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# Electro-Fluidic Micro- and Nanotechnologies for Health and Environmental Monitoring

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10/16/2017

# Acknowledgements

## Rutgers NanoBioelectronics Group

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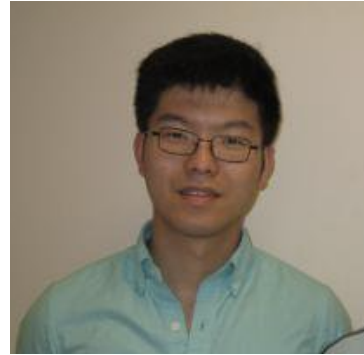
### Rutgers Microelectronics Research Laboratory Staff

### Upenn Singh Center for Nanotechnology Staff

Noah Clay, John Russell, Merideth Metzler

### Stanford University

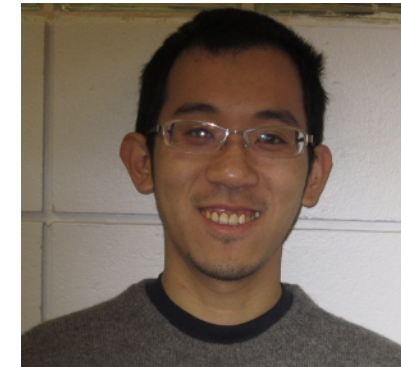
**Mentors:** Robert Dutton, Roger T. Howe, Ronald W. Davis



Zhongtian Lin



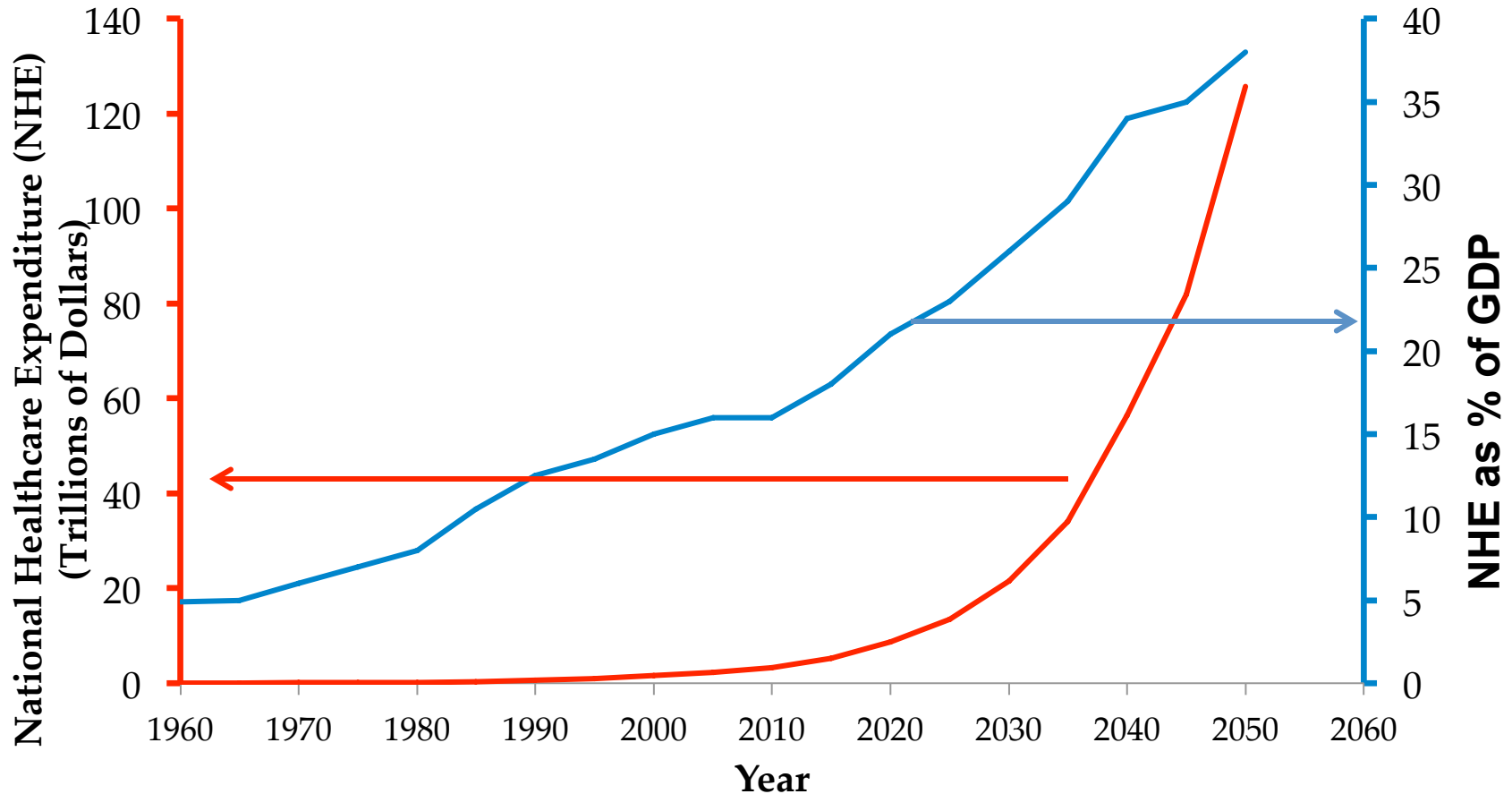
Azam Gholizadeh



Pengfei Xie



# National Healthcare Crisis

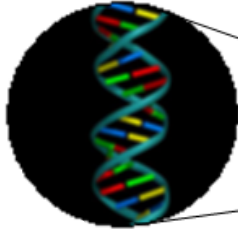


- By 2050, sum of Medicare, Social Security, Medicaid and interest on the national debt will consume 100 percent of tax revenue.

