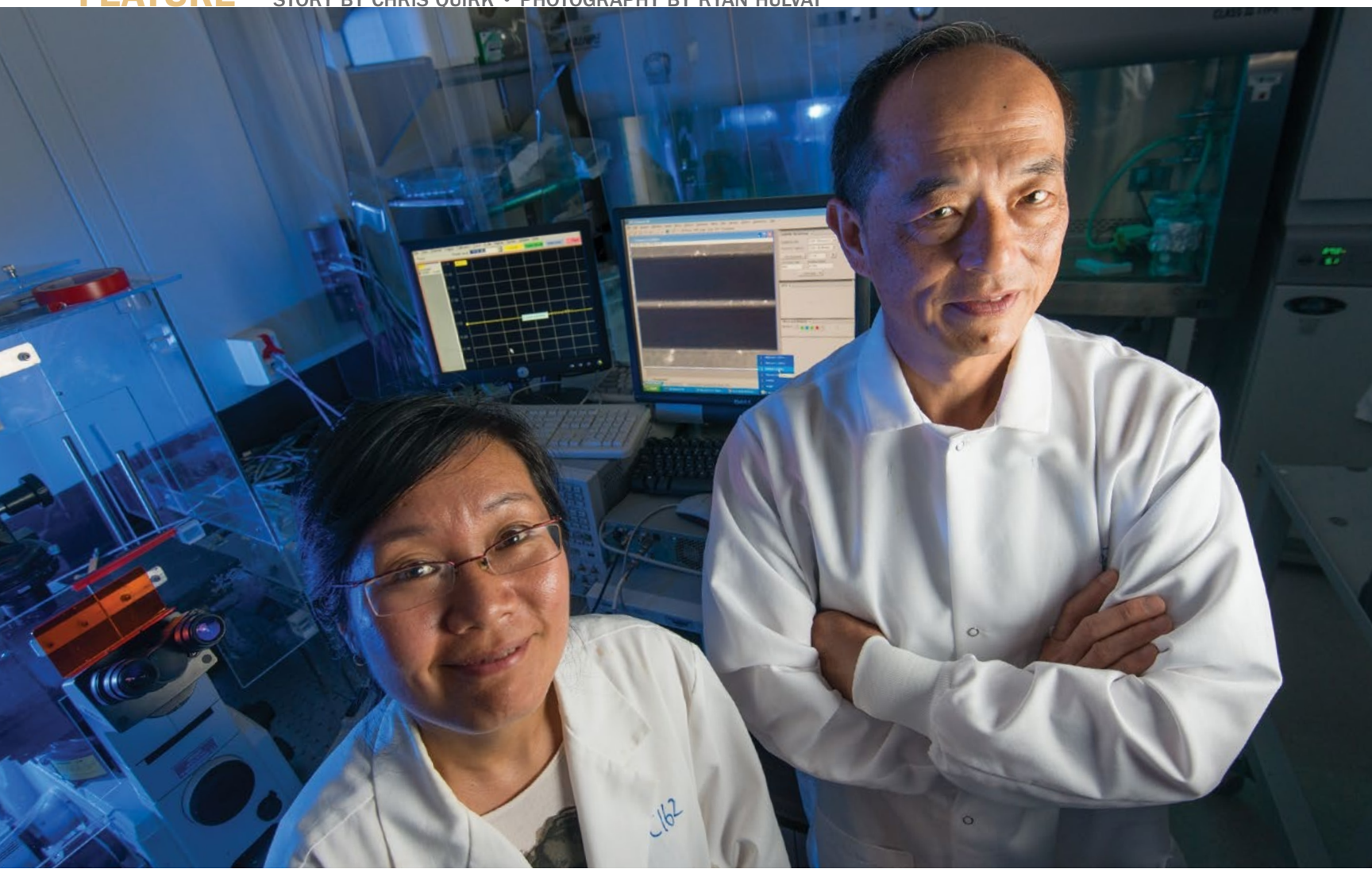
STORY BY CHRIS QUIRK • PHOTOGRAPHY BY RYAN HULVAT

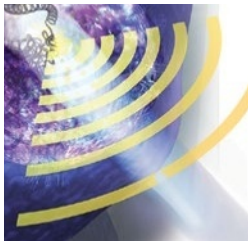


THE POWER OF A PULSE

A TEAM LOOKS PAST THE CELL MEMBRANE TO DNA SEQUENCING.

Xuanhong Cheng and James Hwang have developed a technique that enables live cells to be probed with focused beams in the terahertz range.

Nature does not reveal its secrets to just anyone, and many of its mysteries are beyond our ability to perceive them with our unaided senses. Scientists have built massive tools—like orbiting telescopes and supercolliders—that can reveal hidden enigmas from the intergalactic scale down to the minuscule workings of subatomic particles.



If a team of Lehigh researchers is successful, one of the next high-tech tools to unveil the unseen will be a device that can identify substances at the molecular level—and potentially decipher DNA—and that will fit into the palm of your hand.

James Hwang, professor of electrical and computer engineering; Xuanhong Cheng, assistant professor of materials science and engineering and bioengineering; and Cristiano Palego, a research scientist, are in the early stages of developing a handheld sensor that can identify bacteria quickly.

