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A dual-mode wearable sensor with coupled ion and pressure sensing

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Abstract

Simultaneous monitoring of the body's biochemical and biophysical signals via wearable devices can provide a comprehensive assessment of an individual's health state. However, current multifunctional sensors for synchronous biochemical and biophysical sensing rely on discrete sensing units, posing a limitation in increased complexity in device assembly, signal processing, and system integration. In this study, we report a dual-mode and self-powered wearable sensor with ion and pressure-sensing capabilities by interfacing a hydrogel film with a solid ion-selective electrode. The hydrogel film can not only collect natural sweat from the skin but also offer a piezoionic response to pressure. We show that wrist pulse-induced pressure response can be incorporated into the noise of the response to sweat sodium ions, allowing for the simultaneous measurement of heart rate and sweat electrolytes. This work provides an example of simplifying the development of wearable multimode sensors through the rational design of classic electrochemical sensors.

Keywords: Wearable sweat sensor, ion selective electrode, piezoionic response, hydrogel

INTRODUCTION

Skin-mounted wearable sensors are integrated analytical devices that can monitor various physiological signals in a real-time and continuous way^[1-5]. Their point of care feature, along with non-invasive or minimally invasive operations, provides a promising pathway to user-friendly healthcare and



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diagnostics^[6-8]. Wearable sensors can be classified into physical and biochemical types based on target physiological signals. Specifically, wearable physical sensors are designed to monitor biophysical signals such as body motions, blood pressure, heart rate, or body temperature^[9-13], while biochemical sensors focus on the analysis of biomarkers in body fluids to indicate the health state at the molecule level^[14-17]. The comprehensive evaluation of the body state for precious health management and diagnosis calls for next-generation hybrid wearables capable of physical and biochemical sensing concurrently^[18,19]. A straightforward way to achieve this goal is integrating various sensors with different sensing mechanisms into a single device^[20-22]. However, this add-on design inevitably results in increased complexity in fabrication, signal processing, and device integration.

Among various biofluids, sweat may be the best choice for wearable sensing to indicate the dynamic body state at the molecular level^[23]. This is because sweat contains a wealth of biochemical information that is composed of various metabolites (glucose, lactate), electrolytes (sodium, chloride, potassium), proteins, hormones, and peptides^[24]. Moreover, compared to other biofluids such as tear and saliva, sweat can be easily accessed in a non-invasive and on-demand manner and readily analyzed using skin-interfaced electronic devices. Among various sweat electrolyte ions, the level of sodium ions (Na^+) can reflect the body's electrolyte balance, osmolality regulation, and acid-base equilibrium, which is also a biomarker for the diagnosis of cystic fibrosis^[25-27]. Among the biophysical signals, the pulse caused by the periodic flow of blood can reflect the health state of the heart, and pulse monitoring has wide applications in the diagnosis of cardiovascular diseases, physical fitness, and health management^[28]. Simultaneous detection of these two basic yet important physiological signals may give a full picture of the health state of an individual. However, this can only be done using two sensors with existing strategies.

Herein, we show that a single wearable sensing unit can detect sweat Na^+ concentration and heart rate simultaneously. This was achieved by introducing a hydrogel interface to a solid Na^+ selective electrode. In previous reports, the introduction of a hydrogel film between skin and electrochemical sensing electrodes has proven to be an efficient way to continuously collect and analyze natural sweat^[16,29]. Thus, the hydrogel interface is quite attractive to eliminate the use of chemical, exercise, or thermal stimuli for sweat induction and may offer unique insight into body physiology at the rest state^[30]. In this work, considering hydrogels also have the piezoelectric response to pressure^[31-33], we show that the wrist pulse-induced potential signal with a periodic pattern can also be monitored during the sensing of sweat Na^+ . Thus, the pulse and sweat Na^+ concentration can be easily analyzed from the single potential response. We believe this dual-mode sensor has the potential to pave the way for the next generation of multifunctional wearable sensors for synchronous biophysical and biochemical sensing.

