Lab Notes

NEWS FROM AROUND LINCOLN LABORATORY

BIOMEDICAL DEVICES

An Instrument to Transform Back Surgery

The design of a new laser-based scope could offer a less invasive, more precise way to remove tissue that causes back pain and immobility

A casual conversation between friends sparked the development of an innovative tool that could change the way doctors perform surgery to alleviate lumbar spinal stenosis, a condition resulting from the narrowing of the spinal canal. At a backyard cookout, Matthew Johnson, a technical staff member at Lincoln Laboratory, was talking with childhood friend Patrick Codd, then a neurosurgeon at Massachusetts General Hospital in Boston. Codd was explaining the difficulty of accessing the spinal column to remove overgrown connective tissue that compresses the spinal cord and nerve roots, causing severe back and leg pain and weakness, even paralysis. "There's got to be a better way," Codd commented.

Johnson, an engineer who has always been intrigued by solving problems, began to think about that better way. "I had zero background in anatomy, medical devices, or lasers," Johnson said. "I was working on electrical engineering solutions for a variety of systems, including lasers." But the problem gnawed at him. Could a laser beam excise, or ablate in medical terminology, the obstructive connective tissue? Doctors already were using lasers to remove damaged soft tissue or kidney stones. What type of instrument could navigate the spinal canal and direct a laser to safely and efficiently remove the tissue?

Johnson sought advice from colleagues with experience in lasers and anatomy, and he worked closely with Codd and former Laboratory staffer Wes Hill to design a laser-based tool that could access the spinal column and then ablate the compressive tissue. He took a proposal for this tool to the Laboratory's Advanced Concepts Committee, which grants internal funding for experimental research. The committee approved the project that could lead to improved treatment for the 8.3 million Americans who suffer from lumbar spinal stenosis, many of whom are military personnel whose training and active-duty assignments have often triggered the onset of the condition as early as age 40.

Tara Boettcher of the Laboratory's Human Health and Performance Systems Group was Johnson's go-to person for the anatomical aspects of the tool. "I handled all biology aspects of the program to execute it here at MIT Lincoln Lab," Boettcher said. "Matt and I adapted a room so that lasers and biology could co-exist following all safety regulations to perform the experiments."

The standard initial treatment for lumbar spinal stenosis is physical therapy. If physical therapy is not effective, the next step is often an epidural steroid injection administered through a needle into the space around the spinal cord. This injection of an anti-inflammatory medicine is usually prescribed after the stenosis has progressed enough to cause the patient difficulty walking or some neurologic damage. Injections are generally administered every few months until they are no longer effective. At this point, surgery is often the next step.

"Surgical decompression is reasonably a measure of last resort," Johnson explained. "Though only a small amount of compressive tissue needs to be removed, surgery involves significant bone and tissue destruction, general anesthesia, and a long recovery time, and sometimes it even necessitates spinal fusion."

To develop a surgical tool capable of ablating compressive

tissue in the spinal canal without destroying healthy tissue, the researchers at Lincoln Laboratory collaborated with Codd on the practicalities of the laser sacroscope. Their goal was to shift the treatment model toward early surgical intervention that would relieve pain, preempt further physiological damage, require less extensive surgery and rehabilitation, and ultimately reduce hospital costs.

The prototype laser sacrascope was built around a commercially available ureteroscope. The sacrascope's features are designed for the three primary phases in surgery to remove compressive tissue: access the spinal canal, identify the compressive tissue, and remove it.

With an outer diameter of roughly 3 millimeters, the sacrascope can access the spinal canal through a 2-centimeter incision in the skin that covers a naturally occurring hole in the sacrum (a bone at the base of the spine) called the sacral hiatus. Once the device has entered the sacral hiatus, the surgeon can gently guide the device up the spine along the dorsal (upper) wall of the spinal canal. The sacrascope's shape conforms to the curvature of the spinal canal, allowing the device to smoothly track along the dorsal canal wall and not get caught on any nerve roots.

"To allow the surgeon to positively identify the compressive tissue, we wanted the sacrascope to provide high-fidelity video imagery," Johnson said. The sacrascope uses a sensor capable of advanced image processing. The sensor detects the relative brightness and darkness of tissue that is close to (bright) or farther from (dark) the device's tip to create an accurate video image.

The sacrascope's features are designed for the three primary phases in surgery to remove compressive tissue: access the spinal canal, identify the compressive tissue, and remove it.

"Because the sacrascope is introduced into a compressed anatomy, we developed two petals that, when actuated, hinge laterally away from the side of the distal tip of the device while the device face concurrently slides backward. This mechanical action reveals a clear area for direct visualization and a safe surgical area, with the spinal cord and nerve roots protected from the laser fiber by the lower petal," Johnson explained.

To remove the compressive tissue, two concentric nitinol (a nickel titanium alloy) tubes advance from the working channel of the sacrascope. The straight, stiff outer tube carries a laser fiber and has a predefined radius of curvature. By sliding the inner tube relative to the outer tube and rotating the tube assembly, the laser fiber can be steered anywhere within the field of view of the imaging sensor.

For control of the inner and outer tubes, the Lincoln Laboratory engineers developed a unique mechanical handle at the far end of the sacrascope. The handle is designed so that relatively large movements by the operator result in very fine, controlled movement of the laser fiber within the spinal canal. This handle enables precise targeting of only the intended tissue, without the need to reposition the entire device for each new target area.

Although lasers have been commonly used for some procedures on humans, their effect on tough, rubbery tissue like that compressed in stenosis, the ligamentum flavum, was not well documented. Therefore, the sacrascope development team devoted substantial effort to performing experiments to understand the properties of ligamentum flavum and the impact of laser beams on that tissue type.

One consideration in using lasers is the effect of the beam's heat on tissue. "We wanted to minimize damage to tissue adjacent to the tissue being ablated," Johnson said. "We looked at the absorption characteristics of the ligamentum flavum and selected two promising lasers; one commonly used in medicine, and one that isn't currently used in medicine but may offer a large advantage in terms of precision."

The team then tested the lasers on ligamentum flavum obtained from the spine of a pig. To evaluate how lasers affected "living" tissue, the experiments were done on tissue taken no more than four hours after the animal's death and were completed within 10 hours after the tissue was acquired. The

researchers irradiated the tissue to assess the amount of energy needed to ablate a specified area of tissue and the amount of thermal damage to adjacent tissue.

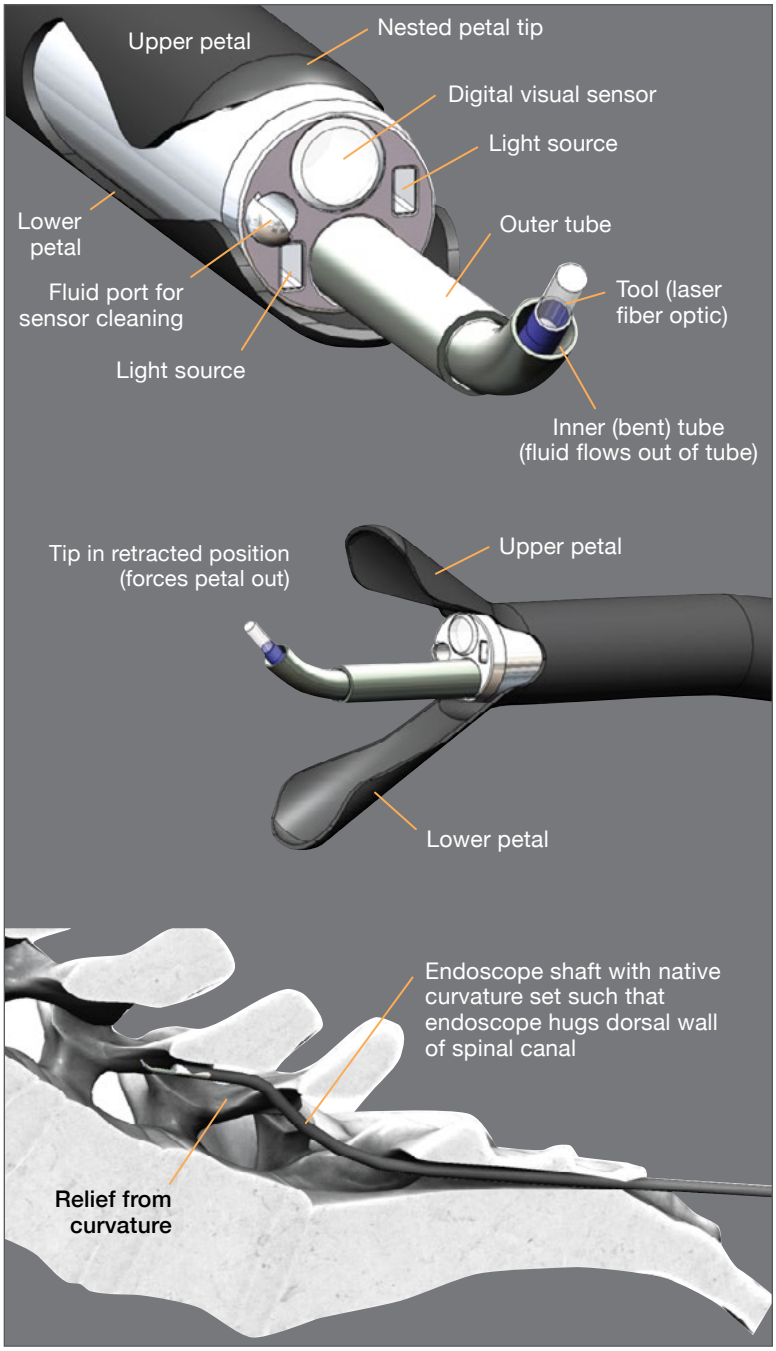
The Ho:YAG laser, which irradiated the ligamentum flavum through a 600-nanometer-diameter fiber-optic cable, rapidly heated, thus ablated, the tissue. This laser is already used for surgical procedures, and its beam is easily transmitted through a standard multimode fiber optic. However, the Ho:YAG laser caused significant thermal necrosis and charring of the adjacent tissue.

