Bioelectronic Devices for Personalized and Precision Medicine: from Wearable Sensors to Medical Nanorobots

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Outline

- **Wearable Biosensors**
  - **Technology Development**
  - **Fitness and Health Monitoring**
- **Synthetic Nanomachines**
  - **Technology Development**
  - **Biosensing and Drug Delivery**
- **Current Research Focus**

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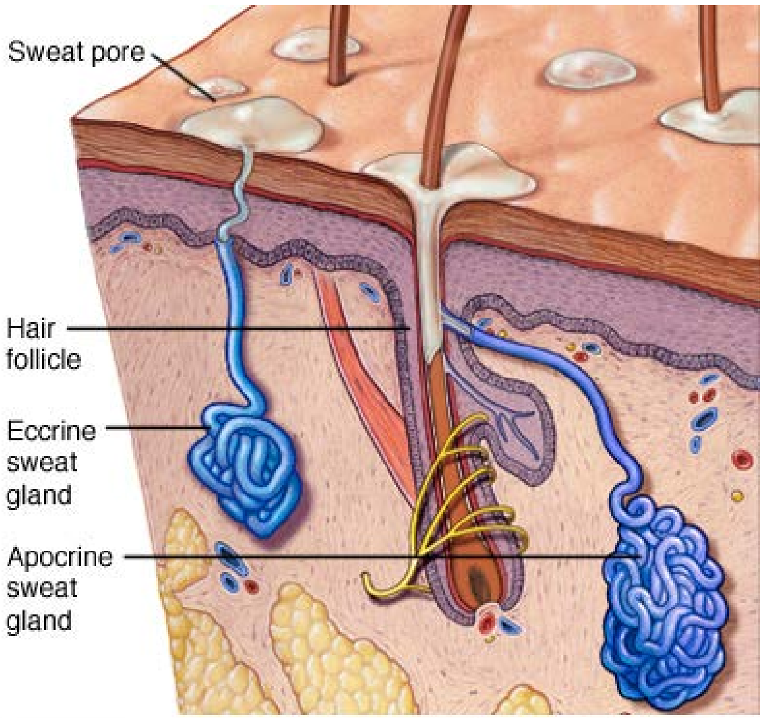
Wearable Biosensors for Personalized Medicine

Commercial health monitors can mainly track **physical activities and vital signs**

Challenges and opportunities: physiological monitoring at molecular levels

Human Sweat



Electrolytes

- Na^+, Cl^-, K^+, NH_4^+, Ca^{2+}, H^+

Metabolites

- Lactate, glucose, urea, uric acid, creatinine

Small Molecules

- Amino acids, cortisol, DHEA

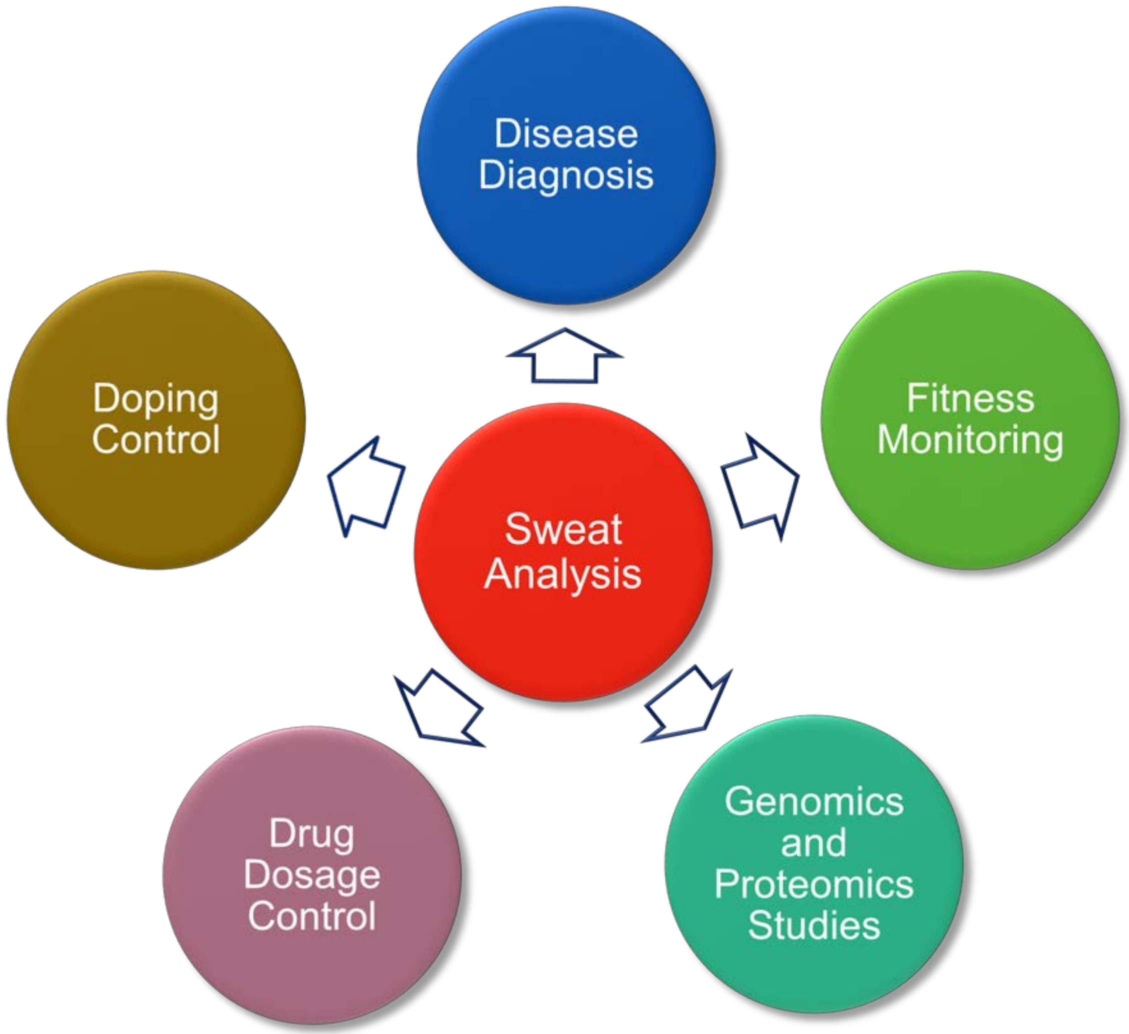
Proteins & Peptides

- Interleukins, tumor necrosis factor, neuropeptides

Xenobiotics

- Heavy metals such as Cu, Hg, Cd, Zn, Pb, As, Ni
- Ethanol
- Drugs
- Cosmetics

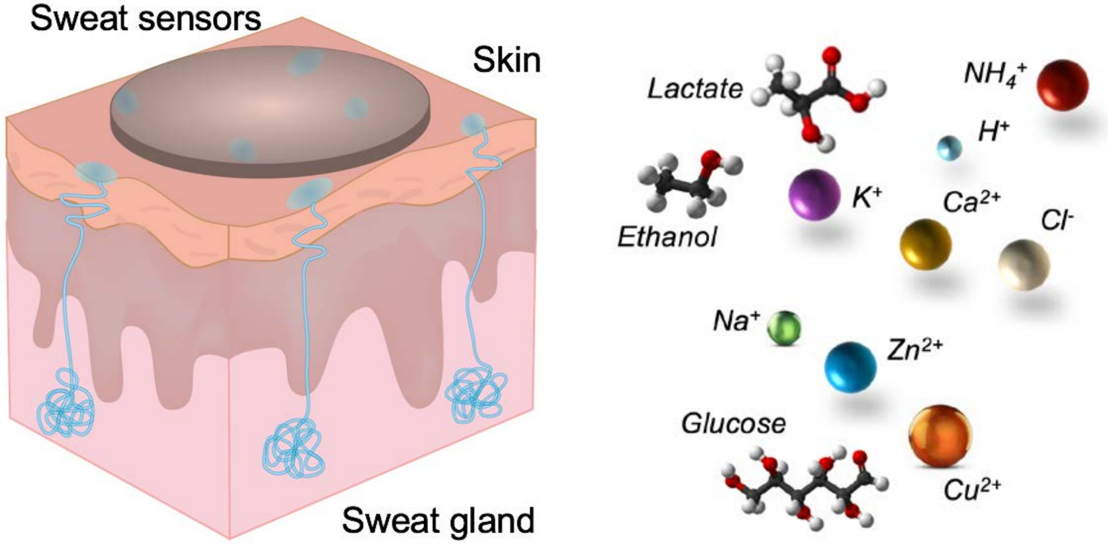
The Current Healthcare Applications of Sweat Test



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

Wearable Sweat Biosensors

Real time, non-invasive, continuous health monitoring



Gao et al. IEDM 2016.

Fully Integrated Wearable Sensors or Perspiration Analysis

- **Real time in situ monitoring**:
  - Metabolites (glucose, lactate)
  - Electrolytes (Na^{+},K^{+})
  - 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.

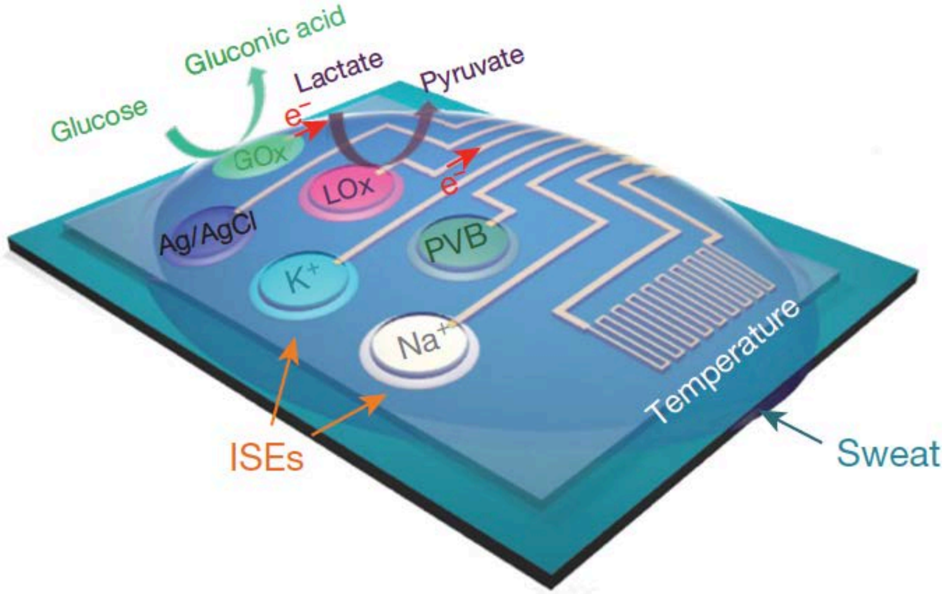
Wearable Sweat Biosensors: System Level Integration

The platform consists of **disposable sensor patch** and **reusable flexible printed circuit board**.

The selection of targeted biomarkers

- Metabolites (glucose, lactate)
- Electrolytes (Na^+,K^+)
- Skin temperature.

Gao et al. Nature, 2016, 529, 509.



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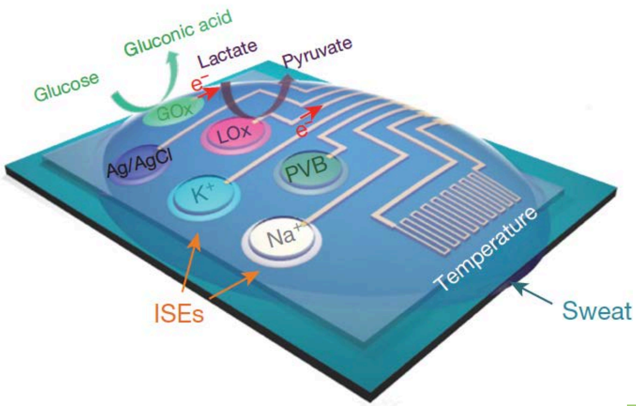
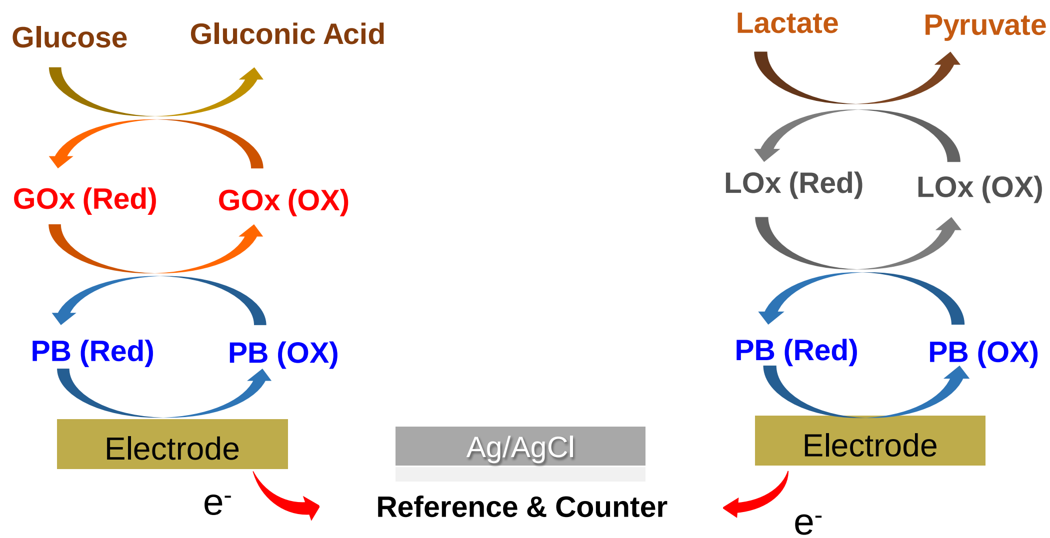
System Level Technology Development - I

Flexible Sensors – Enzymatic Sensors (Glucose and Lactate Sensing)





Glucose Sensors **Lactate Sensors**

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

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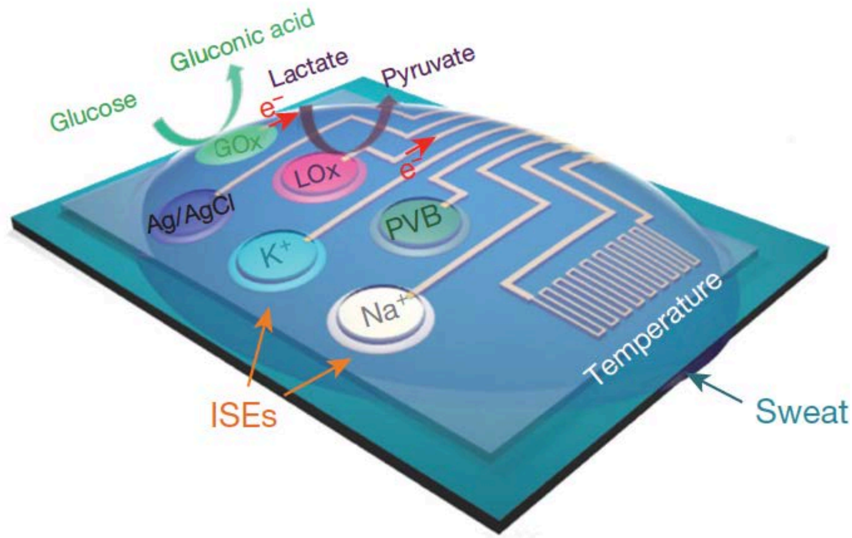
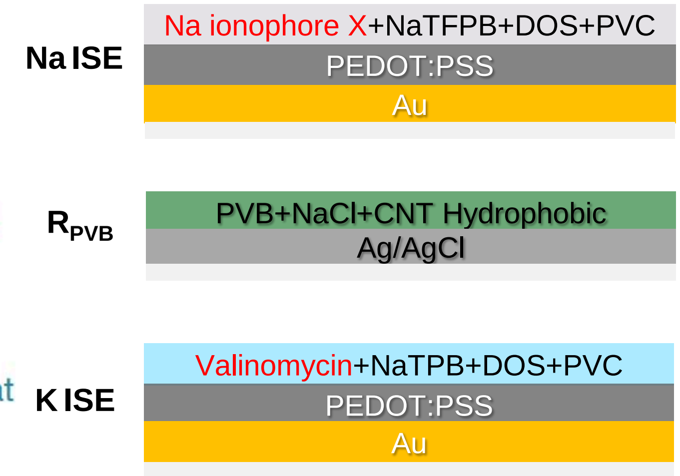
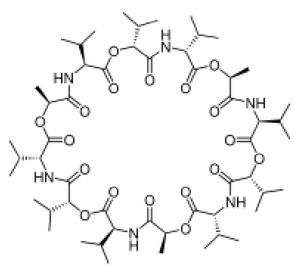
System Level Technology Development - I

Flexible Sensors – Ion Selective Sensors (Na^+ and K^+ Sensing)





Metal ion is encapsulated in a molecular cavity whose size is matched to the ion size