EXPERIMENTAL

Chemicals and materials

Selectophore grade sodium ionophore X, 3,4-ethylene-dioxythiophene (EDOT), poly (sodium 4-styrene sulfonate) (NaPSS), sodium tetrakis [3,5-bis(trifluoromethyl)phenyl] borate (Na-TFPB), polyvinyl chloride (PVC), bis(2-ethylhexyl) sebacate (DOS), acrylamide (AM), N, N'-Methylenebisacrylamide (Bis), poly (ethylene glycol) diacrylate (PEGDA), and (2-hydroxy-2-methylpropiophenone) (HMPP) were obtained from Sigma-Aldrich. Polyvinyl butyral (PVB) and sodium chloride (NaCl) were obtained from Aladdin (Shanghai, China). Tetrahydrofuran and methanol were obtained from Macklin (Shanghai, China). A CHI 660D electrochemical analyzer (CH Instruments) was used to carry out electrochemical measurements. A commercial blood pressure and pulse meter (YE 660D, Yuyue Medical Co., Ltd., China) was used for the pulse test.

Preparation of the hydrogel

The p(AM-co-PEGDA) hydrogel was prepared by dissolving 10 wt% AM, 0.2 wt% Bis, 1 wt% PEGDA, and 1 wt% HMPP in deionized water. AM and HMPP are the monomer and photoinitiator, respectively. Bis and PEGDA are the cross-linking agents. Then, the solution was injected into the glass cell with a spacer thickness of 0.2 mm, followed by UV polymerization for 30 s [Supplementary Figure 1]. Under the UV light, the photoinitiator (HMPP) absorbs the UV energy and forms free radicals to initiate the polymerization reaction. After polymerization, the hydrogel was immersed in distilled water for seven days, with water replaced every 12 h to remove unreacted monomers and photoinitiators. The hydrogel was cut into the films (0.5 cm × 1 cm) for on-skin applications, and each hydrogel film initially contained ~20 μL water or NaCl solution, which was obtained by weighting the hydrogel films before and after dehydration.

Preparation of the Na⁺ selective electrode

Graphite ink (LOCTITE EDAG423SS E&C) was screen-printed on the poly (ethylene glycol) terephthalate (PET) film, followed by drying at 90 °C for 30 min. The reference electrodes were printed with silver/silver chloride ink (LOCTITEEDAG 6037SS E&C) followed by drying at 80 °C for 30 min [Supplementary Figure 2]^[34]. Then, the poly(3,4-ethylene-dioxythiophene) PEDOT:PSS was deposited on the working electrodes as an ion-electron transducer through the galvanostatic electrochemical polymerization in a solution containing 100 mM NaPSS and 10 mM EDOT. A constant current of 35 μA was applied, and the depositing time was 285 s. We prepared the Na⁺ selective membrane solution by dissolving 1.0 wt% Na ionophore X, 0.55 wt% Na-TFPB, 33 wt% PVC, and 65.45 wt% DOS in tetrahydrofuran and a PVB-based coating solution by dissolving 79 mg PVB and 50 mg NaCl in 1.0 mL methanol. Finally, 2.0 μL of Na⁺ selective membrane solution and 2.0 μL of PVB solution were dropped on the working electrodes and reference electrodes, respectively, followed by overnight drying at room temperature [Supplementary Figure 3].

On-body test

To perform the sweat rate test, a piece of filter paper (Cytiva, 0.5 cm × 1 cm) was attached to the wrist to absorb sweat for an hour. During this process, the paper was weighed every ten minutes. Before each test, the sweat collection area at the wrist was cleaned with 75% alcohol and deionized water, followed by removing the water using absorbent cotton. Then, the sensor was positioned on the wrist and covered by a waterproof adhesive layer to prevent water evaporation. Before the on-body test, the hydrogel was immersed in 1 mM NaCl solution. All experiments were conducted in strict compliance with the relevant laws and with the approval of the Scientific Ethical Committee of Southeast University. Three healthy volunteers were recruited to participate in the on-body tests.

