Wearable sensing technology is an essential link to future personalized medicine. However, to obtain a complete picture of human health, it is necessary but challenging to track multiple analytes inside the body simultaneously. Here, we present a wearable plasmonic-electronic sensor with “universal” molecular recognition ability. Flexible plasmonic metasurface with surface-enhanced Raman scattering (SERS)–activity is introduced as the fundamental sensing component in a wearable sensor since we solved the technical challenge of maintaining the plasmonic activities of their brittle nanostructures under various deformations. Together with a flexible electronic sweat extraction system, our sensor can noninvasively extract and “fingerprint” analytes inside the body based on their unique SERS spectra. As a proof-of-concept example, we successfully monitored the variation of trace-amounts drugs inside the body and obtained an individual’s drug metabolic profile. Our sensor bridges the existing gap in wearable sensing technology by providing a universal, sensitive molecular tracking means to assess human health.

INTRODUCTION

Wearable sensor technology is an essential link to future personalized medicine (1, 2). Such sensors need to overcome the fundamental mismatch between the typically rigid silicon-based sensor and the soft, elastic organism, thus softly laminating onto the biointerfaces [such as epidermis (3–15), eye (16), nerve (17–19), and tooth (20)] for a seamless assessment of human health. Application examples include the continuous monitoring of vital signs (such as heart rate and body temperature) (3–8), perspiration (9), and physical activities (10–15). Despite the success of physical wearable sensors, noninvasive molecule tracking techniques (such as disease markers and drugs), which can provide insight into the dynamics of the human body at a more profound molecular level, still lag behind. These capabilities are vital for personalized precision medicine, allowing for more accurate diagnosis or tailoring therapy based on an individual’s unique conditions. Current popular sweat-based electrochemical (EC) wearable sensors that measure currents or potentials at highly specific electrode surfaces to transduce analyte concentrations have enabled the continuous tracking of some electrolytes (K⁺ and Na⁺) (21–25), metabolites (lactate and glucose) (9, 26–28), and drugs (29) in sweat; however, these sensors are often limited to detecting one analyte at a time. To obtain a complete picture of a dynamic heath, it is necessary but challenging to combine several sensing mechanisms and detection approaches into one sensing platform (9). Therefore, the development of a new regime with universal target specificity instead of having only one target, thus enabling the simultaneous tracking of multiple targets, will represent the next watershed for wearable sensors.

Flexible plasmonic metastructures have currently attracted considerable interest because of their capabilities of controlling, manipulating, and concentrating light at the nanometer scale and their ability to be stretched, bent, or deformed into arbitrary shapes; thus, plasmonic metastructures have enabled great new functionalities that were previously not possible (30–35). The enormous increase in the electromagnetic (EM) near field of plasmonic metasurfaces has resulted in increases in many other prominent optical properties, thus opening opportunities for developing new wearable sensing mechanisms. For example, the surface-enhanced Raman scattering (SERS) effect offers both ultrahigh detection sensitivity (signal-molecule detection) (36) and high specificity (SERS fingerprint spectrum) at the same time (37), which has been intensively used in bio/chemical sensing (38). Although it has been expected that flexible plasmonic metastructures would be integrated with flexible electronics for a new generation of multifunctional devices (39), the application of flexible plasmonic metamaterials in wearable devices is currently rare. An essential requirement for wearable sensors is that they are resilient to mechanical strains and distortions that accompany on-body use. However, it is difficult to maintain the integrity of the delicate nanosized structures in plasmonic metasurfaces against constant body movements and daily activities.

Here, we present a wearable plasmonic-electronic integrated sensing platform with an almost “universal” molecular recognition ability. This integrated platform is enabled by the integration of a flexible SERS-active plasmonic metasurface that serves as the key sensing component and a flexible electronic system capable of automatically extracting sweat and analytes from the body, as shown in Fig. 1A. Since we have decoupled the stringent mechanical requirements that give rise to wearable challenges, a flexible plasmonic metasurface and the onboard SERS effect can be introduced as the fundamental transduction component and mechanism in this type of continuous wearable sensor for the human body. Because of the unique SERS spectrum of each molecule, the extracted targets in sweat can be “fingerprinted” by our wearable sensor. Through the use of this sensor, as a proof-of-concept study, real-time tracking of the variation in drug concentration inside a human body to obtain an individual’s drug metabolic profile can be achieved. Our integrated
A wearable sensor can bridge the existing gap in personalized diagnosis or therapy by providing real-time tracking of important molecules inside the body. This sensing platform shows excellent potential for monitoring physiological cues or drug concentration in a closed-loop feedback drug delivery system.

