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Researchers propose an approach to surgically removing cancerous tissue based on real-time imaging of tissue oxygen concentration-based fluorescence signal.

Real-time hypoxia imaging for surgical guidance

In the surgical treatment of cancer, distinguishing between tumors and healthy tissues is critical. Fluorescent markers can help to do this, by enhancing the contrast of tumors during surgery. Some markers show a phenomenon called “delayed fluorescence” (DF) which relies on detecting “hypoxia” (or low oxygen concentration), a condition often presented by tumors. The real-time imaging of hypoxia can provide a high contrast between tumors and healthy cells. This can allow surgeons to remove the tumor effectively. However, real-time hypoxia imaging for surgical guidance has not yet been achieved.

In a new study published in Journal of Biomedical Optics (JBO), researchers proposed an optical imaging system that enables real-time imaging of tissue oxygen concentration for tumors presenting both chronic or transient hypoxia. The team achieved this by making use of an endogenous molecule called protoporphyrin IX (PpIX), which exhibits DF in the red to near-infrared region.

“This is a truly unique reporter of the local oxygen partial pressure in tissues. PpIX is endogenously synthesized by mitochondria in most tissues, and the particular property of DF emission is directly related to low microenvironmental oxygen concentrations,” explains Brian Pogue, Chair of Medical Physics at University of Wisconsin-Madison, Adjunct Professor of Engineering Sciences at Dartmouth College, and senior author of the study. “Healthy cells will show little to no DF, because it is quenched in the presence of molecular oxygen.”

The technical challenge in detecting DF is due to its low intensity; background noise makes it difficult to detect without a single photon detector. The team overcame this problem using a highly sensitive time-gated imaging system, which allows signal detection within a specified time window only. This greatly reduces the background noise and enables a wide-field direct mapping of oxygen partial pressure (pO2) changes with the acquired DF signal. The result is real-time metabolic information, a useful map for surgical guidance.

Lead author Arthur Petusseau, a doctoral candidate in Engineering Sciences at Dartmouth College, explains: “Acquiring both prompt and delayed fluorescence in a rapid sequential cycle allowed for imaging oxygen levels in a way that was independent of the PpIX concentration.” Petusseau’s team demonstrated the efficacy of their technique using mice models of pancreatic cancer, which exhibited hypoxic tumors. The DF signal obtained from the cancerous cells was over five times stronger than that from surrounding healthy oxygenated tissues. The signal contrast was further enhanced when the tissues were palpated before imaging to further enhance transient hypoxia.

According to Frédéric Leblond, Professor of Engineering Physics at Polytechnique Montreal and JBO Associate Editor, “The results reported by Petusseau’s team suggest hypoxia imaging as an efficient approach to identifying tumors in cancer treatment. PpIX DF detection uses a known clinical dye and an already-approved in-human marker, with great potential for surgical guidance, and more.” Petusseau notes that the imaging of pO2 in tissues could also enable control of tissue metabolism. This, in turn, would help us better understand the biochemistry involved in oxygen supply and consumption.

Read the full article


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Health and fitness are becoming more manageable, thanks to wearable devices and mobile applications promoting physical activity, calorie counting, and more. These technologies commonly rely on tracking activity and other biomarkers, such as heart rate and blood oxygenation, via body-worn sensors. Many of these sensors are optical in nature, so their functionality depends on the interaction of light with multiple layers of skin tissue and their constituents.

How reliable are wearables? Currently, reliability may depend on whether the body in question is overweight or has darker skin. Recent studies indicate that some wearables have higher levels of error, especially for bodies that have darker skin tones and elevated body mass index (BMI)—and error rates increase as you move from overweight individuals to those with severe obesity.

Toward improving the accuracy of health-dependent biomarkers in wearable devices, a team from Florida International University and Texas A&M University recently reviewed current knowledge of different skin layer parameters that cause changes in optical properties. As reported in *Journal of Biomedical Optics* (JBO), they found that optical properties, such as absorption, scattering, autofluorescence, and optical propagation of the light through the skin, change with excess body fat.

Obesity increases the thickness of many skin layers, making some of the vasculature in the dermis harder to reach by light used in some of the wearables. Water concentration in the epidermal skin layer is also a factor: individuals with obesity have lower skin hydration. Similarly, the concentration of blood vessels in the skin is impacted by increased obesity. All these changes influence light absorption.