RESULTS AND DISCUSSION

Overview of the dual-mode sensor

Existing strategies for wearable sweat Na⁺ detection include optical techniques, e.g., fluorescence or colorimetric analysis^[35,36], and electrochemical methods using potentiometric ion selective electrodes (ISE)^[37] or organic electrochemical transistors^[38]. Among these sensing methods, ISE-based Na⁺ sensors are particularly attractive due to their simple electrode and circuit design, low cost, and ability for continuous sensing^[34].

Here, we designed the wearable dual-mode sensor with ion and pressure sensing functions by interfacing a hydrogel film to a solid Na⁺ selective electrode [Supplementary Figure 4], which was attached to the wrist to monitor the sweat Na⁺ and pulse simultaneously [Figure 1A]. In our design, the hydrogel film can be used not only for sweat collection but also for pressure sensing by utilizing the piezoionic effect of the hydrogel. The piezoionic electromechanical response of hydrogel is due to the difference in mobilities of cations and anions in the hydrogel that generates a streaming potential when pressure is applied^[32] [Figure 1B].

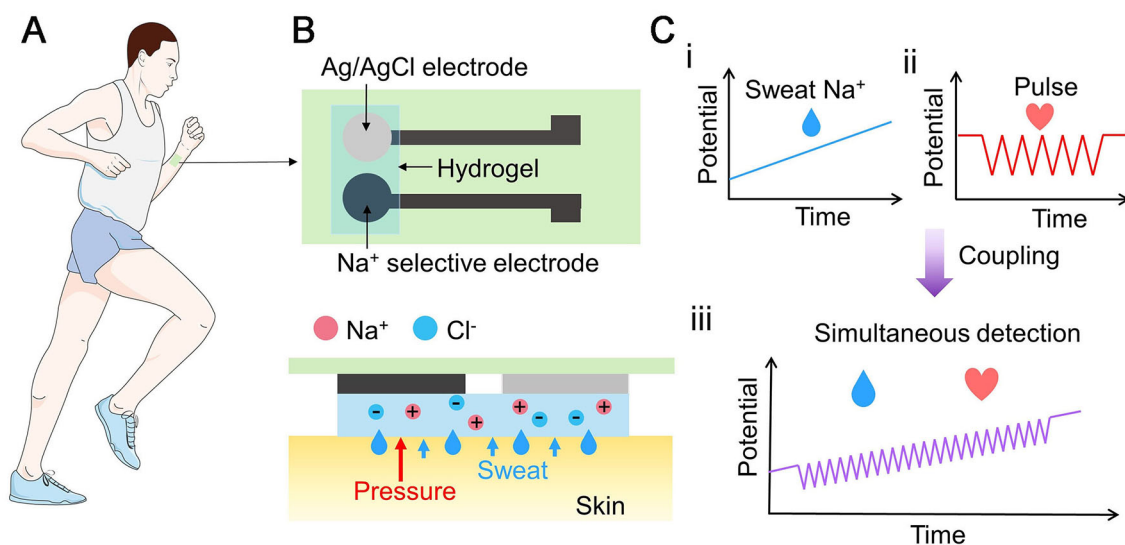


Figure 1. Schematic illustration of the dual-mode wearable sensor. (A) Schematic illustration showing the dual-mode sensor working as a wearable device; (B) Structure and working mechanism of the dual-mode sensor; (C) (i-iii) Schematic illustration of the dual-mode sensor detecting (i) the sweat Na^+ , (ii) periodic pressure, and (iii) the two physiological signals simultaneously.