The immediate application is to detect pathogens in a combat zone or other security-related venue, and the team has received initial and follow-up grants from the U.S. Defense Department. Assisting in the research are Caroline Multari and Yaqing Ning, Ph.D. candidates, and Caterina Merla, a visiting scientist from ENEA, an Italian government research agency.

The first phase of the project was to create a sensor to

determine if a given cell is alive or dead.

"It's a primary task," says Cheng, "because for a pathogen to be dangerous it generally has to be viable."

Testing for viability is typically done with optical instruments, which are bulky and do not lend themselves easily to miniaturization. Another method is to fire electrical pulses in a range of frequencies at a cell and see what bounces back, like radar. This technique, called a frequency domain electrical test, can be susceptible to false positives. Multiple dead cells, for example, can sometimes return a numerical value indicating a live cell.

To overcome this problem the team is using a time domain technique, firing a pulse at controlled intervals at target cells and analyzing the results.

"We're not experimenting with the frequency too much at the moment, as it has a thermal effect," says Palego. "The time-domain pulse excites the cell's components without heating up the cell."

"The beauty of time domain," says Hwang, the project's principal investigator, "is that you can easily generate a short pulse that encompasses many frequency components. But you have to disentangle the frequency domain data from the time-domain pulse; otherwise, it's a big mess. For that we need to do frequency domain studies."

The analysis of cell viability looks first to the cell membrane. If the membrane has been breached or has lost its integrity in some way, it's a good sign the cell is no longer viable. When excited by a pulse, the signature of the returning vibrations can show if a cell membrane has been compromised, much like the difference in tone between an intact drum head, which resounds emphatically when struck, and a split one, which returns a flaccid thud.

Working on mammalian cells, which are relatively large, the team has succeeded in this initial phase of the project. The next step is to obtain more information about the interior of the cell beyond the membrane. After the team targets smaller cells and organisms, eventually at the molecular level, it will seek to optimize and miniaturize its device.

Exciting molecules requires a focused beam in the terahertz range, says Cheng. "Larger wavelengths, even at the gigahertz level, will wash over molecules like a huge, rolling wave without creating any measurable activity in the molecule."

Terahertz waves, however, don't propagate well in fluid, or even humid air, and fluid is necessary to keep the target cells intact. The solution, says Hwang, hinges on positioning.

"We want to remove as much of the fluid between the sensor and the target as possible, keeping the cell alive, and getting the sensor right on the target," he says. "We're working on innovative technology to make that happen."

Making the tool workable as a handheld device increases the challenge. Calibration is an issue with sensors, so developing a technique that enables the device to quickly calibrate itself is crucial. Moreover, all the components must be scaled down, and data analysis, which is now done manually, must be automated.

"Eventually, we see all of this being miniaturized onto a single chip," says Palego. "CMOS [complementary metal-oxide semiconductor] technology is very suitable for this kind of project and it is a common trend."

"One of the strengths of our team," says Cheng, "is the close relationship we have with collaborators who can do state-of-the-art CMOS production quickly and efficiently. Once we have the chip designed, we can go to large scale production rapidly."

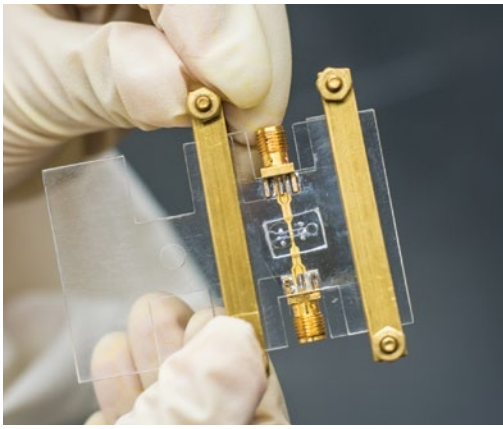
The long-term goal of the project is to perform abbreviated DNA sequencing on target cells and to identify them unambiguously.

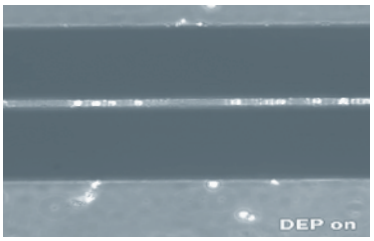
"This is the outer reaches of what we hope to do," says Cheng. The process would start by creating a small pore in the target cell with a tightly focused electric pulse. Cell contents could then be extracted from the cell interior through the pore. Because DNA has an electrical charge, a charged probe can coax it out.

"Graphene is an interesting material for this," says Palego, "and it could allow us to activate the pore, and use it as a tool." The pore itself could be used to obtain particular bits of information—such as the length of time it takes for a section of the unfurled DNA strand to pass through the pore—while doing an abbreviated sequencing of the DNA or highlighting a unique identifier.

"The technology is there, but there is plenty to do to get all the parameters right," says Cheng.

Military applications are the impetus for the project, says Palego, "but there are many other possibilities. On the medical side, these include not just identifying cells but monitoring cells to check medication effectiveness, which could be done at home. Other potential applications include therapeutic uses, such as pulsing electromagnetic energy into cancer cells to disrupt their viability."





Using CMOS technology, the researchers hope to develop a chip with sensors that can identify cells, confirm their viability and perform abbreviated DNA sequencing.

Cheng elaborated further: "The civil and medical possibilities are very broad. For example, instead of going to a lab for a blood analysis, you could have it done virtually anywhere with a tool like this. This would increase point-of-care possibilities for underserved populations."