While it is well known that skin pigmentation governs light absorption, the team found that none of the data they reviewed addressed melanin production in the epidermal skin layer as dependent on or correlated with increasing BMI. They note that the high prevalence of obesity among African Americans and Hispanics makes melanin a noteworthy chromophore to factor into adequate light transport models for biomarkers.

Advocating for better evaluation of the limits of wearable health technologies when used by individuals with obesity, the team calls for experimental validation of their results, so that future models and optical methods may be confidently tailored to populations with obesity.

This is increasingly urgent as the prevalence of obesity is rising. In the US, according to the Centers for Disease Control and Prevention, it rose from 31 percent in 1999–2000 to over 42 percent in 2017–2018, and severe obesity increased from 4.7 percent to 9.2 percent.

According to corresponding author Jessica C. Ramella-Roman, whose Medical Photonics Laboratory at Florida International University led the study, “On the whole, this study highlights the need for better inclusion of diverse populations in all types of fundamental studies. Technology embodies assumptions regarding the optical properties of the skin and other biological environments, and those assumptions are based on research that was limited in terms of diversity. A more personalized approach is needed to better serve all groups.”
Kernel Flow: a wearable device for noninvasive optical brain imaging

A new wearable helmet-shaped device monitors brain activity

Recent advances in brain imaging techniques facilitate accurate, high-resolution observations of the brain and its functions. For example, functional near-infrared spectroscopy (fNIRS) is a widely used noninvasive imaging technique that employs near-infrared light (wavelength >700 nm) to determine the relative concentration of hemoglobin in the brain, via differences in the light absorption patterns of hemoglobin. Most noninvasive brain scanning systems use continuous-wave fNIRS, where the tissue is irradiated by a constant stream of photons. However, these systems cannot differentiate between scattered and absorbed photons. A recent advancement to this technique is time-domain (TD)-fNIRS, which uses picosecond pulses of light and fast detectors to estimate photon scattering and absorption in tissues. However, such systems are expensive and complex and have a large form factor, limiting their widespread adoption.

To overcome these challenges, researchers from Kernel, a neurotechnology company, developed a wearable headset based on TD-fNIRS technology. This device, called “Kernel Flow,” weighs 2.05 kg and contains 52 modules arranged in four plates that fit on either side of the head. The specifications and performance of the Kernel Flow system are reported in the Journal of Biomedical Optics (JBO).

The headset modules feature two laser sources that generate laser pulses less than 150 picoseconds wide. The photons are then reflected off a prism and combined in a source light pipe that directs the beam to the scalp. After passing through the scalp, the laser pulses are captured by six spring-loaded detector light pipes that are 2 mm in diameter and then transmitted to six hexagonally arranged detectors 10 mm away from the laser source. The detectors record the photon arrival times into histograms and are capable of handling high photon count rates (those exceeding 1 × 109 counts per second).

To demonstrate its performance, the Kernel Flow system was used to record the brain signals of two participants who performed a finger-tapping task. During the testing session, histograms from more than 2,000 channels were collected from across the brain to measure the changes in the concentrations of oxyhemoglobin and deoxyhemoglobin.

While the results are promising, Field acknowledges the need for more testing as near-infrared light is absorbed differently by certain hair and skin types. “We are currently collecting data with Kernel Flow to demonstrate additional human neuroscience applications. We are also in the process of evaluating the performance of the system with different hair and skin types,” he says. Kernel Flow packages large-scale TD-fNIRS systems into a wearable form, delivering the next generation of noninvasive optical brain imaging devices. Systems like Kernel Flow will make neuroimaging much more accessible, to enable widespread benefits in health and science. For instance, the FDA recently authorized a study using the Kernel Flow system to measure the psychedelic effect of ketamine on the brain. JBO guest editor Dimitris Gorpas of the German Research Center for Environmental Health remarks, “This is the world’s first wearable full-head coverage TD-fNIRS system that maintains or improves on the performance of existing benchtop systems and has the potential to achieve its mission of making neuromeasurements mainstream. I am really looking forward to what the brain has yet to reveal.”