The frequency-quadrupled Nd:YAG laser, which focused the laser beam through an aperture and lens, achieved a clean ablation with minimal heating (thus charring) of the adjacent tissue. However, this laser wavelength is difficult to transmit at sufficient power levels through traditional fiber optics.

Prior research on lasers for surgery to mitigate spinal stenosis has not produced a usable tool. "Three things have made other approaches unsuccessful," Johnson explained. "The doctors could not get an endoscope into the spinal canal well enough to see what they were doing. They were unable to steer the laser successfully, and the tissue got charred."

The sacrascope uses a camera that is small and produces high-quality imagery, and its design allows for the laser to be precisely steered to the area of interest. The final challenge is figuring out the best type of laser to use. The Lincoln Laboratory researchers are no longer directly involved in developing the sacrascope, but they have filed patents on the technology and hope a biomedical device company will pick up the project to investigate that best laser and develop a marketable sacrascope.

Boettcher sees the development of the tool as a valuable



An endoscope was modified to build the laser sacrascope (top left); the callouts point out the modifications. In the middle is shown the action of the petals that deploy from the side of the sacrascope's face, clearing a safe surgical field. At bottom, the laser sacrascope is inserted into the spinal canal through the sacral hiatus and ascends the spinal canal along the dorsal wall.

investigation. "One of the cool things about MIT Lincoln Lab is the ability to combine experts from many different fields to work on ideas that can be prototyped and someday have an application," she said. "We published a paper on our work in *Lasers in Surgery and Medicine*, and the technology has been licensed. I hope to see it in the clinic someday soon."

Another outcome of the sacrascope project is the creation of a new bioengineering facility within Lincoln Laboratory. Boettcher explained that the space she and Johnson adapted for the sacrascope experiments "has now been made more official and permanent, called the BEAMM Lab."

The Biophotonic, Electric, Acoustic, and Magnetic Measurement (BEAMM) Lab is a facility that will allow staff to apply the Laboratory's capabilities in optics, lasers, radio frequency, imaging, and image processing to investigate how biological tissue reacts to the application of different energy types.

"The BEAMM Lab is a unique resource that will enable multimodal, multispectral characterization of biological materials," said Catherine Cabrera, leader of the Biological and Chemical Technologies Group. "Biomedical imaging has been identified as a key area in which the Laboratory could have a significant impact by leveraging its resources."

MEDICAL IMAGING

Fluorescence Imaging for Surgery

A near-infrared fluorescence imager helps surgeons quickly locate microtumors

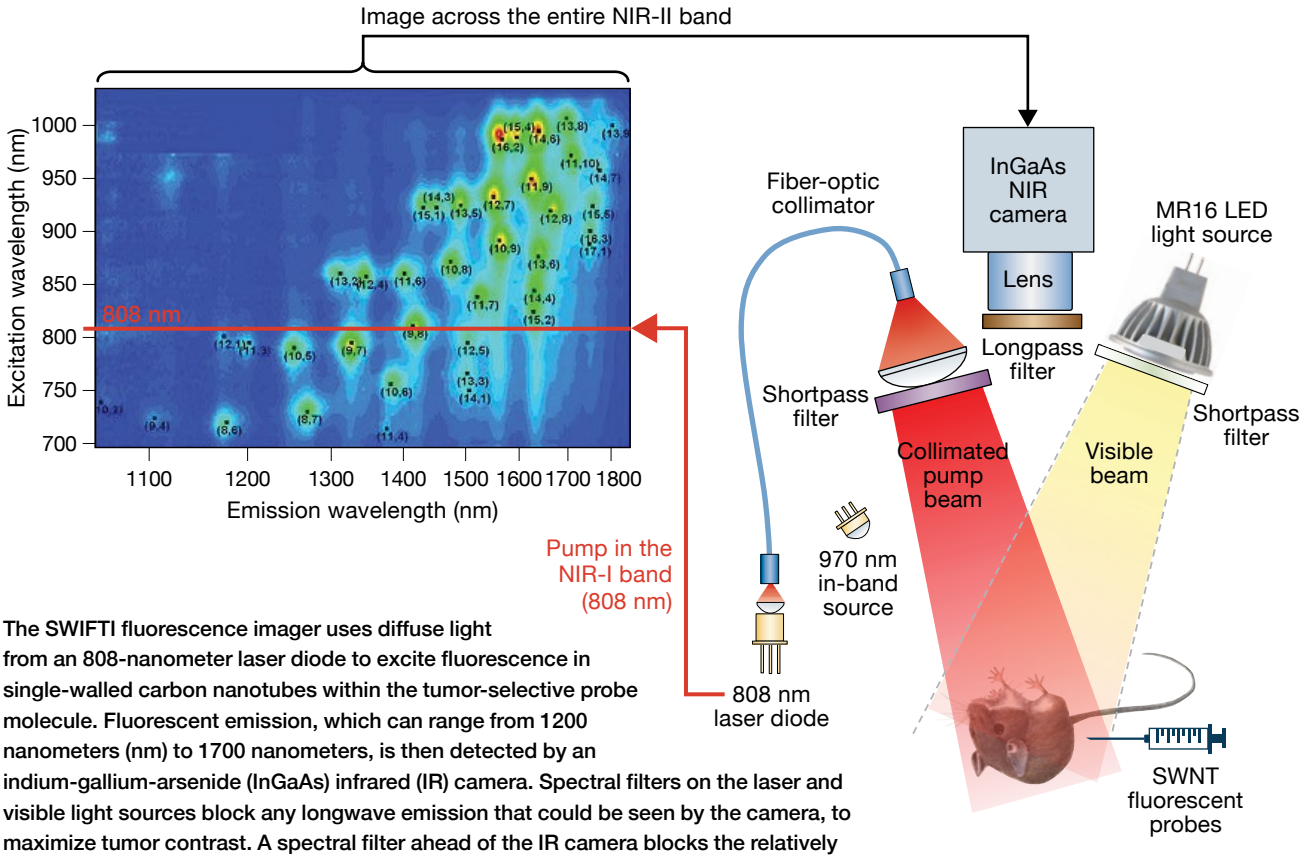
Clinical treatment of advanced cancers involves removing a large amount of affected tissue. The surgeon must remove as much cancerous tissue as possible while at the same time preserving enough healthy tissue to provide a good clinical outcome, minimize patient trauma, and speed recovery. Affected tissue can present with tumors ranging in diameter from many centimeters (e.g., a golf ball) to submillimeter (e.g., a single poppy seed). Recent clinical studies indicate that removing submillimeter-sized "microtumors" can significantly increase post-operative survival. However, small tumors are extremely difficult for a surgeon to differentiate by eye from healthy tissue within a complex surgical field. This difficulty greatly impedes the detection and removal of the tumors.

