John Edwards

Medical Optical Imaging

Signal processing leads to new methods of detecting life-threatening situations

Optical imaging, a medical technique that's used to obtain detailed images of organs, tissues, cells, and molecules in the presence of visible light, is an emerging technology with the potential to enhance patient treatment, diagnosis, and disease prevention.

Offering numerous advantages over radiological imaging techniques, optical imaging uses nonionizing radiation to reduce a patient's radiation exposure, thereby allowing for more frequent studies over time. Optical imaging also has the ability to differentiate suspicious soft tissues from native soft tissues as well as tissues labeled with either exogenous or endogenous contrast media. Scattering differences and photon absorption provide specific tissue contrasts and potential capabilities for studying functional and molecular level activities. Optical imaging is a multimodal and highly responsive imaging technique that can be easily combined with other imaging approaches to create complete multidimensional views of objects and areas of interest.

Signal processing is now helping to make optical imaging even more useful and versatile, allowing more detailed images to be captured and expanding the technology's use into new patient treatment and medical research areas.

Identifying cancer biomarkers

At the University of Arizona, Prof. Jennifer Barton is using advanced optical imaging to identify imaging biomarkers of ovarian cancer, one of the most deadly gynecological cancers. The project's goal is to extend lives while preserving quality of life. "Right now, there is no effective ovarian cancer screening technology that is useful for all women," says Barton, a professor of biomedical engineering and interim director of the BIO5 Institute.

When detected early, ovarian cancer can often be treated effectively with surgery and chemotherapy. Yet, given the lack of good tools for catching it at its early stages, fewer than half of women diagnosed survive five years.

Barton is collaborating with researchers in the university's departments of physiology, medical imaging, and obstetrics and gynecology to identify imaging biomarkers, subtle changes in tissue that can be detected by sensitive optical methods, for ovarian cancer in mice. Barton's team has developed a tiny, highly flexible falloposcope—a wand-like imaging device that uses high-resolution optical imaging techniques—to obtain in vivo images of ovaries and fallopian tubes (Figure 1). By analyzing physical and biochemical changes over time to create a road map of the changes that happen during ovarian cancer, the researchers hope to be able to detect cancer in the fallopian tubes, where many researchers believe it originates.

"My optical imaging work utilizes two modalities: optical coherence tomography (OCT) and multispectral fluorescence imaging (MFI)," Barton says. OCT measures the interference of broadband light from a reference mirror with light from the tissue. "The reflectivity of tissue as a function of depth is then encoded in the interference frequency, where that interference is measured as a function of wavelength," she notes. "In my current setup, we use a spectrometer detector and measure the spatial frequency modulations on a linear charge-coupled device (CCD) array."

Resampling is necessary to convert from a measured function of wavelength to a function of wavenumber. Then a Fourier transform is performed to obtain the reflectivity as a function of depth. "Each measurement off the linear CCD array provides one depth scan, or column of a cross-sectional image," Barton says. "We have to scan the beam in one or two dimensions to obtain a 2-D or 3-D image."

For MFI, the researchers have to control which excitation wavelength is used to illuminate the tissue. "In our falloposcope, lasers are coupled into a single high numerical aperture multimode fiber that directs light to the tissue," Barton says. An imaging fiber bundle collects the reflected or fluorescence light, which is measured with a high-sensitivity CCD camera. A filter wheel in front of the camera selects out reflected light or fluorescence light at a specific wavelength range. "We need to adjust gain and exposure time of the CCD as the signals in reflected light are orders of magnitude higher than fluorescence light," she notes.

Frame grabbers are typically used for the OCT linear CCD array, the MFI

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UNIVERSITY OF ARIZONA

FIGURE 1. University of Arizona Prof. Jennifer Barton holding a highly flexible falloposcope her research team has developed to image the biomarkers of ovarian cancer, one of the most deadly gynecological cancers.

CCD camera, and a multipurpose data acquisition (DAQ) board to generate control signals for scanning or excitation of a source/filter wheel and to generate any needed synchronization signals. "It is always a struggle to increase signal-to-noise, dynamic range, and contrast in imaging systems," Barton says. These attributes affect how fast—and deep—one can image-in OCT. "We are limited in the amount of light power we can put on the tissue, so signal processing techniques that efficiently extract the signal from noise, background, and unwanted artifacts are always important," she explains.

"In the past, systems were slow enough that one didn't have to pay too much attention to data acquisition and signal processing," Barton observes. "Nowadays, with linear CCDs running at 100-KHz frame rates and 2k pixels, there needs to be more careful consideration of hardware and software processing," she notes. "This is not extraordinary as compared to some signal processing applications, but it means that imaging teams have to have new skill sets."

