Wearable, stretchable sensor enables quick, continuous, noninvasive detection of solid-state skin biomarkers

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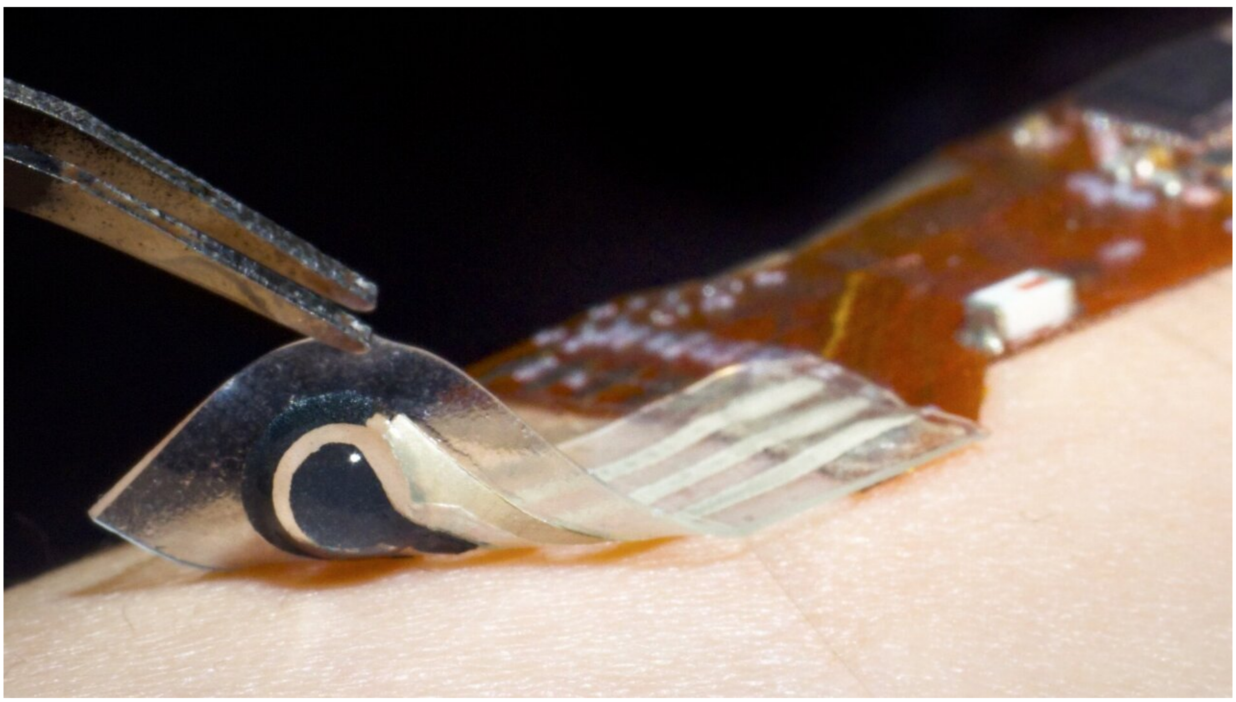

The sensor comprises an ionic electronic bilayer hydrogel that can detect solid state biomarkers from the skin. The sensor is connected to a flexible printed circuit board which transmits data wirelessly to a user interface. Credit: NUS iHealthtech

Detecting diseases early requires the rapid, continuous and convenient monitoring of vital biomarkers. Researchers from the National

University of Singapore (NUS) and the Agency for Science, Technology and Research (A*STAR) have developed a novel sensor that enables the continuous and real-time detection of solid-state epidermal biomarkers (SEB), a new category of health indicators.

Jointly led by Assistant Professor Liu Yuxin from the NUS Institute for Health Innovation & Technology as well as N.1 Institute for Health and the Department of Biomedical Engineering under the NUS College of Design and Engineering, and Dr. Yang Le, Principal Scientist and Head of the Sensors and Flexible Electronics Department of A*STAR's Institute of Materials Research and Engineering (A*STAR's IMRE), the research team's innovation offers a noninvasive method to monitor health by detecting biomarkers such as cholesterol and lactate—directly on the skin.

The team's wearable, stretchable, hydrogel-based sensor overcomes the limitations of current methods that rely on biofluid samples, such as blood, urine and sweat. This makes it a promising alternative for wearable, continuous, and real-time health monitoring, facilitating the early detection of conditions such as cardiovascular diseases and stroke.

It can also efficiently monitor athletes' lactate levels, an indication of exhaustion and tissue hypoxia, which affect their performance. This development is especially pertinent to areas including chronic disease management, population-wide screening, remote patient monitoring and sport physiology.

The team's findings were published in the journal *Nature Materials* on 12 June 2024. A*STAR's Institute of High Performance Computing and Institute of Molecular and Cell Biology, as well as Nanyang Technological University, Singapore also contributed to the research.

