A wearable, freestanding electrochemical sensing system

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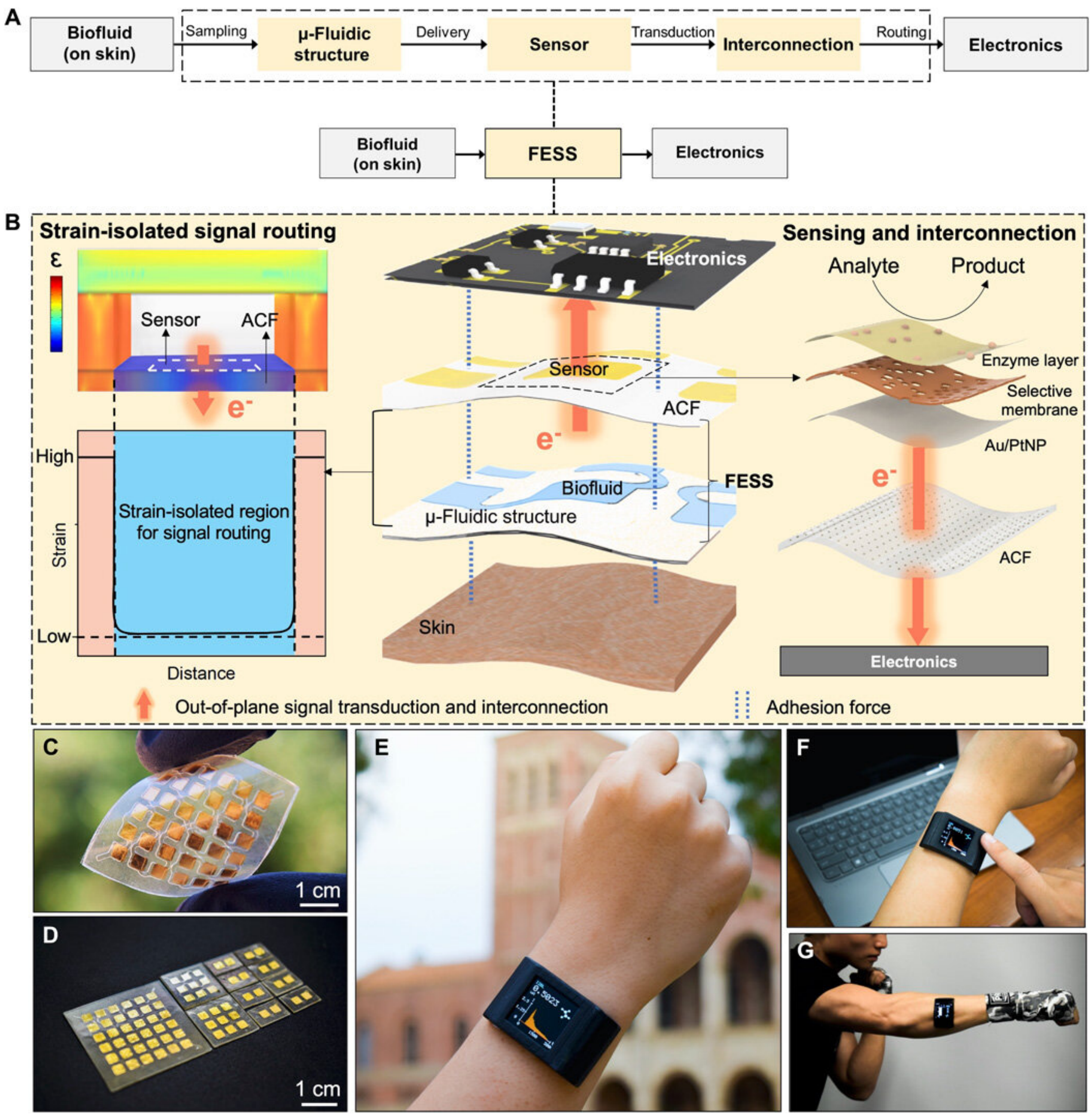
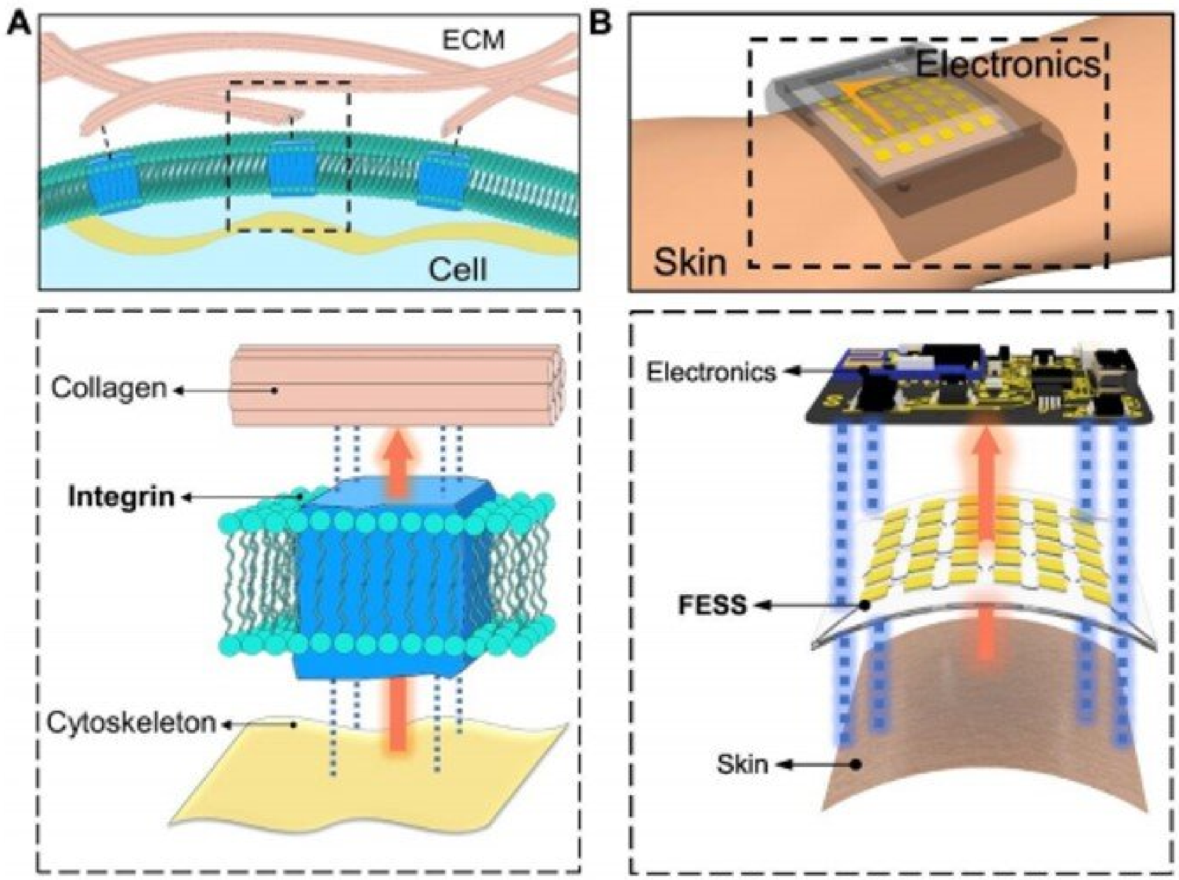


