Wearable plasmonic-metasurface sensor for universal molecular fingerprint detection on biointerfaces
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Plasmonic metamaterial–integrated wearable SERS sensing device. (A) Schematic drawing showing the working principle and design of the device, (B) which consisted of two major components (sweat extraction component and SERS sensing component) and was styled to look like a yin-yang symbol. The inset figure highlights the key sensing interface near the metafilm. (C) Optical image of the device and (D) enlarged optical image of the sweat extraction component. A thin hydrogel layer loaded with molecules (acetylcholine chloride) that stimulate sweat gland secretions is mounted on the spiral fractal mesh electrode. Note that to highlight the contrast for exhibition, only one of the electrodes was mounted with the hydrogel layer and the plasmonic metafilm. Photo credit: Yingli Wang, Zhejiang University. (E and F) High-resolution transmission electron microscopy (TEM) images of the SERS sensing component mounted at the center of the electrode, which is the plasmonic metafilm formed by an ordered silver nanocube (NC) superlattice. Scale bars, 1 cm (C), 5 mm (D), 50 nm (E), and 5 nm (F). Credit: Science Advances, doi: 10.1126/sciadv.abe4553

Wearable sensing technology
Wang et al. presented a wearable plasmonic electronic integrated sensing platform with an almost "universal" recognition ability. Wearable sensing provides a link to the future of personalized medicine, but such sensors must overcome a fundamental mismatch between a rigid and soft elastic surface to laminate into biointerfaces such as the skin, eye, nerve and tooth to seamlessly assess human health. The devices allow researchers to continuously assess vital signs including the heart rate and body temperature, perspiration and physical activities. Despite the success of physical wearable sensors, non-invasive molecule tracking techniques that provide insight into human body dynamics at the molecular level remain to be realized. These capabilities are vital for personalized precision medicine. In this simultaneously, to obtain a complete picture of human health. In a new report on Science Advances, Yingli Wang and a team of scientists in biosystems, engineering and information science at the University of Cambridge and Zhejiang University in the U.K. and China, presented a wearable plasmonic-electronic sensor with "universal" molecular recognition capability. The team introduced flexible plasmonic metasurfaces with surface-enhanced Raman scattering (SERS) activity as the fundamental sensing component. The system contained a flexible sweat extraction process to noninvasively extract and fingerprint analytes inside the body based on their unique Raman scattering spectra. As proof of concept, they successfully monitored varying trace-drug amounts inside the body to obtain an individual drug metabolic profile. The sensor bridged the gap in wearable sensing technology to provide a universal, sensitive molecular tracking process to assess human health.
instance, Wang et al. aimed to develop a new strategy with universal target specificity instead of having one target alone to simultaneously track multiple targets. The team developed a new platform using a flexible surface-enhanced Raman spectroscopy (SERS)-active plasmonic metasurface to serve as the key sensing component and a flexible electronic system to automatically extract sweat and analytes from the body.

Characterization of the SERS sensing component of the device. (A) Schematic illustration showing the SERS sensing principle of the NC metafilm. The analytes in the extracted sweat were drawn to the EM hotspot in NC metafilm from the bottom, which can be in situ detected by SERS technique from the backside metafilm (backward excitation and collection). (B) FDTD simulation of the local electric field enhancement for the EM hotspot in the NC metasurface. (C) SERS spectra of the NC metafilm immersed in the probe molecule (CV) solution with various concentrations (an average of 20 randomly selected locations for each concentration with a 1-s acquisition time and using a 10× objective and laser power of 0.33 mW). (D) Raman intensity map (~1621 cm⁻¹) of the NC metafilm after treatment with the Raman probe (CV, 10⁻⁵ M). (E) Comparison of the SERS responses (~1621 cm⁻¹) to various CV solutions using backward and forward collection approaches. (F) SERS spectra of the human sweat samples containing different drugs (0.2 M lidocaine, 10⁻³ M cocaine, and 10⁻⁵ M methotrexate) and the blank sweat sample (using 10× or 50× objective and laser power of 0.15 to 0.66 mW, with acquisition times of 6 to 30 s). Credit: Science Advances, doi: 10.1126/sciadv.abe4553

The team fingerprinted the unique SERS spectrum using the wearable sensor. As a proof of concept, they detected the variation of drug concentrations in the human body to obtain an individual's drug metabolic profile. The integrated wearable sensor bridged the existing gap in personalized diagnosis for real-time tracking of important biochemical compounds. The scientists used the sensing platform to monitor physiological cues or drug concentrations in the human body to obtain an individual's drug metabolic profile. Then using the integrated wearable sensor, they monitored physiological cues or drug concentrations in a closed-loop feedback drug delivery system.