Innovating to overcome existing challenges

Monitoring biomarkers—chemicals found in blood or other body fluids that capture what is happening in a cell or an organism at a given moment—traditionally involves analyzing biofluids such as blood, urine and sweat. While effective, these methods come with challenges.

Blood tests are invasive and inconvenient, while urine analyses can be cumbersome and lack real-time capability. Probing biomarkers from sweat, though noninvasive, is limited by the difficulty of inducing sweat in inactive individuals and the discomfort of using sweat-inducing drugs. All these pose barriers to the early diagnosis and treatment of diseases.

SEBs offer a compelling alternative. These biomarkers, which include cholesterol and lactate, are found in the stratum corneum, the outermost layer of the skin, and have shown strong correlations with diseases such as cardiovascular disease and diabetes. However, detecting these biomarkers directly has been difficult. For instance, traditional solid electrodes lack the necessary charge transport pathways to enable electrochemical sensing of SEBs.

The NUS and A*STAR research team has overcome this challenge with their novel sensor design. When the device is worn on the skin, SEBs dissolve into the ionic conductive hydrogel (ICH) layer, diffuse through the hydrogel matrix, and undergo electrochemical reactions catalyzed by enzymes at the junction between the ICH and electronically conductive hydrogel (ECH) layer.

Relevant physiological data is then transmitted wirelessly to an external user interface via a flexible printed circuit board, providing continuous monitoring capabilities. The sensor is produced using a scalable and cost-effective manufacturing process called screen printing.

"Our novel hydrogel sensor technology is key to enabling the noninvasive detection of solid-state biomarkers on skin. The ionic conductive hydrogel layer that solvates the biomarkers and the electronically conductive hydrogel layer facilitates electron transport.

"This bilayer enables the sequential solvation, diffusion and electrochemical reaction of the biomarkers. Another highlight is the sensor's sensitivity with biomarkers being detected precisely even in low amounts," said Asst. Prof. Liu.

"This wearable sensor is the first-in-the-world that can monitor biomarkers on dry or non-sweaty skin. The sensor's novel bilayer hydrogel electrode interacts with and detects biomarkers on our skin, allowing them to become a new class of health indicators. The stretchable design enhances comfort and accuracy as well, by adapting to our skin's natural elasticity.

"This innovation can change the way we approach health and lifestyle monitoring, particularly for those living with chronic conditions requiring constant health monitoring," said Dr. Yang.

Reliable, sensitive and user-friendly

Unlike traditional sensors that require biofluid samples, this sensor can continuously and noninvasively monitor SEBs directly on the skin, making it valuable for remote patient monitoring and population-wide health screening.

In clinical studies, the sensor demonstrated strong correlations between the biomarkers detected on the skin and those found in blood samples. This validates the sensor's accuracy and reliability, suggesting it could be an alternative to blood tests for monitoring chronic diseases such as diabetes, hyperlipoproteinemia and cardiovascular conditions.

The sensor's sensitivity is another advantage, as it can detect solid-state lactate and cholesterol at very low levels. This level of sensitivity approaches that of mass spectrometry, which ensures precise monitoring of these biomarkers.

Additionally, the sensor's design reduces motion artifacts, which occur when the user's movements affect the placement of the sensor or its contact pressure to the skin, by three times compared to conventional counterparts. This new finding was successfully modeled mathematically. By minimizing disruptions caused by movement, the bilayer hydrogel ensures consistent and reliable readings, while the stretchable, skin-like nature of the device enhances user comfort.

"One of the possible applications of this technology is to replace the pregnancy diabetic test, commonly known as the glucose tolerance test. Rather than subject pregnant women to multiple blood draws, our sensor could be used to track real-time sugar levels conveniently in a patients' home, with a similar level of accuracy as traditional tests. This also can be applied to diabetes in general, replacing the need for regular finger-prick tests," Asst. Prof. Liu explained.

"Another potential application is to use the sensor in the daily monitoring of heart health, as cardiovascular disease accounts for almost one-third of deaths in Singapore. The research team has embarked on a research program to work closely with cardiologists in establishing clinical correlation between biomarkers—lactate, cholesterol, and glucose—with heart health," said Dr. Yang.

Rolling out next-gen sensors

The NUS and A*STAR researchers plan to enhance the sensor's performance by increasing its working time and sensitivity. Further, they aim to integrate additional solid-state analytes, broadening the sensor's applicability to other biomarkers.

The researchers are also collaborating with hospitals to provide additional clinical validation and bring the technology to patients, particularly for continuous glucose monitoring, as well as quantitative assessment of dynamic resilience.

More information: Ruth Theresia Arwani et al, Stretchable ionic–electronic bilayer hydrogel electronics enable in situ detection of solid-state epidermal biomarkers, *Nature Materials* (2024). DOI: 10.1038/s41563-024-01918-9

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