FESS design rationale, implementation, and application. (A) Schematic of the biomarker information delivery pathway enabled by the FESS, illustrating sampling, sensing, and routing of epidermally retrieved biomarker information to readout electronics through a single entity. (B) Design rationale of the FESS. (C) Representative implementation of the FESS, demonstrating flexibility and no in-plane interconnection. (D) Representative family of FESS devices, containing 1 × 2, 3 × 3, and 6 × 6 electrode arrays. (E) Custom-developed and FESS-enabled smartwatch for biomarker monitoring. (F and G) Deployment of the FESS-enabled smartwatch in stationary (F) and high-intensity exercise (G) settings. (Photo credit: Peterson Nguyen, Kaili Chiu, Yichao Zhao, University of California, Los Angeles.) Credit: *Science Advances*, doi: 10.1126/sciadv.aaz0007

In a new study published on *Science Advances*, Yichao Zhao and a research team in integrated bioelectronics and materials and engineering in the U.S. engineered a disposable, free-standing electrochemical sensing system (FESS). The FESS allowed them to realize a system-level design strategy to address the challenges of wearable biosensors in the presence of motion and allow seamless integration with consumer electronics. The team developed a FESS-enabled smartwatch, featuring sweat sampling, electrochemical sensing and data display or transmission, within a self-contained wearable platform. The team used the FESS-smartwatch to monitor the profiles of sweat metabolites among individuals in sedentary and high-intensive exercise settings.

