# **Skin-Interfaced Wearable Biosensors**

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# **Bioelectronic Devices for Personalized Medicine**

#### Gao Research Group at Caltech Medical Engineering





#### **Device Innovations for Translational Medicine**



# Wearable Biosensors for Personalized Medicine









Commercial health monitors mainly track physical activities and vital signs

Challenges and opportunities: physiological monitoring at molecular levels



# **Human Sweat**



#### Electrolytes

• Na<sup>+</sup>, Cl<sup>-</sup>, K<sup>+</sup>, NH<sub>4</sub><sup>+</sup>, Ca<sup>2+</sup>, H<sup>+</sup>

#### **Metabolites**

• Lactate, glucose, urea, uric acid, creatinine

#### Amino Acids, Vitamins, & Hormones

• Amino acids, Vitamin C, cortisol, DHEA

#### **Proteins & Peptides**

• Cytokines, TNF, neuropeptides

#### **Xenobiotics**

- Heavy metals (Cu, Hg, Cd, Zn, Pb)
- Ethanol
- Drugs



# The Current Healthcare Applications of Sweat Test



Traditional sweat test cannot provide real time information and requires extensive laboratory analysis



# **Wearable Sweat Analysis**

Real time, non-invasive, continuous health monitoring



Bariya et al. Nature Electronics, 2018; Yang et al. Chem Soc Rev 2019; Gao et al. Acc. Chem. Res. 2019; Xu et al. Mater 2020; Tu et al. Adv Funct. Mater. 2020.



# **Fully Integrated Wearable Sensors for Perspiration Analysis**

- Real time in situ monitoring:
  - Metabolites (glucose, lactate)
  - Electrolytes (Na<sup>+</sup>,K<sup>+</sup>)
  - Skin temperature.
- On site signal conditioning, processing, wireless transmission.
- Real time sensor reading calibration.
- Data display on cell phone.
- Data aggregation on cloud server.

Gao et al. Nature, 2016, 529, 509. Featured by Time, New York Times, The Wall Street, Nature, Science etc.





J. Wang et al. ACS Sens, 2016, 1, 1011.



D.H. Kim et al. Nat Nanotech, 2016, 11, 566.



J. Heikenfeld et al. Lab Chip, 2018, 18, 3750.



J. Rogers et al. Sci Trans Med, 2016, 8, 366ra165.



# Sensor Mechanism – Enzymatic Sensors

Amperometric – Chronoamperometry; Two-electrode or three-electrode system



Prussian Blue is used as redox mediator to lower the operation potential (from 0.6~0.7 V to ~0 V) and minimize the interferences from electroactive molecules.



# **Sensor Mechanism – Ion-Selective Sensors**



100,000 times larger than that of the sodium-valinomycin complex.

# **Sensor Mechanism – Voltammetric Sensors**

Some **electroactive molecules** can directly lose or donate electrons on the electrode surface when a redox potential is applied to the sensing electrode.

Voltametric – Different Pule Voltammetry; Square Wave Voltammetry; Three-electrode system



Nature Biotechnology, 2020, 38, 217.

Adv. Mater. 2018, 1707442.

Example electroactive molecules in sweat: some metabolites (e.g., uric acid), nutrients (e.g., tyrosine), drugs/opioids (e.g., caffeine and cocaine), and hormones/peptides (e.g., NPY)



### Large-scale, low-cost manufacturing: Laser-Engraved Lab on Skin



Mass-producible wearables for simultaneous sweat sampling, chemical sensing and vital-sign monitoring





Isabella Yang MedE G5 Forbes 30 Under 30

Laser-engraved graphene allows highly sensitive chemical sensing

Yang, Song, Bo, et al. Nature Biotechnology 2020, 38, 217-224. Chosen as Editor's Choice by Science Translational Medicine



### Laser-Engraved Lab on Skin



Laser-engraved graphene allows highly sensitive chemical sensing



Laser-engraved graphene allows highly robust physical sensing/vital sign monitoring

Nature Biotechnology 2020, 38, 217-224.



### Laser-engraved microfluidics for efficient sweat sampling





The multi-inlet design enables highly efficient sweat sampling

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# Validation of the laser-engraved wearable sensor



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# How to Access Sweat Sample Without Exercise?

Beyond physical exercise: iontophoresis based sweat extraction



Sweat can be induced on demand through iontophoresis.



# **A Wearable Platform for Sweat Extraction & Sensing**

Beyond physical exercise: accessing sweat samples on demand using iontophoresis



PNAS, 2017, 114, 4625



# **Iontophoresis based Sweat Extraction**





# **Applications – Disease Diagnosis**



Sweat Test (CI-) is the gold standard for Cystic Fibrosis diagnosis.



PNAS, 2017, 114, 4625



# **Applications – Gout management**



#### Gout

- The most common inflammatory arthritis affecting tens of millions of people worldwide.
- Characterized by chronic hyperuricemia, an elevated UA level exceeding the physiological saturation threshold.
- The upper end of the normal range is 360 µmol/L for women and 400 µmol/L for men.
- Urate-lowering therapy, flare-up preventions, and dietary or nutritional control



#### **Laser-Engraved Wearable Sensors for Gout Management**



#### Collaborator: Profs. Tzung Hsiai and Zhaoping Li at UCLA Medical Center

#### Nature Biotechnology, 2020, 38, 217.

This platform is used for gout management in a pilot study.

We plan to monitor main metabolic syndrome risk factors for early diagnosis and nutritional intervention.