Although the responses to sweat Na^+ and pressure are all based on the potential variation of the sensor, we can differentiate the wrist pulse from the Na^+ response curve due to its periodic pattern. Moreover, the wrist pulse-induced pressure response is at the noise level of the potential signal, and thus, we can synchronously obtain the sweat Na^+ level and heart rate [Figure 1C]. To our knowledge, this is the first report using a single wearable electrochemical sensor to achieve simultaneous chemical and biophysical sensing. In addition to dual-mode sensing, this sensor is also operated in a self-powered way without using complicated peripheral circuits for signal readout.

Detection of the Na^+ in the hydrogel

We utilized the biocompatible p(AM-co-PEGDA) hydrogel film to interface the skin and sensing electrodes for collecting natural sweat and pulse monitoring. Cross-sectional SEM image indicated the porous architecture of hydrogel with a mean pore size of $13.7 \mu\text{m}$ [Supplementary Figure 5]. In addition, the pore sizes of the hydrogel equilibrated in NaCl solution with varied concentrations (0, 1, 5, and 10 mM) changed slightly, and the mean pore size ranged from 13.5 to $15.3 \mu\text{m}$ [Supplementary Figure 6]. The *in vitro* cytotoxicity assay was performed with NIH 3T3 cells using a standard Cell Counting Kit-8 (CCK8) assay, and the results indicated the good biocompatibility of the p(AM-co-PEGDA) hydrogel [Supplementary Figure 7]. Furthermore, the on-skin test indicated there was no irritation reaction, such as erythema and edema, after wearing for 2 h [Supplementary Figure 8]. In addition, the water content of the p(AM-co-PEGDA) hydrogel remained nearly unchanged after ten days, indicating its good stability [Supplementary Figure 9].

To characterize the Na^+ selective electrode's response to the Na^+ in the hydrogel, we immersed the hydrogels in NaCl solution with different concentrations (4, 8, 16, 32, and 64 mM) and then attached the hydrogels to the electrode surface. The open-circuit potential monotonously increased as the Na^+ concentration in the hydrogel increased [Figure 2A]. Figure 2B shows the potential value plotted against the logarithm of Na^+ concentration with a correlation coefficient of 0.999, indicating that the quantitative analysis of Na^+ in the hydrogel can be achieved. It is noted that these results were consistent with those obtained by directly detecting the corresponding NaCl solutions using the Na^+ selective electrode [Supplementary Figure 10]. In

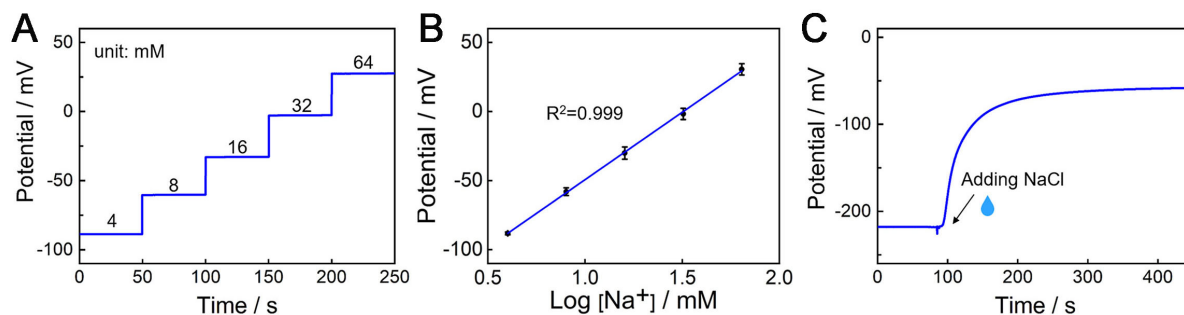


Figure 2. Detection of the Na⁺ in the hydrogel. (A) Open-circuit potential in response to hydrogels containing NaCl solutions with different concentrations; (B) Plots of the potential value as a function of the logarithm of the Na⁺ concentration in the hydrogel; (C) Potential change after adding NaCl solution to the hydrogel.

addition, the Na⁺ selective electrode exhibited not only selectivity of Na⁺ but also good anti-interference to other cations [Supplementary Figure 11].

