Ewa Stępień (left) and Paweł Moskal seen through their plastic-based PET scanner.

PHOTO: ZACK SAVITSKY/SCIENCE

MEDICAL PHYSICS

Twist on PET unlocks hidden signals

Overlooked emissions from exotic positronium atoms open unexpected window for diagnosing cancer and other diseases

ZACK SAVITSKY, in Kraków, Poland

Paweł Moskal opens a closet in the corner of his lab and looks back with a grin. "This is something very special since the communistic times," he says, reaching for a rustic, lead-walled safe designed to hold nuclear materials. From the safe, he pulls out a small, yellow wafer with a single black dot of radioactive sodium-22 at its center. Later, he will inject the sodium into human tissues, where the glow from its decay will be captured by a positron emission tomography (PET) scan.

For 50 years, physicians have used PET scanners to detect diseases such as cancer and Alzheimer's. But Moskal, a physicist here at Jagiellonian University, has quietly pioneered a technique to squeeze additional information out of the devices. By probing the lifetime of an exotic atom called positronium that forms within the body during PET scans, Moskal thinks he can use this new information to better identify different types of cancer, monitor disease progression, and guide treatment plans.

The technique is catching on with several other labs around the world. If Moskal and those colleagues can convince the medical industry to buy in, "it could really open up a new dimension in nuclear medical imaging," says Katia Parodi, a physicist at the Ludwig Maximilian University of Munich who collaborates with a group in Japan that does positronium imaging. "Now I think many people are appreciating the huge potential."

Traditional PET scans rely on radioactive tracers that decay in minutes to hours by emitting a positron (the antimatter counterpart of an electron). When the positron encounters an electron in the body, the two annihilate in a flash, sending two photons flying in opposite directions. Detected by sensors in the PET scanner, they are traced back to their origin in the patient. By binding the tracers to molecules the body naturally processes, such as glucose, scientists can monitor the rate of metabolism in different tissues to look for hallmarks of disease. For instance, cancer cells metabolize glucose much faster than normal cells. As a result, diseased regions eat up more tracer and glow more brightly on the scan.

Because PET scans trace biological function rather than structure, they can provide earlier warnings than other imaging techniques. But they aren't perfect. Because of their limited resolution and ambiguous factors that influence metabolism rates, they must be confirmed with biopsies. Furthermore, access to PET scanners is limited. Seventy countries have none at all, and most—including Poland—have fewer than one device per million people. Struck by this disparity, Moskal hunted for a way to democratize the machines, which cost a few million dollars.

About half of that cost comes from rare-earth crystals used to register photons. Moskal realized he could replace those crystals with less sensitive but cheaper plastic detectors. To the surprise of his colleagues, by 2016, Moskal and collaborators had stacked the plastic detectors in layers to build a prototype PET scanner with sufficient sensitivity. Moskal says their latest version, expected in 2028, should cost just 10% to 20% as much as commercial machines and have even higher sensitivity.

Moskal sought a way to put the additional light-gathering power of his plastic PET sensors to use. From his background in nuclear physics, Moskal knew of a process traditional scans overlook. Positrons and electrons don't always instantly annihilate—about 40% of the time, they instead bind to form a temporary, atomlike state called positronium. Within a few nanoseconds, the positronium collapses and annihilates itself, giving off a delayed pair of photons.

Working with Jagiellonian medicinal physicist Ewa Stępień, Moskal began to investigate physiological features that control the speed of that positronium decay. Positronium forms in the gaps between molecules in tissues, where it can hide from stray electrons that cause it to decay. Its lifetime is shorter in denser tissues with smaller pores and in voids with reactive molecules such as oxygen. As some tissues become cancerous, their pores shrink and oxygen levels fall, and Stępień and Moskal wondered how these factors would affect positronium lifetimes.

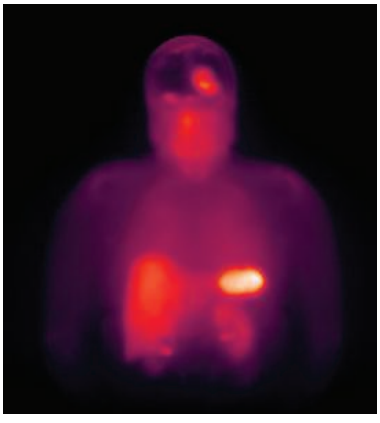
Measuring those lifetimes with their machine required some tweaks. PET scans usually detect only the two photons given off by annihilation. But by turning to a tracer that emits an additional photon at the time a positronium atom forms, Moskal and Stępień could clock the elapsed time between this "prompt" photon and the annihilation photons to calculate the positronium lifetime. They designed

their scanner specifically to look for the prompt photon, which is typically disregarded as noise.