SUMMARY
Many brain-imaging techniques have uncomfortable scanning procedures and require expensive devices. Researchers from Kernel, a company based in the US, have developed a wearable headset called “Kernel Flow” that monitors brain activity using functional near-infrared spectroscopy technology. The device’s performance matches that of conventional time-domain functional near-infrared spectroscopy systems and can facilitate high-resolution optical brain imaging.

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A noninvasive and reagent-free technique for the efficient detection of COVID-19

The novel coronavirus, or SARS-CoV-2, which causes the highly contagious COVID-19, has infected millions of people worldwide. The global spread of this deadly pandemic has triggered widespread research on infection control. However, controlling the spread of COVID-19 is challenging for many reasons. Some patients show a variety of non-specific symptoms ranging from headaches to a cough. However, many patients with COVID-19 remain symptom-free even after getting infected, but still may have the potential to infect others. This makes initial triage and diagnosis difficult. And while reverse transcription polymerase chain reaction (RT-PCR) techniques are currently the gold standard, they have certain limitations.

RT-PCR involves the transportation of samples to a clinical laboratory for testing, which poses logistical difficulties. It also requires the use of reagents, which could be in short supply and may be less effective when the virus mutates. Moreover, RT-PCR tests can be time-consuming and less sensitive in asymptomatic individuals, rendering them unfeasible for widespread rapid screening.

Thus, biomedical researchers are trying to devise novel methods for better detection of COVID-19 infections in point-of-care settings, without the need to send away samples for testing. Recently, researchers from Canada developed one such technique using saliva samples. Unlike nasopharyngeal swabs, saliva sampling is safer and noninvasive. In their article published in the Journal of Biomedical Optics, they describe a new reagent-free detection technique that is based on machine learning (ML) and laser-based Raman spectroscopy.

Raman spectroscopy is routinely used by researchers to determine the molecular composition of samples. Put simply, molecules scatter incident photons (particles of light) in a unique manner that is dependent on underlying chemical structures and bonding. Researchers can sense and identify molecules based on their characteristic Raman “fingerprint” or spectrum, which is obtained by shining light at samples and measuring the scattered light. Raman spectroscopy is efficient in identifying specific chemical groups, which are indicative of underlying chemical structures and bonding.

COVID-19 can cause chemical changes in the composition of saliva. Based on this knowledge, the research team analyzed 33 COVID-19-positive samples clinically matched with a subset of a total 513 COVID-19-negative saliva samples collected from the Pointe-Saint-Charles COVID-19 testing clinic in Québec, Canada. The Raman spectra they obtained were then trained on multiple-instance learning models, instead of conventional ones.

Senior author Frédéric Leblond, with appointments at Polytechnique Montréal, Centre de recherche du Centre hospitalier de l’Université de Montréal, and Institut du cancer de Montréal, Canada, explains this more simply: “Our machine learning method uses information from each individual Raman spectrum. It does not use averaged data, and so it can integrate more information from the saliva samples to give a highly accurate output.”

The results from this method indicate an accuracy of about 80 percent, and the researchers found that taking sex at birth into consideration was important in achieving this accuracy. Although saliva composition is affected by time of day as well as the age of the test subject and other underlying health conditions, this technique can still prove to be a great candidate for real-world COVID-19 detection.

Katherine Ember, a postdoctoral researcher at Polytechnique Montréal, Canada, and first author of the study, sums up, “Our label-free approach overcomes many limitations of RT-PCR testing. We are working to commercialize this as a faster, robust, and low-cost system, with potentially higher accuracy. This could be easily integrated with current viral detection workflows, adapted to new viruses and bacterial infections, as well as accounting for confounding variables through new machine learning approaches. In parallel, we are working on reducing the testing time further by using nanostructured metallic surfaces for containing the saliva sample.” These findings can facilitate better COVID-19 detection in addition to paving the way for new tools for other infectious diseases.
Optical tools for measuring blood oxygenation

Hemoglobin imaging and sensing helps identify significant biomarkers via a growing range of optical techniques.

At the level of your entire body or any particular organ, blood oxygenation provides a vital sign of health or disease. It is recognized as the fifth vital sign, after temperature, blood pressure, pulse rate, and respiratory rate. Blood oxygenation happens thanks to hemoglobin, a protein in red blood cells that carries oxygen from your lungs to the rest of your body.