To simulate the process of the hydrogel collecting the sweat, we dropped 2.0 μ L of 100 mM NaCl solution on the hydrogel. The potential increased once the NaCl solution was added to the hydrogel [Figure 2C]. Then, the potential stabilized after \sim 150 s due to the diffusion and equilibrium of Na⁺ in the hydrogel film. The measured Na⁺ concentration is 8.36 ± 1.1 mM ($n = 5$), which is close to the theoretical value of 9.09 mM. Furthermore, we attached the sensor to the wrist of a volunteer to detect the volunteer's sweat Na⁺ concentration. Based on the measured sweat rate [Supplementary Figure 12], the volume of sweat absorbed by the hydrogel can be calculated. We then tracked the sweat Na⁺ concentration of the volunteer undergoing different activities, including exercise and drinking water [Supplementary Figure 13]. The volunteer's sweat Na⁺ concentration was 8.0 mM before the exercise. After 30 min of exercise, the sweat Na⁺ concentration increased to 9.6 mM. Then, the sweat Na⁺ concentrations returned to 7.5 mM due to the water intake and regulation of hydration. The measured sweat Na⁺ was slightly below the typical physiological range of sweat Na⁺ (10-100 mM)^[39]. This may be due to the low sweat rate since the test was conducted when the volunteer was at the rest state, and previous reports have shown a positive correlation between sweat Na⁺ concentration and sweat rate^[40].

Pressure sensing of the dual-mode sensor

In addition to the sweat collection, the hydrogel containing free Na⁺ and Cl⁻ can also be used as a pressure sensor by generating potential in response to mechanical pressure stimuli. Due to the different mobility of the Na⁺ and Cl⁻, an ion gradient is established, and a voltage signal is generated in the hydrogel under pressure, namely, the piezoelectric effect of the hydrogel^[32]. Herein, we used the Na⁺ selective electrode to detect the generated potential of the hydrogel by interfacing the hydrogel on the electrodes. When we exert pressure on the working electrode, a decrease in potential is detected since the diffusion rate of Cl⁻ is lower than that of Na⁺ [Figure 3A].

To show the piezoelectric effect of the hydrogel, a cyclic pressure/release test at a pressure of 15 kPa over ten cycles was conducted, and the potential response is shown in Figure 3B. The pressure induced a decrease in potential, and the potential could rapidly return to its original level in a short time (< 0.5 s) once the pressure was removed. We also applied different pressures on the hydrogel containing 1 mM NaCl solution. The potential change linearly increased with rising pressure ($R^2 = 0.997$) and exhibited a sensitivity of 6 μ V/kPa over a pressure range from 5 to 100 kPa [Figure 3C]. We further attached this pressure sensor to the human wrist to detect the pulse, and a waterproof film was added between the skin and hydrogel to