The team is now seeking additional funding to build hospital-ready falloposcopes so that research can be conducted on human subjects. Barton is hopeful that the technology will lead to an earlier and more accurate diagnosis of ovarian cancer. "Our technique can either serve as a primary screening method, or as a follow-up to other tests," she says.

Imaging arteries

Plaque accumulating inside artery walls can cause arteries to thicken and harden. When a plaque accumulation ruptures, it can restrict or even block blood flow, leading to a heart attack, stroke, or other serious medical issues. Accurate diagnoses are limited by the fact that there are no imaging tools available to consistently and accurately detect plaque at risk of rupturing in living patients.

An enhanced imaging technology—intravascular photoacoustic (IVPA) imaging—can generate three-dimensional images of artery interiors, potentially helping physicians to diagnose plaques on the verge of rupturing. The drawback is that developers have so far struggled to develop imaging instruments that are capable of illuminating arteries to a useful depth and at fast enough speeds while also meeting clinical requirements.

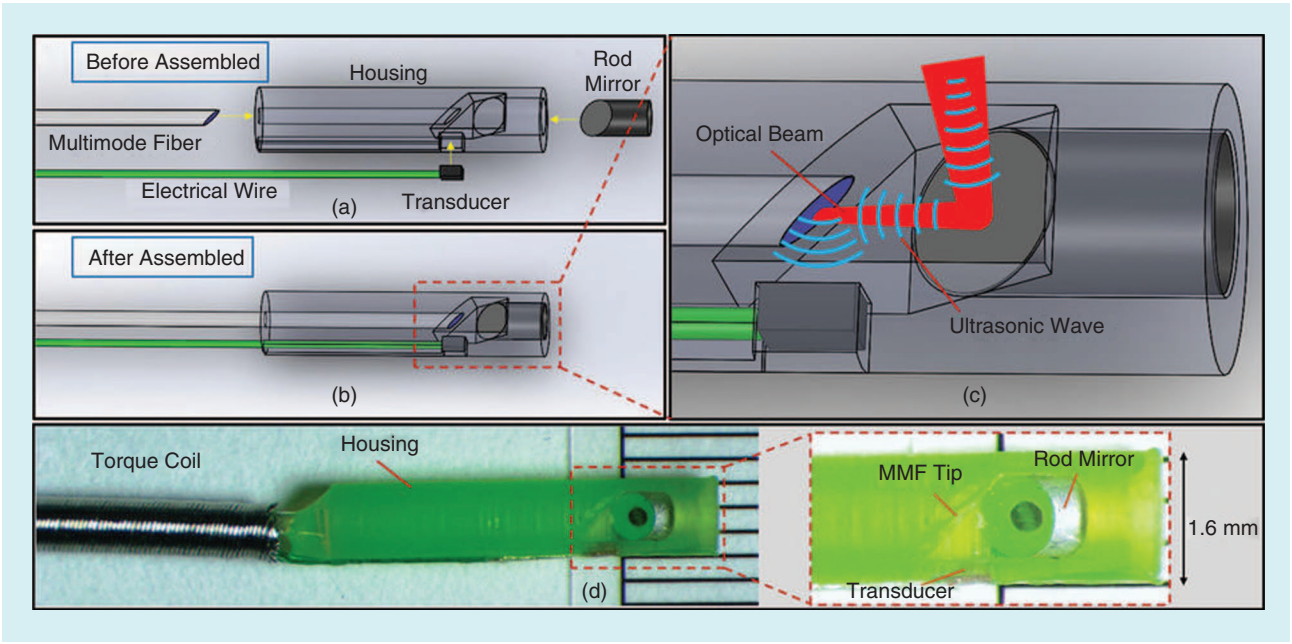
Now, using signal processing and other advanced tools and approaches, a team of researchers from Purdue University, the Indiana University School of Medicine, and the Shanghai Institute of Optics and Fine Mechanics has developed a new type of collinear catheter (Figure 2), featuring a design that promises to greatly improve the sensitivity and imaging depth of IVPA imaging.

"Our photoacoustic catheter probe integrates both photoacoustic and ultrasound modalities within a very tiny space—1 mm in diameter in our most updated version," says Yingchun Cao, a postdoctoral fellow working in the research group led by Prof. Ji-Xin Cheng of Purdue University. "The most important feature of our catheter is that we used a collinear design for the optical-acoustic wave overlap to greatly improve the imaging sensitivity and depth," notes Cao, who is the lead author of a research paper on the project.