The plasmonic metamaterial-integrated wearable sensing device contained two major components including a thin layer of hydrogel loaded with molecules to stimulate sweat gland secretions. The team attached these constructs to two spiral fractal mesh electrodes to serve as the sweat extraction component. Wang et al. used the iontophoresis process (transdermal drug delivery) for this extraction; widely used as a non-invasive sweat sampling method in devices for diagnostic and therapeutic purposes. They formed a plasmonic meta-film using an ordered silver nanocube superlattice to serve as the sensing component mounted in the experimental setup. The strong electromagnetic fields localized in the nanocube gave rise to the SERS (surface-enhanced Raman scattering) effect to detect molecules approaching the metafilm surface. They placed the two components on a thin ultralow-modulus polymer film to form a thin, breathable and physically tough support for nonirritating skin adhesion. Using the electrodes, the team applied a mild electric current to deliver acetylcholine chloride in the hydrogel layer to secretory sweat glands for rapid, localized sweat generation.
Mechanical characteristics of the device. (A) Optical images of the sensor under deformation. (B) FEM strain distribution analysis of the guard ring area of the stretchable electrode under various distortions, indicating that the guard ring can isolate large deformations to the soft elastomer, thus avoiding potentially destructive plastic strains to the SERS sensing component. (C) SERS responses of the sensor under various deformations. (D) Characteristics of the SERS sensor after the cyclic stretching test. (E) Resistance changes in the electrode under various deformations. (F) Resistance changes in the electrode after the cyclic stretching test. (G) Photographs of the sensor mounted on human skin and (H) under various conditions. Photo credit: Xiangjiang Liu, Zhejiang University. Scale bars, 1 mm (B) and 1 cm (G and H). Error bars are defined as ±SD. Credit: Science Advances, doi: 10.1126/sciadv.abe4553

The SERS sensing component and mechanical properties of the wearable sensor

The sensor of the wearable device depended on the SERS effect generated by the ordered silver nanocube superlattice metafilm, based on which the team detected the target of interest in extracted sweat. At first, they assembled a single layer of the closed-packed nanocube array at the liquid/air interface and subsequently transformed the construct to a thin flexible polymer supporter. The scientists then verified the average gap size between the nanocubes using high-resolution transmission electron microscopy (TEM) images and performed finite-difference time domain (FDTD) numerical simulations. The mechanical compliance and skin contact of the metafilm allowed high-fidelity measurements. The team then developed the SERS film and transferred it onto a hydrogel loaded with an agonist agent attached to fractal mesh electrodes. They used an ultrathin spiral design to increase the tolerance of the sweat-inducing system to mechanical deformations and accomplished this by developing an "interconnected island" design stage to form a brittle SERS film with a soft and elastic electronic system. The team confirmed the durability of the electronics after 100 testing cycles, without any observable signal degradation to perfectly fulfil the duties required of a wearable sensor.

In vivo sensing performance of our sensor. (A) Schematic illustration showing the working principle of the sweat extraction system. (B) Variation in skin moisture content after periodic sweat induction (using the hydrogel containing 10% acetylcholine chloride, iontophoresis current of 0.5 mA for 5 min). (C) Induced sweat-secretion characteristics in response to different iontophoresis times (0 to 10 min). The secretion duration represents the total time of skin conductance above baseline (measurements stopped at 60 min). (D) Real-time monitoring of nicotine in human skin using our integrated sensor (with sweat extraction) and (E) control groups (without turning on the iontophoresis current for sweat extracting). The spectra were collected using laser power of 0.33 mW and a 10× objective (acquisition time, 1 s). (F) Evolution of the characteristic Raman peak of nicotine after sweat extraction of the test group and control group (without turning on the current or without attaching nicotine patch). Credit: Science Advances, doi: 10.1126/sciadv.abe4553

Biological sensing application
Wang et al. next recruited healthy volunteers for in vivo (physiological) measurements to demonstrate the sweat extraction capability of the device. The scientists used nicotine as the model drug and monitored the actual concentration of the drug in skin relative to drug delivery, uptake and metabolic rate per individual. During the experiments they used a wearable SERS sensor coupled to a compact power supply and wireless control unit on the forearm of the volunteers. The device showed the SERS spectrum of nicotine in the sweat to match the spectrum of the nicotine standard. The results indicated how the sensor trained the metabolic behavior of nicotine to allow the wearable sensor's capability to monitor the dynamic pharmacokinetics of drugs and their metabolic profile. The sensor, however, only effectively detected targets stored in the shallow sub-epidermis; therefore, the researchers will need to understand how this value correlates with drug concentrations in blood or interstitial fluid during further studies.

**Outlook**

In this way, Yingli Wang and colleagues displayed a wearable plasmonic-electronic integrated sensor as a next-generation wearable device. When compared to existing wearable electrochemical sensors, this sensor showed broader target specificity and higher stability. The integrated device bridged the existing gap in personalized diagnosis and precision medicine to track important molecules inside the body in real time. The team proposed applications to monitor physiological cues and drug concentrations in a closed-loop feedback drug delivery system and expect the wearable sensor to inspire a range of multidisciplinary applications.

**More information:** Editorial, Taking personalized medicine to heart. *Nature Medicine*, doi.org/10.1038/nm.4495


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