of the problem is that images are made by different methods at different scales, making comparisons across scales difficult.

"In current practice," he says, "we use optical microscopy to examine organelles and cells and nonoptical imaging techniques such as X-ray tomography for tissues and organs. None of the clinical imaging technologies give you the strong contrast of the optical techniques.

"So between the micro domain and the macro domain there's a huge divide, because people can't relate the images acquired at one length scale to those acquired at another.

"My hope is that photoacoustic tomography, which has consistent

contrast over all length scales, can help translate the microscopic lab discoveries to macroscopic clinical practice."

For similar reasons, he thinks photoacoustic imaging will be useful for systems biology, the new movement in bioscience to focus on systems as a whole rather than on individual components.

"We're really just tool builders," Wang says, "who are going to help other scientists make the revolutionary discoveries in biology and medicine. At least that's my hope."

Provided by Washington University in St. Louis