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A digital microfluidics-based electrochemical impedance spectroscopy for cell-based immunoassay detection in a dynamic mode

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MicroTAS 2022

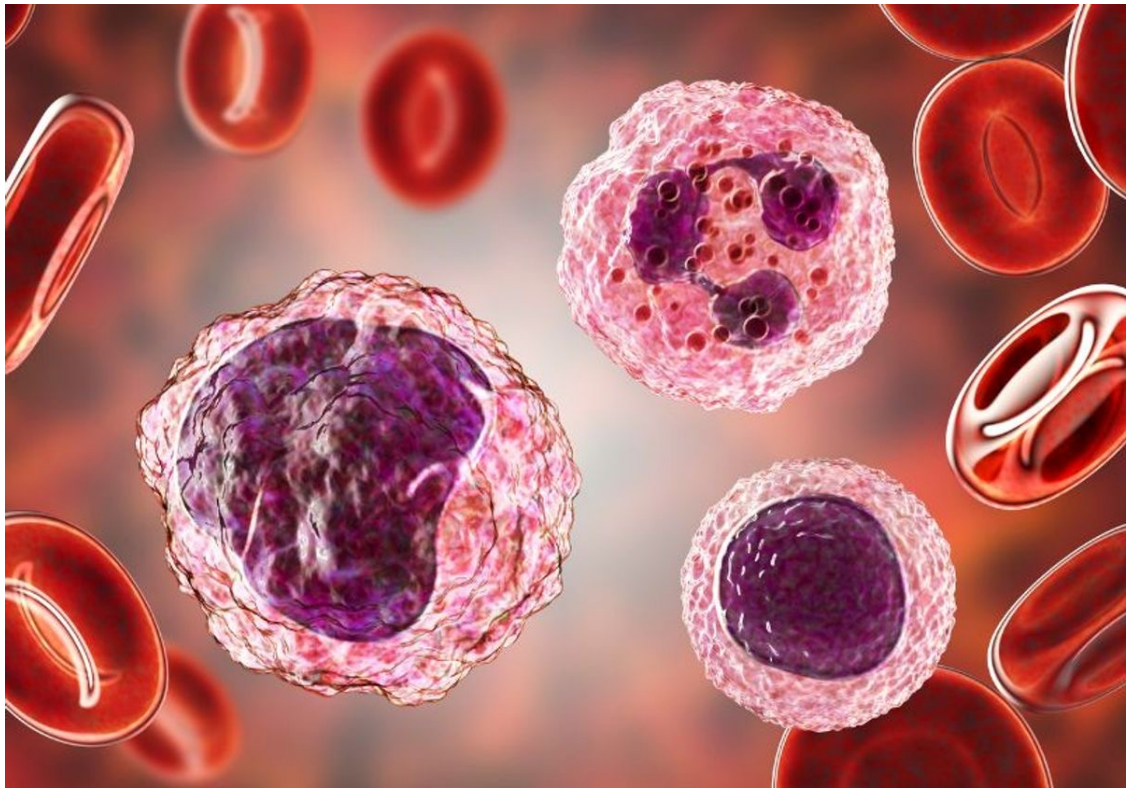
Oct. 25th, 2022

Human peripheral blood mononuclear cells (PBMCs)

- Key drivers of the **immune responses** to pathogens
- Heavily involved in **physiological homeostasis regulatory mechanisms**
- immune-mediated **indicators of therapeutic responsiveness**

Advantages as biomarker:

- Minimally invasive
- Provide a more comprehensive overview of immune status



https://www.the-scientist.com/

Dynamic quantification of PBMC abundance

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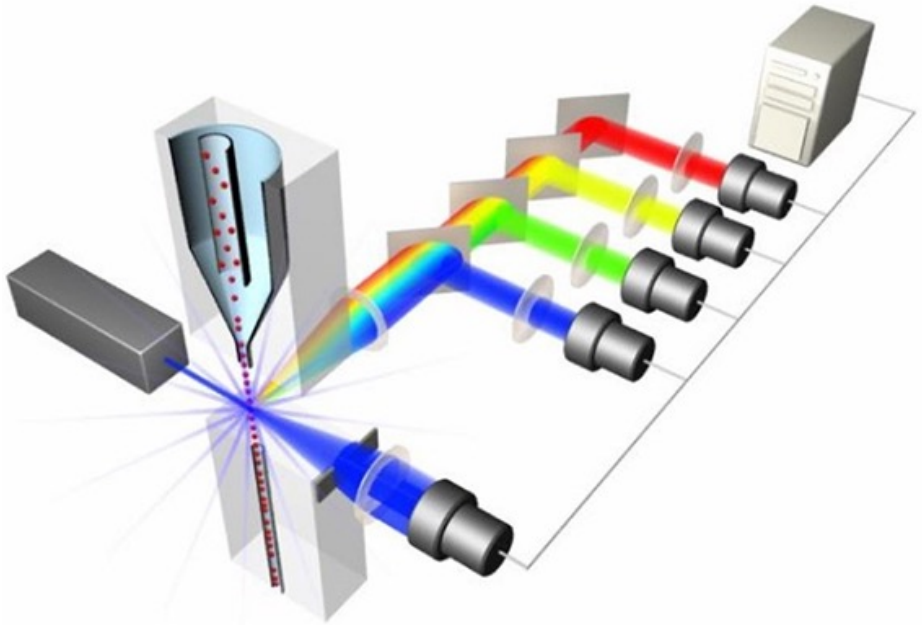
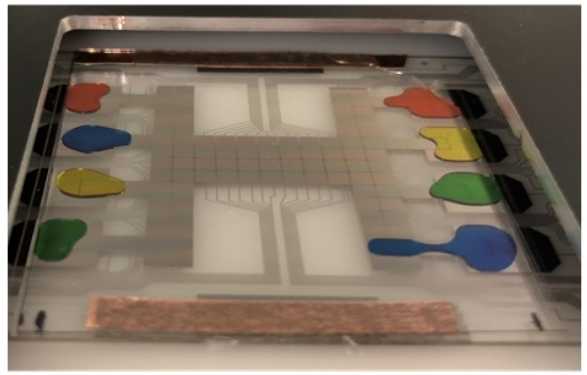
Standard method: **flow cytometry**



- Sensitive and reliable
- Relies on highly specialized and bulky equipment
- Not realistic to monitor PBMC abundance on a regular basis

Our method : **digital microfluidics (DMF)-based electrochemical impedance spectroscopy (EIS)**

Dropbot system



DMF device

- Palm-sized device, automated and parallel operation
- Cost-effective, minimal human intervention
- Ideally for point-of-care (POC) testing

Liu, Y., et al. *ACS omega* 6.39 (2021): 25642-25651.

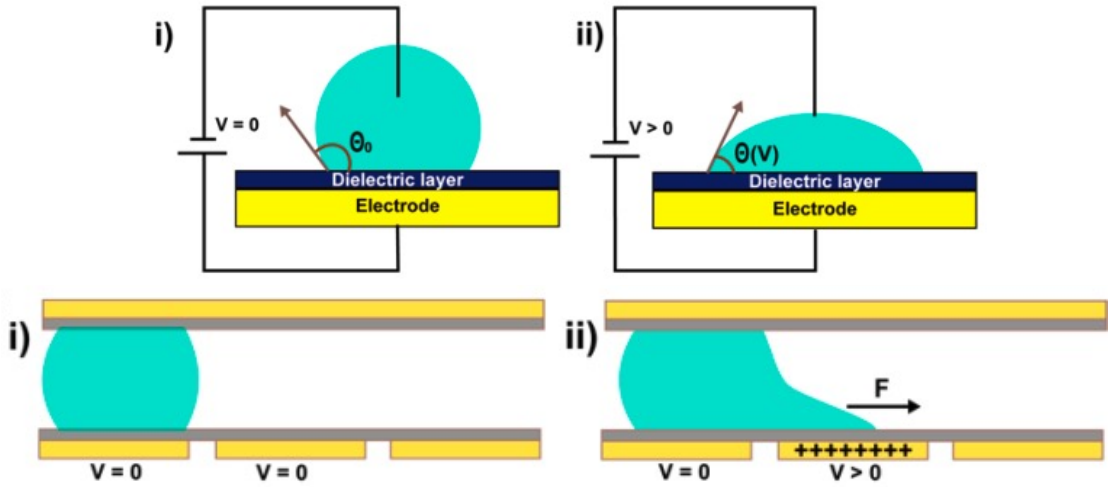
Digital microfluidics (DMF)

Conventional lab-on-chip:

- Permanently etched microchannels
- External modules: pumps and microvalves

Digital microfluidic lab-on-chip:

- Manipulation of liquids as discrete droplets
- Electrowetting-on-dielectric (EWOD):



- Automated and programmable, reconfigured on-demand,

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Electrochemical impedance spectroscopy (EIS)