Valinomycin - K ionophore

According to Nernst Equation:

$$E_{meas} = const + \frac{0.05916}{z} \log A_{unk}$$

charge of ion

Ion activity/concentration

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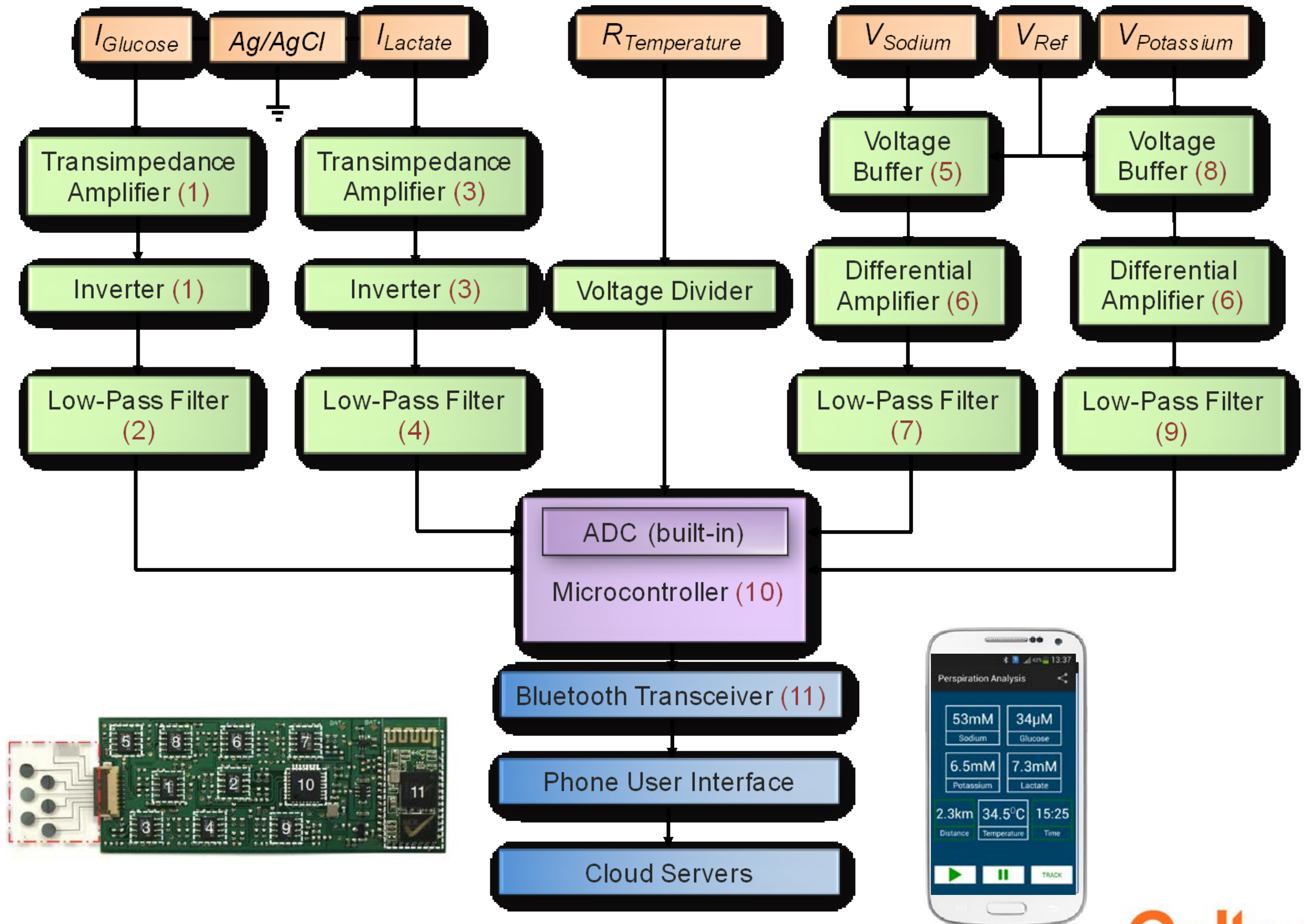
System Level Technology Development - II

Flexible Printed Circuit Board



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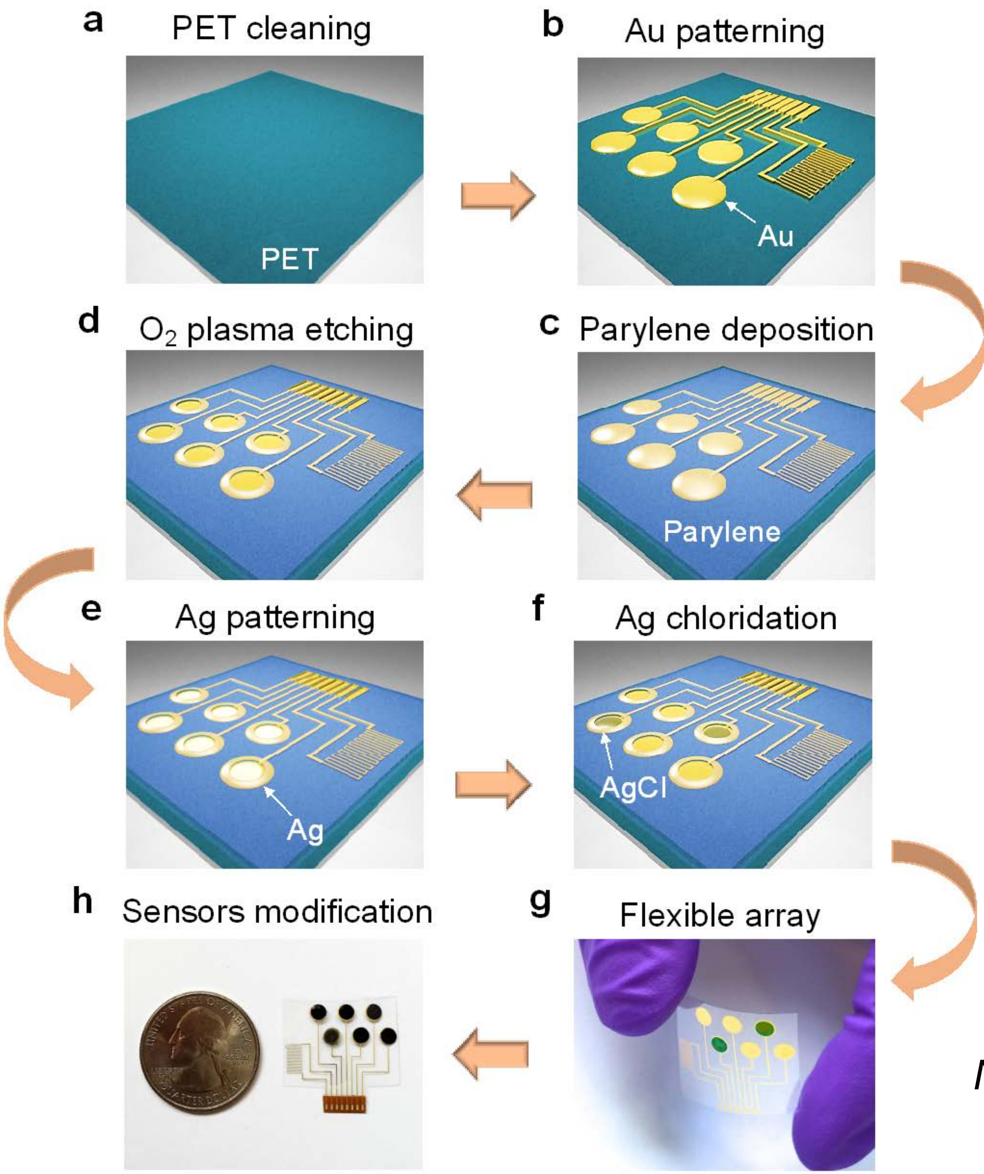
Fabrication process flow for the flexible sensors



Nature, 2016, 529, 509.

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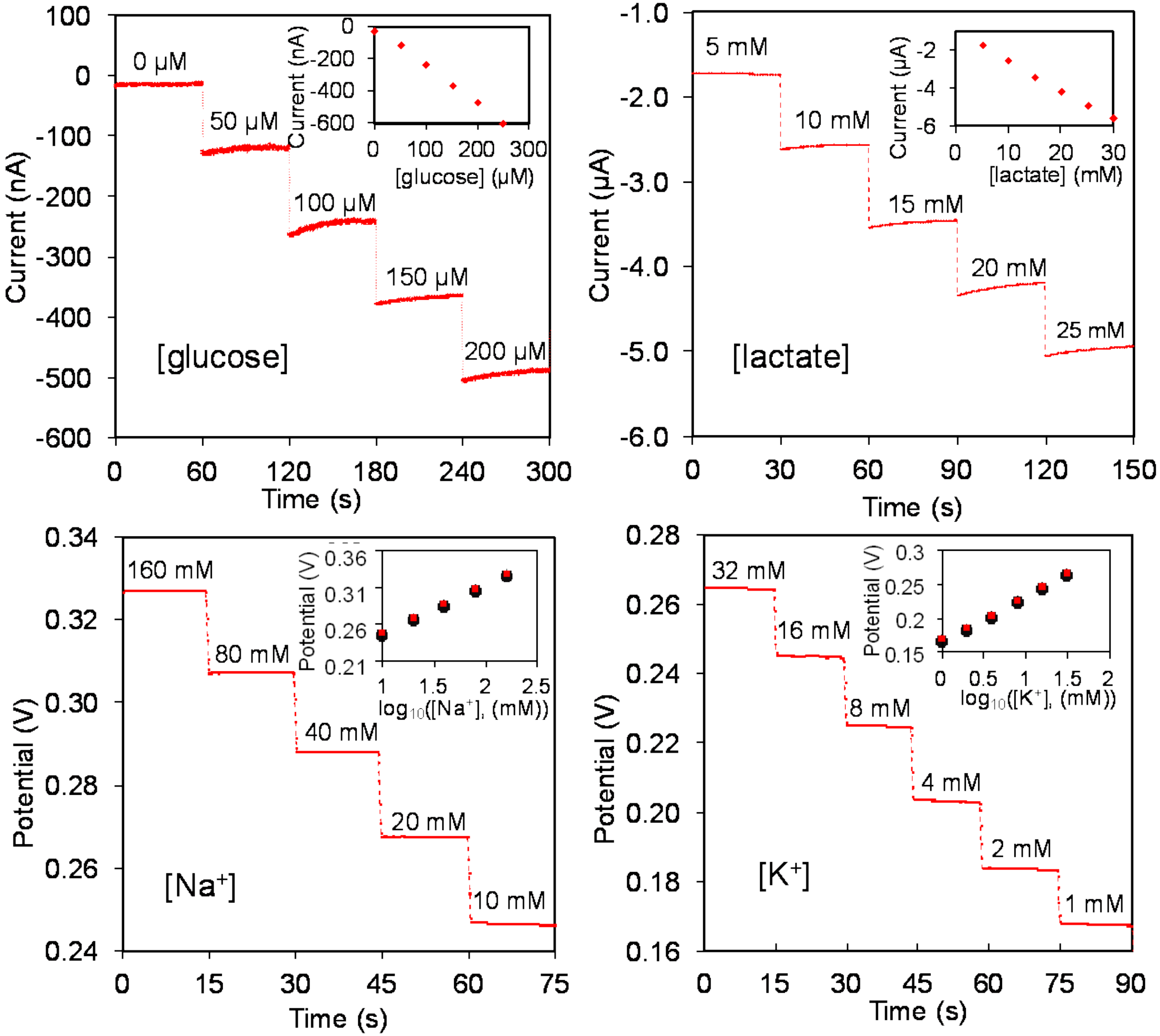
Characterization of the sensors



All the sensors show linear response vs concentration or logarithm of concentration

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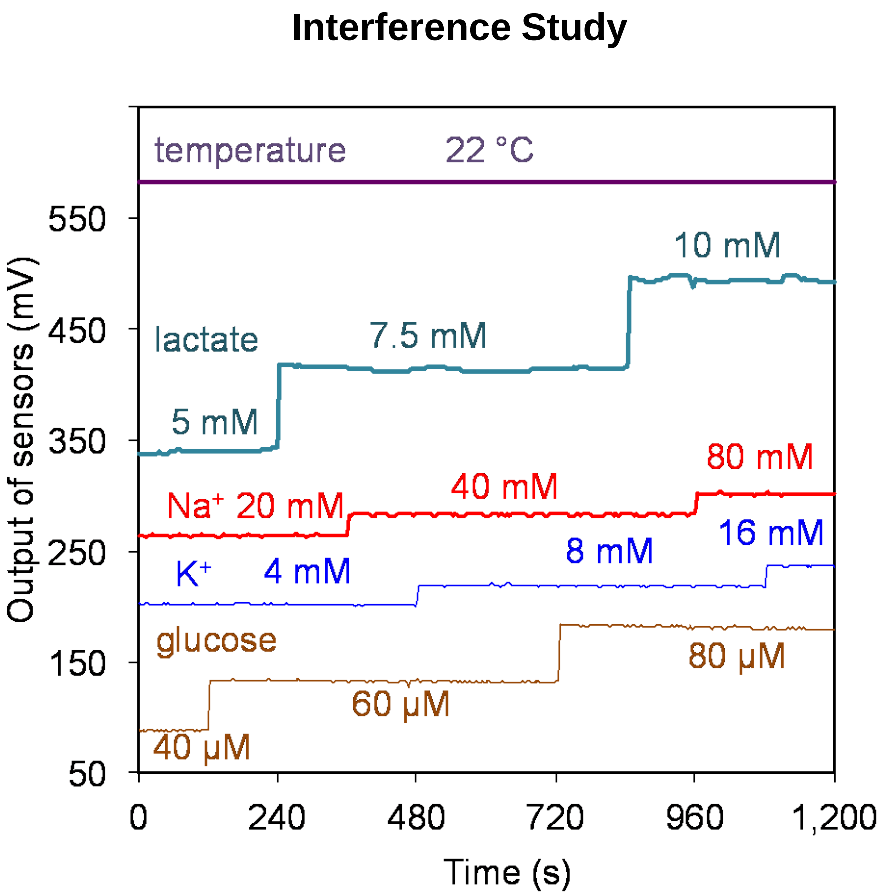
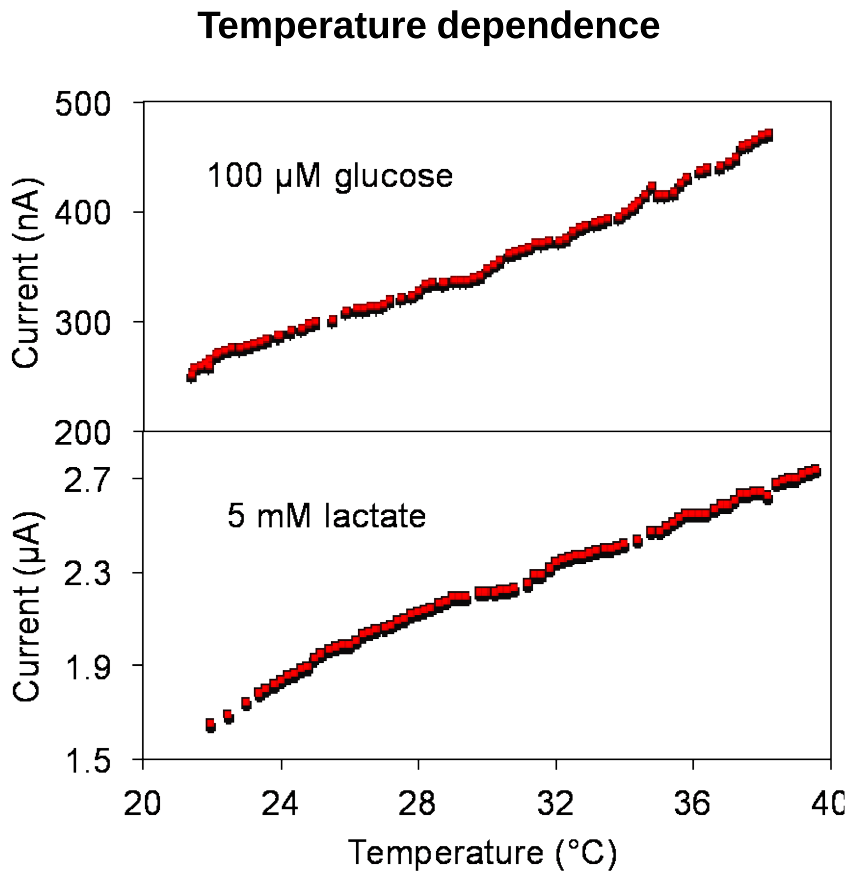
System Level Interference & Temperature Compensation





The chemical sensors have good selectivity.

Real time temperature compensation is necessary.

Gao et al. Nature, 2016, 529, 509.

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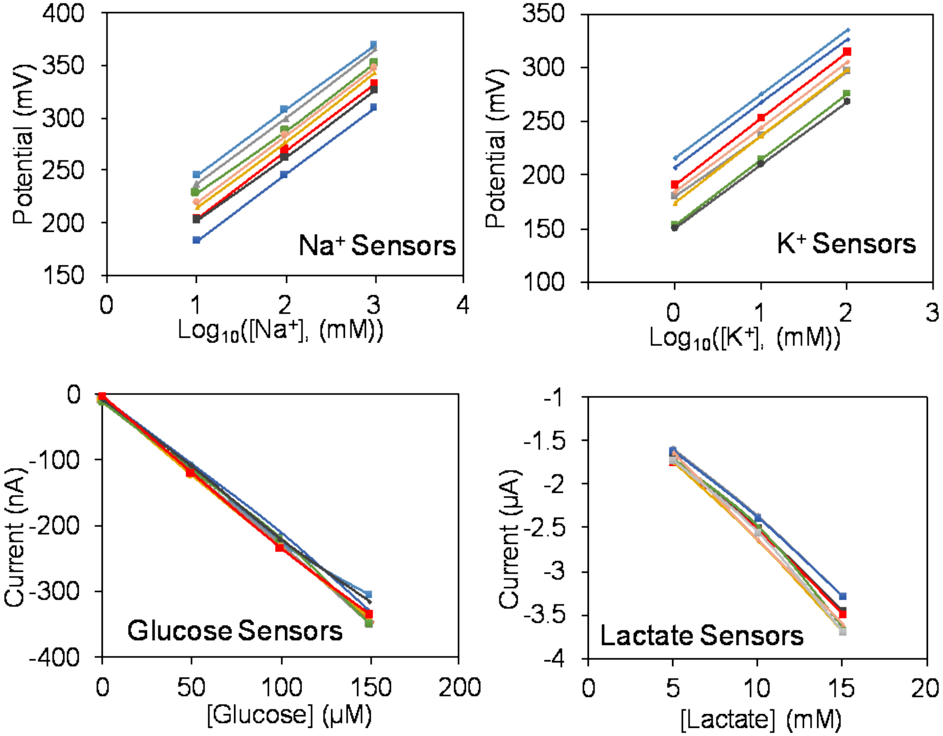
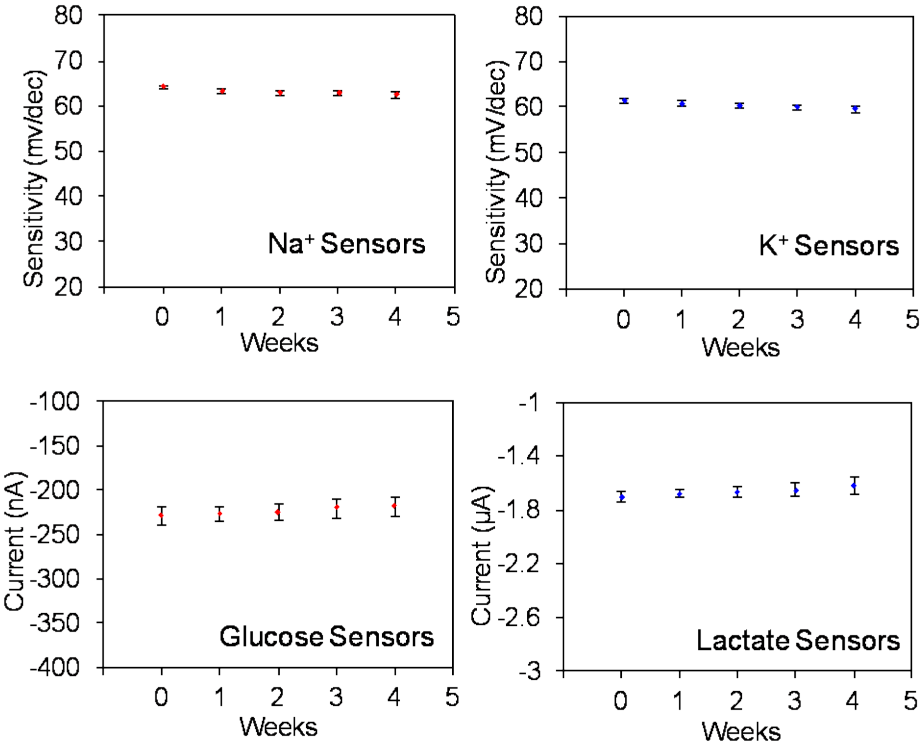
Repeatability, Stability and Calibration of the Sensors

Sensor-sensor variations



Long term stability



Na^+ and K^+ sensors: 1% relative standard deviation in sensitivity
Glucose and lactate sensors: 5% relative standard deviation in sensitivity

For Na and K sensors, **one-point calibration** is needed.