RESULTS
Design and fabrication of the sensor

Figure 1B shows the design of the plasmonic metamaterial–integrated wearable SERS sensing device, which consists 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. Figure 1C presents optical images of the obtained integrated wearable device. Figure 1D shows two stretchable spiral fractal mesh electrodes (shown as a dualism “yin-yang” illustration), served as the sweat extraction component. The extraction is based on an iontophoresis process, which is widely used as a noninvasive sweat sampling method in clinics for diagnostic and therapeutic purposes. Second, a plasmonic metafilm formed by an ordered silver nanocube (NC) superlattice serves as the sensing component, which was mounted in a through-hole cut in the hydrogel layer on the centers of the yin-yang electrode. The strong EM fields localized in the NC gaps and corners give rise to the SERS effect that could be used to detect molecules approaching the metafilm surface. Both components were bonded to a thin ultralow-modulus polymer film, which served as a thin, breathable, and physically tough support that also enabled robust, reversible, and nonirritating adhesion to skin. Therefore, by applying a mild electric current using the electrodes, the acetylcholine chloride in the hydrogel layer could be delivered to secretory sweat glands, causing the rapid and localized generation of sweat (27, 40). Thus, the target of interest could be drawn through the epidermis to the skin surface by the extracted sweat, which could then directly approach the sensing component since the hydrogel layer on its top was pre-removed (see insert in Fig. 1A). Details of the fabrication approaches are described in the Supplementary Materials (figs. S1 to S3 and section S2).

Figure 1C presents optical images of the obtained integrated wearable device. As shown in an enlarged figure (Fig. 1D), two stretchable spiral fractal mesh electrodes, an acetylcholine chloride–loaded hydrogel film, and an NC metafilm could be clearly seen. Typical scanning electron microscopy images of the obtained metafilm are shown in Fig. 1E and F, indicating that the Ag NCs formed a close-packed highly ordered array. All these results indicated the success of the fabrication process. More details about the sensor assembly and operations, including the wearable/wireless control units and customer-developed smartphone apps, are described in the Supplementary Materials (section S7).
SERS sensing component of the wearable sensor

The primary sensing principle of our integrated wearable sensor is depicted in Fig. 2A. Our sensor relied on the SERS effect generated by the ordered silver NC superlattice metasurface to detect the target of interest in the extracted sweat, which was fabricated via the Langmuir-Blodgett (LB) approach (section S2.3). A single layer of the closed-packed NC array was first assembled at the air/liquid interface and was subsequently transferred to a thin flexible polymer supporter. The average gap size between the NCs, verified by high-resolution transmission electron microscopy (TEM) images, was ~1 nm (a total of 100 gaps were analyzed; see fig. S5). We performed finite-difference time-domain (FDTD) numerical simulations using the structural parameters extracted from the above TEM images of the NC array (details of the simulations can be found in Materials and Methods). As depicted in Fig. 2B, strong EM fields (EM hotspots) were highly localized in the internanoparticle gaps between NCs; these localized EM hotspots enabled the so-called SERS effect, which could be used to detect molecules approaching the hotspot.

To evaluate the SERS activity of the metasurface, crystal violet (CV) was used as the model analyte to probe the sensor. The corresponding spectra are displayed in Fig. 2C, and a discernible CV Raman signal can still be observed at $10^{-9}$ M. The SERS enhancement factor (EF) was estimated to be $\sim 10^7$ (see section S3.1), which is among the highest EFs measured on similar types of two-dimensional immobilized SERS substrates, suggesting the potential of our substrate for trace organic compound analysis. Further statistical analysis of the obtained SERS mapping of the metasurface (Fig. 2D) indicated good signal reproducibility and high potential for quantitative analysis. The relative SD of the SERS intensity that varied between each spot was only $\sim 3.9\%$. In addition, the variation in the SERS performance between different batches was less than 10% (fig. S4), suggesting the reliability of our fabrication approach.