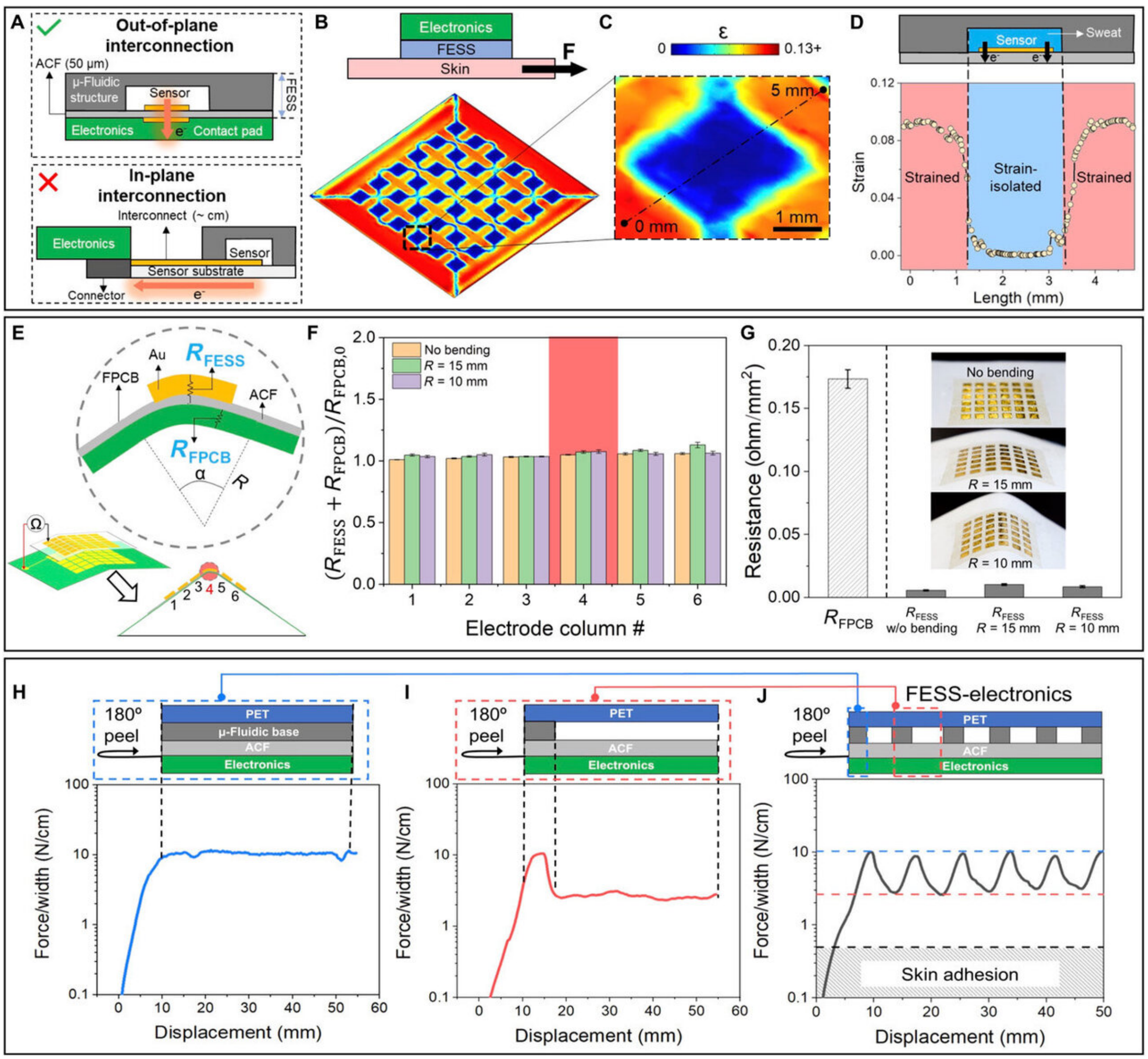
The internet-of-things (IOT) infrastructure can be used in wearable consumer electronics to transform personalized and precision medicine by harvesting physiologically relevant data with minimal user intervention. Scientists have typically used physical sensors in commercial wearable platforms to track a user's physical activity and vital signs. However, to gain insight into the body's dynamic chemistry, researchers require electrochemical sensing surfaces to target the biomarker molecules within non-invasively retrieved body fluids such as sweat. To accomplish this, it is critical to precisely engineer the information delivery pathway from the skin to a readout unit. For electrochemical sensing, the information delivery pathway must sample and deliver the biomarker-rich biofluid to the sensor surface in a microfluidic structure, followed by signal transduction through interconnected elements to the readout electronics. The signal must be maintained along this pathway in the presence of motion-induced strain.



