Wearable electronics

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Wearable sensing of solid analytes

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A bilayer hydrogel sensor is presented for continuous monitoring of solid epidermal biomarkers on human skin.

Biofluids such as sweat harbour various chemical biomarkers, including lactate, cholesterol and glucose[1], which indicate an individual's health status and fitness level. Chemical biomarkers possess complementary information to that obtained by biopotential measurements[2] and medical imaging[3] to predict and diagnose diseases and conditions. Continuous sensing of chemical biomarkers with high specificity and sensitivity underscores their indispensable role in healthcare.

Previous research predominantly focused on liquid sweat sensing[4,5], a method whose efficacy is constrained by the volume of liquid that can be collected. Consequently, sensing sweat from physically inactive subjects presents substantial challenges due to their low metabolic rates and minimal perspiration. Techniques such as iontophoresis and administering sweat-inducing pharmaceuticals are often employed to augment sweat production[6]. However, the prolonged use of iontophoresis may lead to skin irritation, while sweat-inducing drugs can cause severe side effects[7].

Sensing dried and accumulated sweat analytes (that is, solid epidermal biomarkers; SEBs) becomes an attractive alternative. SEBs collected from specific body parts of the subject represent the condition of those particular areas. Unlike liquid sweat, SEBs are less influenced by variables such as hydration status. However, SEBs are generally collected using adhesive tape strips and subsequently analysed via mass spectrometry[8]. Consequently, the in situ continuous sensing of SEBs remains a relatively underexplored area of research.

Owing to the generally slow reaction rates in solids, detecting SEBs is not feasible using conventional solid electrodes. As they report in this issue of *Nature Materials*, Liu and colleagues[9] overcame the challenge by introducing a bilayer hydrogel sensor (Fig. 1a). The sensing scheme comprises four stages. First, the SEBs are solvated by an ionic conductive hydrogel (ICH) layer. The ICH is prepared with either an artificially formulated eccrine perspiration solution (mimicking sweat from the eccrine glands but devoid of target metabolites) to