A unique prerequisite for the plasmonic metasurface used in this type of wearable sensor is its capability to allow the excitation and collection of the SERS signal from the backside metasurface after the sensor is attached to the skin surface (illustrated in Fig. 2A). Therefore, the SERS intensities collected from both sides of the superlattice were compared, and the results shown in Fig. 2E indicated that they were almost identical. This finding suggested that the excitation and collection of the SERS signal would be feasible from either side of the metasurface. The main reason was the unique structure of the ultrathin and noncontinuous metallic nanostructures. As shown in fig. S6A, the small gap between the NCs allowed the illumination light to pass through and permitted the excitation of the SERS hotspots on the top and bottom of the NC. Even a double-layer NC superlattice could produce a much weaker signal (by a factor of 10) when excited from the back of the superlattice (fig. S6C). According to the FDTD simulation shown in fig. S6B, the misalignment of the two NC layers’ gaps greatly reduced the light reaching the bottom, therefore substantially reducing the strength of the resulting SERS hotspot.

One advantage of our plasmonic metamaterial-integrated wearable sensor is its broad molecular identification capability due to the unique Raman “fingerprint” spectrum for each molecule. Figure 2F shows the SERS spectra of various drugs dissolved in human sweat. Each drug exhibited a unique Raman spectrum, as well as the blank sweat sample whose spectra are dominated by lactate and urea (see figs. S13 and S14 and tables S2 and S3 for comprehensive Raman...
band assignment). These results highlighted the high specificity of our sensor; thus, a wide range of targets could be detected without using specific surface chemistries.

The mechanical compliance and conformal contact of the meta-film with the skin are critical factors for a high-fidelity measurement. As indicated in fig. S3 (B and C), a thin polymethyl methacrylate (PMMA)–supported NC metafilm (~200 nm) could be conformably attached to the skin. After the SERS sensing film was fabricated, it was transferred onto a hydrogel loaded with an agonist agent attached to the fractal mesh electrodes.

**Mechanical properties of the wearable sensor**

Mechanical robustness under various deformations is another important requirement of skin-based wearable systems. To prevent mechanical fractures in the metal mesh, we used an ultrathin spiral design to further increase the tolerance of the sweat-inducing system to mechanical deformations (Fig. 3A). A critical challenge was how to maintain the SERS activity of our sensor under deformation. To minimize the influence of deformation, we adopted an “interconnected island” design stage to mitigate this influence on our SERS sensing component. A small guard ring was used to support and protect the NC superlattice metafilm. As indicated by the stress analysis based on the finite element method (FEM) in Fig. 3B and the experimental confirmation shown in fig. S8, using this design isolated large deformations to the soft elastomer, thus helping the brittle materials avoid potentially destructive plastic strains. Therefore, we successfully integrated a brittle SERS metafilm with a soft and elastic electronic system. As shown in Fig. 3C, the SERS activity remained stable under ~30% strain. In contrast, without the guard ring, the SERS activity began to decay even after a slight deformation (15% strain). We also noticed that the SERS activity remained stable even after 1000 stretching-relaxation cycles (~30% strain; Fig. 3D). Further analysis indicated that the spiral fractal mesh could operate normally under an ~50% strain (Fig. 3E). When the strain was >55%, a large-area circuit breakdown accompanied by a sudden increase in the resistance was observed. The reliable durability of the electronics was confirmed in Fig. 3F, which revealed no observable signal degradation after 100 testing cycles. These results indicated the mechanical robustness of the electronic system of our sensor images, perfectly fulfilling the duties required of a wearable sensor.