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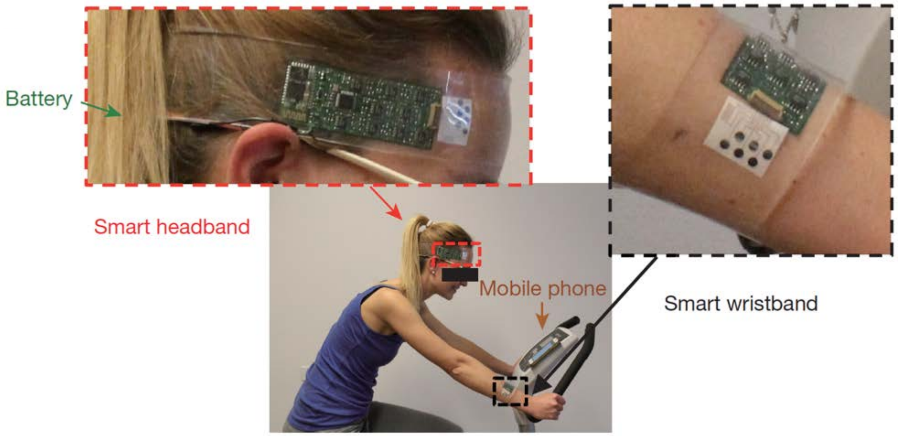
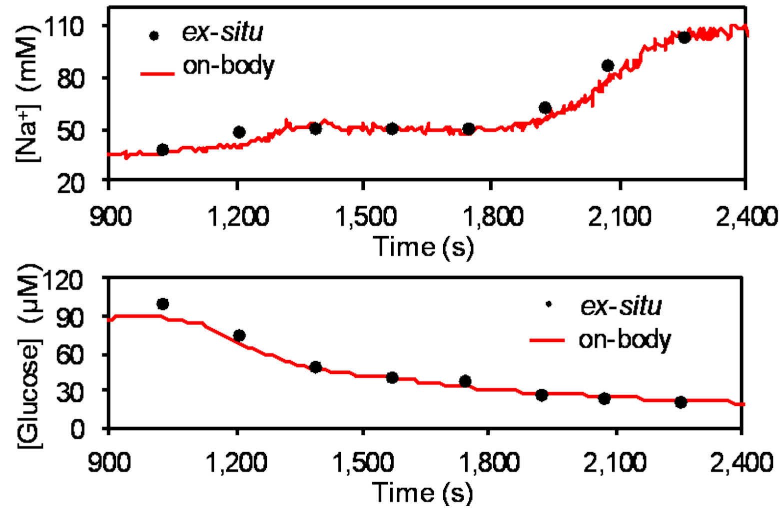
Real time on body sweat analysis

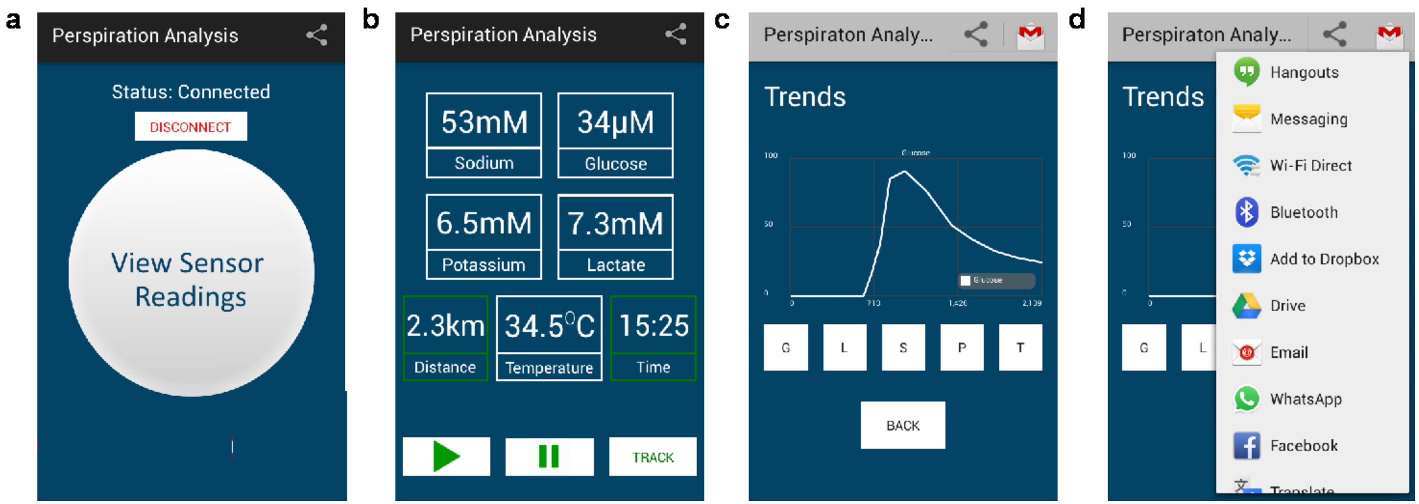
'Smart Wristband' and 'Smart Headband'



On Body Validation using Collected Sweat



The Custom-Developed Mobile App



Gao et al. Nature, 2016, 529, 509.

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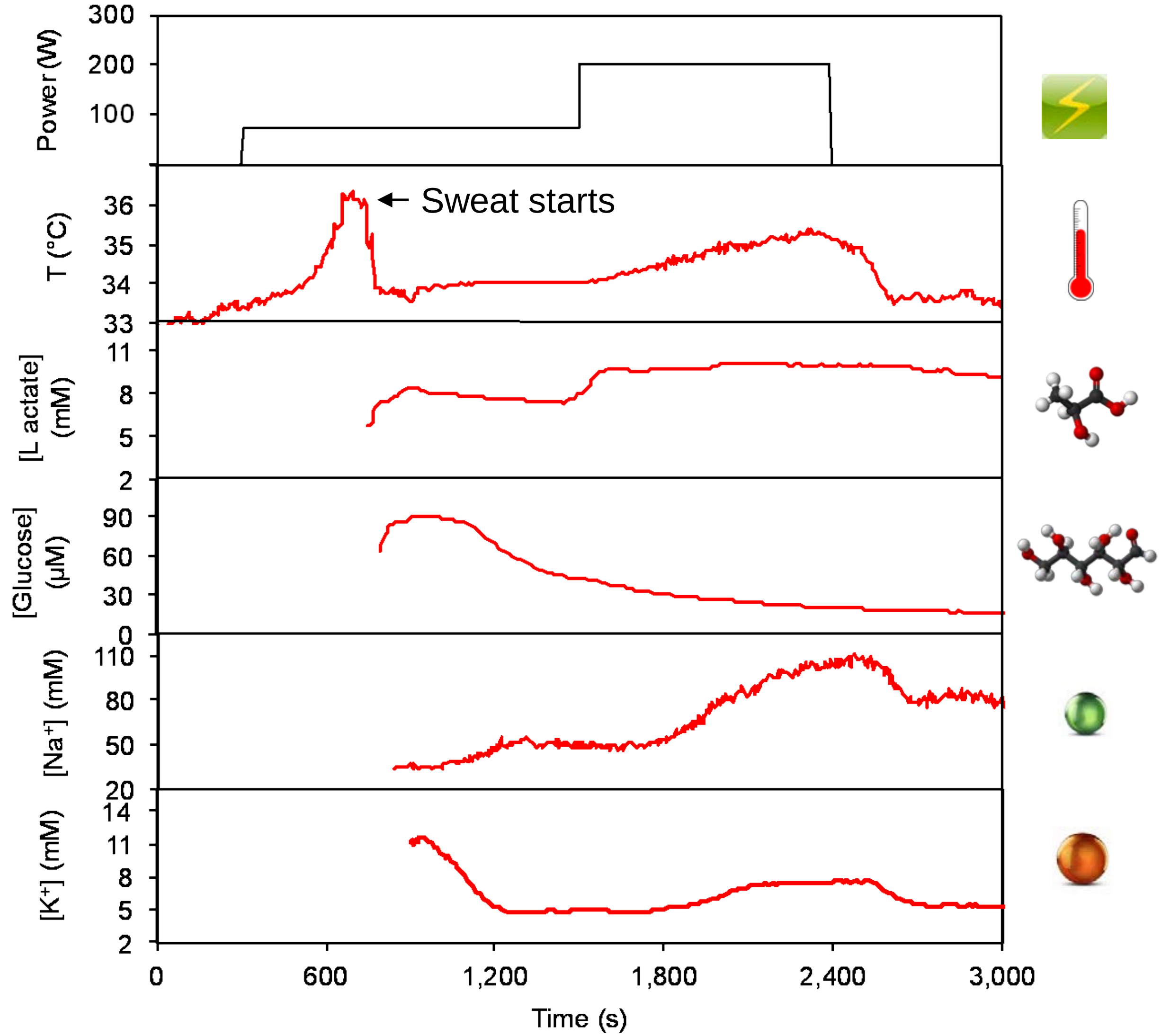
Real time multiplexed sweat analysis during indoor cycling



The device can be used to measure detailed sweat profiles and to collect big data.

Gao et al. Nature, 2016, 529, 509.

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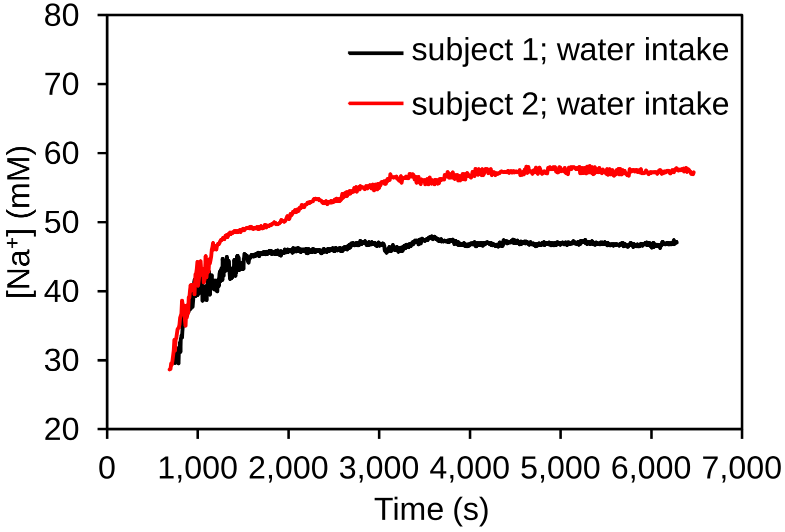
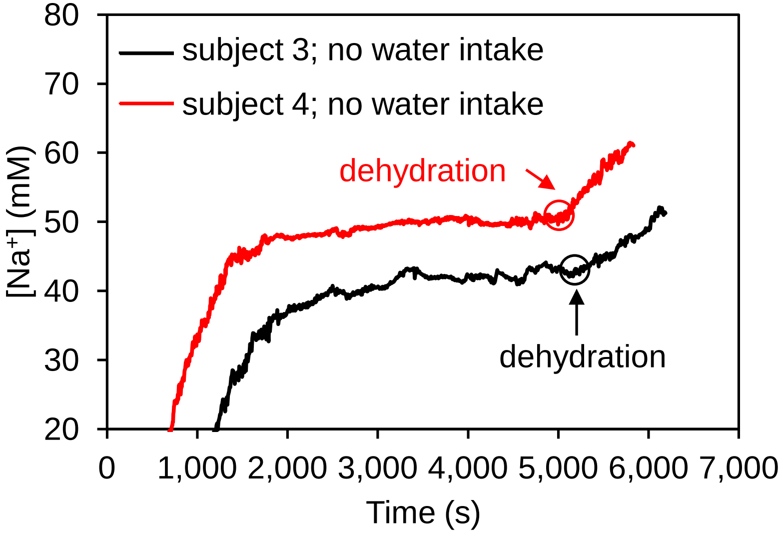
Example Application: Dehydration Monitoring





Sweat sodium can potentially serve as a biomarker for dehydration monitoring.

Gao et al. Nature, 2016, 529, 509.

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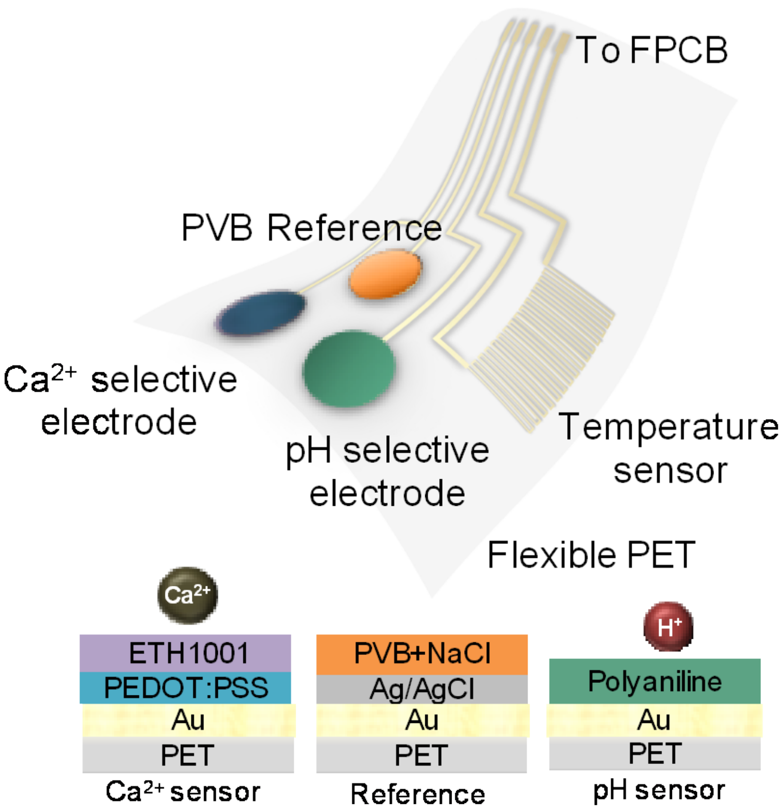
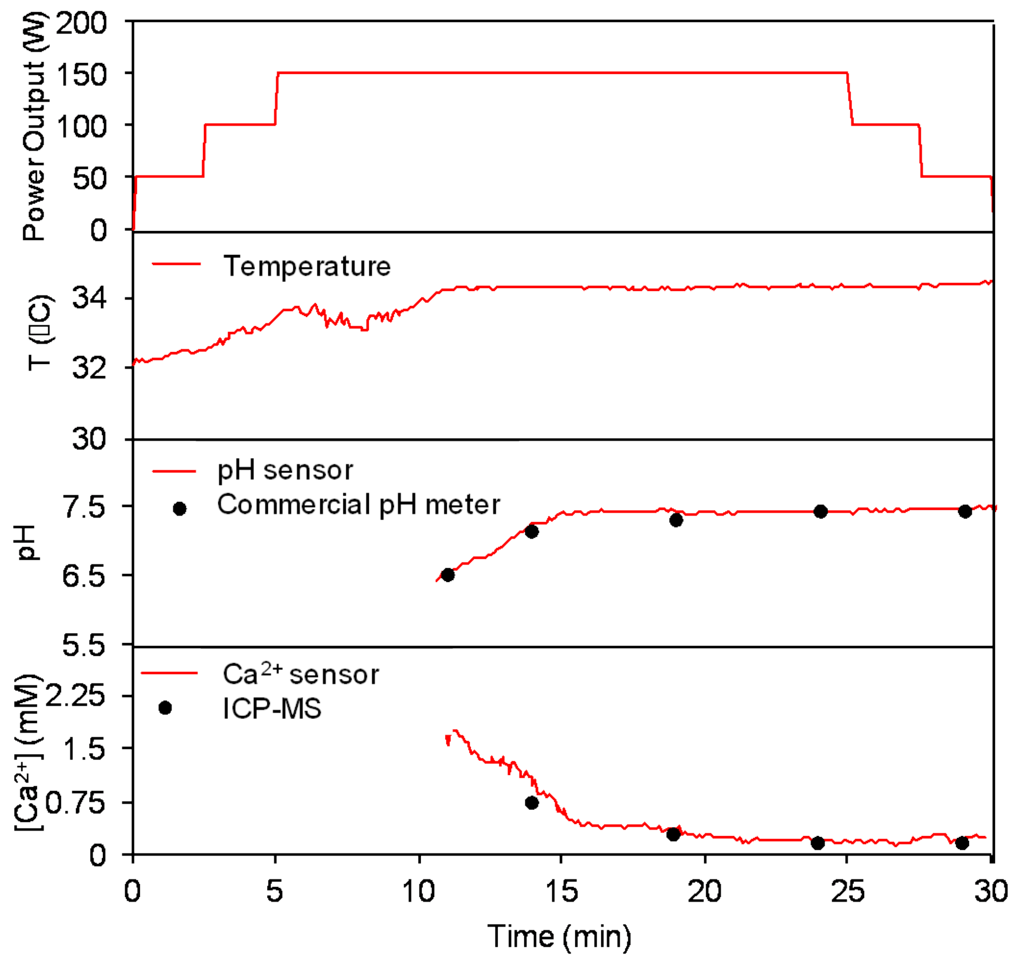
Wearable Sensors for Ca^{2+} and pH Monitoring

Kidney function monitoring

Ca^{2+} level in body fluids is dependent on pH





Simultaneous monitoring of Ca and pH is essential for accurate Ca analysis.