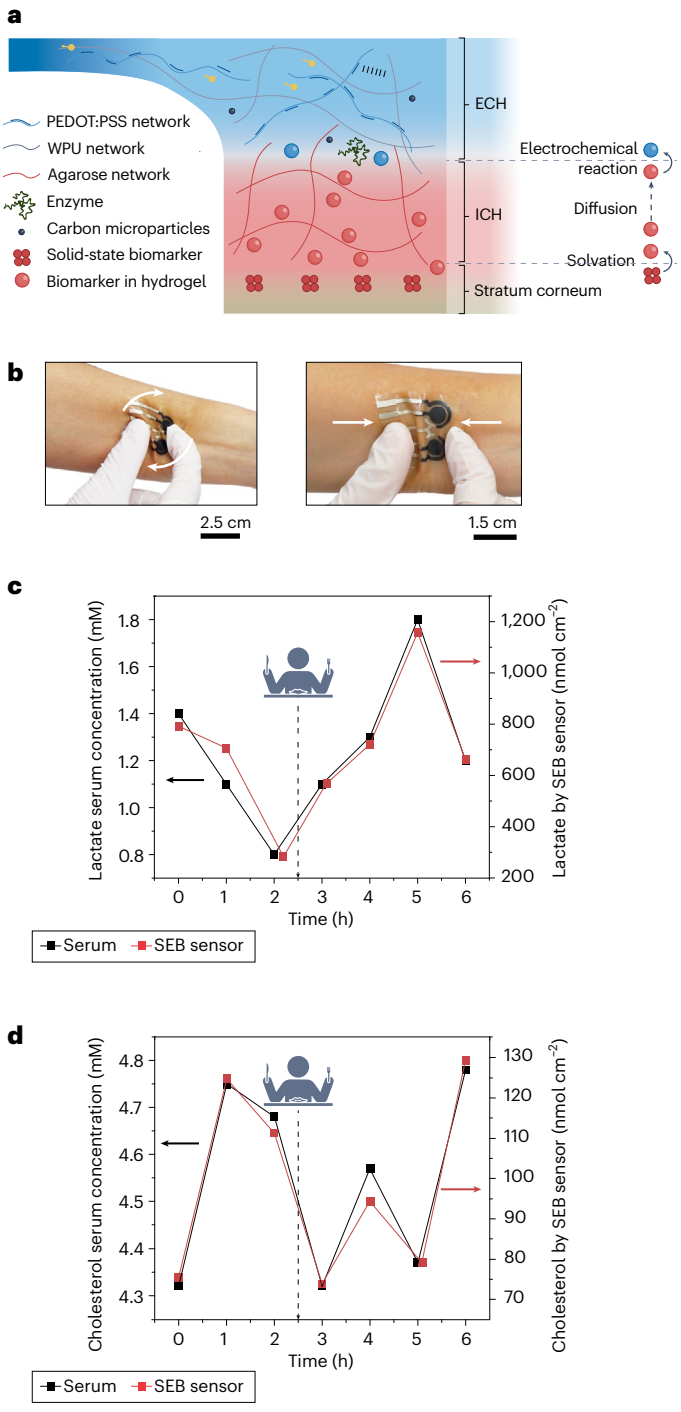

Fig. 1 | Overview of the bilayer hydrogel sensor. a, Schematic of the cross-sectional structure of the bilayer hydrogel sensor in contact with the skin. Solid-state biomarkers on the stratum corneum are solvated by the ICH. These biomarkers then diffuse to the interface between the ICH and the ECH, where they initiate electrochemical reactions with enzymes. Reaction byproducts are depicted as carbon microparticles, and the flow of electronic charges during these reactions is represented by yellow dots within the ECH. WPU, waterborne polyurethane. **b**, Application of the bilayer hydrogel sensor on a human forearm, illustrating the sensor's flexibility during twisting (left) and compression (right). **c**, Measurements from the blood serum strips (black curve) and bilayer hydrogel sensor (red curve) for lactate. The results show a high correlation. **d**, Measurements from the blood serum strips (black curve) and bilayer hydrogel sensor (red curve) for cholesterol. The results show a high correlation. The dashed line in **c** and **d** indicates the time when the subject intakes food. Figure adapted with permission from ref. 9, Springer Nature Ltd.

solvate hydrophilic analytes (for example, lactate), or with a mixture of surfactant and ethanol to emulsify and solvate hydrophobic analytes (for example, cholesterol). Second, the solvated SEBs diffuse through the ICH layer to the interface with the electronically conductive hydrogel (ECH) layer. Third, the SEBs at the ICH/ECH interface undergo electrochemical reactions with enzymes that provide sensing specificity. Incorporating multiple enzymes allows for the simultaneous sensing of various analytes. Finally, the ECH, composed of hydrogel and poly (3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS), detects these reactions by leveraging its hybrid conductivity properties — ionic from the hydrogel and electronic from the conductive PEDOT:PSS. Electrochemical mediators such as iron (III) ferrocyanide enhance electron transfer rates and reduce reaction overpotentials, thus improving the sensor's sensitivity and dynamic range. The PEDOT:PSS transfers charges from the electrochemical reactions to metal electrodes connected to a flexible printed circuit board, which subsequently digitizes and transmits data wirelessly to a cell phone via Bluetooth.

The bilayer hydrogel sensor adheres seamlessly to the skin (Fig. 1b), maintaining relative stability through over 100 stretching cycles at 20% strain. Moreover, the hydrogel sensor demonstrates a reduced water shear flow velocity and strain deformation at the sensor–skin interface, rendering it less susceptible to motion artefacts than conventional liquid-state electrochemical sensors. The hydrogel sensor exhibits a detection limit of 1.415 nmol cm^{-2} with a sensitivity of 93.8 nA $nmol^{-1}$ cm^{-2} for lactate (Fig. 1c) and a detection limit of 0.707 nmol cm^{-2} with a sensitivity of 201.34 nA $nmol^{-1}$ cm^{-2} for cholesterol (Fig. 1d). Such results correlate well with those obtained from standard blood strip tests (Fig. 1c,d).

Despite its innovation, the bilayer hydrogel sensor could be further pursued in the following aspects. First, the SEBs require time to dry and accumulate on the skin surface, leading to an average of and thus deviations from those dynamic analyte concentrations in the human body in real time. Controlling the solvation kinetics of the solid analytes allows the bilayer hydrogel sensor to resolve the concentration of each analyte along the thickness direction. This capability could potentially reveal the dynamics of those analytes in the human body. Second, one-time measurements may not yield accurate data without prior knowledge of the sensing history. Consequently, the data analysis system must account for previous measurements and the time elapsed between them. The results should be adjusted accordingly. Incorporating machine learning-based data interpretation systems or other sensing modalities for calibration might solve this problem. Third, this work did not establish a correlation between solid-state glucose and blood serum glucose in human subjects, possibly due to the hydrogel sensor's low sensitivity to glucose molecules. Using a more glucose-sensitive enzyme or adjusting the hydrogel composition to increase the glucose diffusion efficiency might be a solution. Fourth, it would be valuable to enhance the hydrogel sensor's clinical relevance through large-scale patient trials to validate its accuracy and reliability over a diverse patient population. Finally, the hydrogel sensor detects the concentration of SEBs by chronoamperometry on a complicated electronic circuit built with discrete components. Commercial off-the-shelf, fully integrated chips are available for this type of electrochemical analysis[10]. Integrating these chips could create a more compact standalone system for real-time wearable SEB analysis, providing great benefits to a wide range of stakeholders.

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References

1. Yin, L. et al. *Nat. Electron.* **5**, 694–705 (2022).
2. Kim, D.-H. et al. *Science* **333**, 838–843 (2011).
3. Hu, H. et al. *Nature* **613**, 667–675 (2023).
4. Gao, W. et al. *Nature* **529**, 509–514 (2016).
5. Xu, Y. et al. *Nat. Biomed. Eng.* **7**, 1307–1320 (2023).
6. Kim, J. et al. *Biosens. Bioelectron.* **253**, 116166 (2024).
7. Roustit, M. et al. *Br. J. Clin. Pharmacol.* **77**, 63–71 (2014).
8. Sjövall, P. et al. *Sci. Rep.* **8**, 16683 (2018).
9. Arwani, R. T. et al. *Nat. Mater.* https://doi.org/10.1038/s41563-024-01918-9 (2024).
10. Bill, D. et al. *Anal. Chem.* **95**, 13003–13009 (2023).

Competing interests

The authors declare no competing interests.