In addition to the above design, the sensing component and sweat induction component were transferred onto an intrinsically
soft and breathable waterproof film, substantially enhancing the robustness, tolerance to mechanical deformability, and comfortability of the device while being worn. Optical images of the sensor mounted on the forearm are shown in Fig. 3 (G and H). The images (center) illustrate the responses to compression and extension of the skin induced by pinching. In all cases, the sensor followed the natural deformations of the skin without constraints. Wearing the sensor for hours also caused no skin damage (fig. S19). Above all, these materials and design strategies minimized the influences induced by the strain that occur during deformations, thereby providing a reliable platform for sensing and for the long-term operation of wearable sensors.

In vivo sensing application
The integrated system-level demonstration of the wearable SERS sensor is demonstrated in Fig. 4A. Healthy volunteers were recruited for in vivo measurements. The experiment protocols were approved by the Human Research Ethics Committee of Zhejiang University (ZGL201905-4). All subjects were informed of the risks and benefits and provided informed consent. First, to demonstrate the sweat extraction capability of our device, the skin hydration of the stimulated area was monitored by a commercialized skin moisture meter (Zinnor Industrial & Scientific) based on the variation of skin impedance, which has been frequently used in previous reports as an index to evaluate sweat rate (41). Immediately after each stimulation, the stimulated area was wiped, quickly dried, and measured by the skin moisture meter. As shown in Fig. 4B, a marked increase in skin moisture content could be observed shortly after stimulation. Moreover, periodic sweat durations could be realized by using the same stimulating parameters (10% acetylcholine chloride–loaded hydrogel, 0.5-mA iontophoresis current for 5 min). As shown in Fig. 4C, we were also able to tune the active sweat-secretion window from a few minutes to tens of minutes by adjusting the iontophoresis time (see also fig. S9). Notably, a high iontophoresis current (>0.5 mA) might induce skin irritation despite the use of a buffered hydrogel to prevent burns caused by adverse pH effects.

As a model to study, we used the sensor for in situ monitoring of the drug concentration in sweat. Nicotine was selected as the model drug for this study. Nicotine replacement therapy in the form of transdermal nicotine patches or gums is still widely used for smoking cessation (42). By monitoring the actual concentration of drug in the skin, the drug delivery, uptake, and metabolic rate for each individual could be assessed. This valuable information could play a key role in future personalized medical treatments, which would allow the tailoring of therapeutic windows to individual patients.

For these purposes, an integrated wearable SERS sensor coupled with a compact power supply and wireless control unit (see fig. S11A) was transferred to the forearm of the volunteers. Then, a nicotine patch containing approximately 10 mg of nicotine (2 cm by 3 cm) adhered 2 cm away from the device, which is in the range of the typical daily dosage of nicotine replacement therapy (7 to 21 mg per 24 hours). Figure 4D shows SERS responses of the sensor immediately after the sweat extraction process. After turning on the device for ~20 min, the SERS spectrum of nicotine was observed in the sweat, which matched the spectrum of the nicotine standard shown in the same figure. For comparison, we also repeated the above experiment without iontophoresis for sweat extraction. As shown in Fig. 4E, the SERS spectrum of nicotine could barely be observed much later (~40 min), and the signal intensities remained much lower compared to the above results. It was expected because the natural sweat

Fig. 4. 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).
rate of the human body would be much slower than sweat secretion due to stimulation. Figure 4F also shows the variation in the nicotine band at 1030 cm$^{-1}$ over time. As another control group, we also collected the sensor responses without attaching a nicotine patch to the volunteer arm. In this case, the nicotine spectral fingerprint was not observed for the entire experiment (see fig. S12C). All these results indicated the feasibility of our wearable sensor for in situ monitoring of the drug concentration in sweat.

