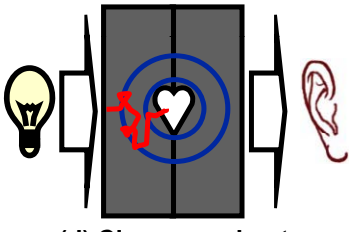
Women who are diagnosed with breast cancer may soon be helped by a discovery made in 1880 by Alexander Graham Bell.

Currently, the removal of the lymph nodes draining the breast is a routine diagnostic procedure to see whether the cancer has spread. The surgery is invasive and often has significant side effects, including fluid retention, swelling and limited range of motion. In most cases -- 80 percent -- the test shows that the cancer hasn't spread. That is a relief to the patient. But both doctors and patients have long hoped for a way to learn these results without surgery.

Now Washington University professors are developing techniques using Bell's photoacoustic effect. The new imaging technology being developed by Lihong Wang and his colleagues will identify the sentinel lymph node (the first one to drain the breast) and guide the doctor in taking a needle biopsy. For most patients, that biopsy will reveal that the cancer has not spread and those underarm nodes can remain in place and keep working to drain the area.

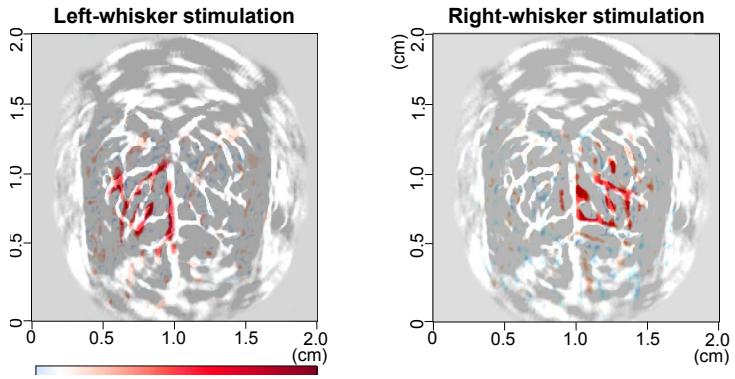
What is the photoacoustic effect, and how does it translate to medical imaging? We are dealing with the world of the very small. When the photon particles in a pulse of light hit a tissue sample, the sample heats up a tiny bit. The heating causes vibration ("thermoelastic explansion), and the vibration gives off sound waves. If the pulse of light is strong enough, the sound waves can be picked up by ultrasound detectors. Then, just as you can exactly locate a flash of lightening by timing thunderclaps, you can detect the source of the ultrasound by triangulation.



Light, even from a laser, bounces around as the photon particles hit objects. But sound waves travel in well-defined fashion

Diagram courtesy of L. Wang

Lasers, even even with a low intensity safe for human use, can excite tissue enough to create detectable ultrasound. Sound doesn't scatter very much, so as detectors map the echo, you are actually listening to the light.

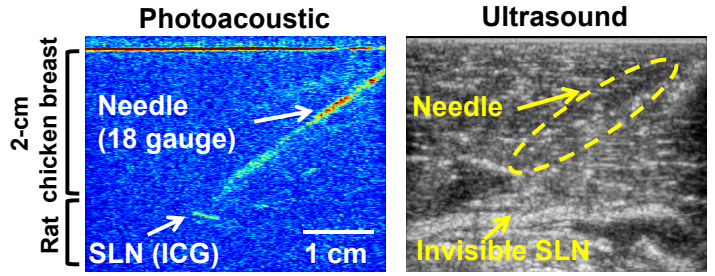


This photoacoustic image of a rat brain, taken with the skin and skull intact, shows in red the different response as the right and left whiskers are touched.

Photos courtesy of L. Wang

Only seven years ago, Wang, Professor of Biomedical Engineering, published an article that began a revolution in medical imaging. He and colleagues used photoacoustic imaging to show all sorts of things in a rat's brain, looking right through the skin and the skull. As far as the laser's light energy could penetrate, the ultrasound image could show brain structures, vascularization, and even localized responses to

stimulation. Since then, research has exploded to the point where more scientific papers are published on photoacoustic imaging than any other type of optical imagining in biomedicine.



SLN represents the sentinel lymph node.

The photoacoustic image is acquired through a slab of chicken breast placed over the rat's sentinel lymph node area. The ultrasound image does not give a clear picture.

Photo courtesy of L. Wang

To show how photoacoustics can guide a needle to a sentinel lymph node, Wang and colleagues first gave a rat an injection of the dye methylene blue just under the skin. Methylene blue, an FDA approved agent, will collect in the sentinel lymph node. Rats being quite small, the node will be quite close to the skin. To show that the laser stimulation will work in deeper human tissue, they overlaid the node area with a chunk of chicken breast about an inch thick, and shone the light through that. Then they followed the needle as it approached the lymph node. As shown, both node and needle are clearly visualized, as contrasted to ultrasound alone. As soon as the university gives approval, they will begin imaging patients, and are working with the Philips company to develop a combination ultrasound and photoacoustic machine.

Photoacoustic imaging is so sensitive that it can show a red blood cell moving through a capillary, as well as the complete vascular structure. It can show oxygenated blood in contrast to oxygen-depleted blood. This property is very useful for detecting tumors. Because tumors metabolize more rapidly than normal tissue, blood vessels emerging from them will have less oxygenated blood.

Nanoparticles can enhance imaging

But tiny tumors may not have a good blood supply. How can imaging be used on tumors that are not yet vascularized?