Bio-inspired in situ sensing and signal interconnection. (A) Conceptual illustration of the physiological information exchange between intracellular/extracellular matrices facilitated by cell adhesive molecules (integrin) via sensing, out-of-plane signal interconnection, and double-sided adhesion. (B) In-situ sensing, out-of-plane signal interconnection, and double-sided adhesion enabled by FESS, as a single entity, placed between skin and electronics. Credit: Science Advances, doi: 10.1126/sciadv.aaz0007

In this work, Zhao et al. developed the freestanding electrochemical sensing system (FESS) and simultaneously adhered it to the skin and to electronics using double-sided adhesion forces without rigid connectors. The FESS sampled and directed epidermally retrieved biofluids for electrochemical sensing, followed by routing to readout electronics through a strain-isolated pathway. They integrated the FESS inside a custom-built smartwatch for sweat induction, sampling, electrochemical sensing, signal processing and data display or transmission. The results showed high-fidelity signal transduction and robust mechanical contact with human skin without constraining user motion. The freestanding sensing system can be linked with future wearable electronics to generate high-fidelity health and wellness-related datasets based on the daily activities of users.

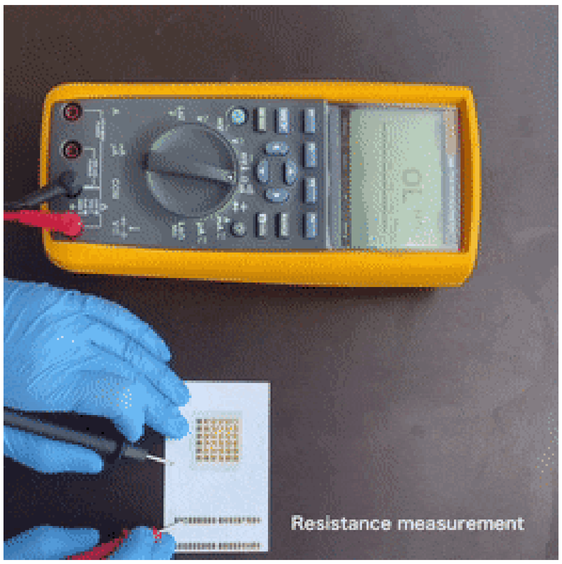
To create an efficient biological pathway, Zhao et al. selected integrin—a cell adhesive molecule that efficiently allowed physiological information exchange between intracellular and extracellular matrices. The FESS device implemented integrin-like functionalities through a strain-isolated region in a microfluidic structure. They engineered FESS as a vertically conductive, double-sided adhesive and flexible microfluidic bioanalytical thin film system composed of multiple vertically stacked films. These films included an adhesive anisotropic conductive film (ACF), a noble metal electrode array film, a biochemical film, a microfluidic film and a skin adhesive film. They taped the complete thin film system onto the readout electronics without connectors and with minimal contact resistance to potentially transform any electrical contact into a chemical or biological sensor. The team developed a proof-of-principle, self-contained biomarker-sensing smartwatch with FESS to monitor the sweat metabolite profiles of individuals in sedentary vs. high-exercise settings.



FESS strain simulation and characterization of strain-isolated signal interconnection. (A) Illustration of the FESS' out-of-plane signal interconnection versus conventional in-plane signal interconnection. Conventional implementations are constrained to signal routing through highly strained regions, while the devised FESS allows for routing via near-zero strain regions. (B) COMSOL-simulated strain (ε) profile of a representative FESS in the presence of an externally applied shear force, illustrating near-zero strain at the bottom of the microchannel (i.e., substrate-biofluid interface). (C) Corresponding zoomed-in view of the strain profile for one "pixel." (D) Strain distribution along the dashed line in (C). (E) Out-of-plane interconnection electrical characterization of FESS performed under different localized bending angles (for an array of 6 × 6 Au electrodes). (F) Interconnection resistances of the bent FESS-FPCB (RFESS + RFPCB), for different localized bending angles (normalized with respect to RFPCB with no bending, RFPCB,0). Error bars indicate standard error of measurements across the six electrodes within each column. (G) Resistance measurements of the FESS electrodes under different bending angles (n = 36), in relation to the FPCB contact pad resistance (RFPCB,0). (H to J) 180° peeling tests characterizing the interconnection adhesion between the PCB and FESS with different backing structures: microfluidic base–ACF (H), microfluidic channel–ACF (I), and a representative microfluidic channel array–ACF (J). (Photo credit: Peterson Nguyen, University of California, Los Angeles.) Credit: *Science Advances*, doi: 10.1126/sciadv.aaz0007