For the quantification of nicotine, we first calibrated the sensor using artificial sweat containing various nicotine concentrations. The results are shown in fig. S10 (A, C, and E), which shows that we could detect nicotine concentrations as low as 100 nM and a linear working curve between 100 nM and 10 mM nicotine was obtained [coefficient of determination ($R^2 = 0.9904$) for quantification. Then, as illustrated in Fig. 5A, a nicotine patch containing ~10 mg was attached to the forearm of one of the volunteers for 2 hours and then removed. Thus, one sensor (sensor A) was mounted directly on the patched area (thoroughly cleaned before measurement), and the other (sensor B) was placed ~2 cm away. Our sensor monitored the variation in the remaining nicotine in sweat over the next 48 hours. As indicated in Fig. 5 (B and C), the nicotine levels at both locations showed the typical exponential decay of the metabolic behavior of drugs, which was in good agreement with previous studies (37, 38). Furthermore, the nicotine levels monitored at these two spots were highly correlated [correlation coefficient ($r = 0.975, P < 0.001$)]. The above results indicated that the prepared sensor could track the metabolic behaviors of nicotine and demonstrated our wearable sensor’s capability in monitoring the dynamic pharmacokinetics of the drug to obtain an individual’s drug metabolic profile.

We also noticed that the nicotine levels at the patched area (sensor A) were higher than those ~2 cm away (sensor B). Since most of the adsorbed nicotine molecules are sorted in the shallow subepidermis under the patch, from where they enter the blood system, the adsorbed nicotine molecules are sorted in the shallow subepidermis A) were higher than those ~2 cm away (sensor B). Since most of the drug to obtain an individual’s drug metabolic profile.

Furthermore, our wearable SERS sensor’s capability can be expanded to SERS-inactive analytes, such as ions (because SERS is a molecular vibrational spectrum). For example, our SERS sensor can incorporate a sort of “probing” molecule to detect the pH value (H$^+$) of sweat, which is also an important factor for human health. Figure 6A presents the design of a multiple sensor array that can be used to track both SERS active and inactive targets. The sensor array is stylized as a floating house in the famous Pixar movie UP. Each “balloon” is an integrated sensor that consists of four layers, as we previously described. In addition to conventional sensors, as also shown in Fig. 6A, the NC metafilm of one balloon is modified with 4-mercaptoypyridine (4-MTP). The variation in decarboxylation Raman spectral signatures of 4-MTP (1004 cm$^{-1}$) can be used to track pH changes of sweat. The calibration and validation of the sensor are shown in fig. S17 (B and C). Furthermore, as shown in Fig. 6B, both types of sensors showed good reversibility. Meanwhile, the cross-talk between different types of sensors is negligible (fig. S18) since the modified metasurface becomes insensitive to other analytes because the SERS hotspots were preoccupied with the probe molecules.

As shown in Fig. 6C, we managed to integrate the power supply, wireless control, and communication system into a small flexible printed circuit board (FPCB) since the power consumption of our sensor is low (see table S1 for the technical specification). This FPCB unit can also be easily mounted on human skin, thereby realizing remote turning on/off the current for sweat extraction via a customer-developed app, as shown in Fig. 6D. With this sensor array, simultaneous tracking SERS-active and inactive analytes can be realized (Fig. 6E). To create controlled variations of the skin’s level, a nicotine

![Fig. 5. In vivo monitoring of the nicotine metabolism process in human skin.](image-url)
patch containing ~10 mg was deliberately attached or removed from the forearm at times. In all cases, there is an initial lag time before nicotine appears in the sweat because of its slow adsorption rate, and a continued increase of concentration after the patch was removed because of residual nicotine in the skin. These observations are highly consistent with the previous report (43).

DISCUSSION

There has been rapidly growing interest in the physiological information obtained from sweat, thereby triggering the development of wearable EC sensors for analytes, including ions, metabolites, and heavy metals. A general problem of a wearable EC sensor lies in the fundamental sensing mechanism, in which the specificity of the sensor is determined by how specific the receptors are in binding to their target. The stability and effectiveness of some receptors, such as antibodies, enzymes, or aptamers, remain unknown in on-body use (44). Some necessary procedures for EC sensors require repeated washing or additional reagents, which is difficult to realize on a considerable sensor mounted on human skin. Seamlessly tracking multiple analytes presents a serious challenge due to the complexity of combining different receptors and detection approaches in a single platform and the cross-talk between them. Therefore, developing a new mechanism that can selectively recognize complex molecules will represent the next watershed for wearable sensors and will allow detection capabilities to be extended to a new class of physiologically relevant analytes.