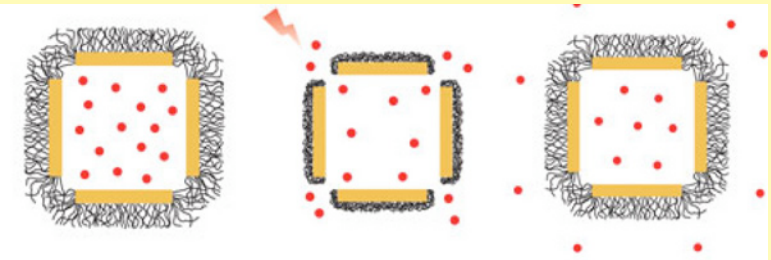
Enter another world of tiny things—nanoparticles. Younan Xia, Professor of Biomedical Engineering at Washington University has developed hollow gold nanostructures that enhance the sensitivity of imaging. Gold has a very strong capability to absorb and scatter light, making it an ideal agent for optical imaging. These tiny (30-60 nanometer) particles can be engineered to bind to certain proteins found only on the surface of cancer cells. As the particles bind, they will enhance the optical properties of the tumors.

Xia and Wang are collaborating to make the visualization of sentinel lymph nodes more sensitive to photoaccoustic imaging by injecting gold nanoparticles intradermally. As the gold particles collect in the node they will absorb light very well, heat up, and vibrate to give a strong ultrasound signal.

Imaging is only the beginning of possible uses for the gold nanocage. Professor Xia has designed it as a box that will empty its contents when heated slightly by a low energy laser. It can be made to attach to specific cells by having a specific targeting agent such as an antibody bound to its surface. Thus a nanocage could, for example, bind to a tumor and deliver a dose of an anticancer drug directly to the tumor itself.

The nanocage is a tiny box with all its corners missing. Each side is about 50 nanometers, or less than one millionth of an inch. The polymer coating on the box is what seals and unseals the contents. At cool temperatures, the polymer forms a dense bushy tangle that effectively seals the corners. When the gold is heated, the polymer collapses and the corner holes are exposed.

Therefore, a nanocage can be loaded with a a drug in a warm solution that enters through the holes. When the nanocage is cooled, the polymer coat becomes bushy and the loaded drug is trapped inside. The drug will be released when gentle warming of the gold metal causes the polymer coat to contract and thus open the corners.



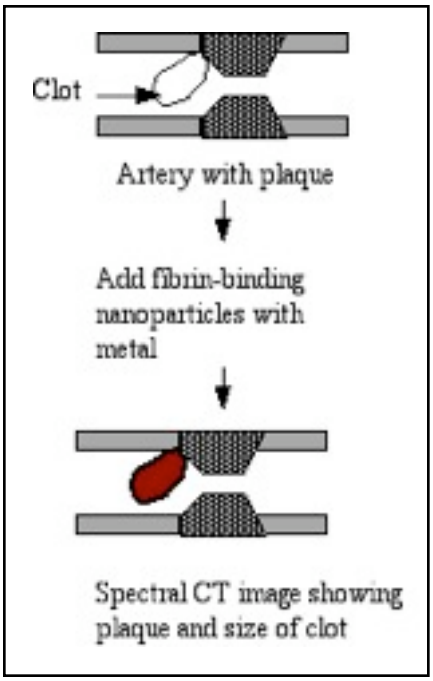
In the diagram, a nanocage is loaded with a drug, represented by the red dots. When it is heated, represented by the lightening bolt, the polymer coating collapses and releases the drug. When the nanocage cools, the polymer coating becomes bushy again, and the corners are sealed off.
Diagram courtesy of Y. Xia.

A Different Imaging Technology using Nanoparticles

Yet another new type of imaging will use nanoparticles to help the patient avoid unnecessary procedures. This new technology, called spectral CT, can tell whether patients admitted to the emergency room for chest pain are actually having a heart attack.

"The vast majority of patients with chest pain do not have heart disease," according to Dr. Gregory Lanza, associate professor of cardiology at Washington U. School of Medicine. The pain may originate in the gut, in the chest muscle, or elsewhere. Some heart attacks are easy to identify by detection methods such as electrocardiogram. Others are not so obvious. Missing a clogged artery and sending the patient home risks a later heart attack, so most patients with chest pain are admitted to the hospital for extensive testing—an expensive precaution.

A CT scan can tell whether coronary arteries have plaque build-up because plaque has calcium, and the x-rays of the scan will show the calcium as white spots. But the blood clots that are the immediate cause of heart attacks do not show up on x-rays.



Spectral-CT imaging shows both the artery and the clot. This newly developed technology combines the detection and quantification of specific metals with the speed of CT imaging necessary to look at a beating heart or a pulsing artery. Lanza and his colleagues construct nanoparticles that incorporate a metal such as gold or bismuth as well as molecule that will specifically bind to fibrin, the characteristic protein of a blood clot. Fibrin is never found in normal circulating blood; it is split off from a precursor only when a clot is formed.

In a spectral-CT scan the image will show the CT x-ray in black and white. A narrowed arterial wall will show in that scan. The spectral part of the CT scan will quantify the metal bound to any fibrin and show it as a colored image superimposed on the black and white image. The radiologist can then tell how big the clot is and whether it requires treatment.

Lanza feels that this new technology and others on the drawing board will revolutionize cardiology. Wang predicts that photoacoustic imaging will have myriad applications, including detecting colon cancers that are below the surface scanned in a colonoscopy. Magnetic resonance imaging of the carotid artery with another type of nanoparticles developed in Lanza's lab may show physicians which of their patients are at great risk for stroke.

These new developments in imaging enhanced by nanotechnology should enable diagnosis and treatment to be much more precisely tailored to the individual patient. In other words, these technologies may enable diagnosis to move further along the spectrum from art to science.