In this setup, the vertical conductivity of ACF facilitated out-of-plane signal interconnections to avoid undesired body-motion-induced strain effects on the signal pathways. The team characterized the mechanical adhesion property of FESS to ensure the adhesion forces between the FESS and electronics were higher than those between FESS and dry or actively sweating skin. The team tested the force required to peel the ACF layer from the FESS on a printed circuit board and the results showed a strong FESS-based interconnection to electronics, as suited for on-body applications.

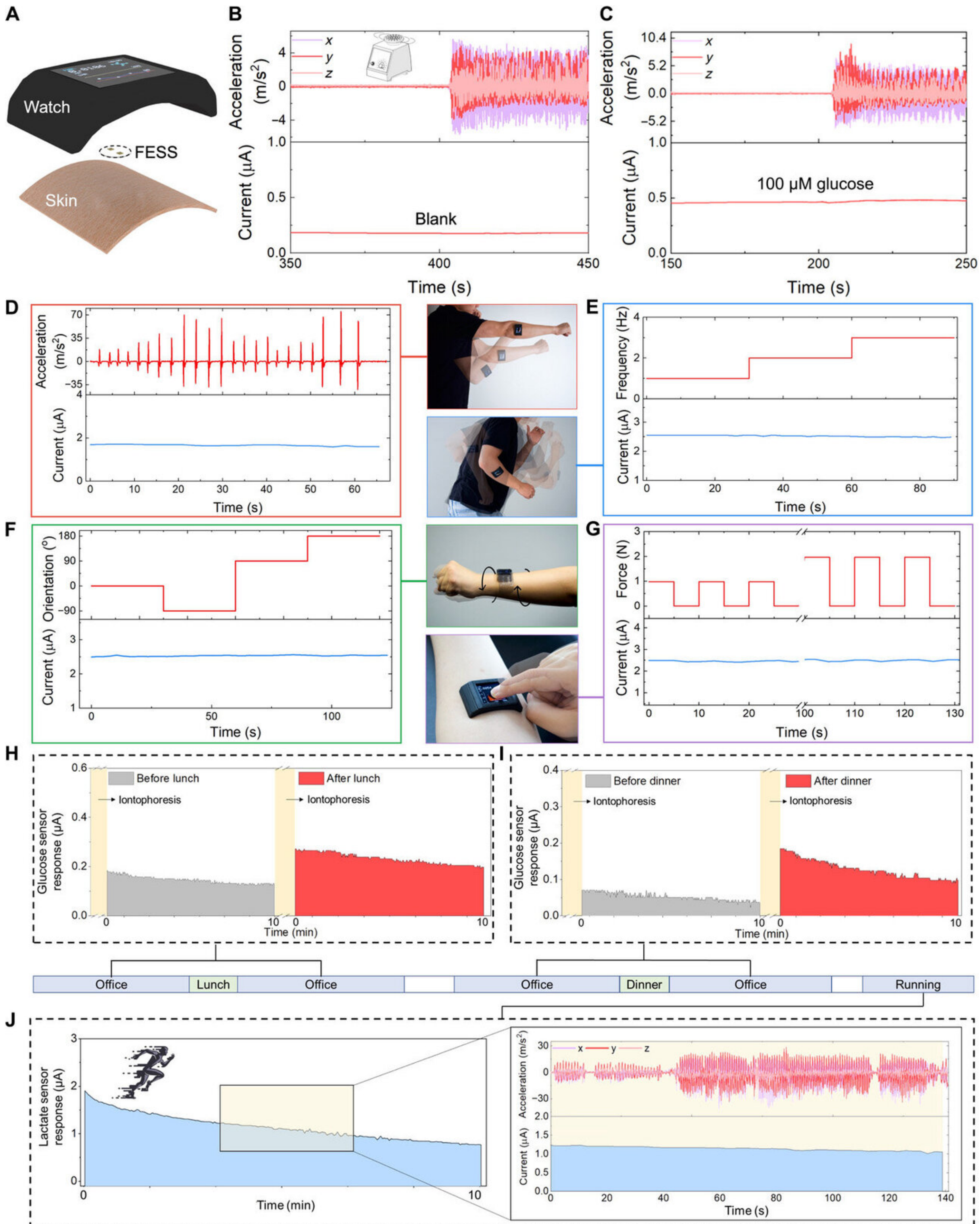
Zhao et al. then tested the signal transduction capability of the FESS. They patterned noble metal electrodes onto the ACF to achieve biochemical-to-electrical signal transduction, followed by deposition of biochemical films to analyze biomolecular targets of interest. They tested the electrochemical activity of metal-patterned ACF for two commonly used electrode surfaces on unmodified gold (Au) and platinum (Pt) nanoparticle-modified Au. The electroanalytical methods investigated in the work provided sample-to-answer biomarker readouts to obtain real-time insight into the alterations in sweat biocomposition.