The Second-Window Infrared Triband Fluorescence Imager (SWIFTI) enables surgeons to quickly scan the entire surgical field for tumors of any size and to accurately distinguish microtumors from healthy tissue.

SWIFTI takes advantage of unique fluorescent chemical "probes" that make the tumors light up on the SWIFTI video display. These chemical probes were developed by MIT researchers led by Angela Belcher, head of MIT's Department of Biological Engineering, and are made of single-walled carbon nanotubes (SWNTs) that bind to tumors but leave healthy tissue alone. When struck by a laser, the probes emit a fluorescent glow in the second near-infrared (NIR-II) wavelength band.

"To the best of our knowledge, no other intra-operative near-infrared fluorescence imagers currently operate in the NIR-II band with similar sensitivity, simple optical design, and precision for dual-mode fluorescence plus contextual imaging," said Andrew Siegel, who developed SWIFTI with fellow staff member Nandini Rajan. "SWIFTI was developed to explore the many advantages of NIR-II band fluorescence imaging for biomedical applications."

The first near-infrared (NIR-I) band, loosely defined as ranging from deep red at 650 nanometers out to 960 nanometers in the near-infrared, is the original biological "window" in tissue. However, this window actually extends beyond 1800 nanometers. In deference to the original biological window band, the longer wavelength region spanning from 950 nanometers to around 1800 nanometers is called the NIR-II band. In this band, there is deeper light penetration and less fluorescence generated by the tissue itself. However, to detect light at these wavelengths, special fluorophores and NIR-II-sensitive detectors are required.



The SWIFTI fluorescence imager uses diffuse light from an 808-nanometer laser diode to excite fluorescence in single-walled carbon nanotubes within the tumor-selective probe molecule. Fluorescent emission, which can range from 1200 nanometers (nm) to 1700 nanometers, is then detected by an indium-gallium-arsenide (InGaAs) infrared (IR) camera. Spectral filters on the laser and visible light sources block any longwave emission that could be seen by the camera, to maximize tumor contrast. A spectral filter ahead of the IR camera blocks the relatively strong 808-nanometer light from being seen because the InGaAs detector material still exhibits some response at 808 nanometers.

Existing intra-operative fluorescence imaging systems operate in the NIR-I band. These systems all employ silicon-based charge-coupled-device or complementary metal–oxide semiconductor cameras, so they all rely on fluorophores with very narrow Stokes shifts (the shifts in wavelength between the excitation light and fluorescent emitted light). NIR-II window operation requires a different camera capable of detecting longer wavelengths. But it also allows the use of new fluorescent probes with much larger Stokes shifts, greatly simplifying the optical design. Also, since healthy tissues autofluoresce much less in the NIR-II band, the image contrast is very high, greatly improving tumor detection.

MIT's SWNT fluorophores combined with Lincoln Laboratory's SWIFTI imaging system exploit the many imaging advantages of the NIR-II band. The wide, approximately 800-nanometer Stokes shift provided by the SWNT probes allows the use of inexpensive optical filters with both good spectral blocking and broad acceptance angles. These filters reduce excitation light leakage and improve sensitivity because broader acceptance angles allow more light from the tissue to reach the camera.

As an added bonus, NIR-II wavelengths penetrate human tissue much deeper than visible light can, so tumors shadowed by a thin layer of tissue will still glow diffusely in SWIFTI video imagery, and many subsurface tumors can still be detected.

To use SWIFTI, the surgeon first applies the probe solution to all tissue in the surgical field and, after a short time, rinses away the excess unbound probe solution. When the surgeon depresses a footswitch, an infrared excitation laser at 808 nanometers illuminates all of the tissue in view of the camera. The tumors, now covered in fluorescent probes, re-emit some of this laser light within the NIR-II band. Healthy tissue, which has no fluorescent probes bound to it, appears dark on the display.

Even small tumors glow brightly, distinctly recognizable against dark healthy tissue, making them much easier for the surgeon to both find and resect (remove) with confidence. Because the sharp, high-contrast imagery also reveals any unresected tumor, this image helps minimize the surgical margin (the healthy tissue surrounding the tumors that is also resected to ensure that the tumor has been completely removed), potentially improving patient outcome.

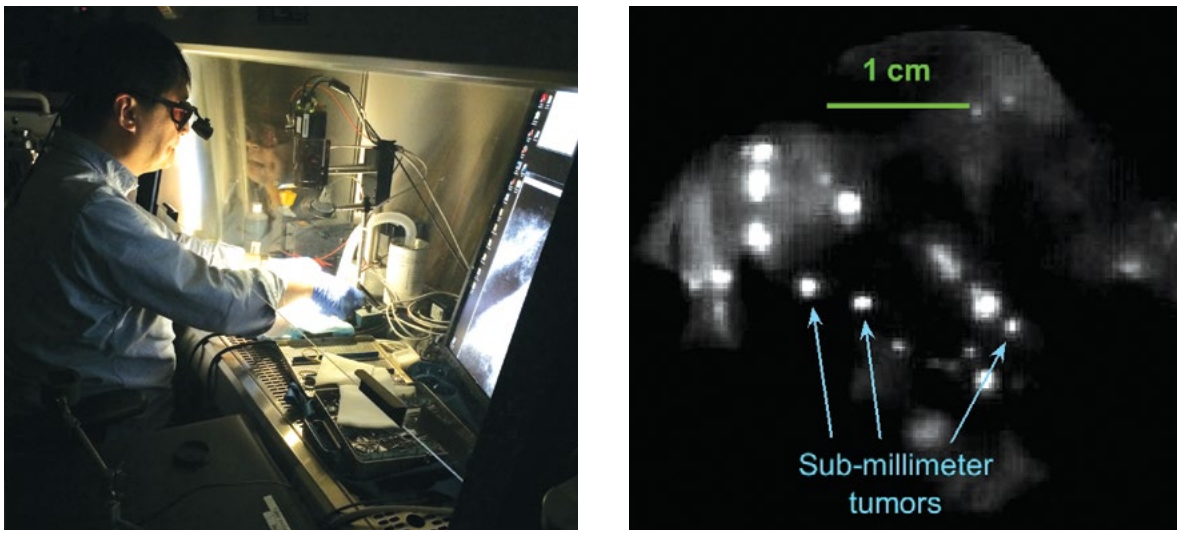
As the SWIFTI camera can still weakly detect light from the infrared laser used to excite the fluorescence, an optical filter is placed in front of the camera lens to block any wavelengths shorter than 830 nanometers. The result is a sharp, clear image in which all the surgeon sees is the bright fluorescent glow from the tumors against a dark, nearly clutter-free background.

In addition to the laser excitation source, SWIFTI also includes two more lights: a white LED light to illuminate the entire surgical field and a low-power 970-nanometer light source that only the NIR-II camera can see. Each source is separately dimmable and controlled by a footswitch.

The white LED light appears similar to a halogen surgical light, but it emits far less infrared light than incandescent lamps do, so it does not interfere with the fluorescent image. The in-band NIR-II light creates a grayscale image of the tissue that reveals surface glint (caused by moisture) and tissue contours similar to those seen in a visible monochrome image. Surgeons now have the freedom to operate from looking at the SWIFTI display screen. Using the footswitches, they can select a fluorescence view, a contextual grayscale view, or both simultaneously. They no longer need to switch their attention back and forth between the display screen and the surgical field, saving time and reducing fatigue.

"The innovative use of in-band illumination allows one camera to generate imagery that normally requires the input of two cameras in other systems, and it provides perfect spatial registration between grayscale and fluorescence imagery," Rajan said. This ability eliminates the need to maintain precise optical alignment or to remap the image in the digital domain, simplifying the design and reducing the cost of the system.

SWIFTI has been tested by surgeons and oncologists at Massachusetts General Hospital (MGH). Using the system on mice injected with the SWNT fluorescent probes, surgeons were able to remove tumors as small as 0.3 millimeters in diameter. Promisingly, the mice that were operated on using SWIFTI survived 40 percent longer than those who had tumors removed without the help of the system.