# Early Disease Diagnosis: Biomarker Based Screening

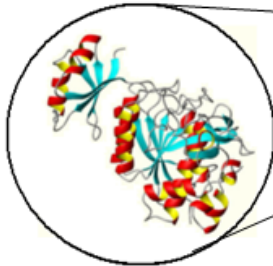
- Biomarkers are any molecular indicators that signals disease presence.
- Discovery, validation, and detection

## Nucleic Acid Biomarkers

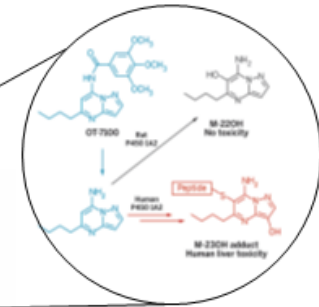


-Genetic Testing

## Protein Biomarkers



-PSA Blood Test  
(Prostate Cancer)  
-hCG Urine Test  
(Pregnancy)

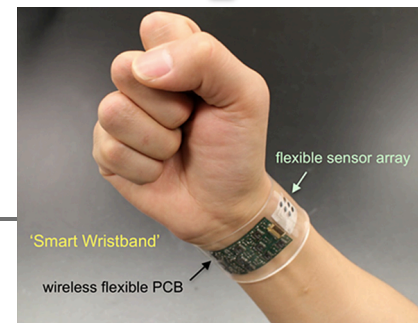


## Metabolites

-Small Molecules  
-< 800 Daltons

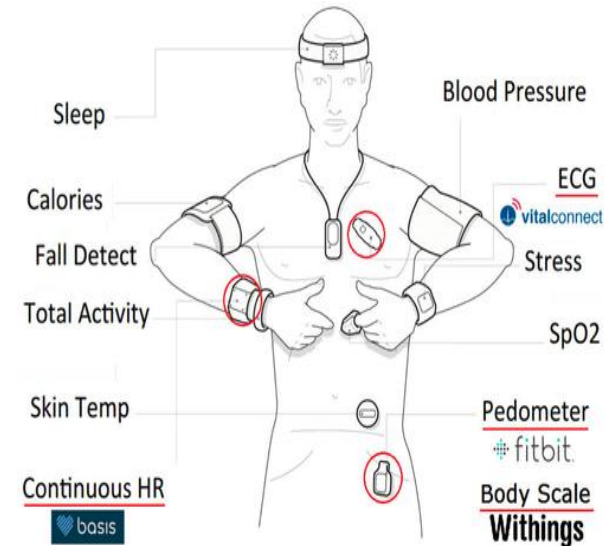
- Precision and Personalized medicine
- Continuous Health Monitoring

Electrical Detection  
Miniaturized Optics



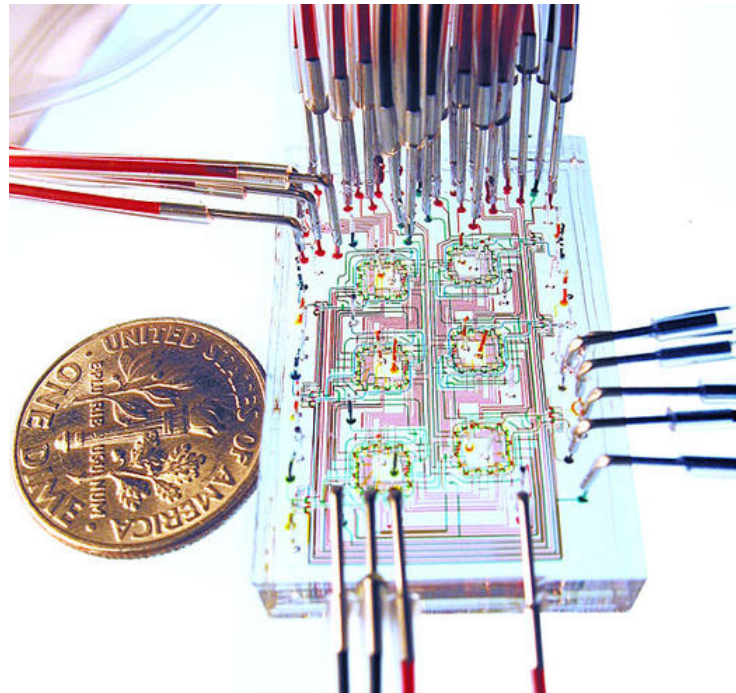
# Micro/Nanosensors for Health and Environmental Monitoring

- Combine biomarker measurement with:
  - Vitals
    - Heart rate/Pulse Oximetry
    - Temperature monitoring
    - Electrolyte concentrations
    - Glucose
  - Genomic Data
  - Environmental Monitoring
    - Measurement of exposure environmental toxins
    - Toxicology
  - Correlation of environmental parameters with biomarker data
- **Crowd Sourcing:** Billions of data points collected from millions of individuals
  - Comprehensive history
  - Predictive algorithms



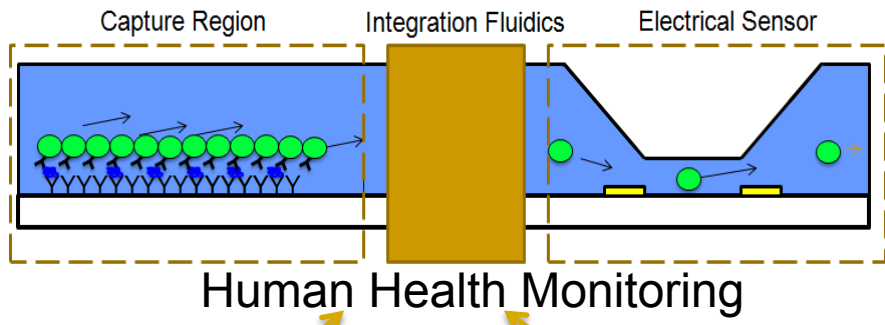
# Lab on a Chip - Microfluidics

- The ability to miniaturize instrumentation and techniques typically performed on a large scale in a lab to the microscale
  - Channels, chambers, mixing, etc..