Testing the resistant measurement of the ACF-based interconnections after mechanical deformation. Credit: Science Advances, doi: 10.1126/sciadv.aaz0007

In the next few experiments, the research team showed the capability of FESS to monitor biomarkers during the user's daily activities. To accomplish this, they integrated FESS into a custom-developed smartwatch as a model IOT device containing and analog/digital circuit, Bluetooth transceiver and a liquid crystal display (LCD) screen for system-level functionalities, including signal and user-command processing, display and wireless data communication. The FESS-based smartwatch performed similarly to a potentiostat. The scientists adhered the complete smartwatch onto the skin without external wrappings or fixtures for wireless biomarker sensing as a self-contained unit. The LCD screen displayed real-time readings and temporal profile of the biomarker measurements, while the Bluetooth receiver relayed the readings to a custom-developed mobile application to upload the data to a cloud-server for further analysis.

The team adhered the FESS-based smartwatch onto a subject's forearm to display its function as a wearable system to monitor biomarkers. The subject could wirelessly control the device to take real-time, sweat-based biomarker measurements relative to the user's daily routine. The user monitored their sweat glucose levels before or after consuming a mixed range of meals and the readout of the smartwatch indicated elevated sweat glucose levels after food intake, in alignment to previous trends. The smartwatch additionally provided user information on sweat lactate readings while running in a field, the results were consistent despite the involvement of high-frequency and high-acceleration-based body motions.



Custom-developed FESS-integrated smartwatch for on-body application. (A) Illustration of the FESS-enabled smartwatch (containing FESS, LCD screen, PCB, and battery units housed within a 3D-printed case). (B and C) Ex situ characterization of the FESS-PCB glucose-sensing system response upon vortical vibration (FESS electrode: 6 mm2, microfluidic channel height: 170 μm, and volume: 4 μl). The vibrational acceleration profiles are presented in the top half, and the sensor responses are captured in the bottom half when tested in PBS (B) and 100 μM glucose in PBS (C). (D to G) On-body signal fidelity characterization of a FESS-PCB lactate-sensing system with a subject performing shadow boxing (D), arm swinging (E), wrist twisting (F), and device pressing (G). The acceleration, frequency, orientation, and force profiles are presented in the top half, and sensor responses are captured in the bottom half. (H to J) Monitoring the subjects' metabolite profiles through various daily events and in different settings. Iontophoretically induced sweat glucose were measured before and after lunch (H) and dinner (I). (J) Sweat lactate measurements during exercise (a representative motion-induced acceleration profile is shown on the right). (Photo credit: Peterson Nguyen, Kaili Chiu, and Yichao Zhao, University of California, Los Angeles.) Credit: *Science Advances*, doi: 10.1126/sciadv.aaz0007

In this way, Yichao Zhao and colleagues examined the biomarker information delivery pathway and recognized near-zero strained regions inside a microfluidic-sensing module to engineer a strain-isolated path to preserve the fidelity of biomarker data. The thin-film system that formed the free-standing FESS entity was bioinspired by integrin-like functionalities for signal transduction and signal interconnection via double-sided adhesion. The FESS efficiently bridged the skin and readout electronics to harvest biomarker information. The team coupled the FESS system seamlessly with a custom-developed smartwatch as a wearable biosensor to monitor real-time biomarker readouts throughout a user's daily routine. To commercialize the prototype developed in this work, Zhao et al. propose future clinical trials to map sweat-based biomarker readings and gain information on the physiological status of the users. The advantages of this work, including their ease of integration with wearable electronics and high fidelity readings can be employed to perform large-scale clinical investigations.

More information: Yichao Zhao et al. A wearable freestanding electrochemical sensing system, *Science Advances* (2020). DOI: 10.1126/sciadv.aaz0007

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