(a) (b)

The SWIFTI system facilitates the surgical resection of millimeter-scale tumors in mice (a). Even submillimeter tumors fluoresce brightly against the much darker healthy tissue, as shown in the fluorescence image of a mouse abdomen (b). The liver—visible as the lighter tissue region in the left side of this image—can be distinguished from the surrounding tissue by its slightly higher autofluorescence.

The MIT, MGH, and Lincoln Laboratory team has sought Federal Drug Administration approval for a Phase 1 clinical trial to test the imaging system for use on human patients. The system could be especially impactful for treating cancers that are difficult to diagnose in early stages, such as ovarian cancer. Seventy-five percent of the 250,000 new ovarian cancer cases diagnosed each year are in advanced stages, after a patient's abdomen is already riddled with many, and often tiny, tumors. SWIFTI could help surgeons resect many more of these tumors than can be removed today.

MEDICAL IMAGING

Diamond Sensors for Brain Imaging

A new detector uses a defect in diamond to sense faint magnetic fields emanating from the brain

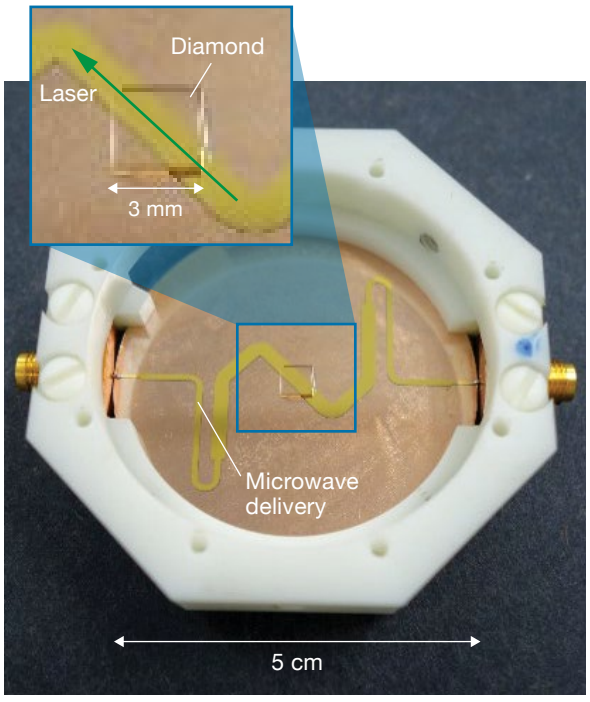
When a neuron fires in your brain, the electrical current produces a magnetic field. Just as the Earth's magnetic field emanates from its core to outer space, the brain's magnetic fields ripple out past the skull, where they can be detected by sensors positioned around the head. Using these sensors, neuroscientists can estimate from which neurons the magnetic fields originated, allowing the scientists to pinpoint brain activity in real time.

This method of imaging the brain, called magnetoencephalography, or MEG, "is a phenomenal technology," said Danielle Braje, a physicist at Lincoln Laboratory, who added that MEG is used to diagnose post-traumatic stress disorder, localize the source of epilepsy, and study autism. Despite its clinical value, there are only a few dozen MEG brain scanners in the United States.

The sensors in today's MEG platforms require highly specialized facilities that cost millions of dollars to build and maintain. These platforms use superconducting quantum interference devices (SQUIDs) that operate at cryogenic temperatures and require constant cooling. Moreover, clinical operation requires a magnetically shielded room, so that external magnetic fields, such as the Earth's, don't obscure the patient's brain signals.

Aiming to make MEG more accessible, a team of researchers from Lincoln Laboratory and MIT is developing a new sensor that could drastically cut operation costs while providing the same magnetic field sensitivity as SQUIDs.

The new sensor is made from diamond with a crystal structure optimized for magnetic field sensing. In nature, a "pure" diamond is composed of a lattice of carbon atoms with numerous defects and impurities. At the Laboratory, the team is growing

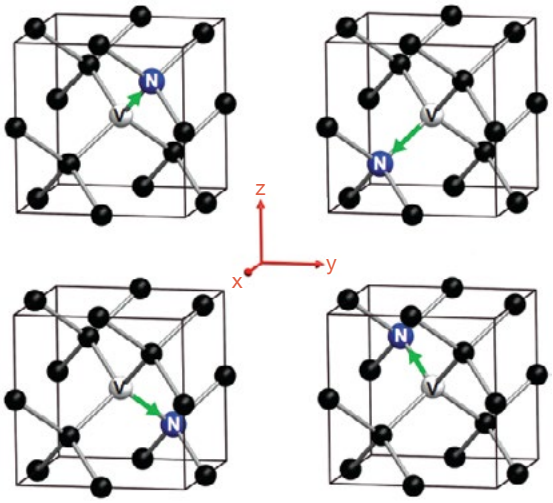


Green laser light is shone through the diamond, situated in the center of the sensor, to initialize the energy states of atoms in the diamond's nitrogen vacancy centers. These energy states transition to different levels in the presence of a magnetic field. By tuning microwave energy on resonance with these transitions, scientists can measure the transitions and therefore measure the magnetic field. This sensor would sit directly on a patient's head.

synthetic diamonds with purposeful defects. When a carbon atom is swapped for a nitrogen atom, an atom-like defect appears in the neighboring lattice site. "This is called a nitrogen vacancy defect or color center, and it is incredibly sensitive to magnetic fields," Braje said. A millimeter-sized diamond sensor contains millions of these nitrogen vacancy defect centers and can aggregate their signals for high-sensitivity detection.

Just as a compass will point north to align itself to a magnetic field, the energy levels of atoms in the nitrogen vacancy center will shift in response to an applied magnetic field. To measure this shift, the ensemble of atoms in a nitrogen vacancy are initialized into their lowest energy state, typically with a green laser. By tuning microwave energy on resonance with the nitrogen vacancy's energy transitions, an interferometric measurement can be made to determine the shift of the energy levels, thus determining the magnetic field.

"One consistent challenge is engineering the sensor to have better sensitivity," said John Barry, who works in the Laboratory's Quantum Information and Integrated Nanosystems Group. The brain's magnetic fields are extremely tiny, about 100 million times weaker than the Earth's. The diamond sensor is expected to be sensitive enough to detect changes of about one billionth of Earth's field after only one second. "Of course, we are always trying to improve the quality of the diamonds that form the heart of the sensor," Barry said. Optimizing the type of carbon and the isotope of nitrogen that are used in the diamond is an important aspect of improving the diamond's quality. "Better diamonds make building a more sensitive sensor much easier," he added.



There are four possible orientations of the nitrogen-vacancy (NV) center defect in each unit cell, or the basic repeating structure, of the diamond crystal lattice. When an NV center in each orientation is used to sense a magnetic field, the direction of the magnetic field can be reconstructed.

While its sensitivity to the strength of a magnetic field is expected to be comparable to that of a SQUID, the diamond sensor can actually describe a magnetic field in more detail because it provides a full vector measurement. A complete description of a magnetic field at any point in space requires two pieces of information—the magnetic field's strength and its direction relative to all three axes. A single SQUID measures field strength and only one directional axis of a magnetic field. A single diamond sensor can measure all three directional axes of a magnetic field because the sensor's nitrogen vacancies are arranged among four different orientations within the diamond's carbon lattice. When nitrogen vacancies in these different orientations are used to sense a magnetic field, its direction can be reconstructed.

The diamond sensor also works at room temperature, in contrast to SQUIDs, which are only sensitive to magnetic fields at extremely cold, or cryogenic, temperatures. Because of this cryogenic requirement, the array of SQUIDs that surround a patient's head are built into a hard helmet under which the patient sits. "It's a one-size-fits-most solution," Braje said. "You have to hope your head isn't too big to not fit but not so small that the sensors are farther away from the skull. Only two MEG machines are tailored for children."

By contrast, the diamond sensor would rest directly on the person's head, strung in a net of hundreds that could conform to that person's head size and shape. This direct contact not only provides a better measurement, but it also allows measurements to be made without the need for a magnetic field–shielded room. "Since nitrogen vacancy sensors are not cryogenic like SQUIDs, they

can conceivably be spread out in a large 3D array covering the patient's head that can allow the background magnetic field to be measured and subtracted, negating the use for the shield," said Barry. "Although such an approach will work in principle, it is expected to be quite difficult to implement in practice."