Inspired by the recent development of flexible plasmonic metamaterials for sensing, we introduced a previously unused effect (SERS) as the fundamental transduction mechanism for our wearable sensor. SERS offers single-molecule detection sensitivity and broad target specificity due to the unique SERS spectrum for each molecule. As previously shown in Figs. 2F, the sweat samples containing various drugs exhibited entirely different SERS spectra, ranging from commonly used anesthesia (lidocaine), a chemotherapy drug with life-threatening side effects (methotrexate), and addictive illicit drugs.
(cocaine and nicotine). Therefore, our sensor can achieve a universal molecular recognition ability compared to EC sensors. Nevertheless, the capability of our wearable SERS sensor can be further expanded toward SERS-inactive targets by incorporating a probing molecule, as demonstrated in Fig. 6. In addition to board specificity, our sensor also exhibited an extremely high sensitivity. For example, as shown in fig. S10 we used our sensor to quantify another chemotherapy drug (mitoxantrone) in sweat. The limit of detection (0.01 nM) that we can achieve is almost two orders of magnitude lower than that of the standard high-performance liquid chromatography method (~1.1 nM) (45), which requires intensive sample pretreatments and much longer operation time compared to ours.

Our wearable plasmonic sensor’s high sensitivity and specificity were barely affected by environmental conditions (such as ion concentration, body temperature, and humidity), as demonstrated in fig. S7 (A to C). In contrast, the EC sensor’s performance that measures the currents or potentials of highly specific electrode surfaces to transduce analyte concentrations is always subject to these factors. Meanwhile, as shown in fig. S7 (D and E), the sample volume (<0.5 µl) required for our sensor is much smaller than that required for EC sensor (~10 µl). The above advantages are essential to wearable sweat sensors because of the constant variable measuring conditions and low sweat rates (44).

The achievement of this work also lies in the integrated wearable system. To the best of our knowledge, this is the first demonstration of an integrated flexible plasmonic and electronic system for wearable sensors. We also establish previously unused engineering design rules and guides for this integrated sensing system to maintain a highly stable plasmonic effect of the metafilm and electronic system under various deformations. The whole system is thin, light, waterproof, robust, and comfortable to wear.

One limitation of our sensing system is the readout system. Currently, a large Raman spectrometer is needed for signal readout, which is not convenient and portable. The realization of onboard Raman excitation and collection in a wearable system is difficult now but still possible in the future with the development of planar optics (46, 47), such as compact foldable metasurface spectrometers, planar waveguides, and organic light-emitting diode sources. A more feasible solution at the present stage is developing a portable “Raman scanner” that allows the bearer to check the sensor as often as it need be. A proof-of-concept design based on a smartphone-based miniaturized Raman spectrometer (PALM-100, Suzhou Weimu Intelligent System Co.) is demonstrated in fig. S20. Future work should be dedicated to the optimization of a system specializing in readout signals from skin surfaces.

For future study, we also suggest that a microchannel system (48) and sweat rate sensor (49) be integrated with our sensor, which allow collecting, storing, and analyzing sweat in a more controlled and accurate fashion (44). For precaution, the spiral fractal Cu electrodes and Ag NC in our sensor could be replaced by more stable metals (such as Au or Pt) to avoid possible corrosion and toxic effects. These modifications should be easily realized by our proposed fabrication approach, as described in the Supplementary Materials. The same air–water interface assembly approach can also prepare the metasurfaces based on Au NPs (such as NCs, nanorods, and nanobipyramids) (50).

In conclusion, we have demonstrated a wearable plasmonic-electronic integrated sensor for a next generation of wearable sensors. Compared with current wearable EC sensors, our sensor shows broader target specificity and higher stability. Our integrated wearable sensor can bridge the existing gap in personalized diagnosis or therapy for real-time tracking of important molecules inside the body. Potential applications range from monitoring physiological cues and monitoring drug concentration in a closed-loop feedback drug delivery system. We believe our wearable sensor will inspire many more applications and open up previously unnoticed horizons in various fields.