Nyein, Gao et al. ACS Nano, 2016, 10, 7216.

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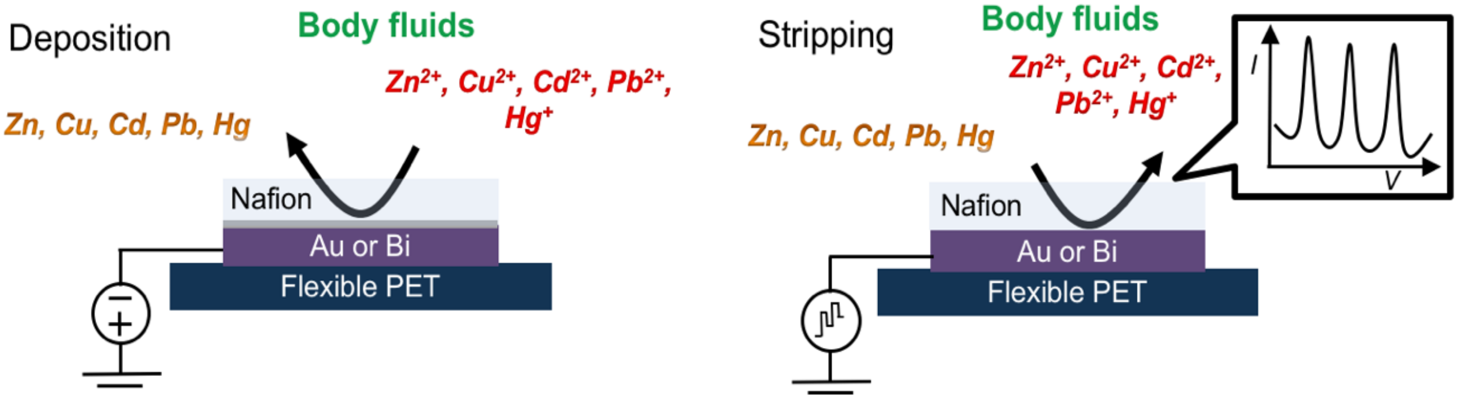
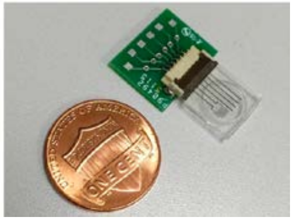
Wearable Sensors for Heavy Metal Monitoring

Heavy metal levels in body fluids are extremely low.





Anodic stripping voltammetry for trace level heavy metal analysis

Gao et al. ACS Sensors, 2016, 1, 866.

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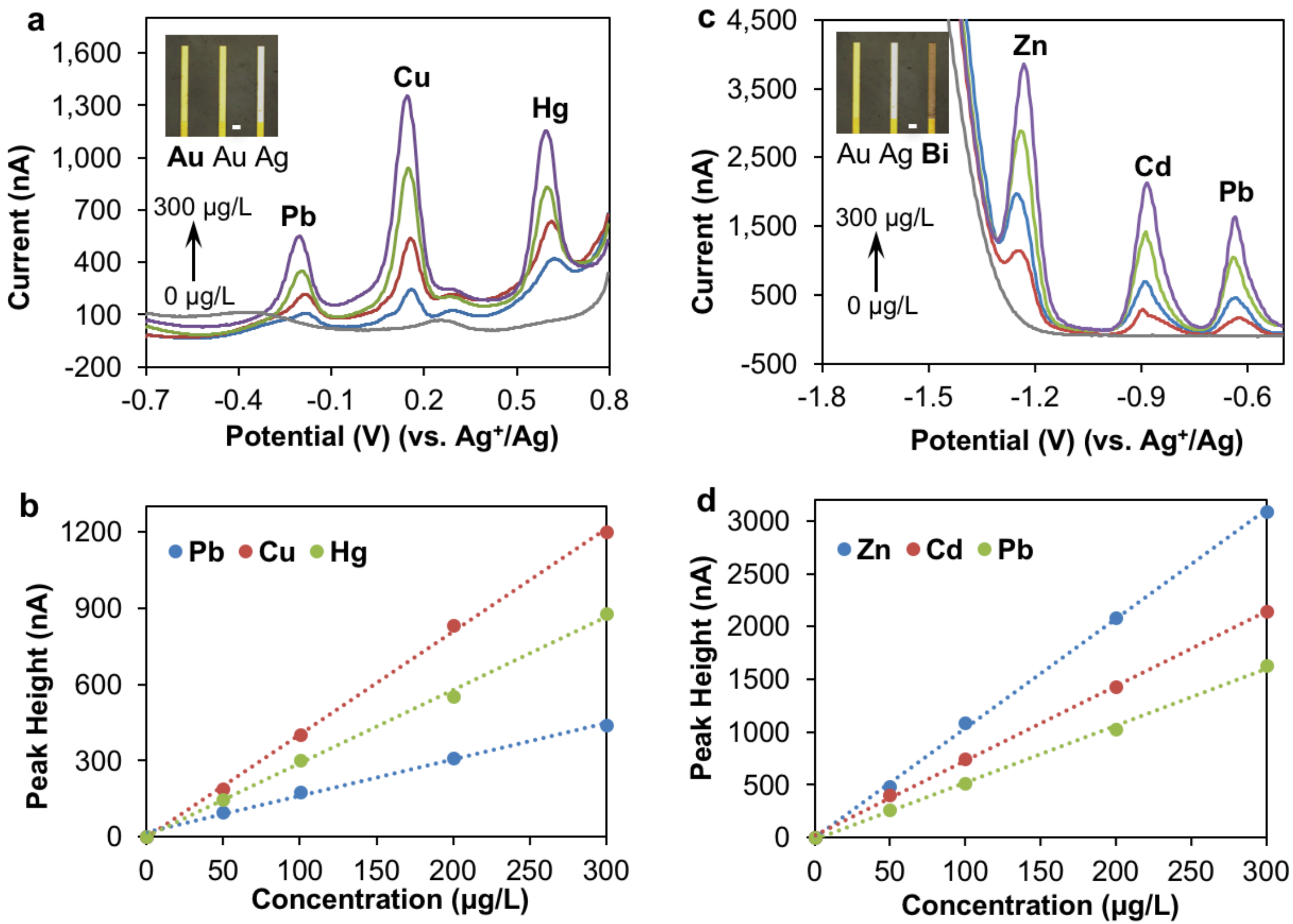
Characterization of the Microsensor Arrays

Au for Pb, Cu, Hg detection

Bi for Zn, Cd, Pb detection



The microsensor array (Au and Bi) can selectively detect 5 heavy metals.

Gao et al. ACS Sensors, 2016, 1, 866.

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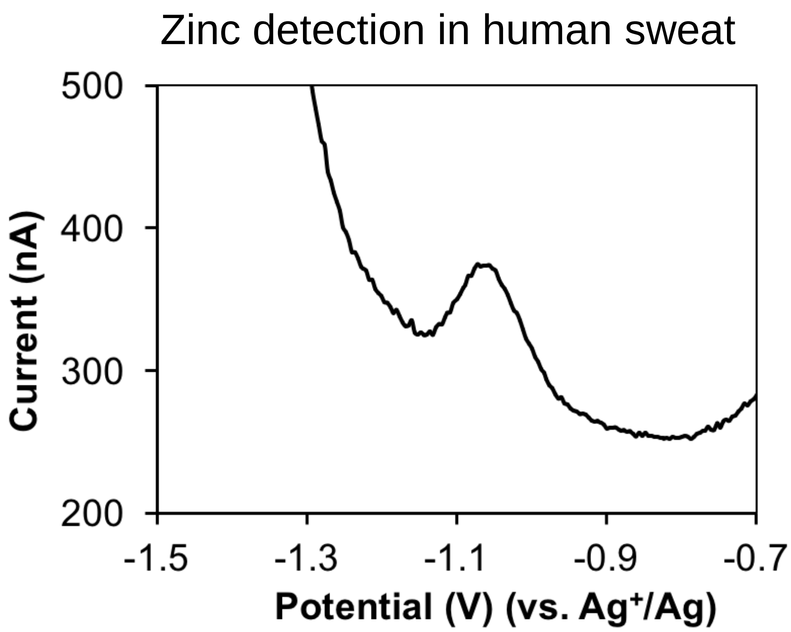
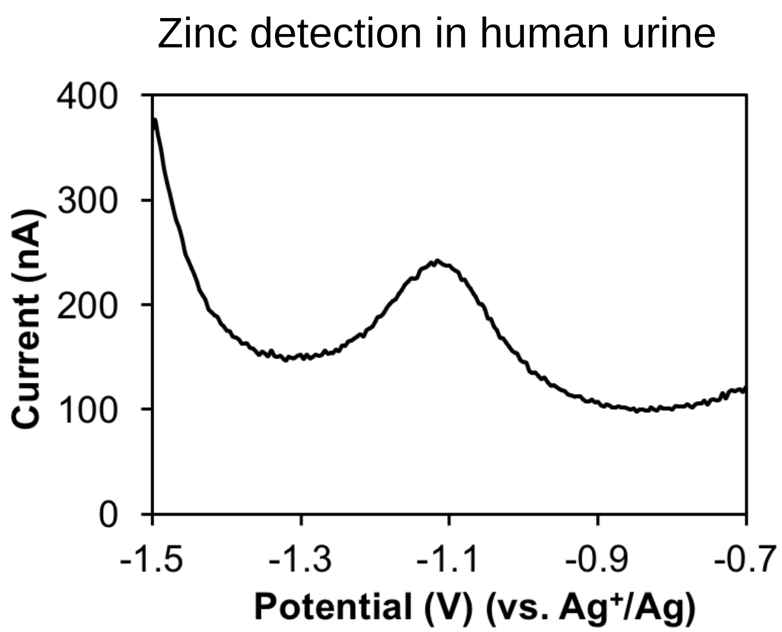
Heavy Metal Monitoring of Body Fluids





Sample	Measurements from the **microsensors** (μg/L)	Measurements from **ICP-MS** (μg/L)
Sweat Cu	249	267
Sweat Zn	274	290
Urine Cu	571	601
Urine Zn	624	634

The wearable sensors can accurately measure heavy metals in body fluids.

Gao et al. ACS Sensors, 2016, 1, 866.

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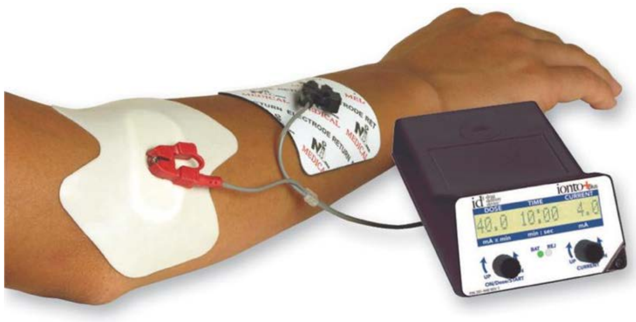
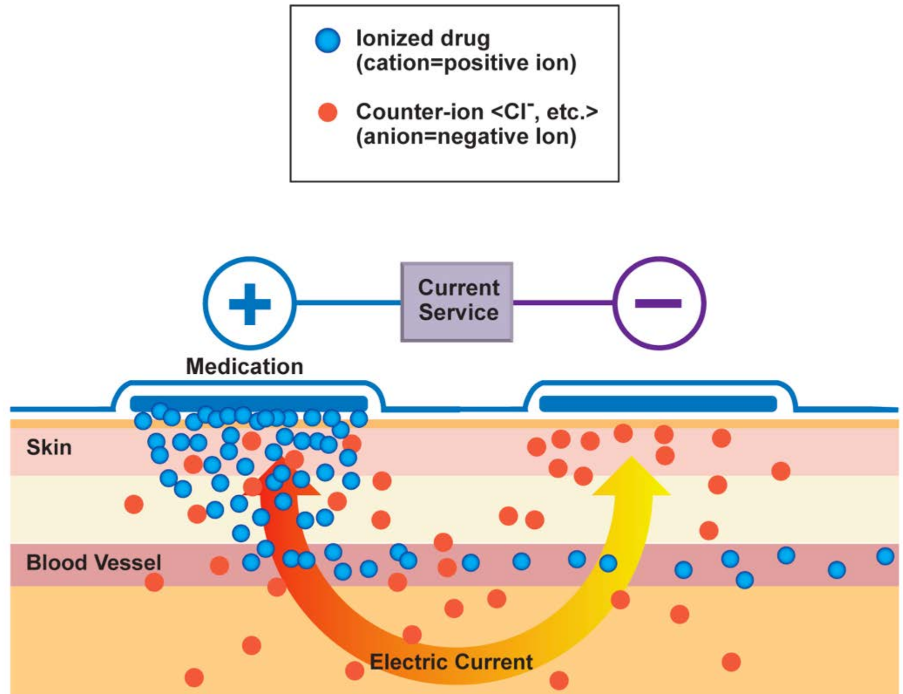
How to Access Sweat Sample Without Exercise?

Beyond physical exercise: **iontophoresis** based sweat extraction





Sweat can be induced on demand through iontophoresis.

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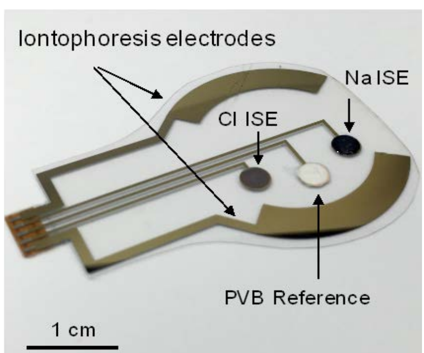
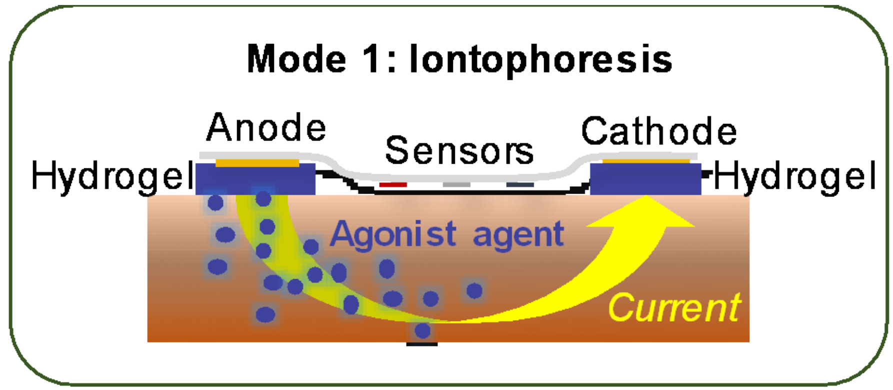
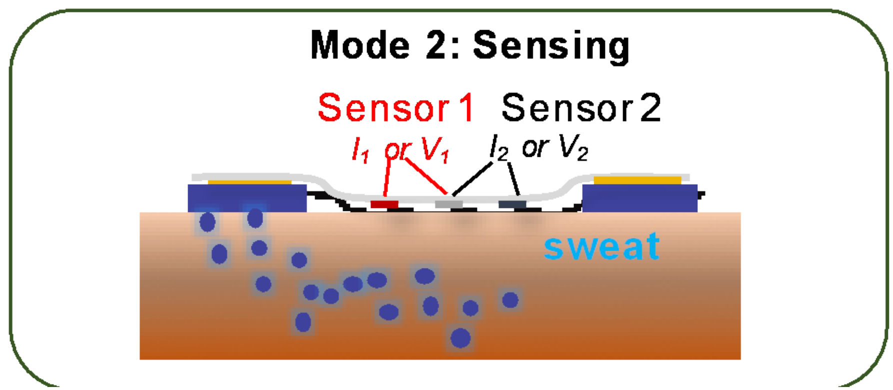
A Wearable Platform for Sweat Extraction & Sensing

Beyond physical exercise: accessing sweat samples **on demand** using iontophoresis







PNAS, 2017, 114, 4625

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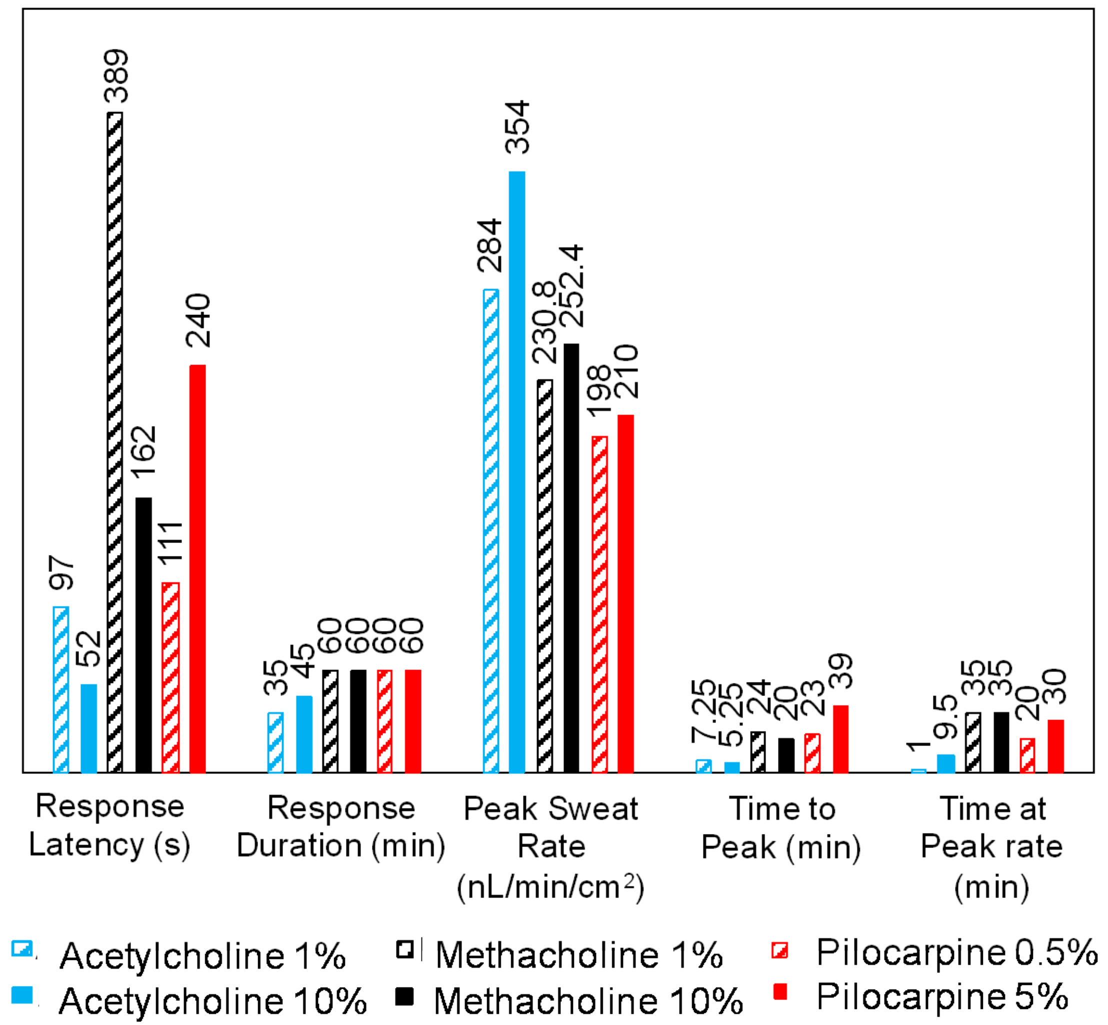
Iontophoresis based Sweat Extraction



Sweat extraction can be controlled by type of drugs and the drug dosage.