Today, the team is collaborating with Massachusetts General Hospital (MGH) in their initial steps to put the sensor into practice. As a baseline, subjects were scanned with SQUID-based MEG machines at MGH. The aim is to make the exact same measurements using a nitrogen-vacancy sensor in a regular laboratory environment—that is, no cryogenics and minimal magnetic field shielding.

Making MEG as commonplace as other radiology techniques, such as X-rays, MRIs, and ultrasound, still requires significant research and development. Other potential alternatives to SQUIDs are atomic vapor cell magnetometers, which use a hot gas of alkali metal atoms to sense magnetic fields.

The ultimate vision, though still far off, would see MEG technology in widespread use as a diagnostic tool in hospitals, doctors' offices, and field medical facilities. The team continues to push their sensor's sensitivity and looks forward to further testing. If successful, nitrogen-vacancy diamond sensors could not only replace the current MEG technology in the scanners in the United States, but, Braje said, could also "put MEG measurements in hospitals and labs around the world."

BIOMEDICAL DEVICES

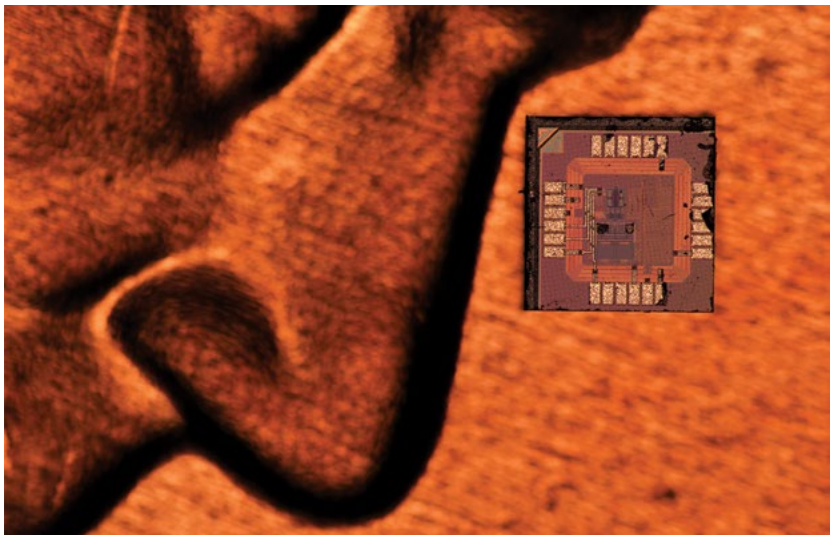
A Nearly Neuron-Sized Brain Sensor

Lincoln Laboratory is developing what could be the world's smallest wireless, implantable device to measure neural activity in the brain

The brain's nearly 100 billion neurons, and the 100 trillion pathways connecting them, are responsible for telling the body precisely what to do, think, and feel. As such a vast and complex system, the brain leaves much for neuroscientists to still understand. However, moving fundamental research forward requires new technologies that enable a closer study of the brain. This need has been recognized by the U.S. National Institutes of Health, which have put nearly a billion dollars of funding toward their BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative since 2013.

Lincoln Laboratory researchers, too, have been pursuing the development of next-generation bioresearch tools. They are developing a new, tiny device—attempting to be as small as a single neuron—for studying neural activity. Implanted inside the brain, the device is designed to detect and wirelessly transmit the electrical signals it picks up from the neurons firing around it.

"One aspect of the overall effort in neuroscience to better understand the brain is about studying electrical signals in the brain, essentially asking, 'How do complex neuronal circuits work?'" said Farhan Adil, who leads this Microelectronics Interfacing



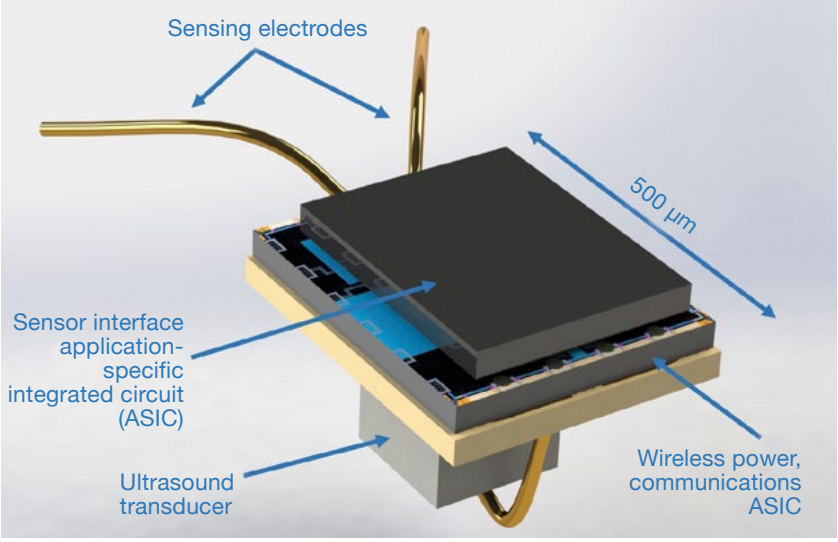
The application-specific integrated circuit, or ASIC, responsible for sensing voltage spikes in the brain is photographed here for scale on the face of a penny, next to Lincoln's nose.

Neural Devices (MIND) program. "To answer this question, we need something very small to put into the brain, and it needs to have high spatial resolution and temporal resolution. So, we need a lot of them and they need to work fast."

Studying individual neurons in living mammals in real time and across the brain is challenging. The only current way to get high-resolution temporal and spatial data is through invasive means—removing part of the skull and implanting, for example, an array of electrodes directly into brain tissue. But these technologies are relatively large and often cause inflammation and scarring, disrupting the cells they are meant to observe. They also require bulky, wired connections to external receivers. "Our goal is to get the signal out wirelessly and truly make the device as passive and nonsurgical as possible," Adil said.

While not quite as small as the 0.1-millimeter size of a neuron, the current MIND prototype measures 1.5 × 0.8 × 0.4 millimeters. If placed on the face of a penny for size comparison, the device would fit squarely on Abraham Lincoln's eye. At this size, the body's natural inflammatory response signal is unlikely to trigger, allowing the MIND device—or a handful of them, implanted around the brain—to operate essentially incognito to the neurons around it.

In simple terms, neurons communicate with each other by using electrical signals. A stimulus to the body is converted to an electrical signal, which rapidly travels down a neuron and is passed to other neurons. This passing action, when the neuron "fires," creates a voltage spike. This spike is what the MIND device is designed to sense, capture electronically, and transmit out of the brain for researchers to study. To do so, the device relies on two custom application-specific integrated circuits (ASICs).



The researchers are working on building and testing a complete MIND prototype, with the sensor interface application-specific integrated circuit (ASIC) and sensing electrodes integrated with the wireless power/communications ASIC and the ultrasound transducer. Shown here is one vision of the final version. Not included in this illustration is the hydrogel that will coat the device.

One of the ASICs is responsible for detecting signals and sits directly on top of the brain tissue. Electrodes from the ASIC sense the voltage spikes from firing neurons. When a voltage spike enters the ASIC, the tiny signal is amplified, converted from an analog to digital signal, and formally detected and time stamped. This sensor ASIC is bonded to a second ASIC that is responsible for relaying power to the sensor and for moving the electrical spike data out of the sensor.

For the ASICs to work, they need power. "The human head is really good at keeping things out, like electromagnetic signals, for example," Adil said. "If you were to put a little RF antenna on the device, the head—with its hair, skin, skull, tissue—would greatly attenuate the signal." Instead, the team is using ultrasound frequencies to wirelessly power the device. These frequencies can penetrate the skull and brain with less signal loss than experienced by RF methods.

A transducer made out of piezoelectric crystal in the MIND device receives the incoming ultrasound frequency. The frequency causes vibrations in the transducer, generating an AC voltage that activates the power and communications ASIC. This ASIC converts the AC voltage to a DC voltage that powers the sensor ASIC, allowing it to collect the neural data.

Ultrasound energy is then used to transmit the data out of the

device by modulating, or varying the phase of, the ultrasound waves that bounce off the MIND transducer. "Not all of the ultrasound energy is collected by the piezoelectric crystal. Some of it will be backscattered," said Mark Hernandez, who has been supporting the program by testing the device components. "We hope to encode the data, 0s and 1s to indicate whenever there is an electrical spike, into that backscattered signal." This signal would be collected again by an ultrasound receiver outside the body and decoded.