# Talk Overview – Research Thrusts

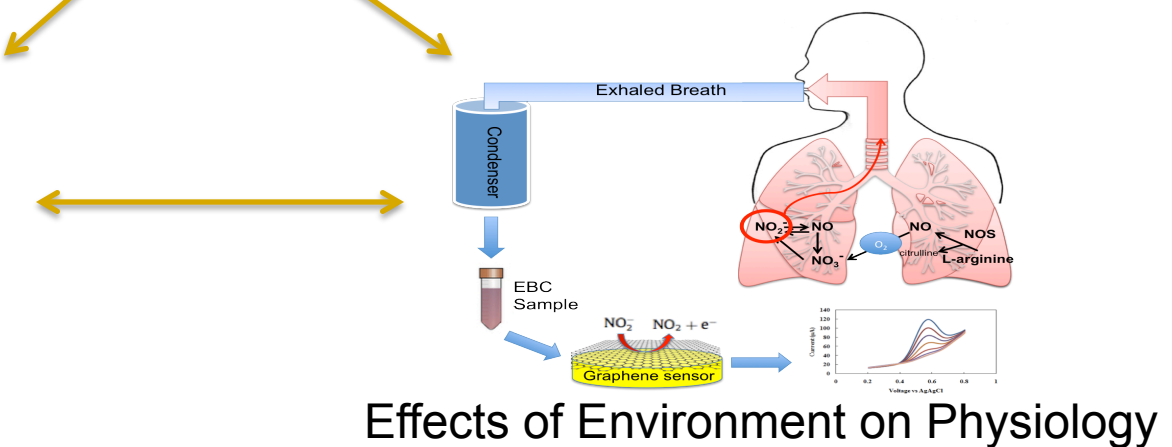
- Fundamental electrofluidic components
- Application/Domain specific sample-to-answer platforms



Human Health Monitoring



Environmental Monitoring

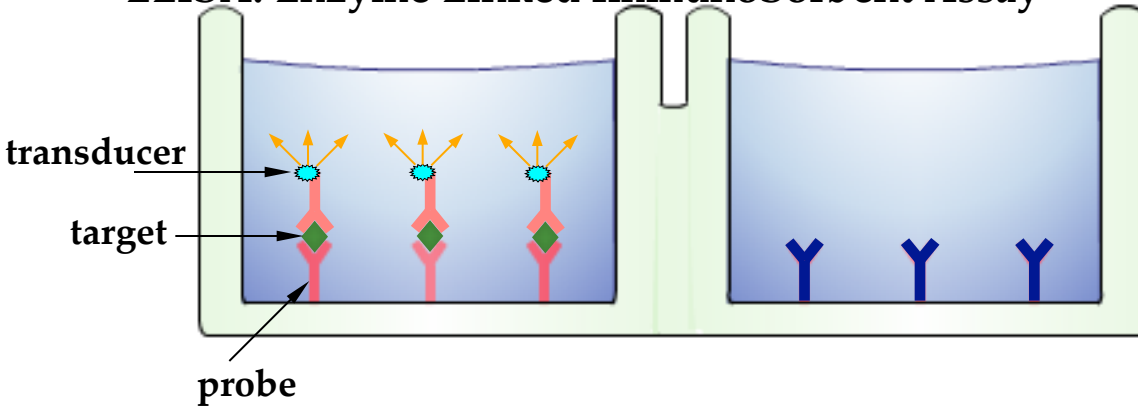


Effects of Environment on Physiology

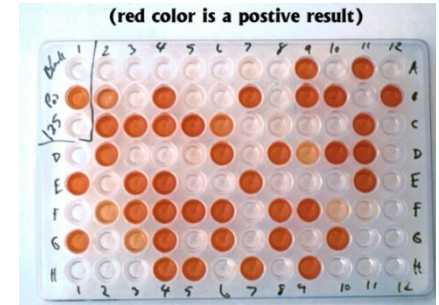


# Enzyme Linked ImmunoSorbent Assay

- ELISA: Enzyme Linked ImmunoSorbent Assay



- Detection limit: 1 pM
- 60 million molecules in 100  $\mu$ l of sample



SpectraMax L  
Molecular Devices  
(\$10-40k)