IVPA imaging functions by measuring ultrasound signals from molecules exposed to a light beam from a fast-pulsing laser. The new collinear probe allows the optical beam and sound wave to share the same path throughout the imaging process, rather than cross-overlapping as in previous designs. The approach increases the instrument's sensitivity as well as the imaging depth, enabling high-quality IVPA imaging of a human coronary artery over 6 mm in depth from the lumen, the normally open channel within arteries, to the perivascular fat that surrounds the outside of most arteries and veins. "This research can be used … to help the doctor for accurate diagnosis of plaque vulnerability and even for imaging-guided intravascular surgery or drug delivery," Cao says.

"The unique advantage of our research," Cao says, "is we can provide quantitative information of lipid deposit within the artery wall, including the size and depth of lipid core with sufficient spatial resolution. The coregistered ultrasound image integrated in the technique can provide morphological structure of the artery for accurate position identification of lipid deposit. "In our most recent research, we can accurately distinguish different lipid compositions by a self-developed numerical approach," Cao notes.

Signal processing is an important part of the research. "A high-quality real-time



PURDUE UNIVERSITY

FIGURE 2. A new catheter probe, developed by researchers at Purdue University, the Indiana University School of Medicine, and the Shanghai Institute of Optics and Fine Mechanics, can generate three-dimensional images of artery interiors, potentially helping physicians to diagnose plaque on the verge of rupturing. (a) The main components of the collinear catheter before assembly. (b) The assembled catheter probe. (c) A zoomed-in view of the catheter tip shows the collinear overlap between optical and ultrasonic waves. (d) The fabricated 1.6-mm catheter probe and the detailed structure of the catheter tip (inset).

displayed image at video-rate or quasi-video-rate speed requires a number of advanced signal processing techniques, including noise shielding," Cao says. "In our current system we use a preamplification device to boost the signal, data sectioning to select the effective data we need, a programmable sampling rate to reduce the data amount, a median filter to remove the random noise speckle and a bandpass filter to remove other noise," Cao says. The team also uses a Hilbert transform to obtain amplitude information, polar coordinate projection for fast coordinate transformation, logarithmic compression and Tagged Image File Format (TIFF) imaging compression to save storage space.

The biggest signal processing-related challenges facing the researchers are enabling effective noise filtering, fast image display, and saving image data to a hard disk, if necessary. "Our imaging system can work at a high frame rate, say, 16 frames per second," Cao says. "That means in every second a huge amount of data will be generated and saved to a computer."

The biggest overall technical challenge is the contradiction between catheter size and sensitivity. The current diameter of 1 mm is for the bare catheter without a protective sheath. After integrating the sheath, the diameter is around 1.6 mm, which is slightly large for a coronary application. The team is now working to shrink the diameter of the catheter, including a sheath, down to ~1 mm to meet the clinical requirement. "The further decrease of the catheter size will result in both apparent photoacoustic and ultrasound loss, because both of these waves are reflected by a micro-mirror imbedded in the catheter," Cao says. Another challenge facing the researchers is the optical wave scattering that occurs when the signal travels through blood, which greatly reduces light intensity and photoacoustic sensitivity during in vivo applications.

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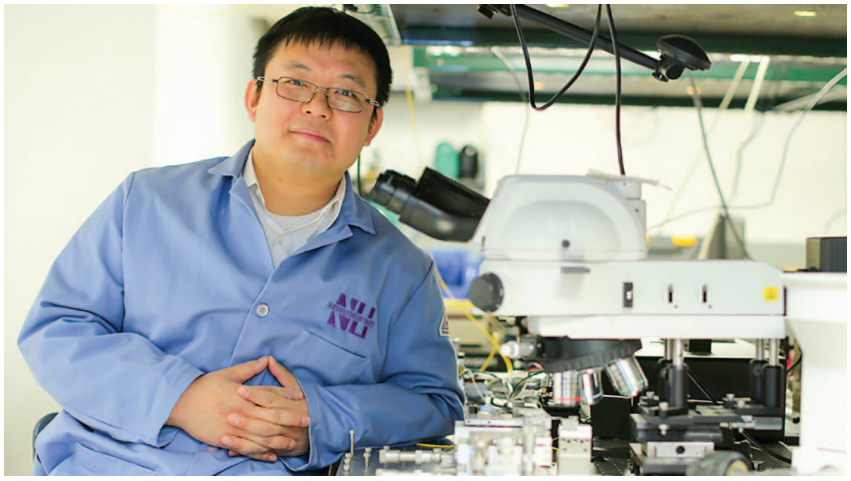
"I believe this technology is very promising for future clinical diagnosis of human coronary artery disease," Cao says, noting that the research is still at a very early stage. "But we are confident to overcome these technical problems and, hopefully, it can go to clinic in the next few years," he adds.