If placed on the face of a penny for size comparison, the device would fit squarely on Abraham Lincoln's eye.

The team is currently demonstrating that they can create sufficient electrical power via ultrasound energy for a device this small. Their modeling shows their device works. "But transmitting and transducing enough ultrasound energy to power the sensor circuitry is very difficult," Hernandez added. The system must have a very low power draw of less than 10 microwatts. If the device is overpowered, it could generate too much heat to be biologically safe. Also, the Food and Drug Administration sets limits on the amount of ultrasound energy to which a person can be exposed.

Once the power demonstrations are complete, the team will turn their attention to miniaturizing the transducer even more (it is currently the largest component of the device). "Our hope is to design a new type of ultrasonic receiver that can be microfabricated and integrated with a conventional complementary metal-oxide semiconductor electronics process," said Siddhartha Ghosh, who is leading the transducer efforts.

Meanwhile, the sensor ASIC has been tested successfully in the lab. Hernandez and colleague Christina Zook led the experiments, first using cultured rat cardiomyocytes, cells that make up the heart muscle and that give off high levels of voltage when electrically stimulated. "We could see that the sensor was picking up the signals from the cells. It could even measure a change in activity. For example, we added norepinephrine, which increases the 'beating' rate of the cells," Hernandez said. The sensor was also able to detect the low-voltage firing of active neurons in subsequent in vitro tests. The results matched those of a gold-standard microelectrode array.

While there are still engineering challenges to overcome, Adil hopes to soon transition a complete MIND prototype out of Lincoln Laboratory and into the research space. In giving neuroscientists a new tool to understand the neuronal circuitry of the brain, the device could also help unveil new connections between brain function and neurological disease. "This new tiny, wireless tool could really help push fundamental neuroscience research to the next level," he said. "There's not a wireless neural sensor of this size out there at the moment."

WEARABLE SENSORS

Progress Toward Wearable Pulse Oximetry

New algorithms and functional fibers clear a way for monitoring blood oxygen saturation on the go

During a routine medical visit, you will likely encounter a pulse oximeter. The sensor is clipped onto your finger to measure heart rate and the saturation of oxygen in your blood, two indicators of cardiorespiratory health. Pulse oximeters are a standard tool for monitoring people in a hospital. However, taking these measurements while a person is on the move, out in the world, remains a challenge.

"Try moving your hand around with the sensor on, and the doctor will ask you to sit still," said Brian Telfer, a senior staff member in the Human Health and Performance Systems Group. Motion corrupts the signal recorded by the oximeter and is one of the main reasons why pulse oximeters have yet to be turned into a wearable technology.

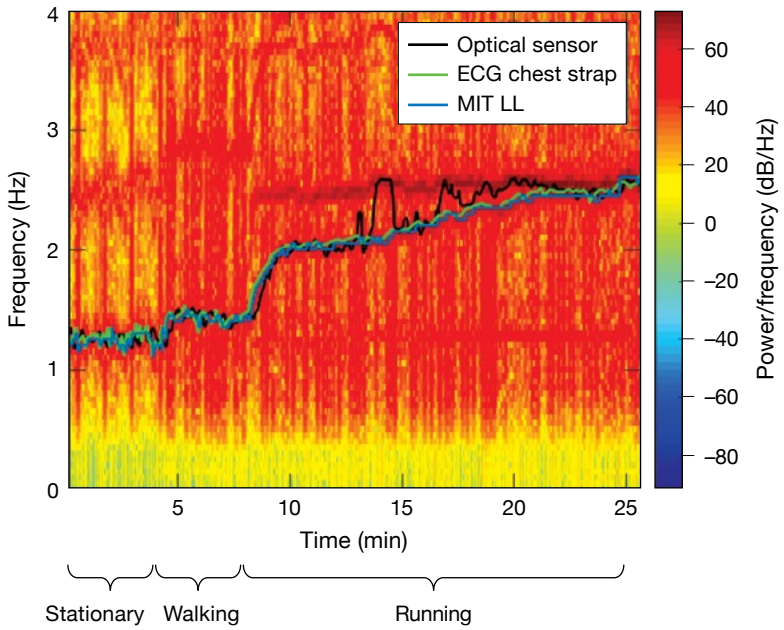
Yet, a wearable pulse oximeter is something both the military and civilian populations need. Real-time oximetry could help predict if

soldiers or hikers are experiencing altitude sickness and need medical attention, or if pilots are suffering from hypoxia and need help before an accident occurs. There are trauma-related applications as well. Changes in the raw oximetry waveforms may be used to detect internal hemorrhaging, which is difficult to anticipate from standard vital signs.

To address these needs, Telfer and his colleagues are teaming with the U.S. Army Research Institute of Environmental Medicine to prototype a wearable pulse oximeter. They are tackling the problem of motion by developing algorithms that can determine the difference between frequencies that are caused by motion and those that reflect heart rate and blood oxygen saturation, referred to as SpO2.

"The crux of our work is to have an accelerometer co-located with the sensor," said James Williamson, who is developing these algorithms. "The accelerometer senses motion and at what frequency. If we can locate and get rid of that frequency in the sensor's data, then we can determine heart rate and SpO2 from the signal."

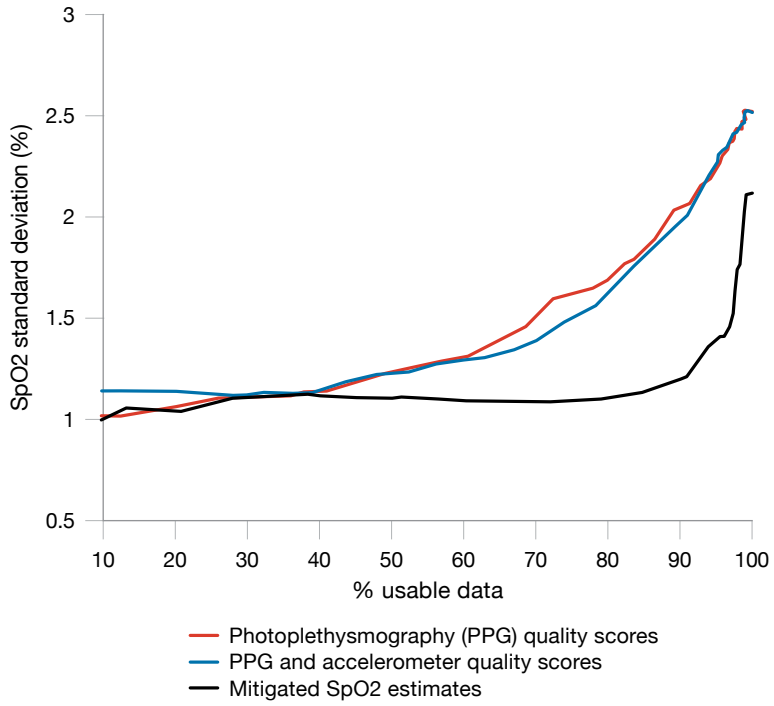
The signals Williamson refers to are optical signals, the same kind used by commercial wearable devices such as Fitbits to estimate heart rate. A light-emitting diode, or LED, reflects onto the wearer's skin, and a photodetector captures changes in light absorption as blood pulses underneath the skin. Algorithms use these changes in light absorption to calculate heart rate (though studies show that these commercial systems' accuracy also suffers from motion artifacts). A similar process is used to measure SpO2, though the device needs to use both red and infrared light, which oxygenated and deoxygenated blood absorb differently.



A spectrogram of the infrared channel from a commercial pulse oximeter chip worn at the forehead shows frequency components from both the wearer's heart rate and from motion artifacts while running. Overlaid are heart rate frequencies measured from the same data collection from a commercial optical sensor (black), an electrocardiogram chest strap (green), and the pulse oximeter chip with Lincoln Laboratory's motion mitigation system applied (blue). The chest strap and the Lincoln Laboratory system accurately follow the heart rate component, while the commercial optical sensor sometimes confuses the heart rate and running components.