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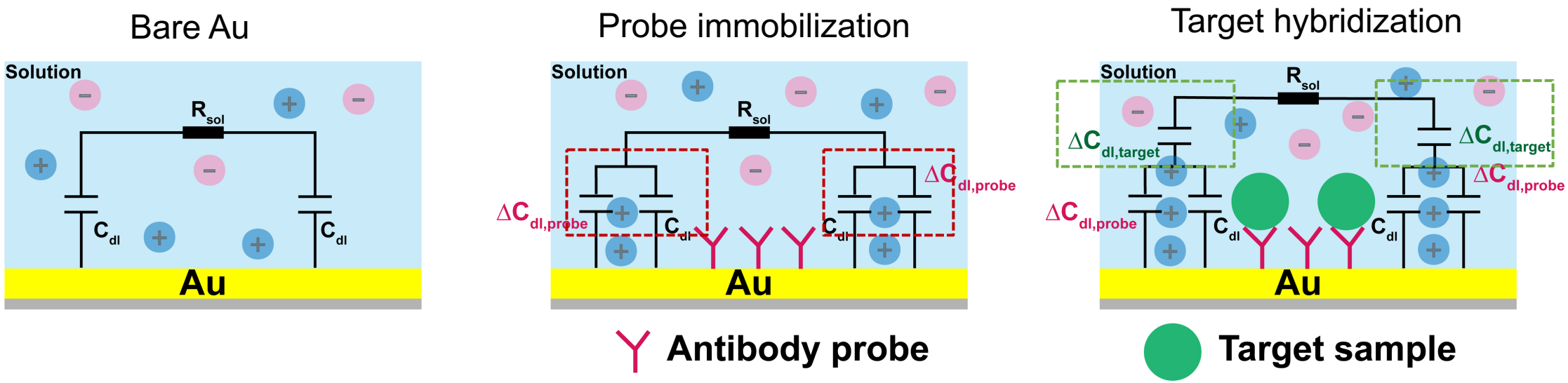
Electronic-based detection

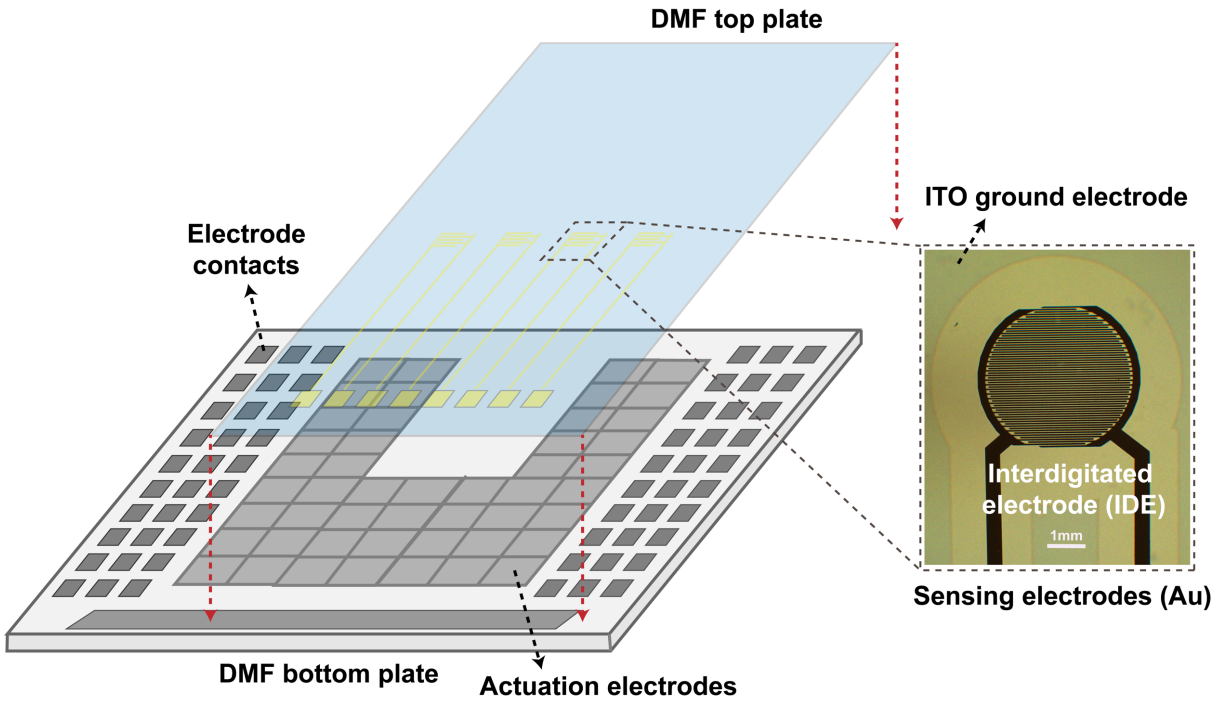
- Easy-to-miniaturize, rapid and real-time detection