PNAS, 2017, 114, 4625

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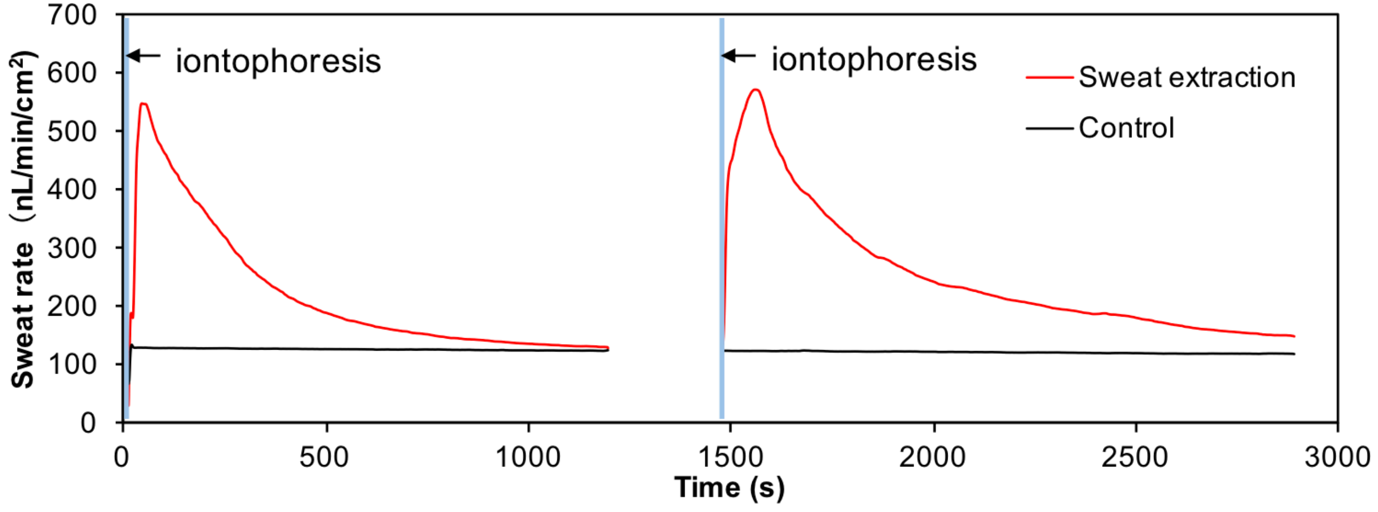
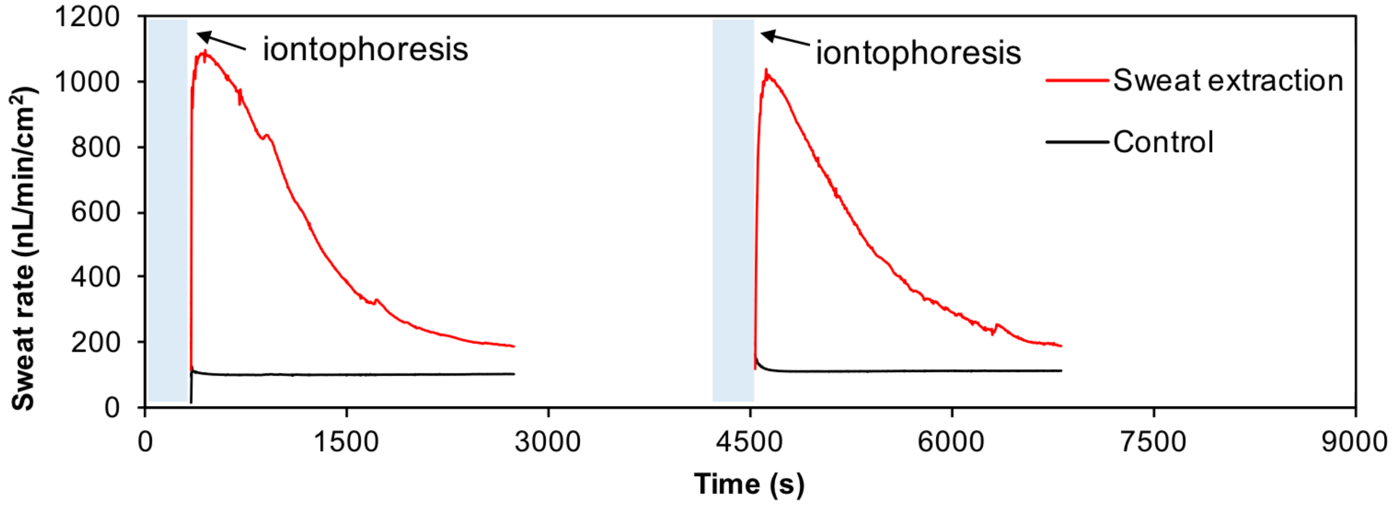
Periodical Sweat Extraction using the Wearable Platform

10 s



300 s



Sweat can be induced periodically.

PNAS, 2017, 114, 4625

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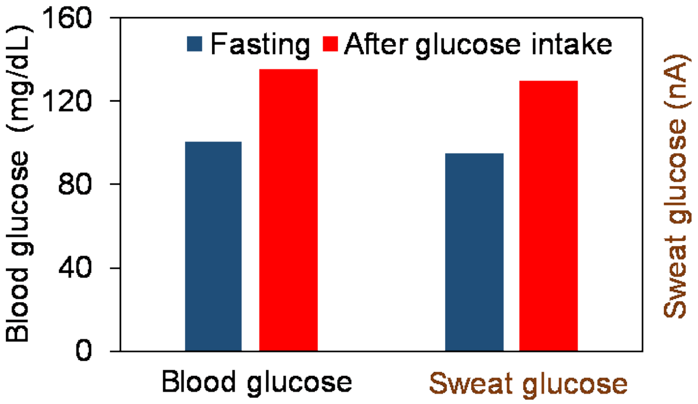
Example Applications of Wearable Sweat Biosensors

Medical monitoring and diagnosis without accessing blood

Non-Invasive Glucose Monitoring



Wearable sweat sensors enable the correlation studies between sweat biomarkers and blood biomarkers

PNAS, 2017, 114, 4625

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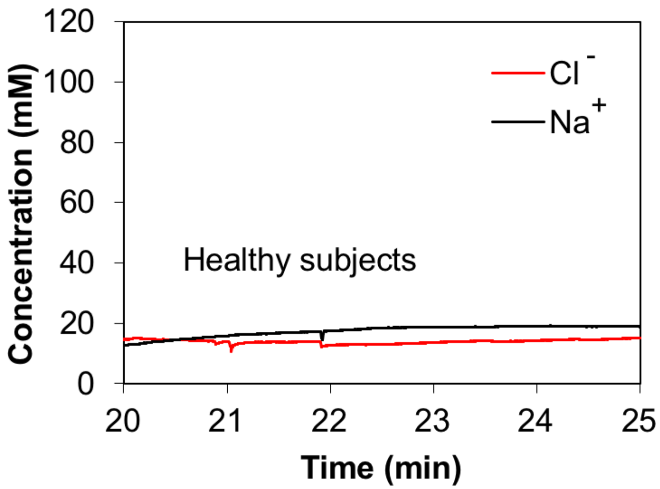
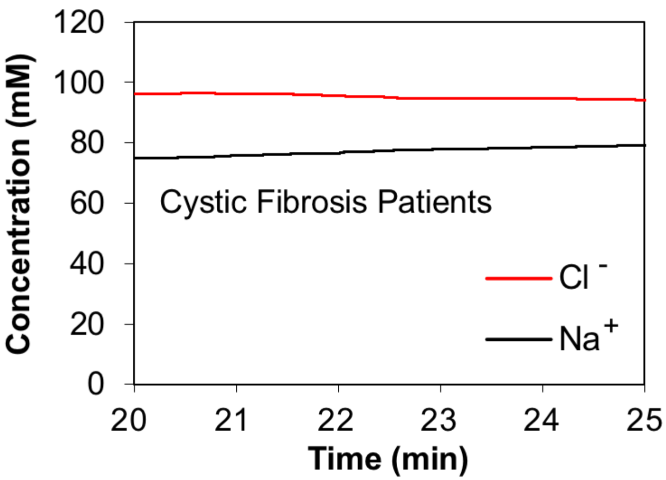
Example applications of wearable sweat biosensors

Medical monitoring and diagnosis without accessing blood

Cystic Fibrosis Diagnosis





PNAS, 2017, 114, 4625

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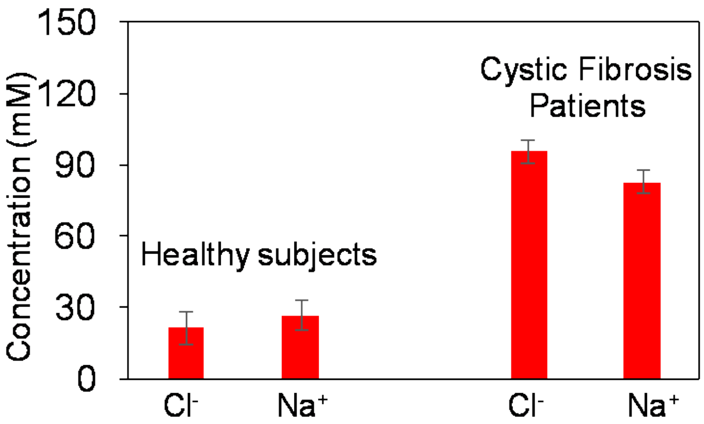
Example applications of wearable sweat biosensors

Medical monitoring and diagnosis without accessing blood

Cystic Fibrosis Diagnosis



Wearable sweat sensors can be used for Cystic Fibrosis screening and diagnosis.

PNAS, in press.

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Wearable Sweat Analysis - Outlook

Gao et al. Nature 2016; Gao et al. IEDM 2016.

- A fully integrated sweat sensing platform for real time, continuous sweat analysis.
- This platform enables numerous physiological & clinical investigations including but not limited to:
  - Fitness monitoring
  - Doping/drug dosage control
  - Aging
  - Stress or depression, neurological disorders
  - Early disease diagnosis

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Outline

- **Wearable Biosensors**
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- **Synthetic Nanomachines**
  - **Technology Development**
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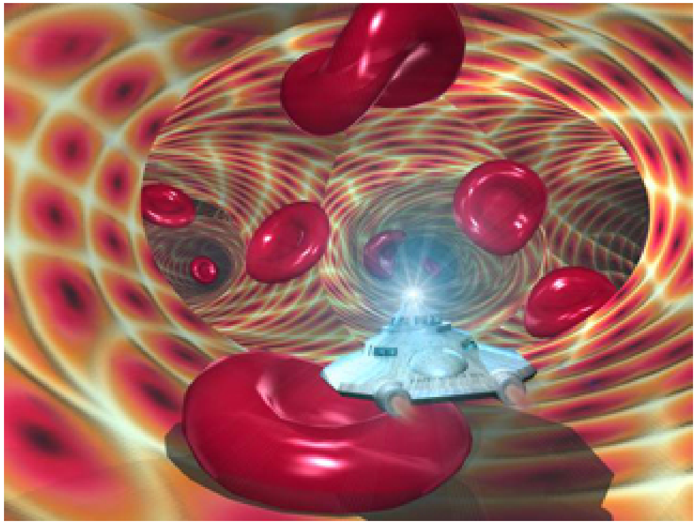
- **Current Research Focus**

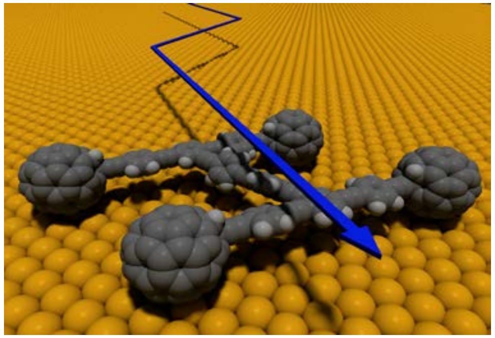
Nanomotors & Nanomachines

Fantastic Voyage, 1966



A miniaturized submarine and its crew are injected into a coma victim in a perilous mission to destroy the blood clot that threatens the patient's life.

Molecular Machines
2016 Nobel Prize for Chemistry



Molecules → **Micro/nanomaterials**

Fulfill the ‘Fantastic Voyage ’ Vision – Nanoscale Propulsion

Life at Low Reynolds Number

- **The challenge of propulsion at nanoscale: low Reynolds Number fluid.**

Navier-Stokes equations

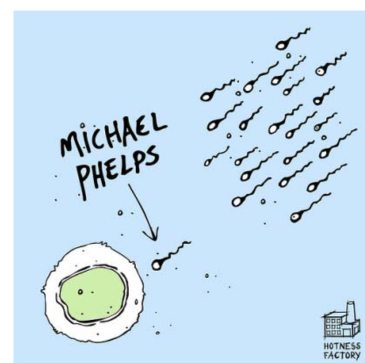
$Re \ll 1$ (the $\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u}$ terms are crossed out)

$$\frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} = -\frac{1}{\rho} \nabla p + \nu \nabla^2 \mathbf{u} \qquad Re = \frac{UL}{\nu} = \frac{Interial\ Force}{Viscous\ Force}$$

- To understand how micro-organisms move in water, we would have to imagine ourselves swimming in a pool of **honey**.
- Swimming strategies used in the macro-scale world may not be applicable in the nanoscale.

Re>>1

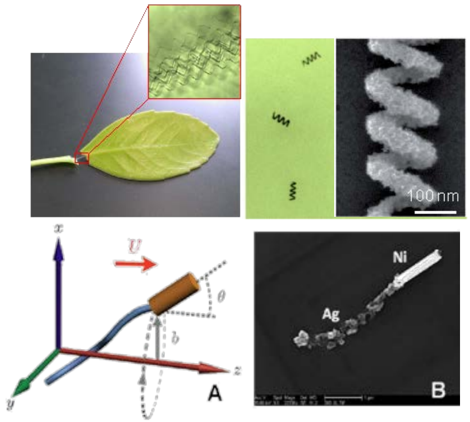
Re<<1



Synthetic Micro/Nanorobots

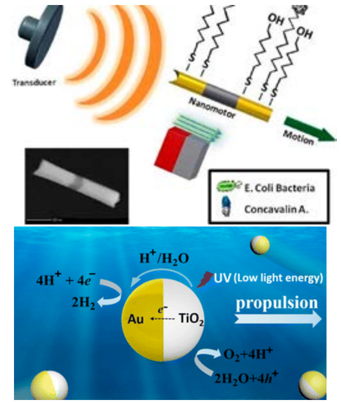
Design

Magnetic Propulsion



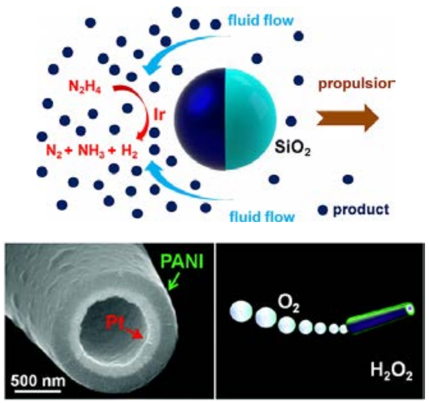
Gao et al. JACS 2010, 132, 14403.
Gao et al. Nano Letters 2014, 14, 305.
Gao et al. Small, 2011, 7, 2047.
Park and Gao, Soft Matter, 2011.

Ultrasound & Light



JACS 2015, 137, 2163.
ACS Nano 2013, 7, 9232.
ACS Nano 2016, 10, 839.
Small 2016, 12, 577.

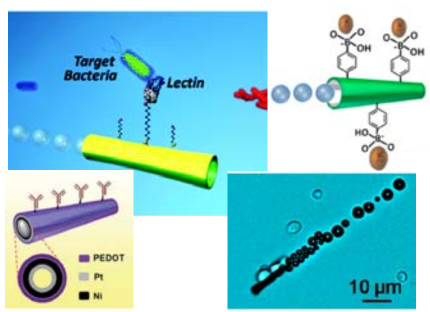
Chemical Propulsion



Gao et al. JACS 2014, 136, 2276.
Gao et al. JACS 2013, 135, 998.
Gao et al. JACS 2012, 134, 897.
Gao et al. JACS 2011, 133, 11862.
Gao et al. ACS Nano 2012, 6, 8432.

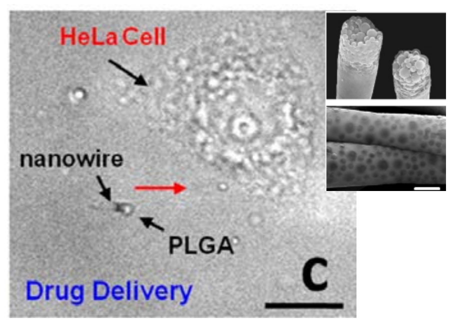
Application

Biosensing



Wang and Gao, ACS Nano, 2012, 6, 5745.
Gao et al. ACS Nano, 2014, 3170.
Nano Letters, 2012, 12, 396.
JACS, 2012, 134, 15217.

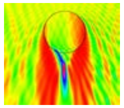
Drug Delivery



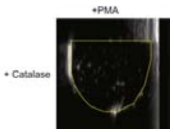
Gao et al. ACS Nano 2015, 9, 117.
Gao et al. Small 2012, 8, 460.
Gao et al. Nanoscale, 2014, 6, 10486.
Small, 2014, 10, 2830.