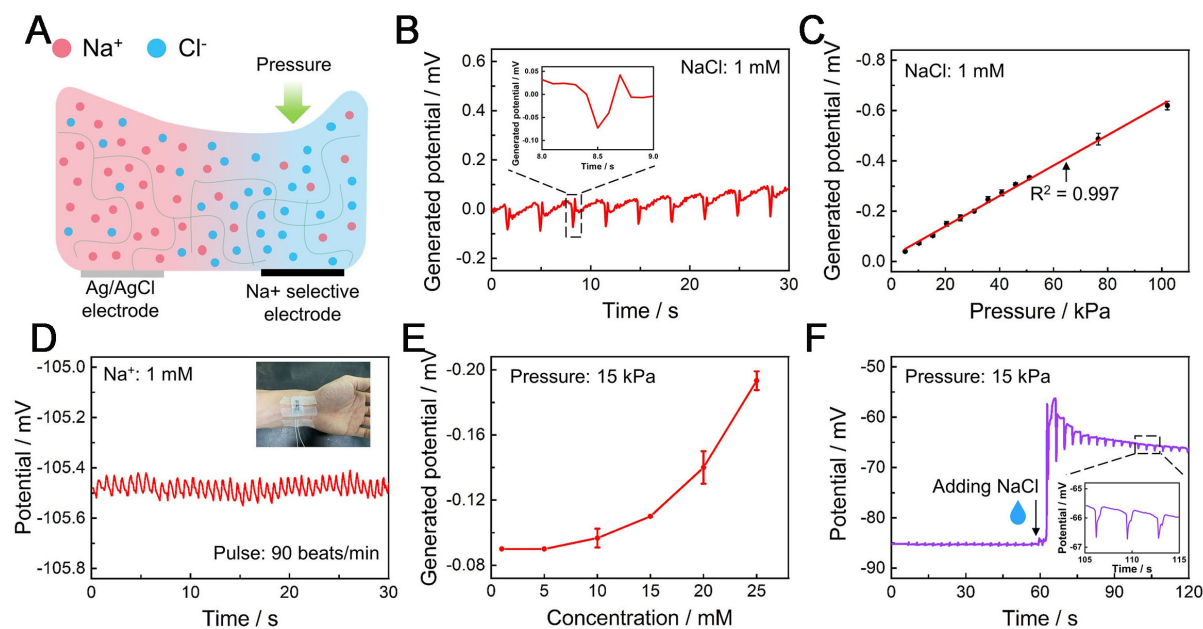


Figure 3. Pressure sensing performance of the dual-mode sensor. (A) Schematic diagram of the piezoionic mechanism of the hydrogel; (B) Cyclic pressure/release test for ten cycles; (C) Generated potential as a function of the applied pressure; (D) On-body pulse detection by fixing the pressure sensor at the wrist; (E) Generated potential as a function of the NaCl concentration in the hydrogel under the pressure of 15 kPa; (F) Open-circuit potential change when applying periodic pressure of 15 kPa with a frequency of 20 and dropping 2.0 μL NaCl solution (10 mM) on the hydrogel containing NaCl solution (1 mM).

avoid the influence of sweat [Figure 3D]. During the test, the dual-mode sensor was worn on the left wrist, and a commercial pulse sensor (HUAWEI Band 8) was worn on the right hand for validation. The potential signal showed a clear and rhythmic change, indicating a pulse of 90 beats/min, which is consistent with the result from the commercial pulse sensor. In addition to detecting the pulse, the sensor can also detect other biophysical signals such as joint movement and swallowing [Supplementary Figure 14]. Moreover, the potential change showed a positive correlation with the NaCl concentration in the hydrogel under the fixed pressure of 15 kPa [Figure 3E].

Furthermore, we applied periodic pressure with a frequency of 20 and added 2.0 μL of 10 mM NaCl solution to the hydrogel with 1 mM NaCl solution, simulating the simultaneous detection of the change in Na⁺ concentration and pressure [Figure 3F]. Before adding the NaCl solution, the stable potential baseline of -85 mV with periodic fluctuation (generated potential of -0.1 mV) responded to the unchanged Na⁺ concentration in the hydrogel and the periodic stimuli of mechanical pressure (15 kPa, 20 beats/min). Once the NaCl solution was added to the hydrogel, the potential baseline rapidly increased and then reached a new equilibrium state of -66 mV with the diffusion of Na⁺. During this process, the generated potential of periodic fluctuation changed with the diffusion of Na⁺ and settled at -1 mV. We calculated that the Na⁺ concentration of the collected solution is 1.95 ± 0.98 mM ($n = 5$) based on the change of potential baseline, which is close to the theoretical concentration of 1.82 mM. Meanwhile, we can read out the pressure frequency of 20 from the period of the fluctuation simultaneously. Note that the piezoionic effect was also observed on the bare carbon electrodes [Supplementary Figure 15]. However, the potential drift was quite large on the carbon electrodes due to the lack of Ag/AgCl and ISE that can provide a stable potential baseline.