Based on the absorption of light by hemoglobin, optical tools make it possible to detect blood oxygenation and blood flow. The pulse oximeter is a well-known example. Simple to use, it clips onto a finger (or toe or earlobe) and peers beneath the skin noninvasively to provide continuous, vital information about levels of oxygen in the blood. An essential item for reducing complications in emergency medicine, it's also routinely used in clinics and at home—screening newborns for heart disease, tracking conditions like sleep apnea, and more.

Beyond pulse oximetry, many newer optical technologies are emerging to detect hemoglobin-based biomarkers and facilitate real-time care for a wide range of debilitating illnesses—from rheumatoid and vascular diseases to neurodegenerative disease and cancer. These methods vary widely—in terms of not only sensitivity and accuracy, but also imaging depth and resolution, as well as physical size and cost—which can make it challenging to select the appropriate tools and understand the relative limitations of different methods.

A group at the University of Cambridge offers a helpful guide to advance the field, with a review of optical tools for noninvasive hemoglobin sensing and imaging, published in the Journal of Biomedical Optics (JBO). Directed by Sarah E. Bohndiek, professor of biomedical physics, the team considers the ability of different technologies to determine hemoglobin biomarkers like oxygenation, weighing factors that influence their practical application.

Pulse oximetry and beyond

Starting with pulse oximetry, the team explores a variety of methods, indicating their strengths and limitations, as well as clinical uses or directions for research and development. Pulse oximetry typically uses alternating LEDs at two different wavelengths to obtain a ratio of oxygenated and de-oxygenated hemoglobin states, based on the way light is absorbed by body tissue, such as a fingertip. Because of the way the light pulses alternate over time, the measurements are vulnerable to motion. Also, skin pigmentation affects light absorption, resulting in less accurate measurements for patients with darker skin. The authors review the record of research and offer perspective on this evolving technology, as it develops toward better-calibrated and more efficient devices.

Some of the other technologies they explore in this comprehensive work include tools for reflectance imaging of hemoglobin. While light can be transmitted through tissue and detected on the other side by a sensor that measures how much light was absorbed, it can also be reflected so that it bounces back to the light detector. This allows the creation of a kind of 3D map based on the qualities of the detected light, which can also provide vital information beyond oxygenation, such as vascular morphology and disfunction.

Reflectance methods include point-scanning spectroscopy, multispectral imaging, and hyperspectral imaging. These are finding a growing number of clinical uses, from nailfold capillaroscopy for real-time imaging of capillaries and blood flow, to endoscopy and retinal imaging. Because hemoglobin can bind to several other molecules—dependent on environmental conditions—such as inflammation in arthritic joints, to guiding surgical procedures.

Where pulse oximetry and reflectance-based imaging fall short, depth-resolved imaging methods can achieve depths beyond a centimeter. Some of these methods are promising for detecting breast cancer as well as other cancer types, but with a wide range of other scenarios where deeper imaging information can contribute to diagnosis—from evaluating inflammation in arthritic joints, to guiding surgical procedures. These technologies can operate on different principles, including photoacoustics (detecting light absorption through sound), diffuse optics, or optical coherence tomography. Each has its strengths and limitations. For instance, whereas the scattering of light in the process of reflectance hinders some imaging techniques, diffuse optical imaging uses that phenomenon to obtain information. Techniques can be used separately or in combinations to obtain complementary results.

Bohndiek and team recognize that the cost and complexity of various technologies, as well as ease of use and interpretability of data, will determine how well they catch on. They highlight new directions for research to overcome present limitations.

According to Brian Pogue, Editor-in-Chief of JBO and Director of the Department of Medical Physics at the University of Wisconsin-Madison, “These techniques are at the vanguard of what has been the most successful in biomedical optics, pulse oximetry and blood oxygenation measurement. The key to advancing this field is to push for improvements to the approaches and technologies that measure deeper, or measure new physiological parameters. This review does a wonderful job of describing this and pointing out new key directions.”

As these light-based technologies develop, they will alter the landscape of healthcare, by increasing equitable access, enabling self-monitoring, and enhancing the detection and treatment of disease.