MATERIALS AND METHODS

Fabrication of the NC superlattice film
A monolayer of the NC superlattice film was assembled according to a previously described procedure with a slight modification (51). First, Ag NCs were prepared via the seed-mediated growth method and were transferred into chloroform. Then, a monolayer of Ag NCs was prepared using an LB deposition trough (KSV NIMA KN2002, Bioin Scientific, Finland). The trough was filled with deionized water. The Ag NCs in chloroform (20 ml) were injected over the water surface. The surface pressure was measured as a function of the area in which the particles were dispersed. The LB film was transferred to silicon, PMMA, and polydimethylsiloxane (PDMS) substrates by the vertical dipping method at 60 mN/m.

Fabrication of the integrated wearable sensor
The fabrication began by fixing a Cu film (thickness, 6 µm) onto a silica wafer with a 10-µm cured PDMS layer as a temporary adhesive layer. The Cu film was then patterned by a laser direct writing technique (LPKF ProtoLaser U4, LPKF Laser & Electronics AG, Germany), which defined the spiral fractal electrodes. A water-soluble tape (3M, USA) enabled the retrieval of the spiral electrodes from the handle substrate and the subsequent transfer to a thin, breathable polymer adhesive tape (3M Tegaderm). Then, a 100-µm hydrogel film containing 10% acetylcholine chloride with the desired shape was transferred onto the electrode. Afterwards, a through-hole was cut in the hydrogel to expose the guard ring on centers of the yin-yang electrodes, where an NC superlattice film can be mounted. The two electrical contact pads of the electrodes allowed an electrical connection to the wireless control unit by an anisotropic conductive film. Details of the sensor assembly can be found in the Supplementary Materials.

Experiments on human subjects
All experiments on human skin were approved by the Human Research Ethics Committee of Zhejiang University (protocol no. ZGL201905-4). Six healthy nonsmoker volunteers were recruited to participate in the study. All subjects were informed of the risks and benefits and provided informed consent. For ex vivo studies, sweat samples were prepared by adding various analytes to the volunteers’ sweat after physical exercise. Then, the samples (~10 µl) were dropped onto the sensor surface for SERS measurement. A typical experimental protocol for the in vivo study was described as follows. Before each experiment, the volunteer’s forearm was thoroughly washed and cleaned by a medical alcohol patch. Then, a sensor connected to the wireless control unit was transferred to the volunteers’ forearm and adequately secured by breathable adhesive tape (3M Tegaderm). For real-time nicotine tracking, a nicotine transdermal patch (1.68 mg/cm²; San Jods) containing approximately 10 mg of nicotine (size, 2 cm by 3 cm) was attached next to the sensor approximately 2 cm away. The SERS spectra were collected using a confocal Raman microscope system (LabRAM HR Evolution, HORIBA Jobin Yvon, France), which...
was equipped with an integrated Olympus BX40 microscope, a three-dimensional motorized stage, and a He-Ne laser (633 nm). The typical laser power we used for in vivo measurement is 0.33 mW, which is safe for the human body. Notably, high-power laser excitation can cause skin damage and, therefore, should be carefully examined before carrying out. Details of the experimental setup can be seen in fig. S11B. For short-term continuous tracking of nicotine (hours), the SERS spectra were collected with continuous sweat extraction (iontophoresis current, 0.5 mA). For long-term low-frequency measurement (days), to avoid contamination from the old sweat sample, it is necessary to flush the sensor with freshly extracted sweat for 20 min before taking SERS measurement (see fig. S16 for details). The details are specified in the figure caption and the Supplementary Materials.

Numerical simulation

FDTD simulations were performed using the commercial modeling package Lumerical solutions. Periodic boundary conditions were used, and only a silver NC was placed in a unit cell. The optical constants of the silver were used in the package. The FEM strain distribution analysis of the spiral electrodes was performed on the basis of the following material parameters, $E_{\text{PDMS}} = 1.8$ MPa and $\nu_{\text{PDMS}} = 0.48$ for PDMS and $E_{\text{Cu}} = 119$ GPa and $\nu_{\text{Cu}} = 0.326$ for copper, and, with refined meshes, ensured computational accuracy. Here, $E$ is the elastic modulus, and $\nu$ is Poisson’s ratio.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/7/4/eabe4553/DC1

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