# **Applications – Therapeutic drug monitoring (TDM)**

Drug dose personalization using wearable sensor

Drug metabolism varies person-to-person (especially in pediatric population) Many drugs have narrow therapeutic index Blood analysis with LC-MS is the gold standard







# Methylxanthine Drug Monitoring with Wearable Sweat Sensors

### **Caffeine monitoring**



# **Applications – Stress and Mental Health Assessment**

### Stress and mental health

Did you know... 95% of disease is stress-related? Anxiety, Depression, PTSD, CVD, Cancers

### How is stress measured?

#### Psychological questionnaires



**PSS: Perceived Stress Scale** 

POMS: Profile of Mood State

ESRQ: Emotional Stress Reaction Questionnaire

PMS-9: Psychological Stress Measure



## mHealth Biosensor for Dynamic Stress Monitoring

Current stress, anxiety, and depression measurements are based on subjective questionnaires. Stress hormone (e.g., cortisol) circadian rhythm is related to metabolic and mental disorders



Blood draw/finger prick induces stress.

Sweat is an attractive, non-invasive source for stress hormone monitoring.

Collaborator: Prof. IsHak Waguih, Professor of Psychiatry at Cedars-Sinai

Torrente-Rodríguez, Tu et al., Matter, 2020, 2, 921-937. Featured in Preview by John Rogers, Matter, 2020, 2, 795.





Dr. Rebeca M. Torrente-Rodríguez Jiaobing Tu MedE G4



### Laser-engraved graphene biosensor for rapid cortisol sensing





LOD as low as 80 pg/mL cortisol

Toward real-time analysis

Strong correlation (r=.973) with ELISA

Matter, 2020, 2, 921-937.





High correlation between sweat/serum and sweat/saliva

Matter, 2020, 2, 921-937.



### Investigation of cortisol dynamics in human sweat: Stress response

Physical stressor (aerobic exercise) Physiological stressor (cold pressor test)



HPA activation during exercise Blunted cortisol response in athletes



Matter, 2020, 2, 921-937.



Cold pressor test

Baseline

Time

# Application – SARS-CoV-2 RapidPlex for COVID-19 Diagnosis



SARS-CoV-2 RapidPlex: a mass-producible graphene-based telemedicine platform - that can simultaneously monitor virus antigen (current infection), virus antibodies (immunity), and inflammatory biomarkers (severity) in less than 10 min in both saliva and blood.

*Matter, 2020, 3, 1981.* Featured on the Journal Cover and Journal Preview





Dr. Rebeca M. Heather Lukas Torrente-Rodríguez MedE G3





Application of SARS-CoV-2 RapidPlex in Blood and Saliva Samples from COVID-19-Positive and -Negative Subjects

#### Matter, 2020, 3, 1981.



# How can we power future wearable biosensors?

A biofuel powered electronic skin



For the first time, the battery-free biofuel-powered soft e-skin system can perform multiplexed biosensing and Bluetooth communication.

Yu et al. Science Robotics, 2020, 5, eaaz7946. Highlighted in Nature Electronics, 2020, 3, 235



Dr. You Yu Caltech

### **Biofuel-Powered Soft Electronic Skin for Wearable Sensing**





### Pt/Co nanoparticle decorated cathode for long-term stability



The transition-metal **Co dopants** could enhance the cohesive energy and thus stabilize the nanoparticles, leading to substantially reduced biofouling in body fluids and higher onset potential for oxygen reduction.

Permselective Nafion layer further improves the long-term stability of the cathode in biofluid.

Science Robotics, 2020, 5, eaaz7946.



#### Power management of the BFC toward powering wearables



What if the BFC can not continuously power the wearables?

Schematic diagram of the PPES system including the BFC array, sensor array, boost converter, instrumentation amplifiers, and BLE module. SOC, system-on-chip; CPU, central processing unit.

The BLE module runs in bursts of activity, periodically waking up from deep sleep mode to acquire measurements with the embedded successive-approximation analog-to-digital converter then wirelessly broadcasting the data to user interface.



In deep sleep mode, the whole PPES system draws a total current of ~100 uA at 3.3 V

### **Biofuel-Powered Soft Electronic Skin for Wearable Sensing**



## **Biofuel-Powered Soft Electronic Skin for Wearable Sensing**



Peak efficiency of 86% at **0.39 V** input voltage and **1.34 μW** of output power with 220 nW of internal average power consumption.

JSSC, 2020, 56, 715.



### Wearable Sweat Sensors Powered by Human Motion



A **highly robust**, **mass-producible**, and **battery-free** wearable platform that efficiently extracts power from body motion through a flexible printed circuit board (FPCB)–based freestanding triboelectric nanogenerator (FTENG). Convert mechanical energy into electrical energy (~416 mW m<sup>-2</sup>) via coupling of inductive and triboelectric effects.

Science Advances, 2020, 6, eaay9842.





Dr. Yu Song



### Wearable Sweat Sensors Powered by Human Motion



Science Advances, 2020, 6, eaay9842.

Caltech

### **Summary - Wearable Sweat Sensors for Personalized Healthcare**



Nature electronics, 2018; Chem. Soc. Rev. 2019



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#### Collaborators

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#### **Clinical Collaborators**

Dr. Tzung Hsiai at UCLA Dr. Zhaoping Li at UCLA Dr. Waguih IsHak at Cedars-Sinai Dr. Jeannine McCune at City of Hope Dr. Harry Rossiter at Harbor UCLA And more...



# Thank you for your attention! Questions?

For more information, welcome to visit: www.gao.caltech.edu