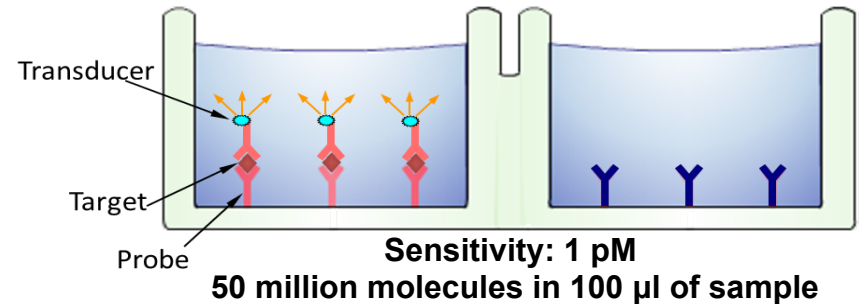
\$50 per data point



# Current Methodologies for Protein Detection

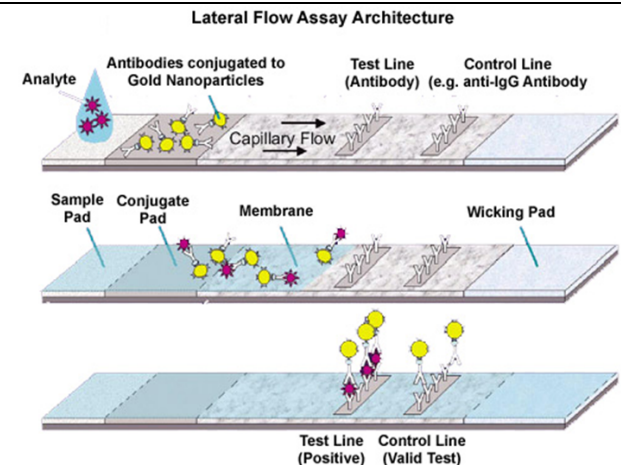
## ■ ELISA

- ❑ Quantitative and Precise
- ❑ Bulky
- ❑ Lacks portability



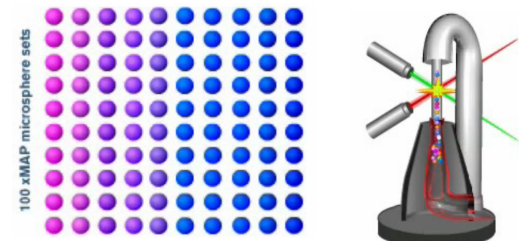
## ■ Lateral Flow Devices

- ❑ Portable, Low Cost, and Disposable
- ❑ Not quantitative
- ❑ Multiplexing Difficult

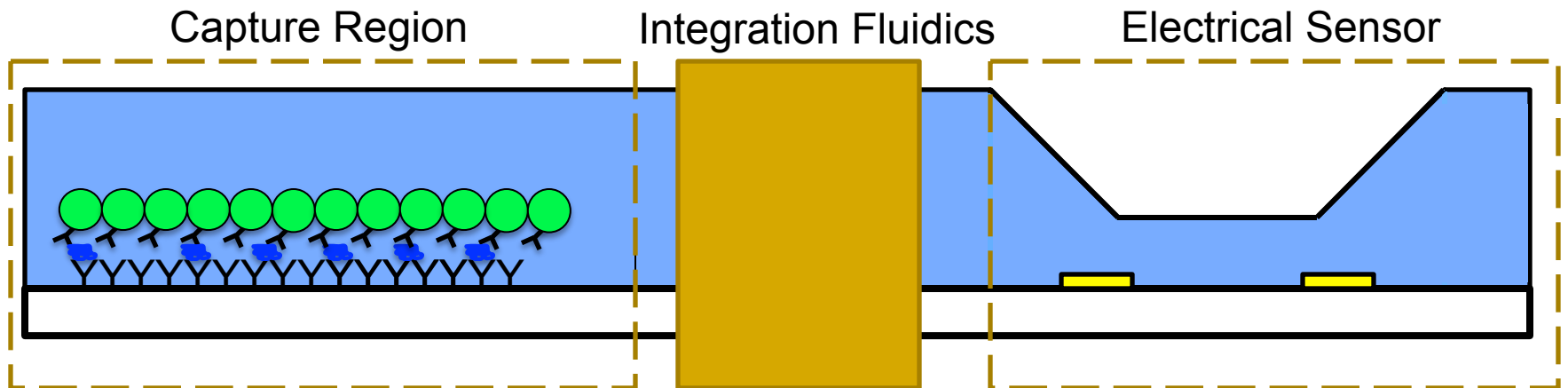
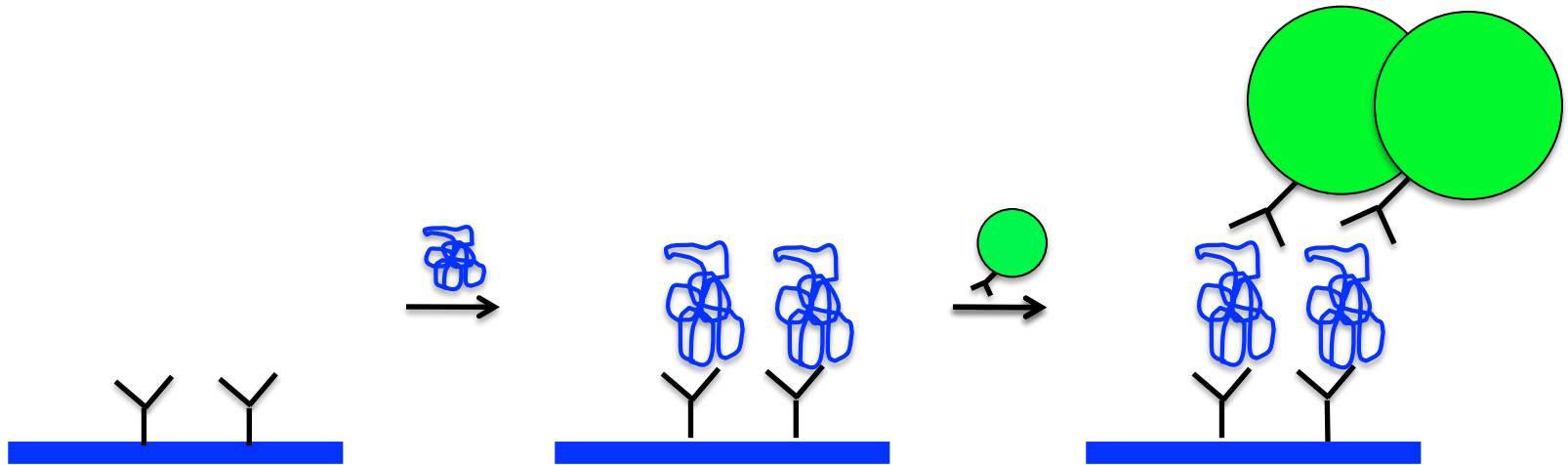