Over the past few years, the team has demonstrated the potential medical value of positronium imaging. In 2021, they reported the first positronium image, comparing heart cancer cells and healthy fat cells extracted from patients. The study showed the cancer cells had significantly shorter positronium lifetime than the healthy ones. Last year, they imaged a brain cancer patient and found that positronium lifetimes in the tumor were shorter than those in healthy brain tissues.

These in vivo images were relatively fuzzy and weak, because the tracer they relied on, gallium-68, emits a prompt photon only in about 1% of its decays. Using a tracer such as scandium-44, which emits an initial photon 100% of the time, would increase the number of registered events and boost the sensitivity by a factor of 100, Moskal says.

With the promise of heightened sensitivity, Stępień dreams of using positronium to do "virtual biopsies," reconstructing tissue composition without the need for surgery. Parodi imagines using positronium not only to monitor how cancer patients respond to radiation therapies, but also to investigate the efficacy of experimental ones.



An image made from triple-photon events is a step toward measuring positronium lifetimes.

The excitement is spreading to other labs. A team at the University of Pennsylvania has used its PET scanner to practice measuring positronium lifetimes in small inanimate objects in preparation for human imaging. In Switzerland, a collaboration between the University of Bern and Siemens Medical Solutions, which sells PET scanners, recently measured positronium lifetimes in the organs of three patients. And at the National Institute of Radiological Sciences in Japan, researchers investigated how positronium could be used to image hypoxia, or oxygen deficiency, which often corresponds with cancer progression and drug-resistance.

The field has been boosted by a wave of full-body PET scanners, which are sensitive enough to register all three positronium photons with minimal upgrades. "Almost by accident, they are able to perform these measurements," says Adrien Hourlier, a physicist at Strasbourg University who led a review of positronium imaging last year. "The advent of full-body scanners really helped buy some credit into the idea."

But the technique still faces hurdles. Chief among them will be untangling the different factors that control positronium lifetime in a given tissue. "It could reveal something meaningful, but at the moment … it's not clear what the signal really corresponds to," says Robert Seifert, a nuclear physician working with the Bern team.

Getting the medical industry on board will be another challenge, because large-scale adoption would require upgrading detectors and retraining staff. It's a battle all too familiar to Moskal, who struggled to commercialize his plastic PET detectors with companies that told him the devices wouldn't raise their bottom line. But he thinks the promise of positronium imaging will eventually carry the day—and maybe help him sell his cheaper detectors, too.

"We are not losing the hope," Moskal says. He and Stępień are currently developing a full-body version of their PET scanner as well as a mobile version. They've also just taken their first images of human tissues with the promising scandium-44 tracers, and they are now racing the groups in Pennsylvania, Switzerland, and Japan to gain regulatory approval for the tracer in live patients.

"We are basically seeing the birth of a new type of imaging," Hourlier says. He likens it to the gradual embrace of the first digital cameras. "Progressively, they're going to get better and better, and then people will see the actual gain." □

RESEARCH BRIEFS

TEETH FILL GAP IN HUMAN HISTORY

Ancient teeth from between 2.6 million and 2.8 million years ago show early members of our genus *Homo* coexisted with a newly discovered species of *Australopithecus*, according to a report this week in *Nature*. In eastern Africa, *Australopithecus afarensis*—the 1-meter-tall upright walking apes whose members included the famous Lucy skeleton—disappeared about 3 million years ago. By 2 million years ago, early *Homo* species were well established. What happened in between is now clearer thanks to 13 fossil teeth found in 2015 and 2018 from a site called Ledi-Geraru in northern Ethiopia. Three teeth belonged to *Homo* species. The rest, the researchers say, came from a previously unknown and still unnamed species of *Australopithecus*. —Bridget Alex

GENETIC CLUES FOUND FOR ME/CFS

The largest genetic study of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has identified clues about the condition, which afflicts millions with extreme exhaustion and difficulty thinking clearly. By analyzing DNA from more than 15,000 people diagnosed with the illness, U.K. researchers identified eight genomic regions associated with the disorder, including some that are linked to immune responses to infection. Although treatments and diagnostics for ME/CFS remain distant, the findings, posted in a preprint last week, will help direct future research and validate ME/CFS as a biological condition, says University of Amsterdam biopsychologist Jos Bosch. It's "an important corrective to psychologizing 'all in the mind' perspectives on the disease," he says. —Catherine Offord

DEVICES LEVITATE IN THIN AIR Researchers have made featherweight devices that could levitate in sunlight indefinitely to probe an understudied region of the upper atmosphere. The centimeter-scale aircraft, made from two thin membranes connected by tiny struts, absorb light on one side and reflect it on the other. That results in temperature differences across the device that are big enough to propel the thin, high-altitude air around and through it, keeping it aloft. Although the devices have only been tested in the lab, their inventors report this week in *Nature* that swarms of them could be outfitted with sensors and deployed to explore the mesosphere, a layer of air 50 to 80 kilometers up that's too thin for planes or balloons and too thick for space-based satellites. —Annika Inampudi