Peering inside cells

Building on research that won an international team the 2014 Nobel Prize in Chemistry, Northwestern University engineers say they have developed an improved version of a superresolution fluorescence microscopy technique that makes it possible to study complex molecular processes in cells.

The new optical imaging technology—spectroscopic photon localization microscopy (SPLM)—is simpler and less expensive than its two predecessors while also offering four times that resolution, claim the researchers. Like the earlier technologies, SPLM is designed to control how fluorescence molecules emit, ensuring that no spatially adjacent molecules emit simultaneously. As a result, each random fluorescence emission can be considered to very likely to come from a single molecule. Based



NORTHWESTERN UNIVERSITY

FIGURE 3. Northwestern University Prof. Hao Zhang says his research team has developed an improved version of a superresolution fluorescence microscopy technique that's used to study molecular processes in living cells.

on this assumption, only the centers of the detected individual molecular emissions are extracted and stored in each acquisition. This process is then repeated thousands of times to accumulate all the "emission centers" into a final image. The spatial resolution is proportional to the number of photons in each emission.

SPLM brings, for the first time, spectroscopic analysis to photon localization microscopy, allowing researchers to image multiple molecular labels simultaneously. The emission spectra of these molecular labels do not have to be significantly different and, in fact, can be largely overlapping. SPLM can analyze the full profile of each emission spectrum to distinguish molecular labels, numerically improving spatial resolution by combining photons from different imaging frames. Additionally, SPLM allows the imaging of multiple molecules, such as DNA, using their intrinsic fluorescence emissions.

"Our contribution to this technology is that we add an additional spectroscopic imaging capability to photon localization," says Hao F. Zhang, professor of biomedical engineering in Northwestern's McCormick School of Engineering (Figure 3). "The earlier technologies cannot distinguish wavelength differences from those emissions."

To solve this deficiency, the researchers needed to design molecular labels with desired, separated emission spectra and use optical filters to separate photon emissions with different wavelengths. One technical constraint the team faced is the limited number of filters that can be incorporated into a single system, which restricts the number of molecules that can be simultaneously imaged. Additionally, spatial resolution cannot be further improved once a particular molecular label has been selected. "We added a specially designed optical grating to the detecting optical path so that both the intensity of emitted photons and their associated optical spectra are detected at the same time," Zhang says.

Optical grating is an optical dispersive component. "When light passes through or is reflected by an optical grating, two beams will be generated simultaneously due to multiple interference," Zhang says. One beam, referred to as the *zeroth-order diffraction beam*, discloses the incident beam's intensity. The second beam, referred to as the *first-order diffraction beam*, reveals the optical spectrum. "We detect both the zeroth- and first-order beams using the same high-sensitivity array detector to obtain the molecular location and its emission spectrum simultaneously," Zhang explains. "Because no optical filter is used in the detection, and the complete profile of photon emission is detected, the number of molecular contrasts is, in principle, unlimited." Additionally, based on the individual emission spectrum, the system can combine imaging frames to numerically increase the number of photons for localization, which improves spatial resolution.

Signal processing plays a critical role in building SPLM's high-quality images. "For example, during the photon localization process, we need to find the best way to fit the point spread function of each photon emission," Zhang says. "To make individual emissions recognizable among different camera frames, we needed to design pattern recognition algorithms to identify optical spectral features among thousands of frames and determine whether they are from the same single molecule or not."

SPLM uses a high-sensitivity array photon detector to capture two images at different regions of the array detection simultaneously. The photo detector has an internal amplification capability. Each single frame acquisition takes about 10 ms, and several thousand such single frames may be generated during a single session. "Once all these frames are acquired and stored, we identify the center of each single-molecular emission and its associate optical spectrum," Zhang says. "We applied sophisticated signal conditioning operations to, for example, reduce background noise and remove detector dark current." Gaussian fitting provides the emission center and associated optical spectrum.

Zhang says the signal processing used in SPLM is far more comprehensive than what's currently available in the field. "The most unique part is that our method takes advantage of the optical spectrum of all single-molecular emissions, besides their locations, into consideration," he says. "As a result, we are not constrained by the limited number of detection channels and pseudo coloring; we know the full spectra of all the detected molecules. There are no alternative approaches because "the optical spectra information is undetectable otherwise," he adds. Zhang says the team is developing an open-source image processing package for SPLM.

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