## ■ Luminex

- ❑ Capable of high throughput multiplex
- ❑ Bulky
- ❑ High cost



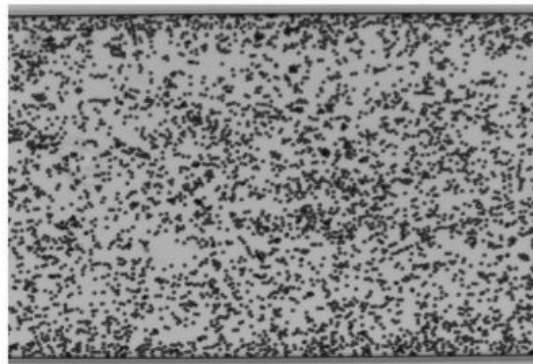
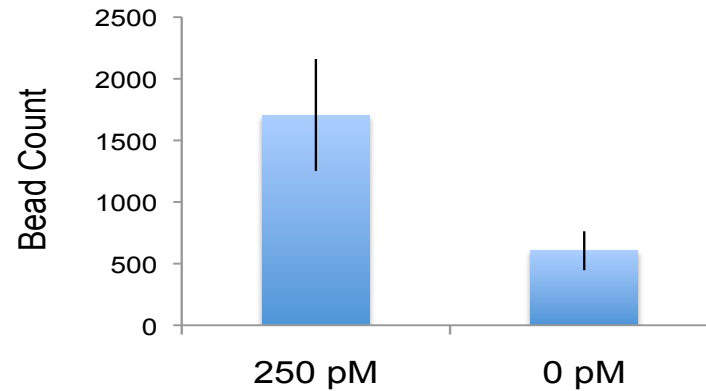
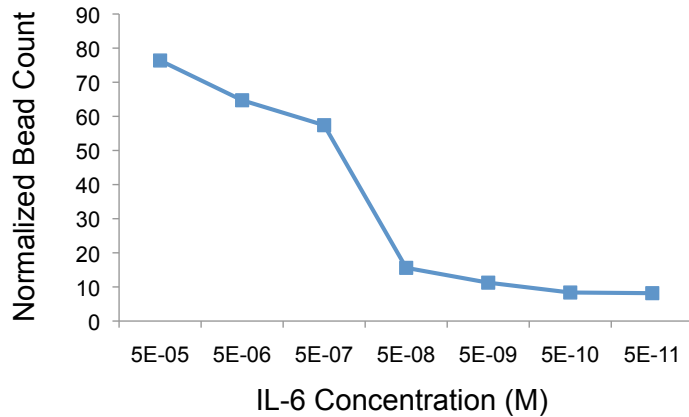
# Digital Decoupled PLISA (Particle Linked Immunosorbent Assay)



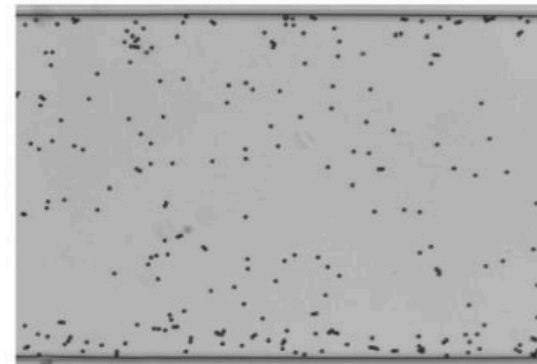
# Digital Detection

**10X Improvement in Sensitivity Compared to ELISA**  
**1 ul of sample required (100X less than ELISA)**  
**1000 X smaller number of molecules necessary**