Impedance (EIS) biosensor

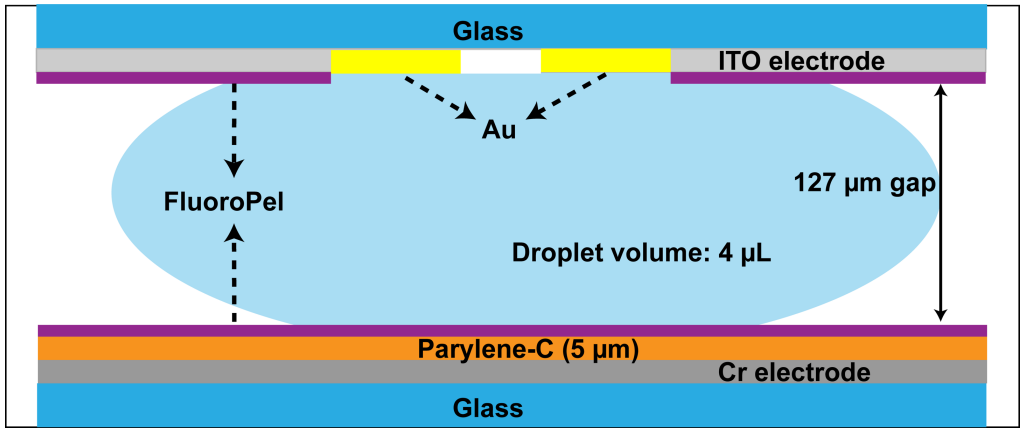
- Utilizes a small amplitude, AC signal to probe the impedance characteristics
- Non-faradaic: change in the **double layer capacitance (C_{dl})** element
- (no direct current needed): ***minimum destructive on electrodes, label-free detection***