Biodetoxification

Nanofabrication



Nanoimaging



Wu and Gao, Adv. Funct. Mater. 2015.
Li and Gao, Nature Comm. 2014.
Olson and Gao et al. Biomaterials, 2013.

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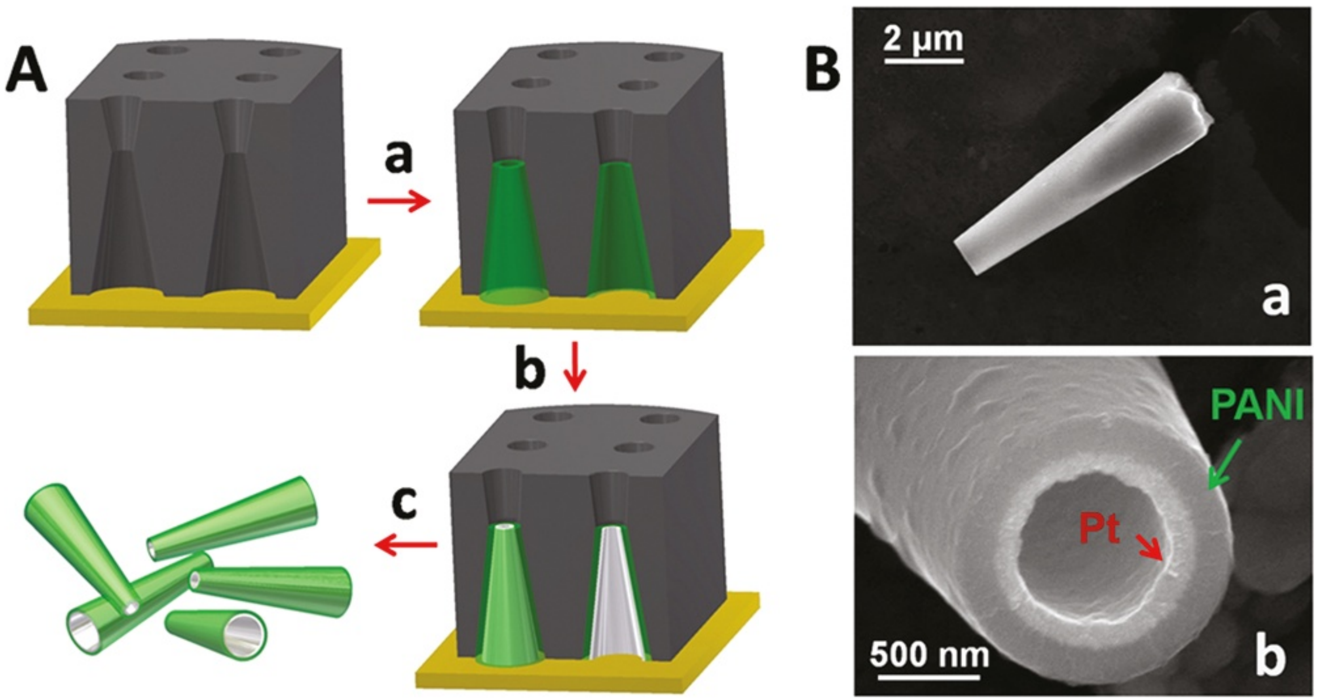
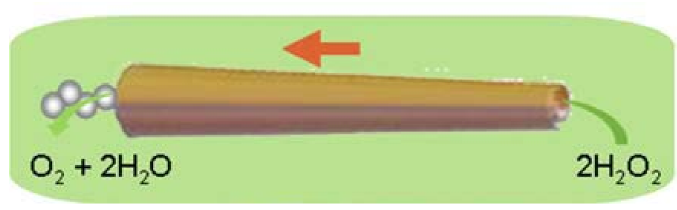
Highly Efficient Polymer-based Microengines

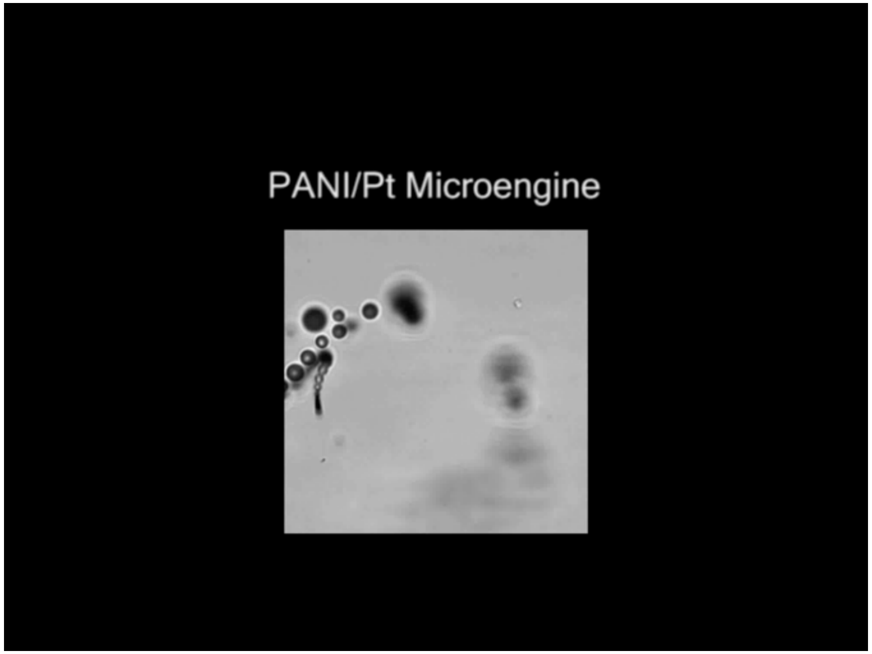


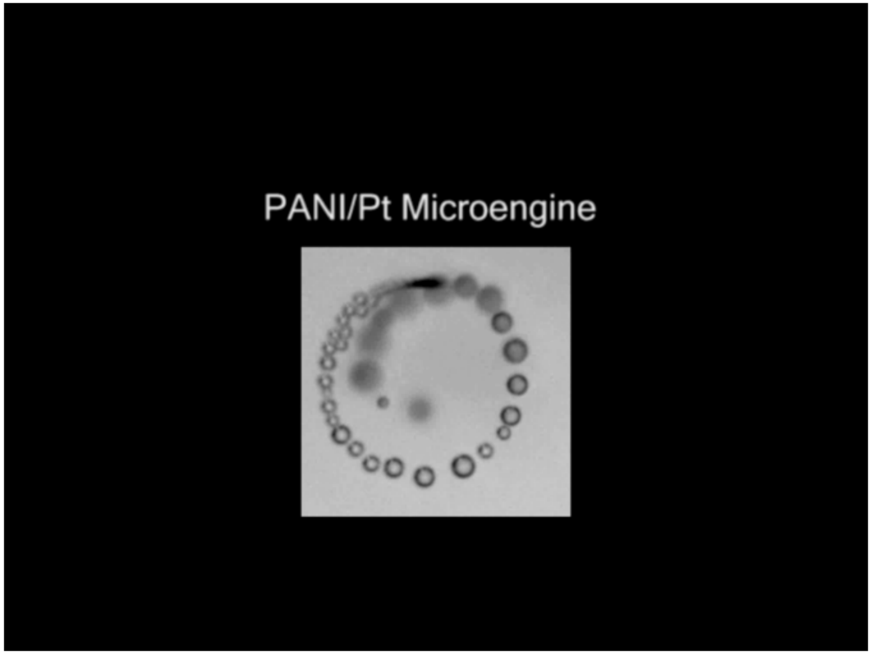


Template Electrosynthesis of Polyaniline/Platinum Microtubes

W. Gao et al. JACS 2011, 133, 11862.

The Propulsion of PANI/Pt Microengines

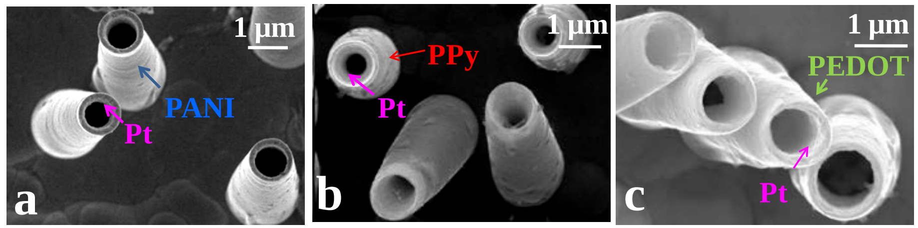


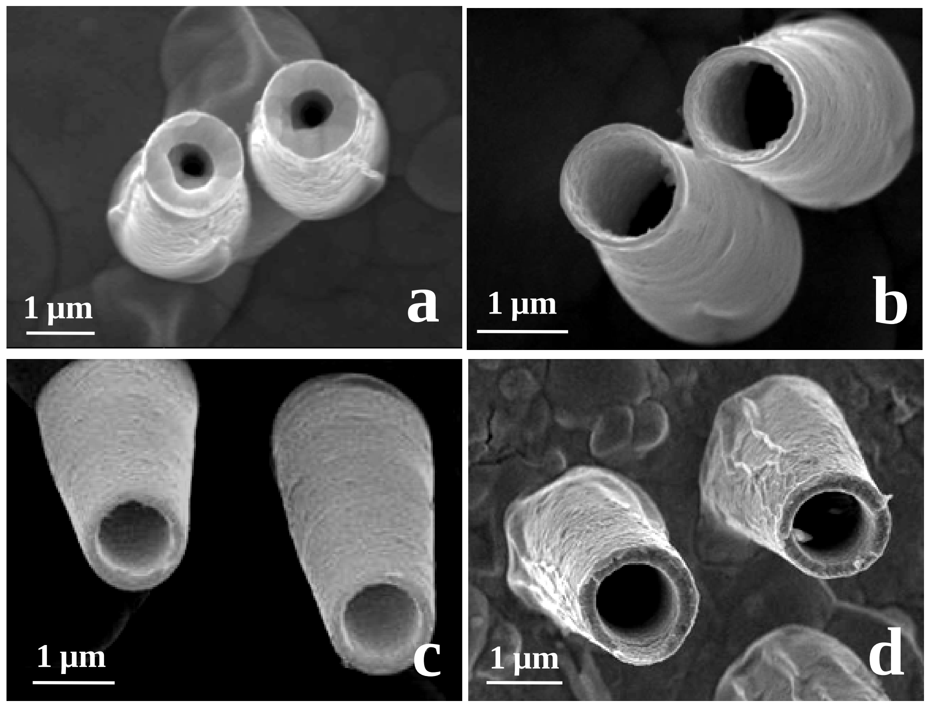


The microrockets display efficient propulsion in PBS buffer, human serum, cell culture media, plasma, saliva and seawater.

W. Gao et al. JACS 2011, 133, 11862.

The Materials Platform: Conducting Polymer Components





Higher surfactant and low monomer concentration provides optimal design for the propulsion (b).

W. Gao et al. Nanoscale, 2012, 4, 2447.

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The World's Fastest Micro/Nanomotors

The Motion of the Polymer based Microrockets in Physiological Temperature

The fastest objects	Max Relative Speed (body length s^{-1})
Human (Bolt)	6
Cheetah	20
Ferrari Enzo	21
Space Shuttle	~200
Bacteria	~100
Polymer based Microengines	**~1400**

W. Gao et al. Nanoscale, 2012, 4, 2447.

W. Gao et al. Chem. Rec. 2012, 12, 224.

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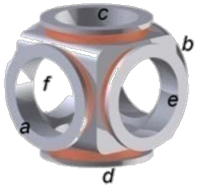
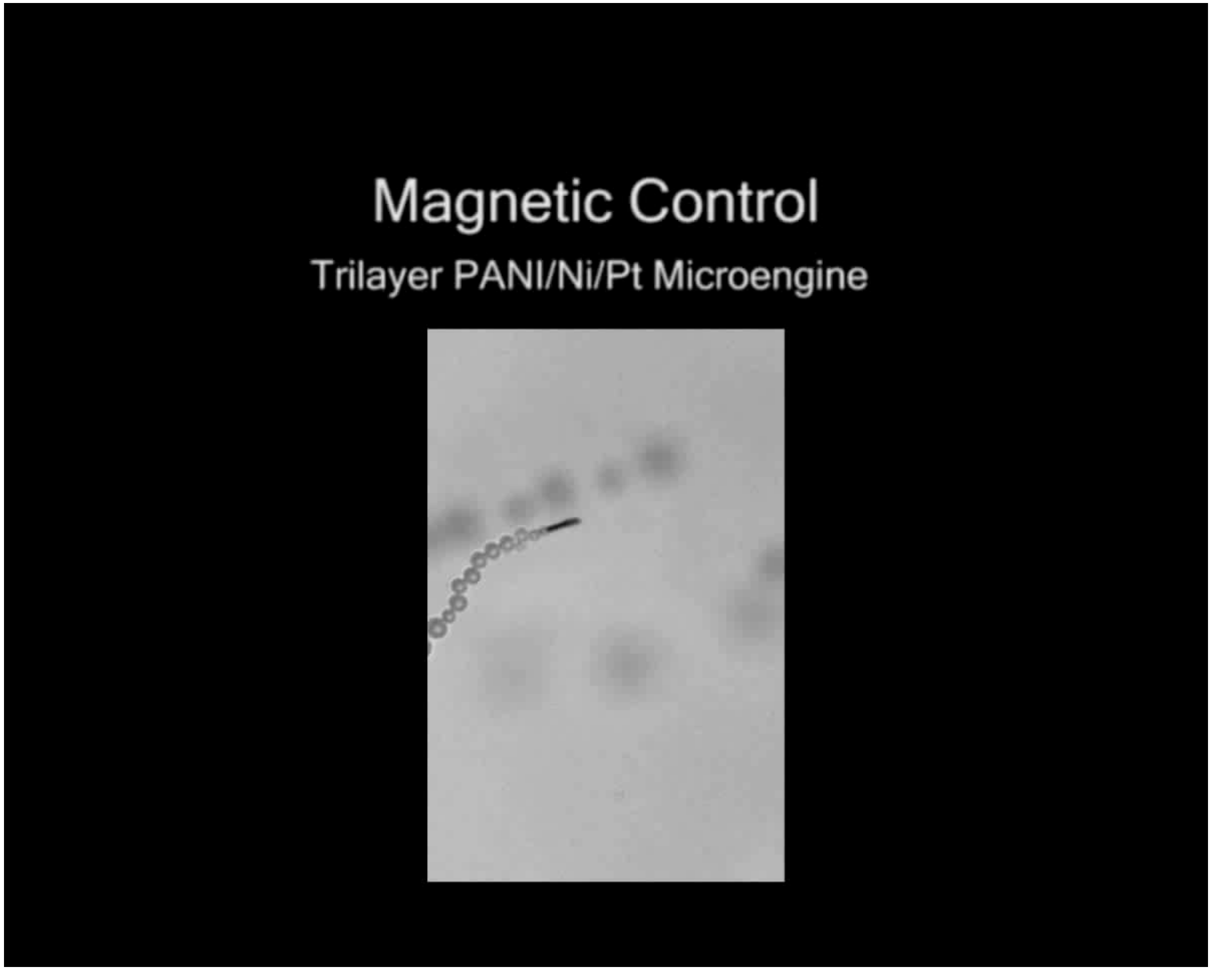
Magnetic Motion Control

PANI/Ni/Pt Trilayer Tubular Microrockets





The propulsion of the microengines can be controlled by external magnetic field.

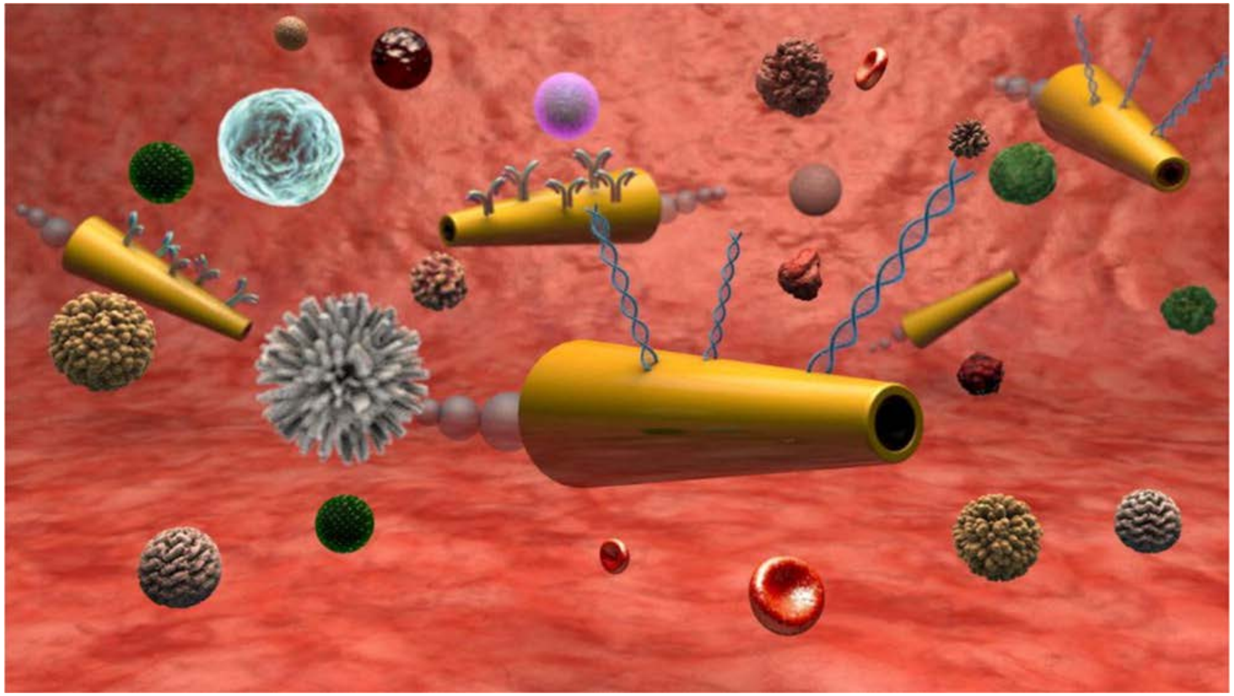
W. Gao et al. JACS 2011, 133, 11862.

Polymer-based Microengines in Microchannels

The microengines have ability to travel within a predetermined path along the microchip channels

Nanoscale, 2013, 5, 1325.