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The BitMap Exercise: progress toward standardization in diffuse optics

International scientific collaborative initiative aims to incentivize the use of standard protocols for assessing and comparing diffuse optics systems used in medical diagnosis.

Among the various optics-based tools used in diagnostics, diffuse optics (DO) is rapidly emerging as one of the most attractive technologies. The technique is based on analyzing how light is absorbed and scattered by biological tissues, which relates to the tissue chemical composition and structure. One of the key advantages of DO is that it is noninvasive (it uses low-power near-infrared light). Moreover, it can be used to probe tissues at depths of up to a few centimeters and can even detect functional activation and oxygenation of brain or muscles. DO is, therefore, likely to assume a central role in the diagnosis and monitoring of patients both at the hospital and at home.

However, even when using the same DO principles to study or diagnose a given disease, clinics and laboratories around the world use vastly different platforms and techniques. This poses a challenge when trying to assess their performance, which is necessary to identify malfunctioning equipment, benchmark developments in DO technology, establish common ground for comparing techniques and instruments, and allow reliable reuse and interpretation of generated open data. Fortunately, a collaboration between 12 European institutions—in the framework of the European Union’s Horizon 2020 Marie Skłodowska-Curie Innovative Training Network “BitMap,” led by Hamid Dehghani, University of Birmingham—is making great strides towards realizing performance assessment and standardization (PAS) in the field of DO. Leveraging over two decades of joint research efforts, the initiative is centered around three protocols developed previously for assessing the performance of DO instruments. This initiative envisions three main actions: Action 1 involves the collection of experimental data, Action 2 focuses on making this data available as open data, and Action 3 revolves around a common analysis of the data using the same tools and techniques.

A study published in the Journal of Biomedical Optics (JBO) presents the results obtained in the context of Action 1. The BitMap exercise presented in this paper is the largest multi-laboratory comparison of DO instruments, encompassing 12 institutions and 28 systems. Through this comparison, the study aims to enforce the culture of PAS in the DO community and beyond and propose a common methodology that can be adopted in other environments. An interesting outcome of this particular work is the conception of simple numeric values, called synthetic indicators, for each of the tests employed. These indicators allow for easy comparison across the gamut of instruments enrolled.

Comparing the performance of different DO instruments is tricky. The researchers settled on three internationally adopted protocols (BIP, MEDPHOT, and NEUROPT) to challenge each DO system. The BIP protocol served to characterize the most basic optical performance of each instrument, whereas the MEDPHOT protocol characterized how well each instrument could recover homogeneous optical properties, i.e., absorption and reduced scattering coefficients. Finally, the NEUROPT protocol tested how well each system could detect inhomogeneities in a sample by focusing on measures related to contrast. Additionally, the researchers agreed on three different phantom kits, each of which was especially tailored for one of the protocols (a “phantom” refers to an artificial structure, typically used for calibration and testing, that emulates certain properties of human tissue).

The experiments consisted in executing an assortment of relevant tests from each protocol on its respective phantom kit, using each of the DO instruments. The researchers then compared the results obtained from these experiments to understand which instruments and techniques showed best performance, how reproducible the results were, and how much variability there was between measurements made using different systems. They found a substantial difference in hardware performances across different systems, which helped them identify some critical issues related to performance assessment in DO.

The researchers plan to deploy the entire dataset gathered through Action 1 into an open data repository (Action 2). This would help them and others to analyze and compare specific aspects of the DO systems (Action 3). One of the ultimate objectives of the project is to identify and mitigate uncertainties and measurement artifacts for each instrument and analysis method, thereby unlocking their full potential.

“Great advances in physics derived from precise measurements of specific physical quantities – planet orbits, speed of light, particle masses, etc. Photon migration through the human body is complicated by the biological variability, but not the basic physics underlying it,” says senior author Antonio Pifferi, Politecnico di Milano, Italy. “We can disentangle the uncertainties and artifacts produced by the instruments and analysis tools from the biological variability, with great benefit for clinical use.” These efforts will open doors to a powerful and reliable DO technology, enabling more accurate and convenient diagnostics.

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The *Journal of Biomedical Optics* (JBO) is an open access journal that publishes peer-reviewed papers on the use of novel optical systems and techniques for improved health care and biomedical research.