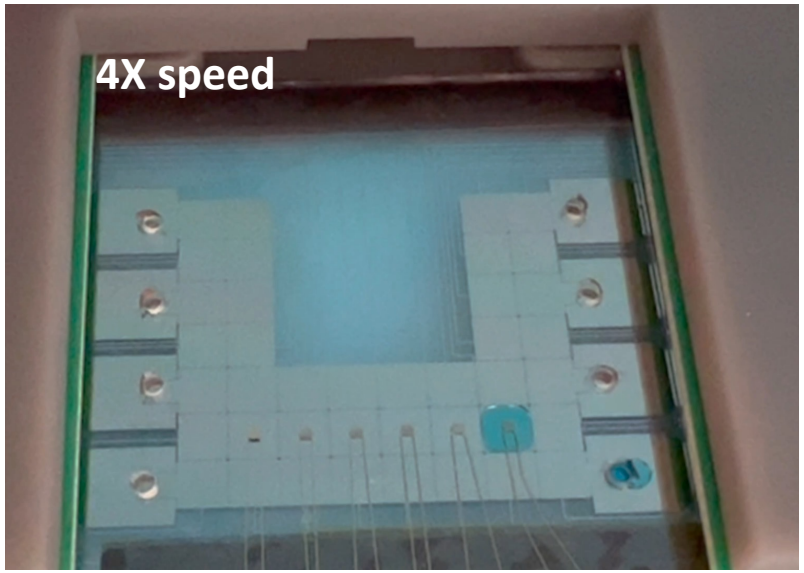


Layout of the integrated DMF device



Cross-section of the DMF device

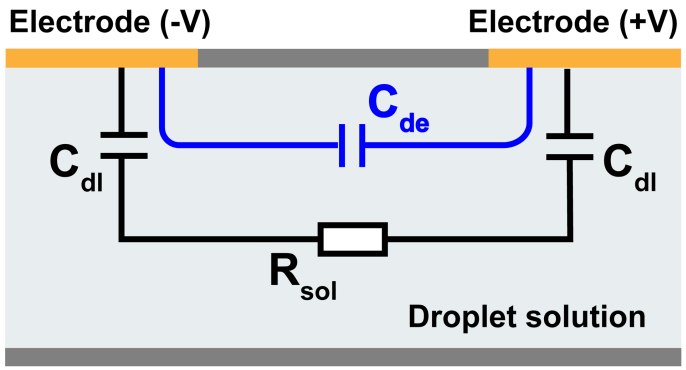


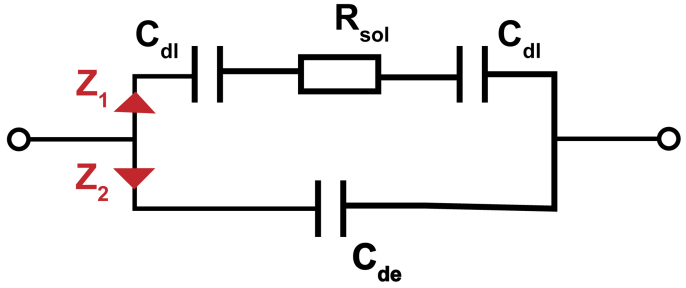


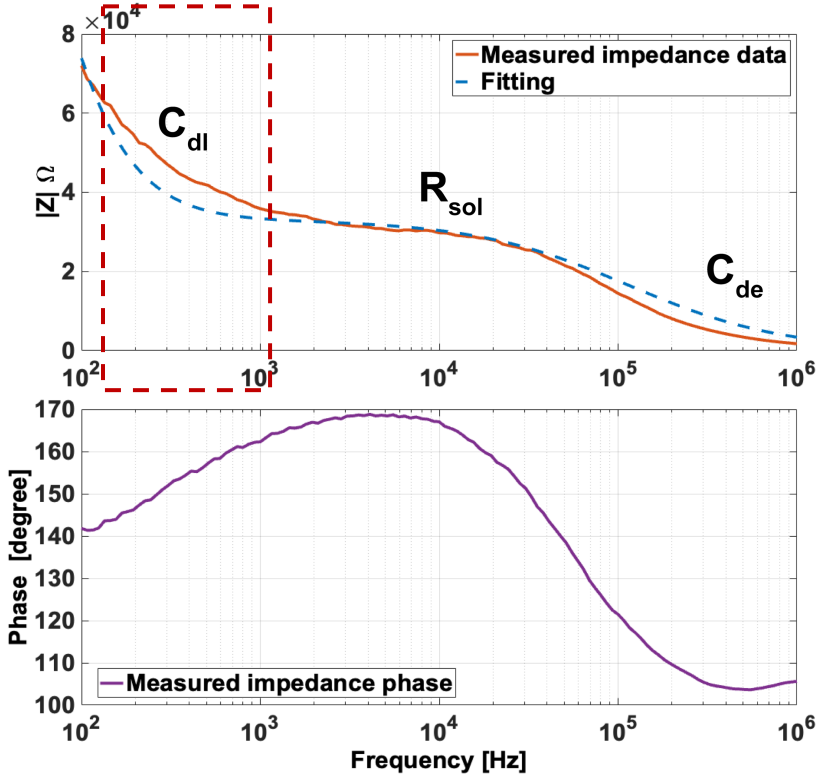
Overview of DMF device:

- **bottom plate**: actuation electrode array
- **top plate**: IDE sensing electrode

Equivalent Circuit and Modeling of IDEs







$$\frac{1}{|Z|} = \frac{1}{|Z_1|} + \frac{1}{|Z_2|}$$

$$|Z_1| = \sqrt{R_{sol}{}^2 + \frac{1}{(2\pi f C_{dl})^2}}$$

$$|Z_2| = \frac{1}{2\pi f C_{de}}$$

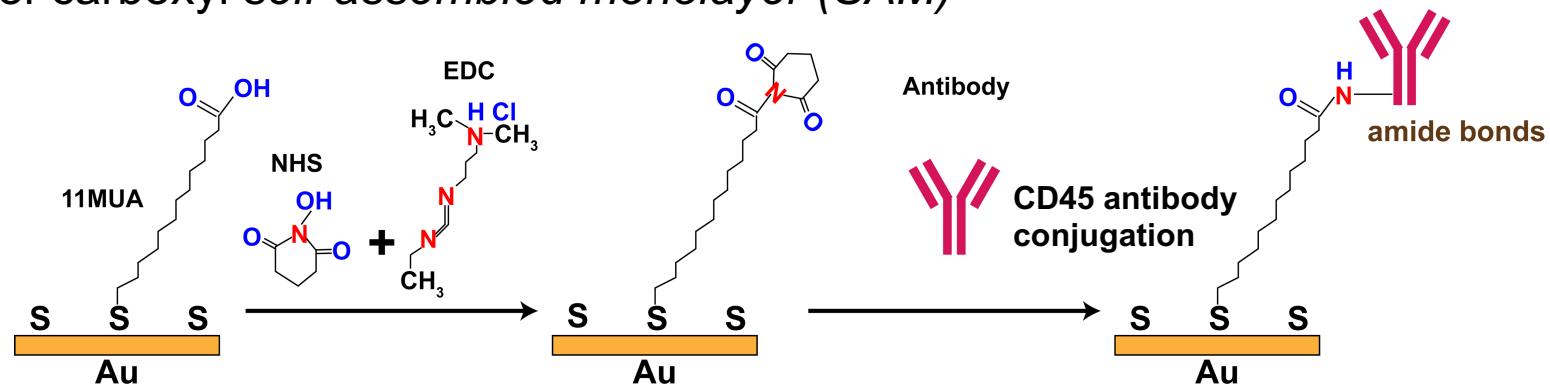
Two parallel branches:

Z_1: capacitive and resistive responses of droplet solution

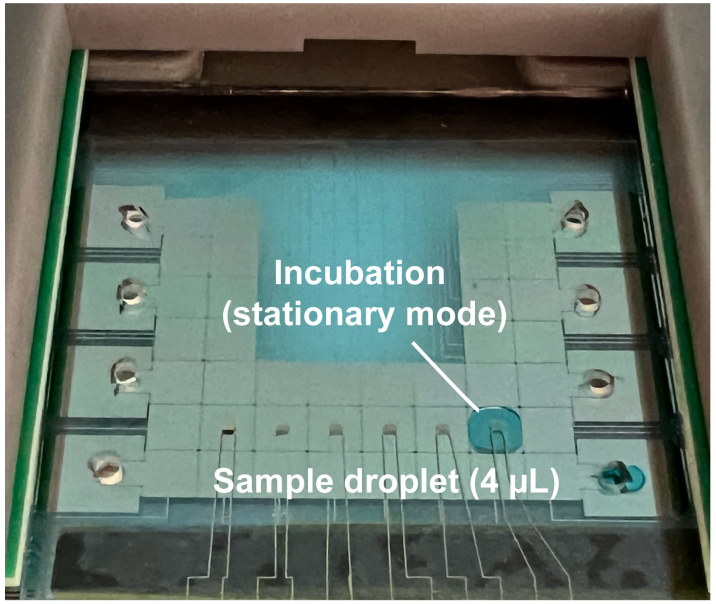
Z_2: solution dielectric capacitance

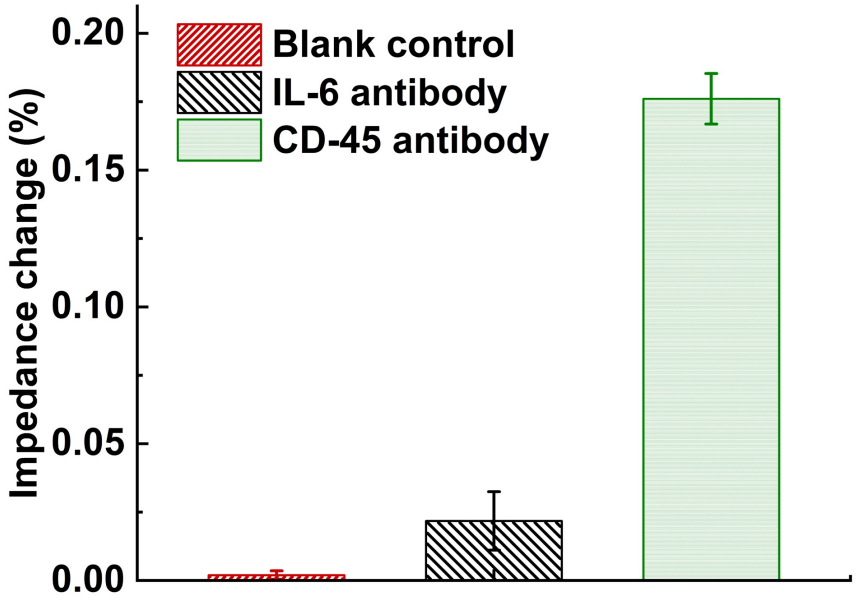
Surface conjugation

Formation of thiol-carboxyl *self-assembled monolayer (SAM)*



PBMC hybridization:



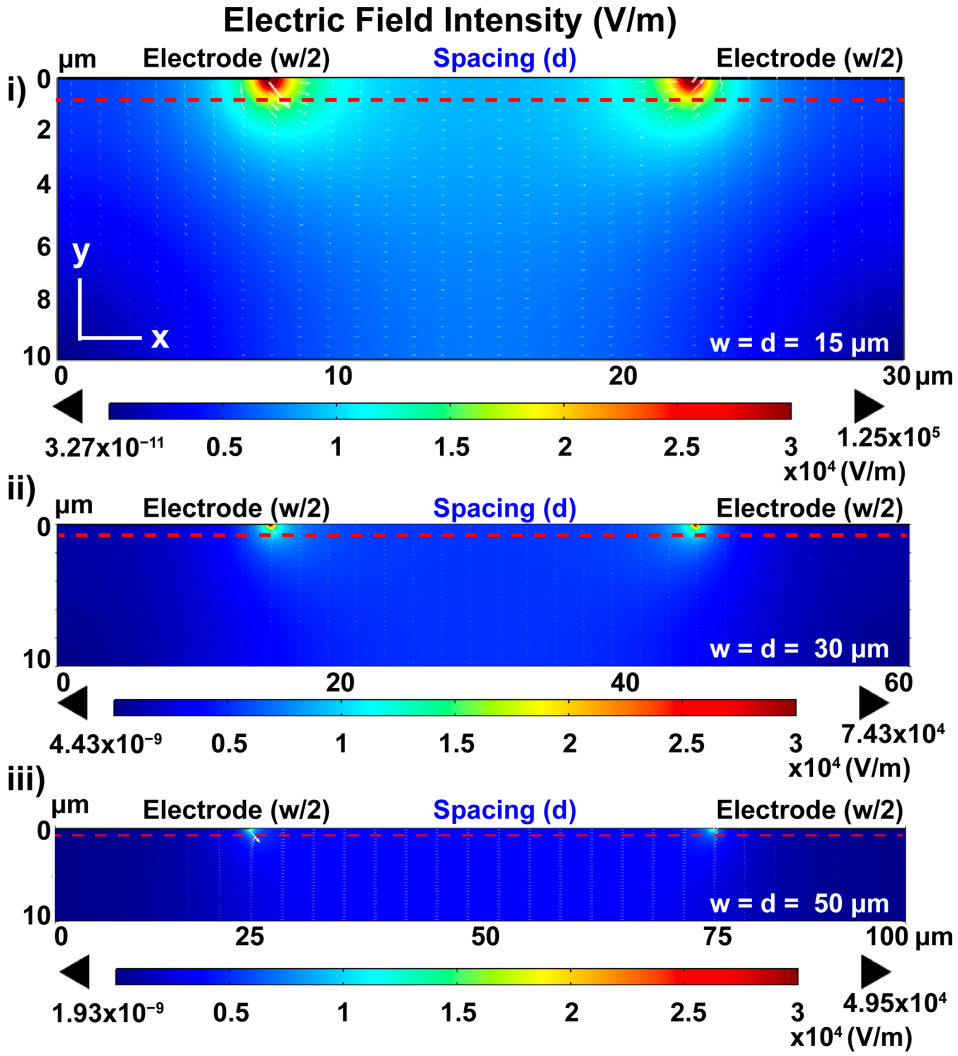


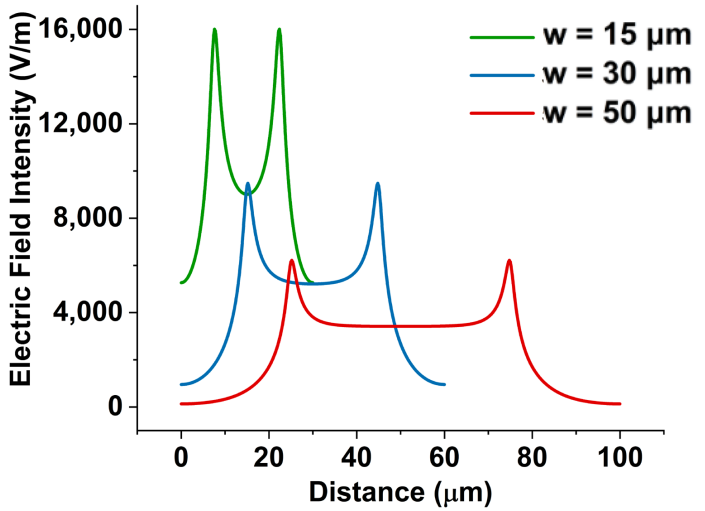
Impedance change (%)

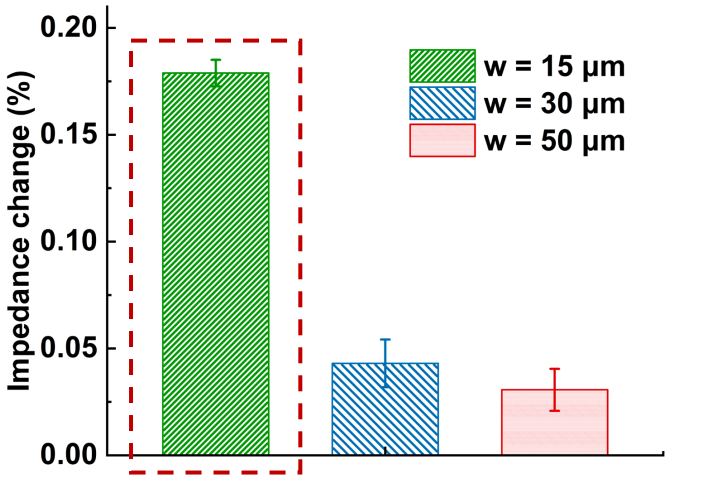
$$= \frac{Z_{cell} - Z_{base}}{Z_{base}} * 100$$

1) Blank control: 0.19%
2) non-specific binding: 2.2%
3) Target binding: 17.6%

Effect of IDE geometry







Over 3-fold sensitivity improvement

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PBMC-Immunoassay in dynamic mode