Separate algorithms for determining heart rate and SpO2 during motion were developed. To assess their algorithms' performance, the researchers had test participants wear headbands or helmets outfitted with a three-axis accelerometer and a commercial pulse oximeter chip pressed against their foreheads. Data were collected as a person stood, walked, and ran on a treadmill. For comparison, the researchers also had each participant wear a hospital-grade pulse oximeter clipped to a finger and an electrocardiogram chest strap, the gold standard for obtaining heart-rate measurements.

As was expected, the chest strap sensor correctly followed the heart-rate frequency, and the finger-worn optical sensor jumped between following the heart-rate frequency and the movement frequency. But when the Laboratory's algorithm was applied to the data recorded by the forehead chip, it allowed the sensor to consistently follow the participant's heart rate and ignore motion-caused frequencies. "We're showing with our method that we can actually measure heart rate better than optical-based commercial systems," Williamson said.



Lincoln Laboratory's mitigation techniques allow for more of the sensor data captured in the presence of motion to be used to accurately estimate SpO2. For normal physiology, SpO2 changes slowly over time, so the standard deviation of SpO2 over a short time window can be used as a metric of SpO2 accuracy. With the mitigation technique applied, the SpO2 standard deviation remains low even when 90 percent of the data is used. In contrast, the SpO2 standard deviation is significantly higher when using alternative techniques, such as optical (photoplethysmography [PPG]) quality scores and PPG and accelerometer quality scores.

A related algorithm was developed to mitigate motion artifacts in the SpO2 computation. The algorithm looks at patterns in 5-second windows of data, analyzing the repetitive peaks in the infrared and red optical frequencies. It then compares these peaks to those in the accelerometer frequencies. If the peaks are too similar, that frame's data are deemed corrupted and are thrown out. The algorithm instead uses nearby uncorrupted 5-second frames to compute SpO2.

SpO2 is calculated as the percentage of oxygenated hemoglobin in the blood; above at least 95 percent is normal. After test subjects began running, average SpO2 estimates from the commercial finger-worn oximeter dropped from an average 97 percent to 93 percent, likely indicating motion corruption. With the Laboratory algorithm applied to the forehead-chip data, SpO2 estimates for test subjects remained consistently at or near 98 percent.

"We are doing more testing to validate the SpO2 measurements," Williamson said, "but the motion mitigation results are promising for enabling wearable pulse oximetry."

The team has also begun turning their attention to prototyping a wearable pulse-oximetry system. Instead of a traditional chip-based device, the system will take advantage of a new area of research and development at Lincoln Laboratory: advanced functional fibers. Here, they are partnering with the Laboratory's Defense Fabric Discovery Center (DFDC) to weave advanced, optical-sensing fibers into the very fabric of a soldier's uniform.

"Many chip devices, like the ones worn on a wrist, are rigid," said Lauren Cantley, a materials scientist who works in the center. "We want a comfortable system and one that can mate to the surface of your skin."

Certain parts of the body are better than others for capturing heart rate and especially SpO2 measurements; a fabric-based system allows the team to expand the possibilities of sensor locations. The fabric's flexibility also helps to ensure the sensing elements are in constant contact with the skin, improving signal quality. Initial investigations by the team have found that the forehead is an ideal sensing location because the reflectivity of the bone yields high-quality signals (thus the team's decision to test their algorithms with a chip pressed to the forehead) and reduces power needs. But once the pulse-oximetry textile is fabricated, more testing can be done on various areas of the body.

To make this textile, DFDC staff are building on a breakthrough technology developed in conjunction with MIT and the Advanced Functional Fabrics of America institute. They embed semiconducting

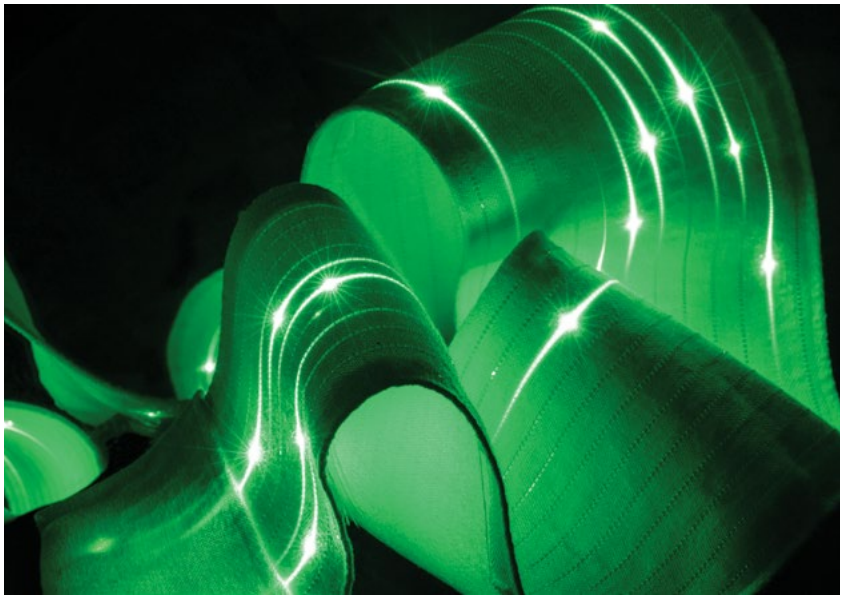
devices—LEDs and photodetectors—into a block of polycarbonate plastic that will be drawn into a fiber. The tiny devices are placed along hollow channels drilled through the block, then copper wire is fed through these channels. As the block is heated and pulled into a thin fiber, the devices are forced into electrical contact with the wire. This fiber now has semiconducting capabilities throughout its length.

To date, the team has proven this fiber's use for optically measuring heart rate. When a user places a finger over a fabric woven with these fibers, the light emitted from the LED-embedded fiber is partially absorbed by blood and reflects back up to a photodetecting fiber in the fabric. Current efforts are focusing on demonstrating that SpO2 can be measured using this fiber technology.

Integrating a pulse oximetry capability into a uniform also has the benefit of not requiring a soldier to carry an additional sensor. "We're adding functionality to something they already have on their body," Cantley said. Along with pulse oximetry, the integration of other physiological sensors into fibers and then into a soldier's uniform is something the DFDC staff are actively working on. The goal is to build a full "body area network," a system of sensors to continuously transmit physiological status updates to medical staff without adding burdensome equipment to servicemembers in the field.

Telfer sees a wearable pulse oximeter being commercially successful as well. The surge in popularity of wearable devices points to people's desire to have real-time data about their health. But it's not just for the fun of knowing—these data can save lives. "Motion mitigation is just one type of the signal processing we are doing," Telfer said. "For blood loss, for example, the Army and other researchers have found that the shape of the waveform changes." Processing these waveform changes and alerting a user may mean that vital steps can be taken before blood loss leads to shock. The researchers are looking into other signal processing techniques that could give greater insight into a user's health.

If a pulse-oximetry textile is realized, it is possible that the clothes you wear to a future doctor's visit will have already told you what the finger clip reveals. Until then, sit still.



Fibers drawn from a preform with embedded LEDs are woven into fabric by using a conventional weave.

DATA ANALYSIS

Expanding the Potential of Medical Data with Polystores

A new approach to integrating medical information from multiple databases aims to improve diagnoses and treatment

Big data, the explosion of digital data available today, has led to significant challenges caused by what is termed the three Vs: volume, velocity, and variety. The massive volume of data generated hampers a system's ability to process, index, and store it all. Datasets streaming into computer networks at high velocity hamstring processing, and the now

commonplace diversity of data—text, images, graphs, and video, for example—constrains a system's capability to manage files efficiently.

No domain is more challenged by these factors than the medical community whose systems must integrate and synthesize a rapidly expanding collection of data to support the decisions medical personnel make. Sensor data, such as MRI scans or electrocardiographs (ECGs), physicians' reports, patient histories, and research findings are just some of the data that are readily available in digital formats.

To deal with this variety of data, programmers working for the medical establishment have developed custom databases for the sensor data, graphs, documents, and transactions that are recorded in medical files. These custom databases deliver 100 times better performance than can general-purpose databases, but the trade-off is that these performance benefits have led to a profusion of data-specific storage engines.