## IL-6 Abundance

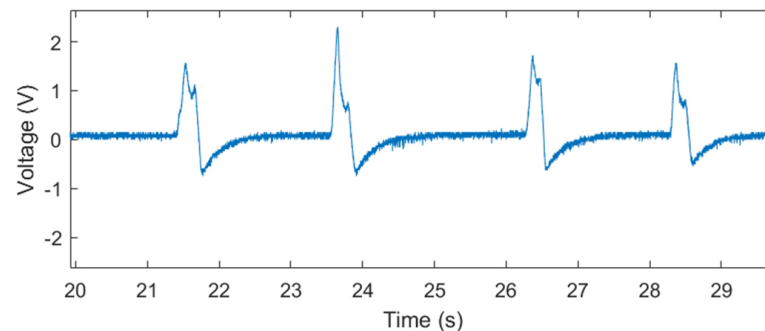
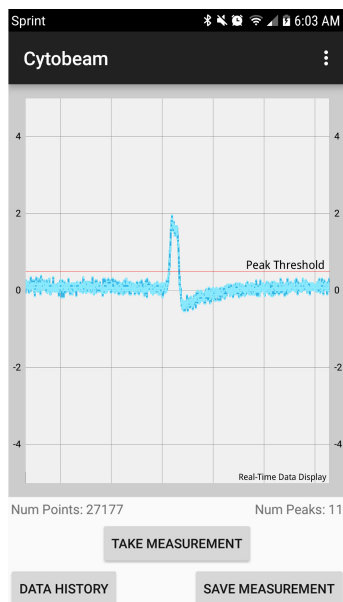
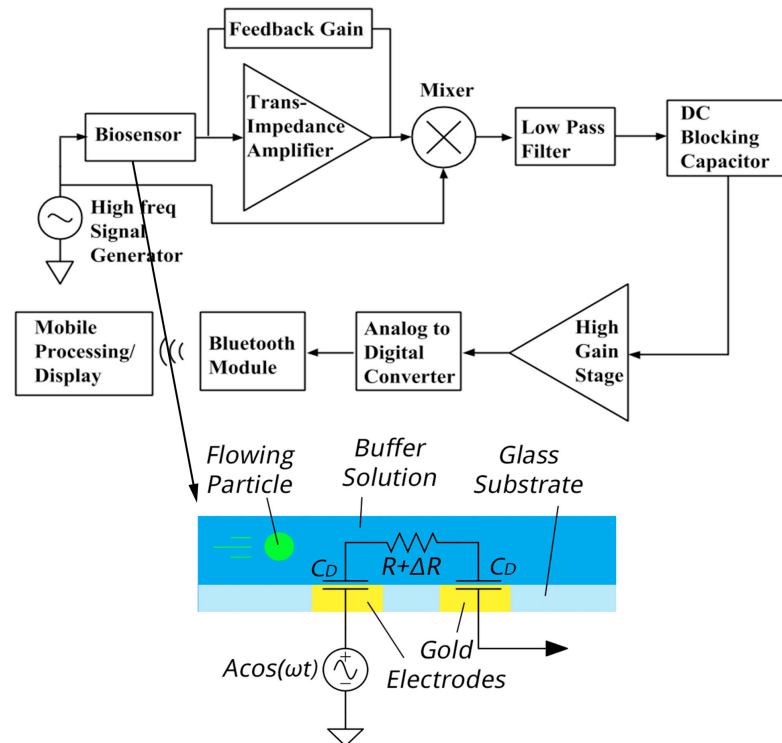
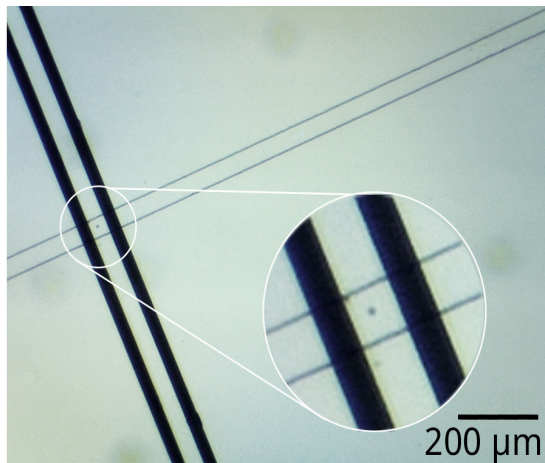
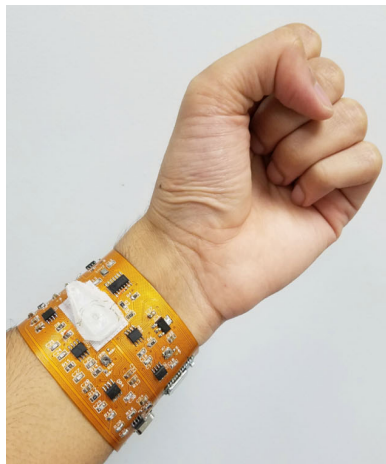