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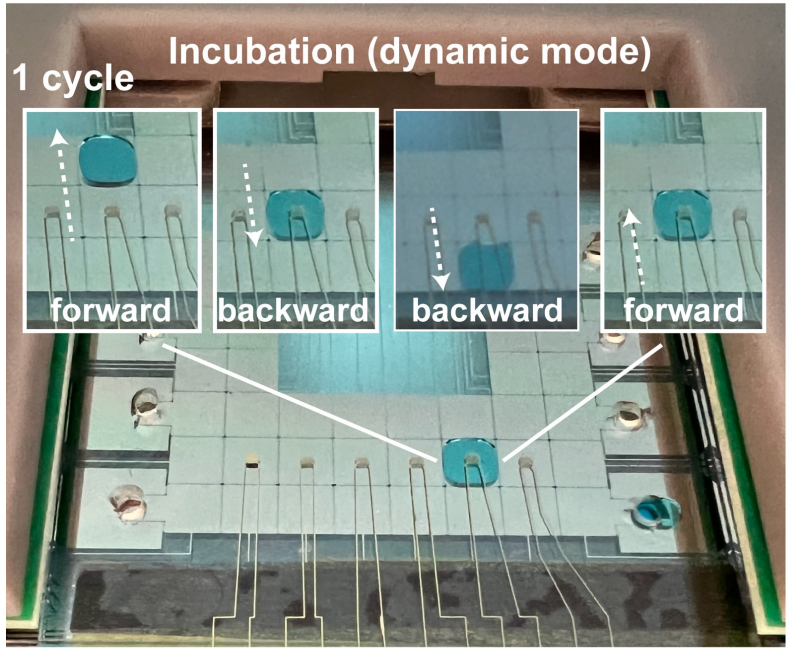
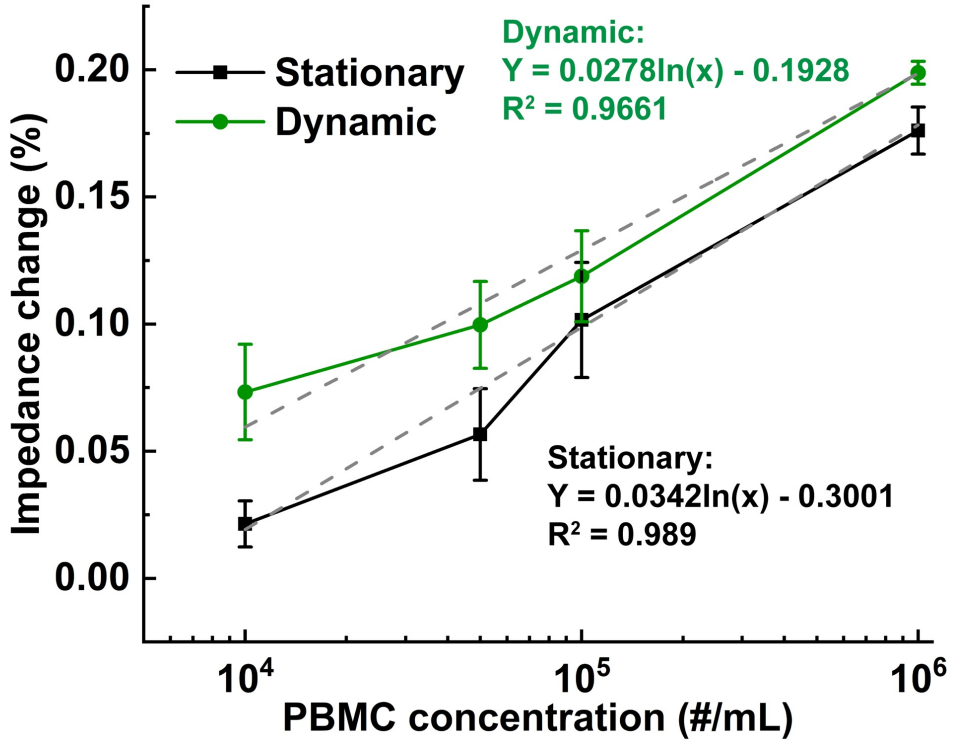
Dynamic incubation mode: *forward-backward-backward-forward*





Comparison of impedance increment (dynamic vs stationary modes)

PBMC Concentration (#/mL)	10^4	5×10^4	10^5	10^6
Impedance Increment (%)	242.7%	64.4%	26.9%	12.9%

Conclusions

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- A novel DMF platform integrated with an EIS-based biosensor for the detection of PBMCs
- **Low sample volume (4 µL)** for **rapid detection (20 min)**
- *Quantitative* detection of PBMC abundance **dynamic incubation modes showed** 2.4-fold **enhanced detection signal** detect as low as **10^4 PBMCs/mL**, approximately *two orders of magnitude less* than the biologically relevant range

Acknowledgements

Alexander Revzin, Ph.D.
Consultant
Department of Physiology & Biomedical Engineering
Mayo Clinic, USA

Seth Hara, Ph.D.
Senior engineer
Division of Engineering
Mayo Clinic, USA

Marina R. Walther-Antonio, Ph.D.
Associate Consultant I
Department of Surgery
Mayo Clinic, USA

Diane Eaker, M.S.
Senior engineer
Electronics Development Unit of the Division of Engineering

Funding resources: Ivan Bowen Family Foundation, Mayo Clinic

- Department of Surgery,
- Microbiome Program, Center for Individualized Medicine

Thank you

Any questions?