"Most modern decision support systems contain five or more distinct data storage systems," said Vijay Gadepally, a senior member of the technical staff in the Lincoln Laboratory Supercomputing Center (LLSC). Large medical establishments, particularly regionalized ones, may employ even more than five. In addition, for organizational or policy reasons, data are often required to be housed in different databases. "For an application developer, this situation translates to developing system-specific interfaces and connectors for every different system," Gadepally explained. Moreover, developing the applications is complicated by the developers' need to understand the nuances of each underlying system.

BigDAWG signals a big shift in the way we think about data management. It simplifies the integration of data distributed across multiple database engines by leveraging translators across common programming and data models.

Gadepally and colleagues in the LLSC were part of a consortium of researchers from Lincoln Laboratory, MIT, and several other universities that has been developing a system composed of multiple storage engines able to support queries spanning multiple data models. Called a polystore, this system is proving to be a viable alternative to the more traditional parallel and federated database systems.

The system developed in this collaboration, BigDAWG (short for the Big Data Working Group), is a reference implementation of a system designed to simplify database management for complex applications. BigDAWG is predicated on several concepts about a solution to the database management problem: one database will not fit all; no single programming language suits all applications; integrating multiple storage engines should not impede a system's functionality; and applications should be portable across different systems. The research team, which looked at using the system for several applications, aimed BigDAWG at the challenge to decision making posed by the increasingly large and diverse amount of data available to the medical community.

They explored how BigDAWG could work with the Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC II) medical dataset. MIMIC II contains physiological signals and vital signs captured from patient monitors of tens of thousands of patients in intensive care units. MIMIC II also contains patients' metadata (e.g., name, age), the text of doctors' and nurses' notes, lab results, and information about patients' prescriptions. Because a hospital typically stores all the patients' historical data and real-time sensor feeds, the hospital's data management system is taxed to support several databases and types of data processing: standard SQL analytics (e.g., how many patients were given a particular drug), complex analytics (e.g., compute a patient's ECG data and compare the results to "normal" ECG readings), text search (e.g., find patients' responses to a drug), and real-time monitoring of physiological conditions.

Each of the underlying databases hosts part of the MIMIC

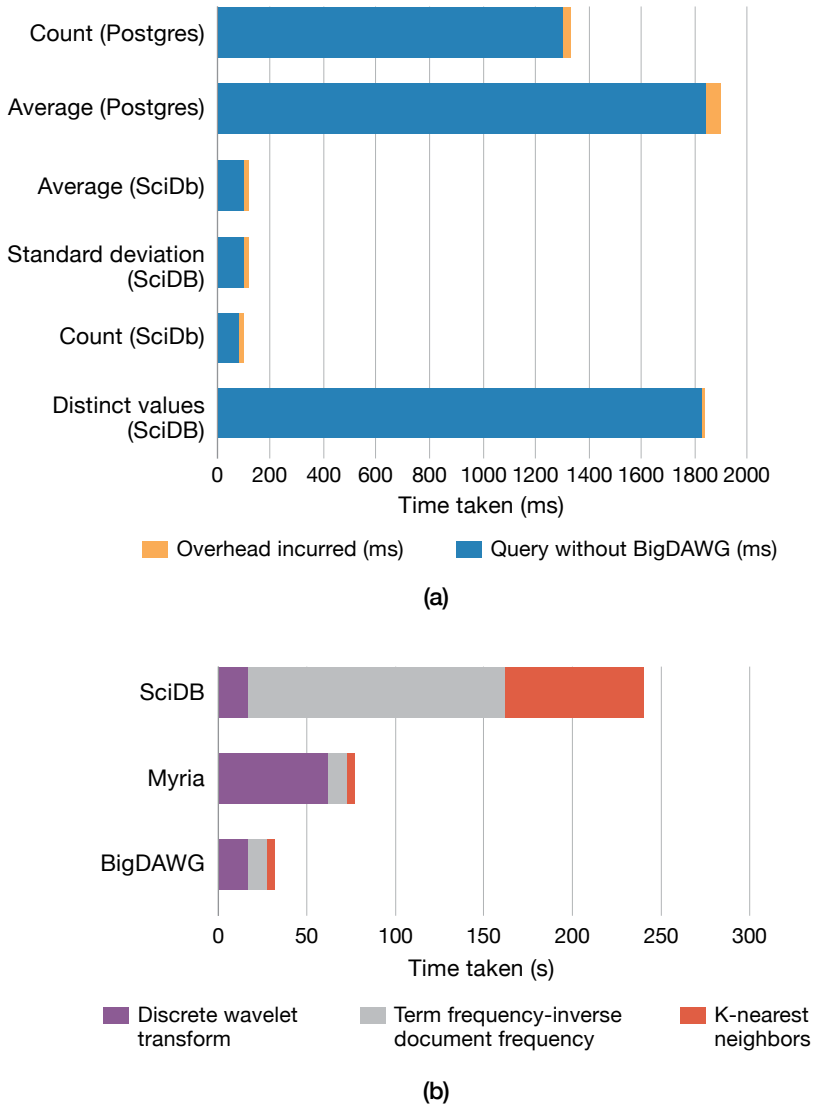
II data corpus—epitomizing "one size does not fit all"— and MIMIC II's multiple databases present a good example of how no one database can comprehensively support complex decision making.

The team applied the polystore solution to a medical analysis that is looking for patients with similar physiological measurements so that doctors might find data useful for predicting which patients may be likely to experience a deterioration of the circulatory system. Using BigDAWG, the analytic first performed a discrete wavelet transformation of an individual patient's electrocardiogram record; then the system generated a wavelet coefficient histogram, performed a function that weights rare ECG changes higher than those commonly seen in ECGs, and correlated these changes across all other patients. Each of these subanalytic pieces was then split across different systems, and the performance of the system was measured.

For the MIMIC II demonstration, the team built a number of interfaces. The browser let the user scan through the entire MIMIC II dataset or drill down to more detailed information. A basic analytics tool enabled the user to spot and explore relationships in medical data, while a tool for complex analytics allowed users to perform data correlations useful for advanced research. Interfaces that facilitate keyword searches and real-time monitoring of sensor data were also included.

"Our results support the notion that overall query performance may be improved by identifying and leveraging relative strengths of disparate database systems within a polystore, and that this improvement does not significantly decrease performance," Gadepally said.

BigDAWG automatically optimizes cross-engine queries and moves data as needed across disparate engines without user intervention. "BigDAWG signals a big shift in the way we think about data management. It simplifies the integration of data distributed across multiple database engines



The charts depict the BigDAWG performance on MIMIC II analytics. The BigDAWG computational overhead for common database queries is presented in (a). The blue bar indicates the time taken without BigDAWG and the orange bar indicates the additional time incurred when using BigDAWG. A comparison of BigDAWG performance for a medical analytic against state-of-the-art SQL and NewSQL databases is seen in (b). For this particular analytic, BigDAWG can cut the overall compute time significantly. V. Gadepally et al., "The BigDAWG Polystore System and Architecture," *2016 IEEE High Performance Extreme Computing Conference*.

by leveraging translators across common programming and data models," Gadepally said.

BigDAWG users can write their applications in popular programming languages for databases, such as SQL, Graph, Array, and Text, because BigDAWG's tools can translate queries among different systems. Although BigDAWG integrates data from diverse engines, it allows developers to exploit the full set of capabilities and the full performance of any database underlying their applications. This benefit is achieved because the BigDAWG modular architecture permits users to customize their database usage; a middleware layer handles various queries, and "islands"—which comprise a data model, a query language or set of operators, and one or more database engines—confine the programming to just the portions of the multiple databases necessary to enable the application.

"We believe that polystores such as BigDAWG will play a big part in the future of complex data management," Gadepally said. "We've held successful workshops at the 2016 and 2017 IEEE International Conferences on Big Data and the 2018 and 2019 Very Large Data Bases conferences. Through these and other outreach efforts, we have been surprised by the number of disciplines and research efforts that are looking for complex data management solutions," he added.

For the near future, the BigDAWG researchers are investigating applications of relevance to the U.S. Navy, Department of Veterans Affairs, and Air Force, and are looking at ways to introduce security and access control for polystore systems.

Polystores such as BigDAWG will play a big part in the future of complex data management.

For the medical community, a polystore solution like BigDAWG, which is available as open-source software at https://bigdawg.mit.edu, may allow developers to create applications that provide clinicians with fast analytics to aid in making decisions about diagnoses and treatments, and that enable medical researchers to make new discoveries.