The Biosensing and Bioisolation using Micro/Nanomotors

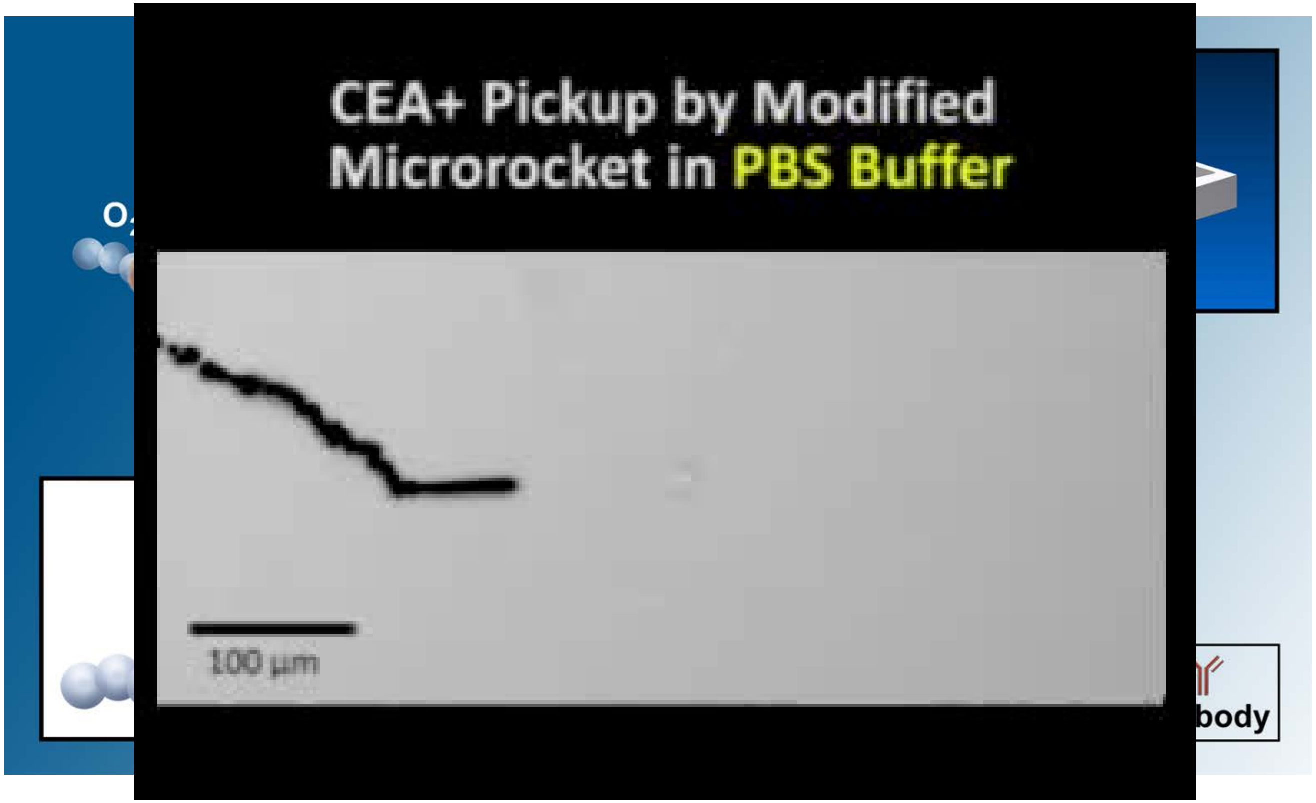


The microrockets functionalized with ss-DNA, aptamer, antibody, and lectin receptors, for 'on-the-fly' isolation of nucleic acids, proteins, cancer cells and bacteria, respectively.

J. Wang and W. Gao, ACS Nano, 6, 2012, 5745; J. Li et al. ACS Nano, 2016

Selection and Isolation of Cancer Cells in Biological Fluids

Circulating tumor cells (CTCs)
Current strategies: complex procedures and bulky equipment.



Capture and transport of a CEA+ pancreatic cancer cell by an anti-CEA mAb modified rocket.

Angew. Chem. Int. Ed. 2011, 50, 4161.

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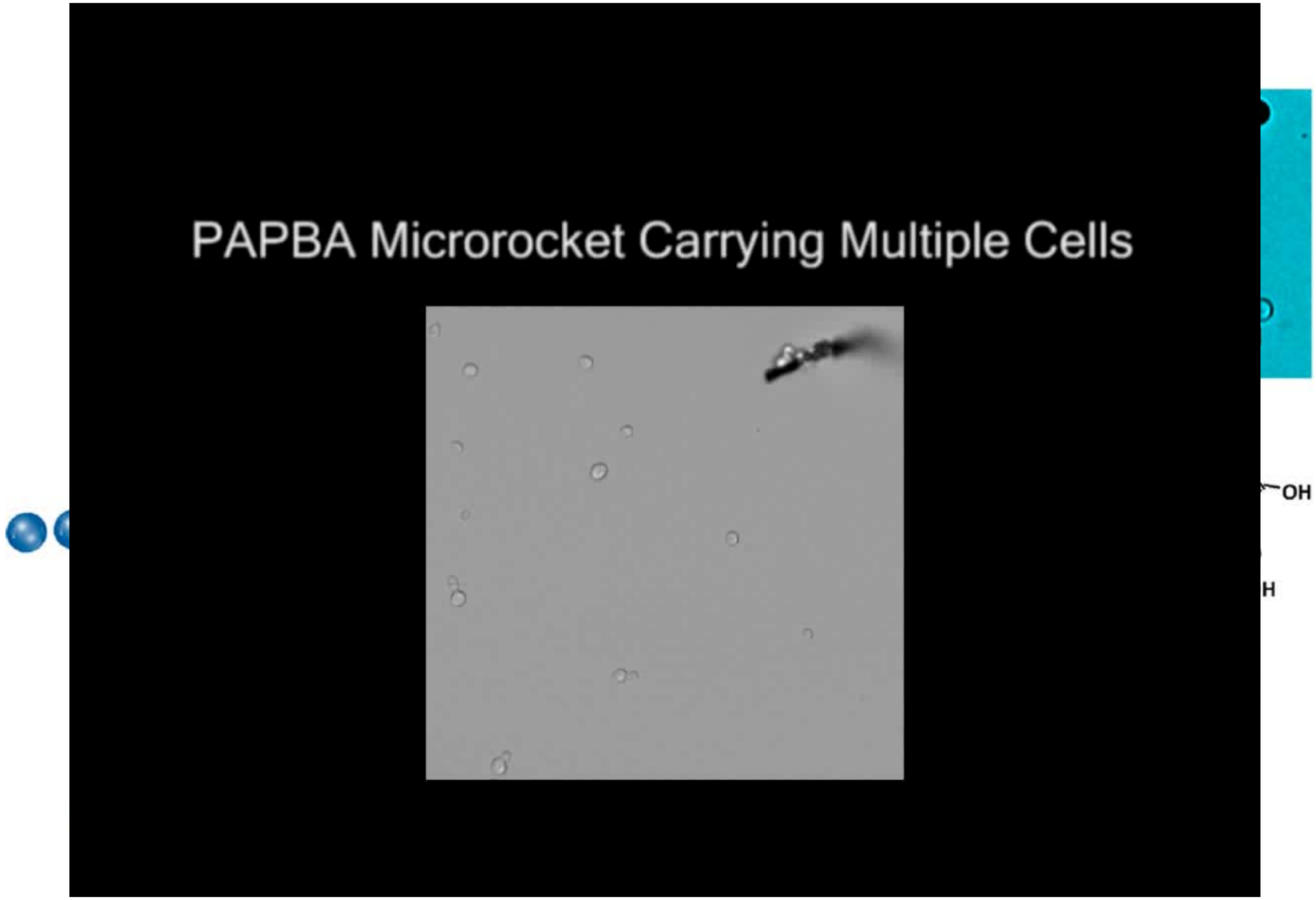
Lectin Modified Microengines for Bacteria Isolation

Campuzano, Gao et al. Nano Lett., 12, 2012, 396.

Caltech

Microrockets with ‘Built-In’ Boronic Acid Recognition for Isolating Sugars and Cells

poly(3-aminophenylboronic acid) - PAPBA



Selective monosaccharide recognition of of the boronic acid-based outer polymeric layer

Kuralay, Gao et al. JACS, 2012, 134, 15217.

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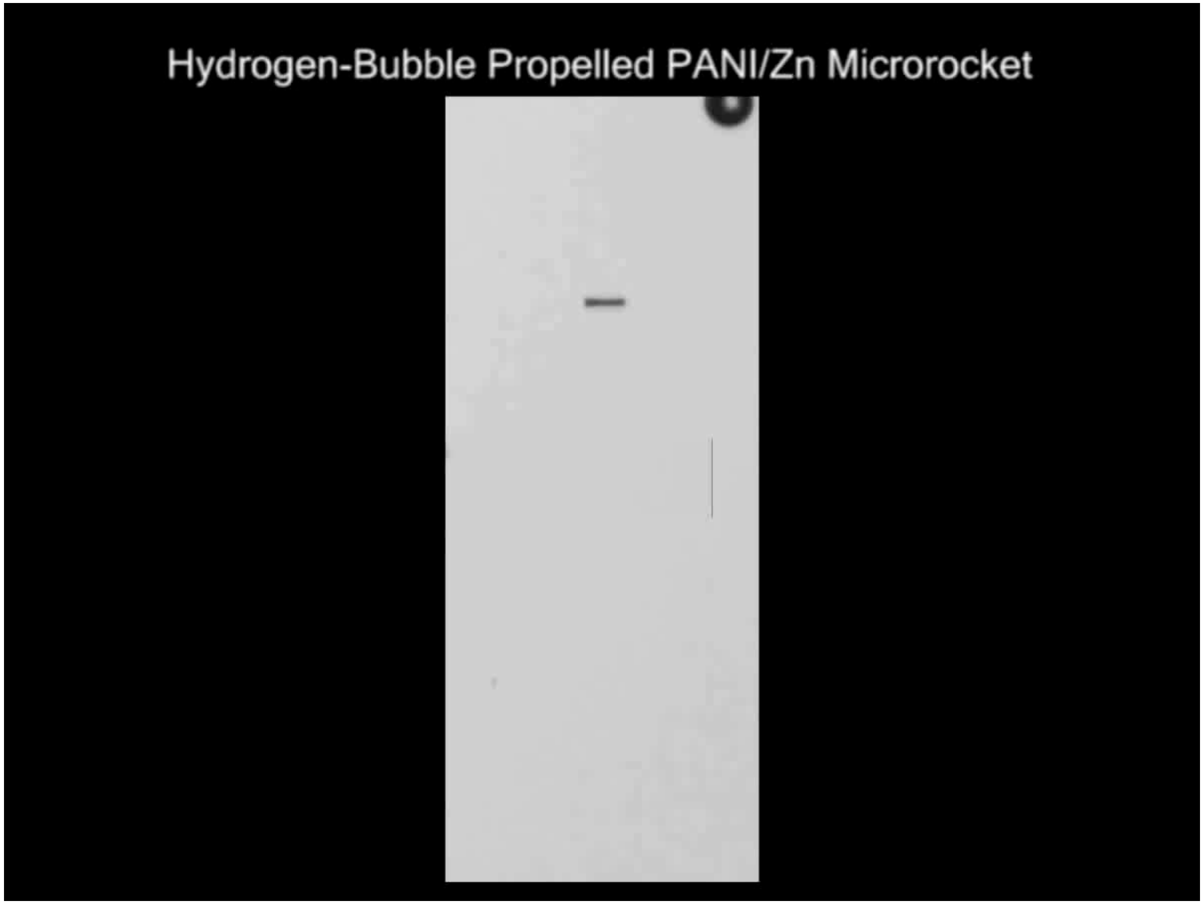
Towards In-Situ Fuel

Hydrogen-Bubble-Propelled Zinc-Based Microrockets

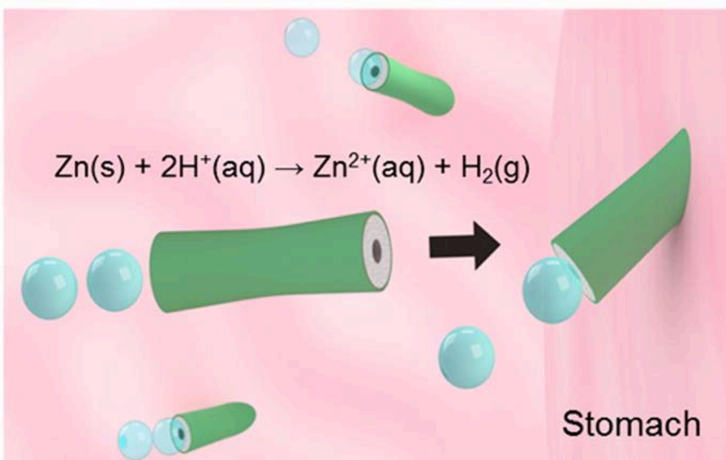
Zn is a biocompatible and biodegradable material in metallic implants in humans.

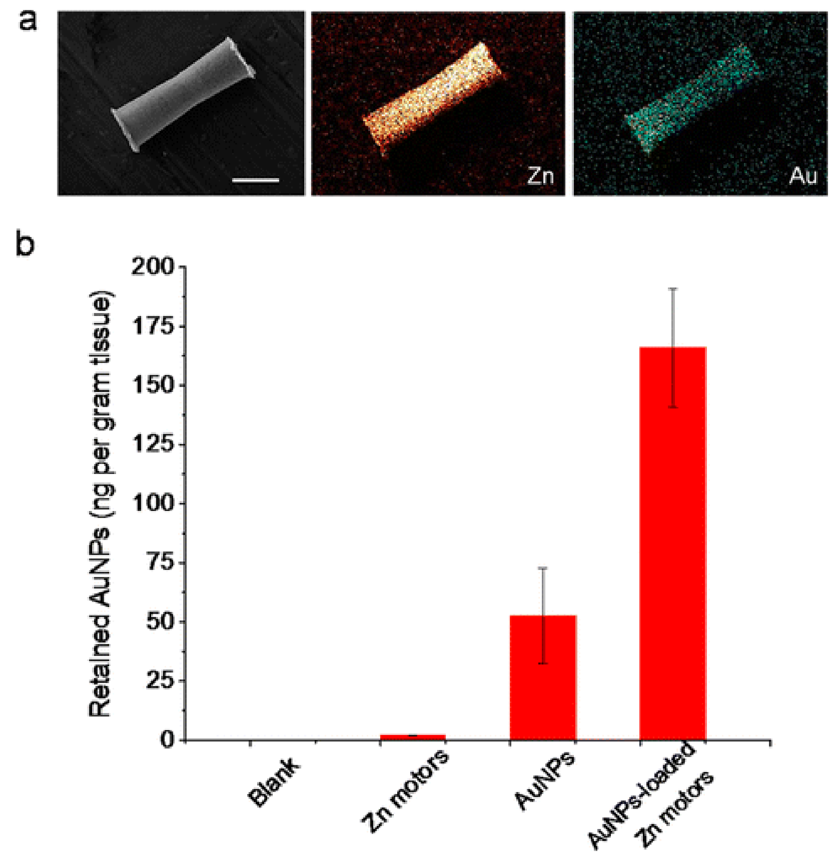


W. Gao et al. JACS, 134, 2012, 897-900.

The First In Vivo Study Using Synthetic Nanorobots

Drug Delivery in Gastrointestinal Tract

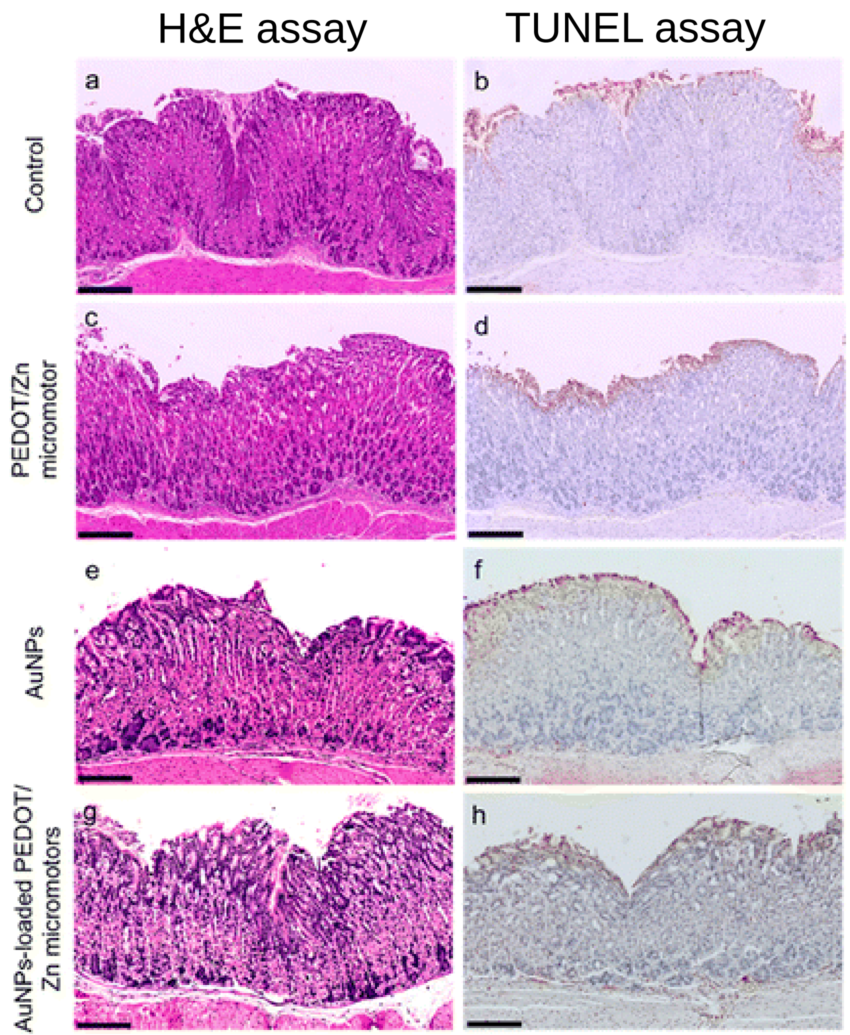




The nanorobots lead to dramatically improved retention of payloads in the stomach lining.

W. Gao et al. ACS Nano, 2015, 9, 117.

In Vivo Toxicity of Synthetic Zn Micromotors



Fully biocompatible: No apparent increase in gastric epithelial apoptosis.