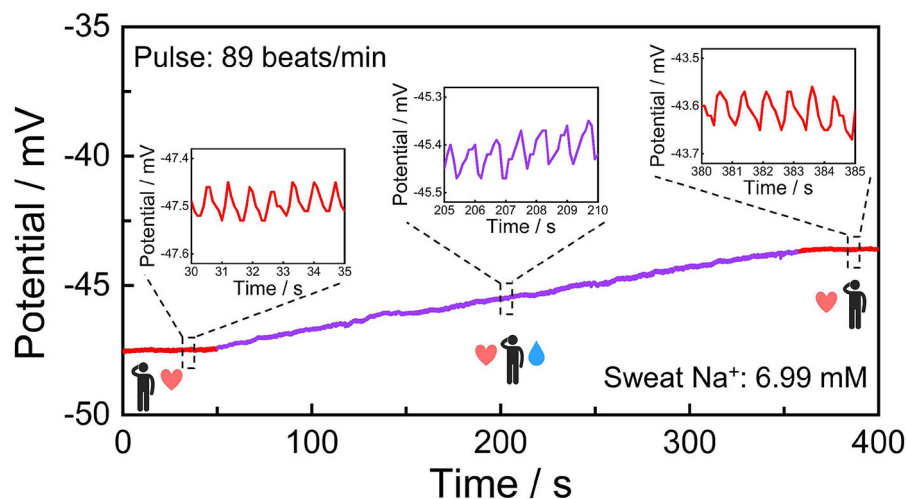


Figure 4. On-body test. The red curves indicate the detection of the pulse. The purple curves indicate simultaneous detection of the sweat Na⁺ and pulse.

On-body real-time monitoring of sweat Na⁺ and pulse

The dual mode sensor was used to monitor sweat Na⁺ and pulse simultaneously by attaching it to the wrist of a female volunteer aged 25 [Figure 4]. Before the test, a waterproof film was added between the skin and hydrogel to prevent the hydrogel from absorbing sweat; thus, the potential baseline remained stable, and the periodic fluctuation was caused by the pulse. Upon removing the waterproof film, the potential baseline gradually increased with time as the hydrogel collected the Na⁺ from sweat. After five minutes, the waterproof film was added again. As a result, the potential baseline stabilized to -43 mV while the pulse potential signal remained. The rising amplitude of the potential baseline from -47 to -43 mV meant that the Na⁺ concentration increased from 1 to 1.10 mM, and the sweat Na⁺ concentration was 6.99 mM. In addition, the pulse information of 89 beats/min can be read out from the number of peaks. Both the Na⁺ concentration and pulse are in agreement with the results measured separately, demonstrating the practicability of this wearable sensor for the simultaneous detection of the physical and biochemical signals. We also demonstrated the on-body tests on the other two volunteers, and the concurrent pulse monitoring and sweat Na⁺ sensing can be achieved for each volunteer [Supplementary Figure 16].

CONCLUSIONS

In summary, we developed a dual-mode sensor capable of the simultaneous detection of both physical and biochemical signals by integrating a hydrogel with a Na⁺ selective electrode. The solid-state Na⁺ selective electrode was endowed with pressure-sensing capability based on the piezoelectric response. In addition, the hydrogel also works as a flexible skin interface for sampling sweat. Thus, we can simultaneously detect the mechanical pressure and Na⁺ concentration using a single sensor. We also demonstrated its application as a wearable device for the simultaneous detection of sweat Na⁺ and pulse. We believe that this integrated dual-mode sensor will pave the avenue for the next-generation multifunctional wearable sensors for applications in healthcare.

DECLARATIONS

Authors' contributions

Conceptualization, methodology, and writing-original draft: Ma B
Methodology and data curation: Huang K

Writing-original draft: Chen G

Investigation: Tian Y, Jiang N

Resources: Zhao C

Writing-review and editing, and funding acquisition: Liu H

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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