W. Gao et al. ACS Nano, 2015, 9, 117.

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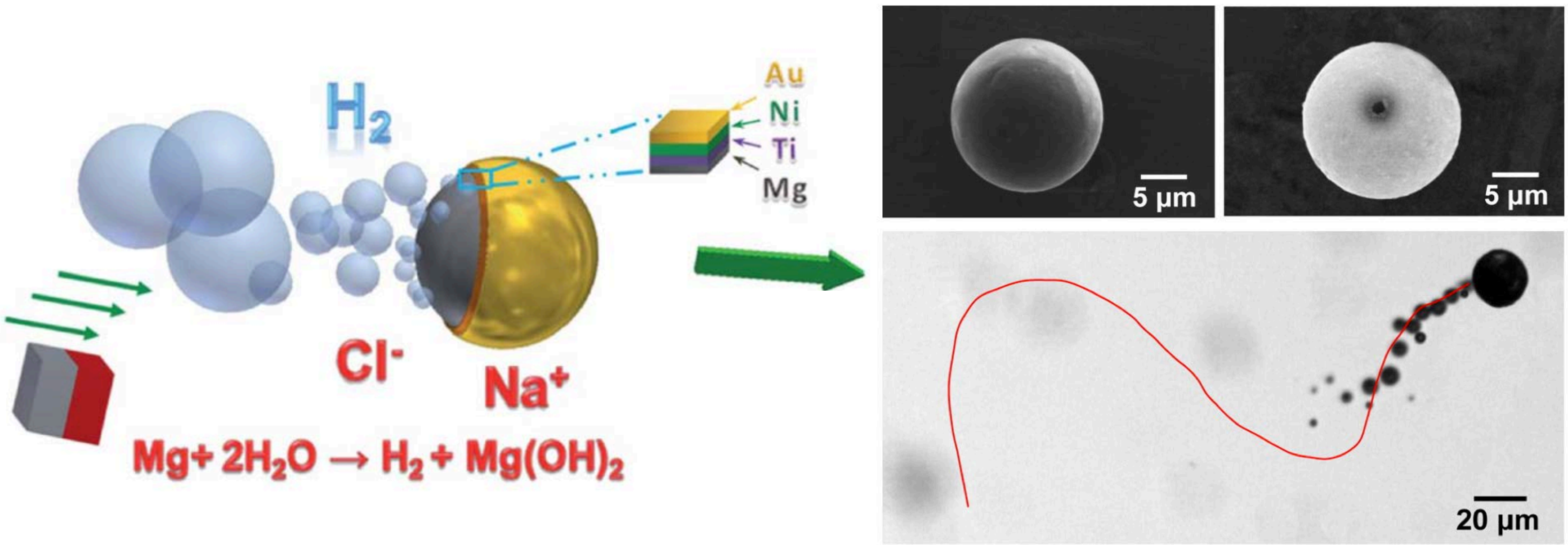
Water Driven Biodegradable Micromotors

Mg is a biocompatible and biodegradable material in metallic implants in humans.



The new micromotors utilize the **galvanic corrosion**, **chloride pitting corrosion** processes to facilitate the Mg-water reaction.

W. Gao et al. Nanoscale, 2013, 5, 4696.

UC San Diego

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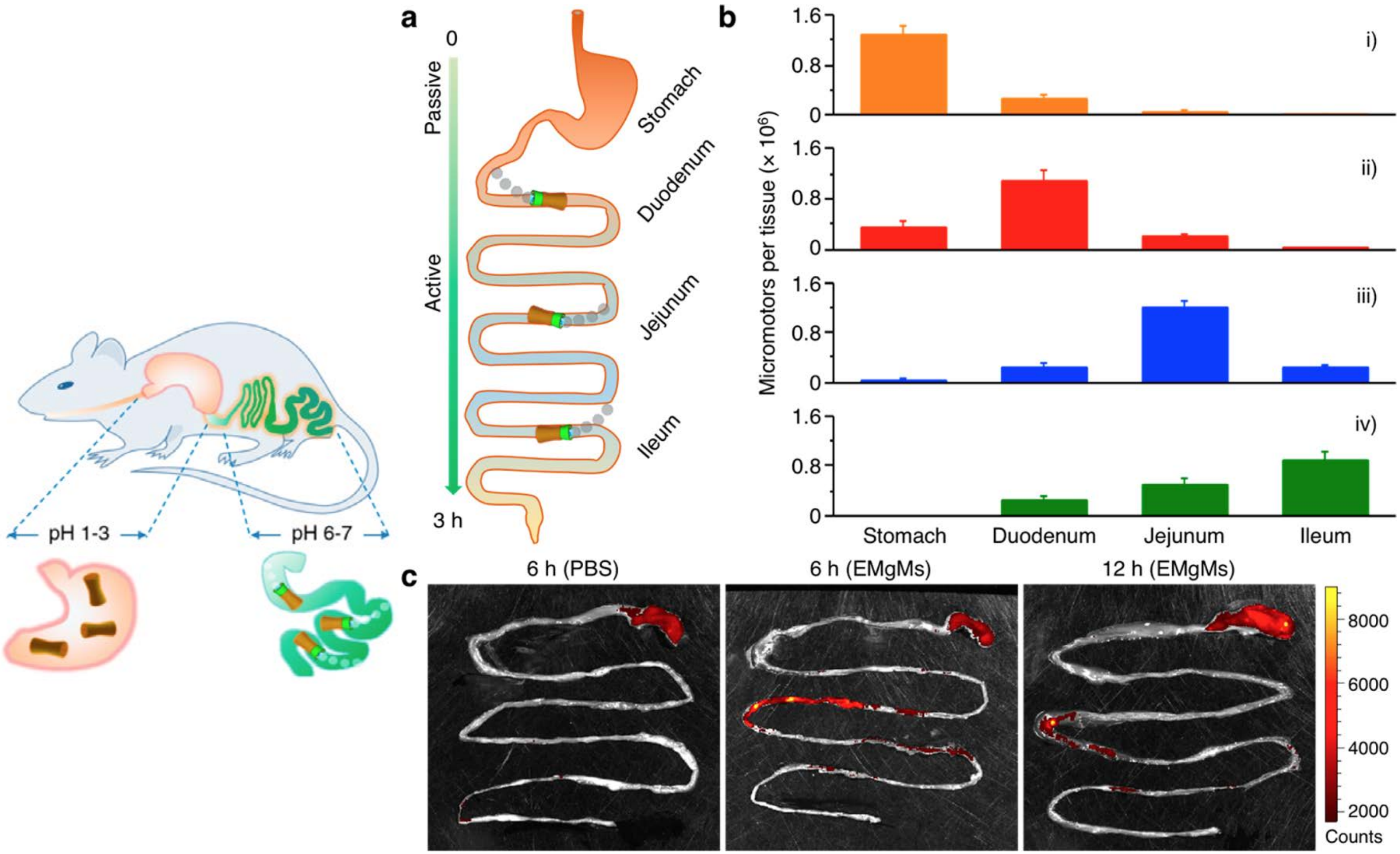
Enteric Mg Micromotors in the GI Tract



Enteric Mg Motors Can Selectively Position and Spontaneously Propel in GI tract

J. Li et al. ACS Nano 2016, 10, 9536−9542

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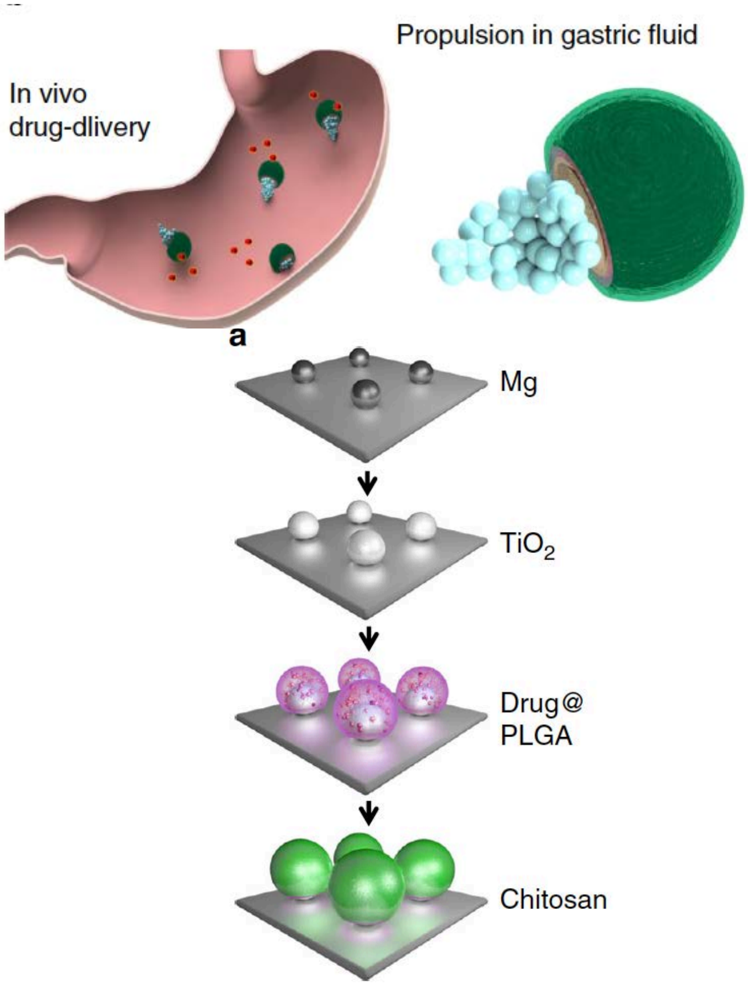
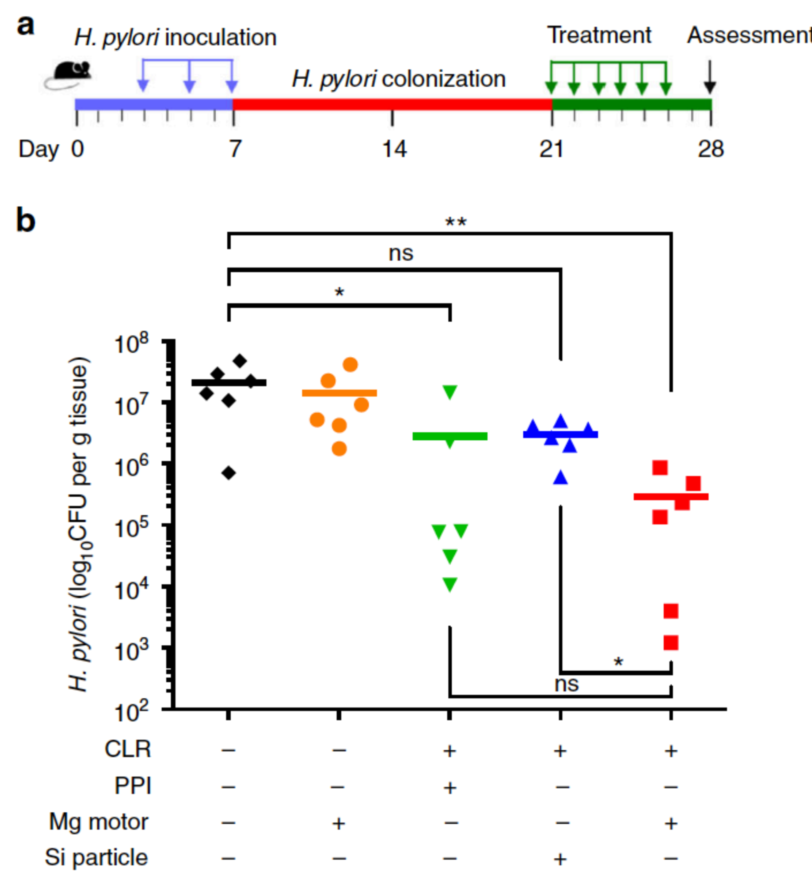
Micromotor-Enabled Active Drug Delivery for Treatment of Stomach Infection





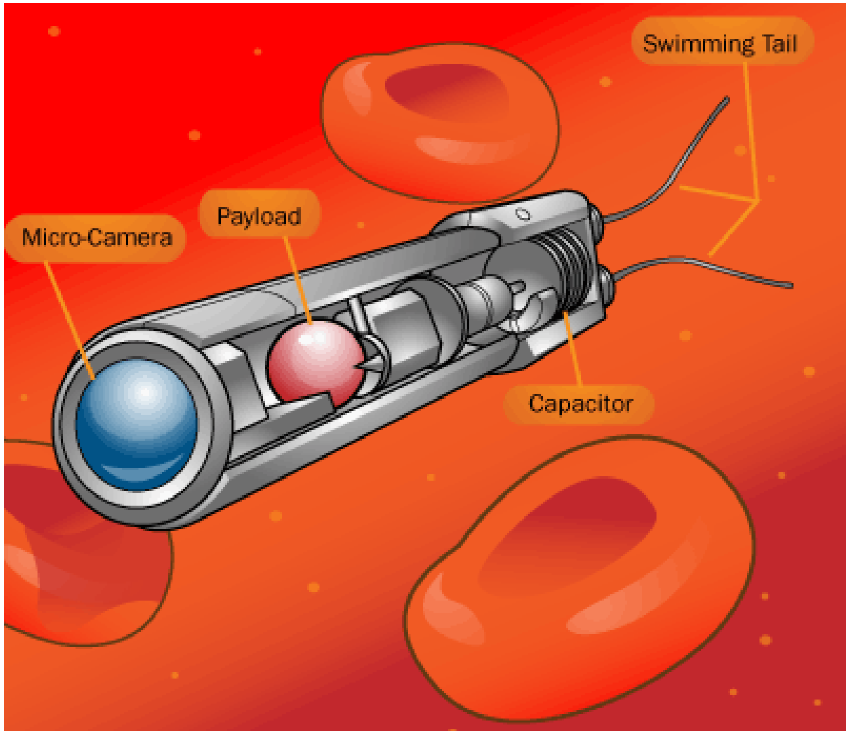
antibiotic drug clarithromycin (CLR)

proton pump inhibitors (PPIs)

Mg Motors Can Deliver CLR Effectively and eliminate the adverse effect caused by PPI

Nature Comm. 2017 8: 272.

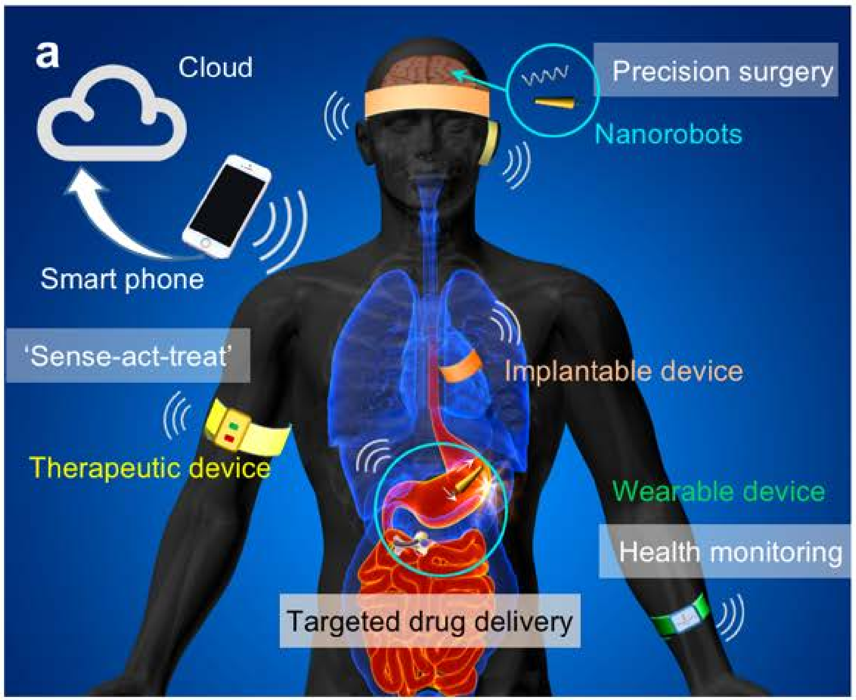
Synthetic Nanomotors - Outlook

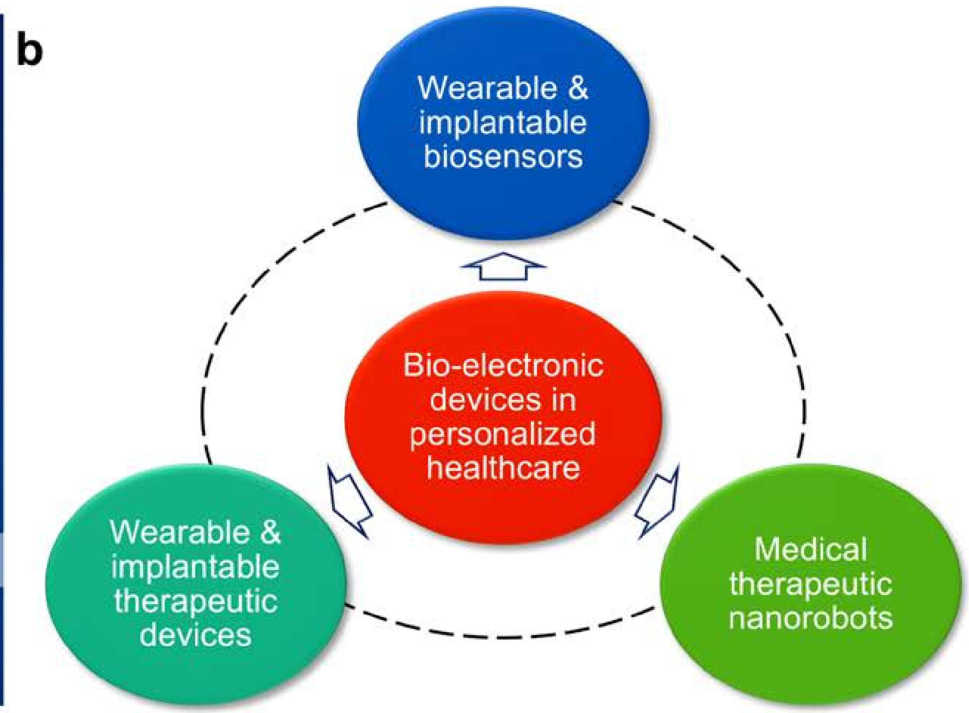


Outline

- **Wearable Biosensors**
  - **Technology Development**
  - **Fitness and Health Monitoring**
- **Synthetic Nanomachines**
  - **Technology Development**
  - **Biosensing and Drug Delivery**
- **Current Research Focus**

Bioelectronic Devices for Personalized and Precision Medicine





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Prof. **Ali Javey**

Prof. **Joseph Wang**

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Thank you for your attention!

Questions?