5 nM IL-6

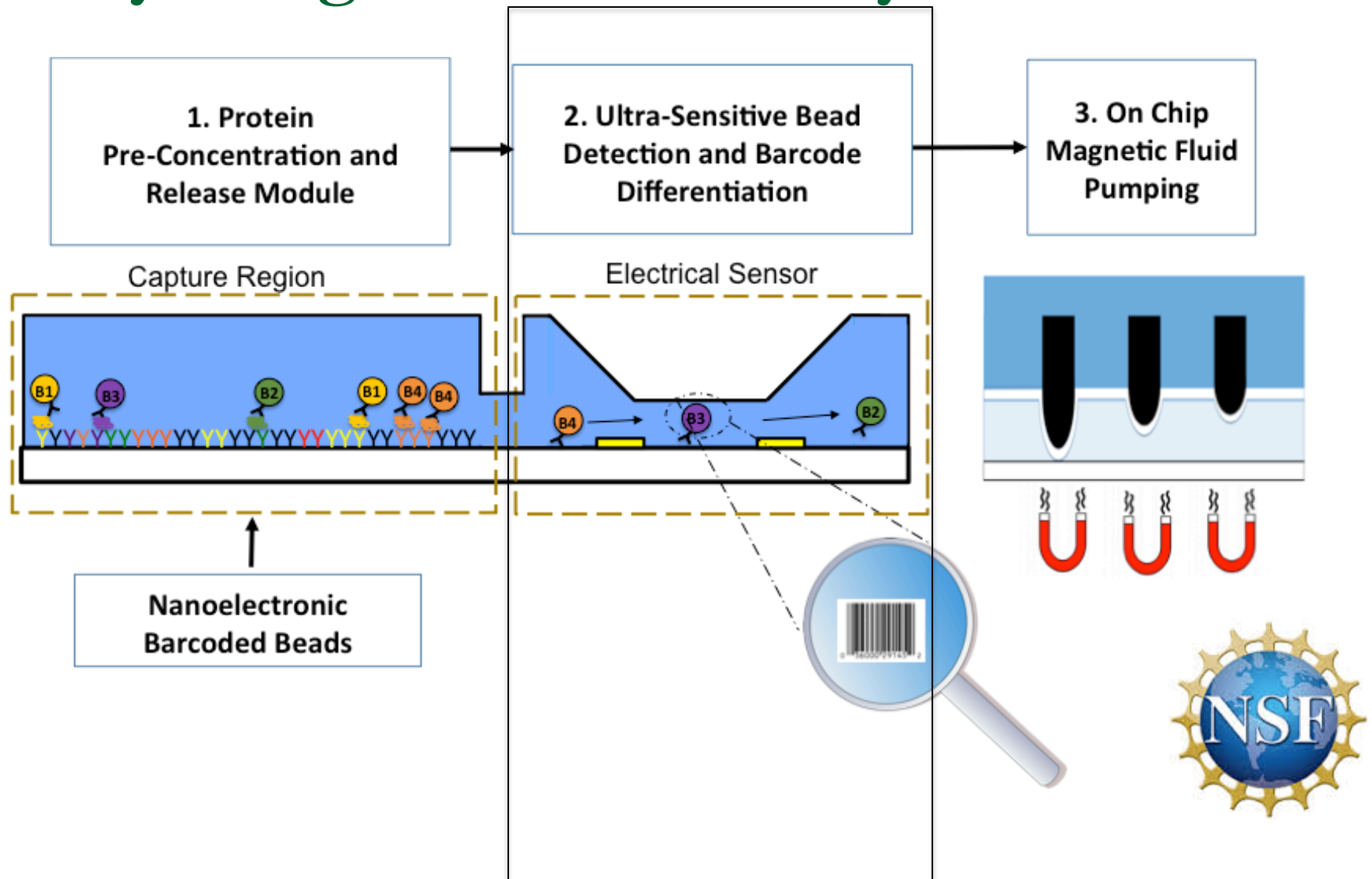


No antigen

# Wearable Wireless Impedance Cytometer

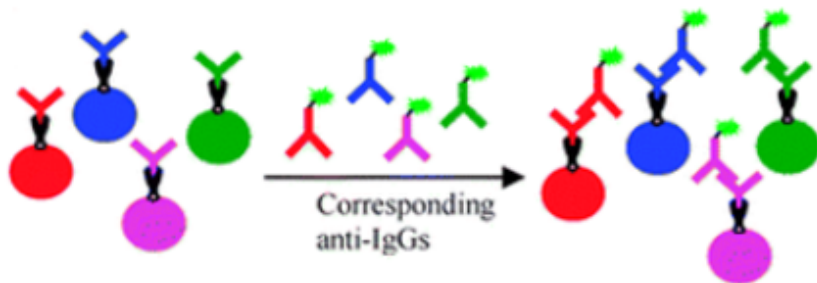


# Fully Integrated Portable System



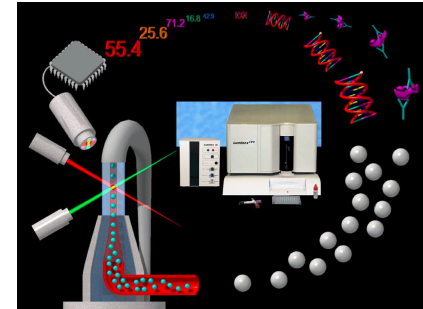
# Particle Barcoding

## Quantum Dots



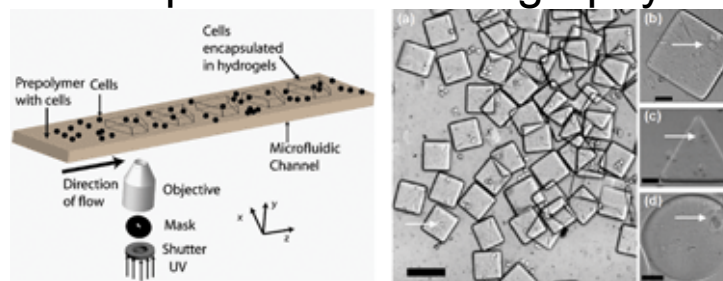
S. Rauf et al. Chemical Communications 2010

## Two-Photon Excitation



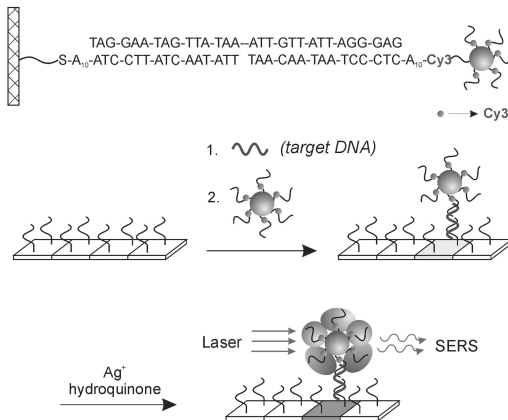
Luminex xMap® Technology

## Stop and Flow Lithography



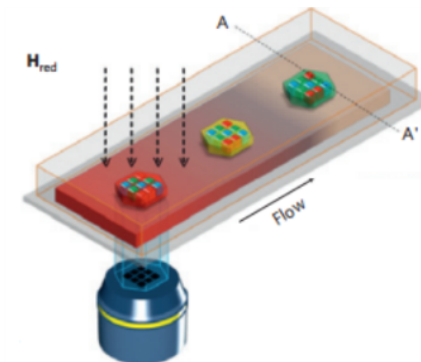
Doyle et al. Lab on Chip 2008:

## SERS Barcodes



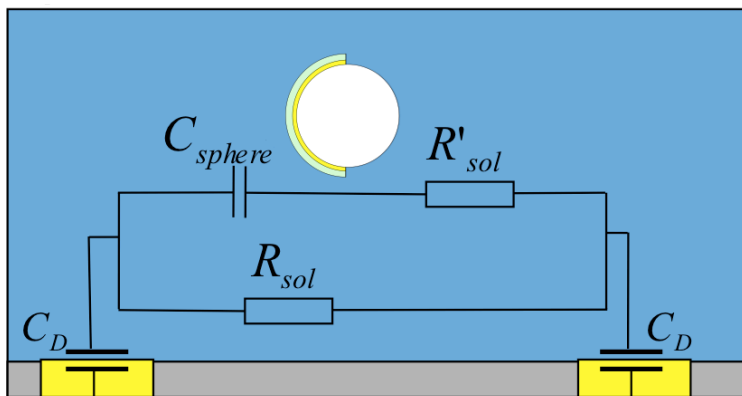
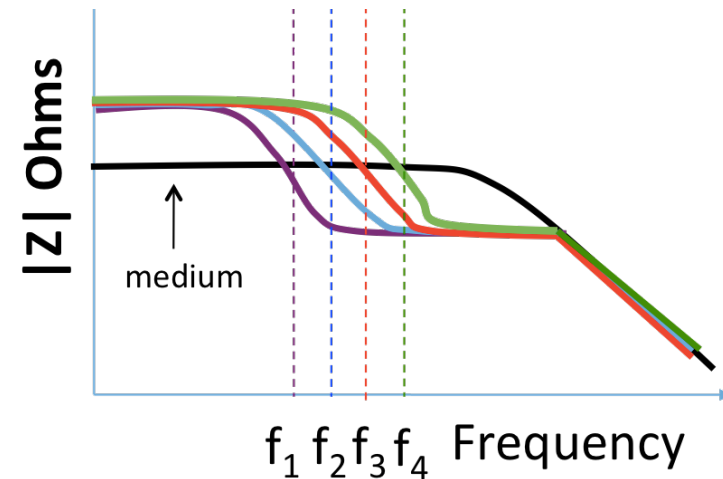
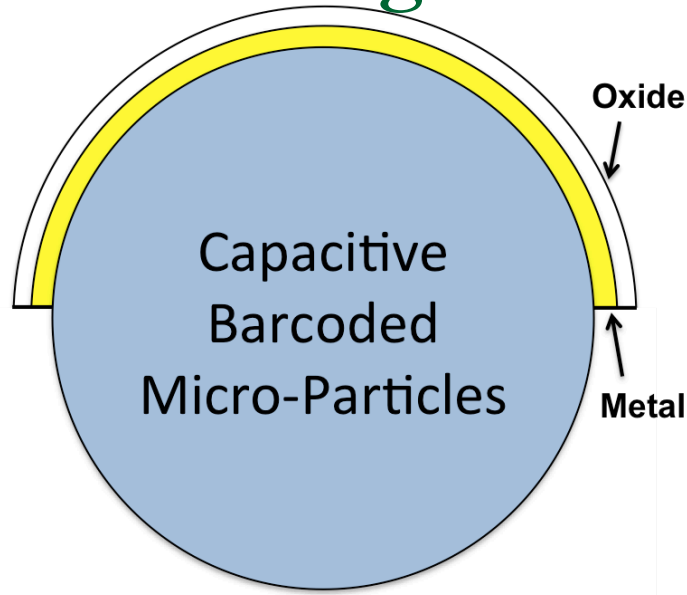
Mirkin et al. Science 2002:

## Optical Barcoded Particles



Howon Lee et al., Nature Materials, 2010

# Multiplexed Protein Detection Using Barcoded Beads



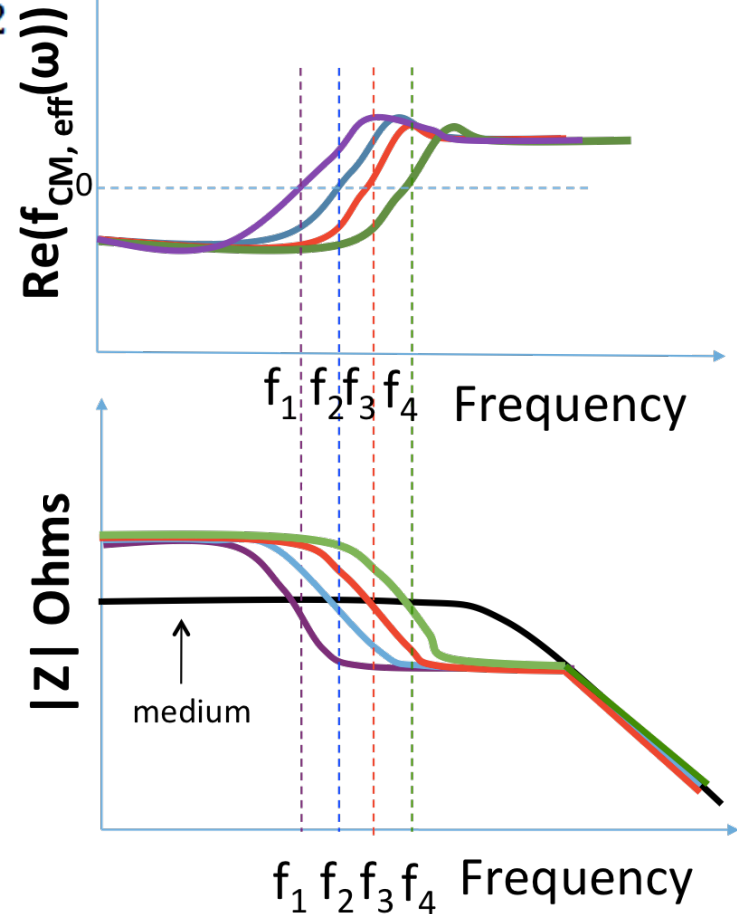
# Dielectric Particle Response to Non-Uniform Electric Field

$$F_{DEP} = 2\pi\epsilon_0\epsilon_m r^3 \text{Re}\{f_{CM}\} \nabla |E_{RMS}|^2$$

$$f_{CM} = \frac{\epsilon_p^* - \epsilon_m^*}{\epsilon_p^* + 2\epsilon_m^*}$$

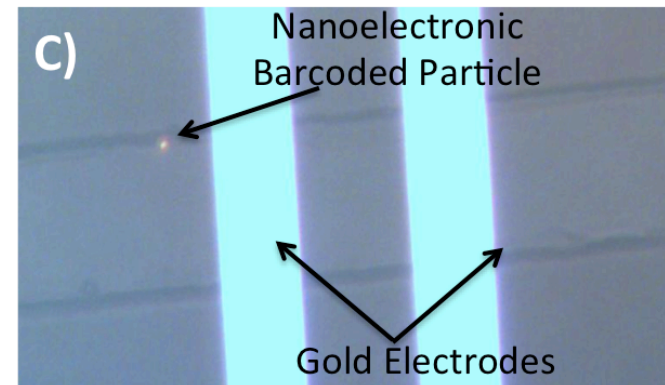
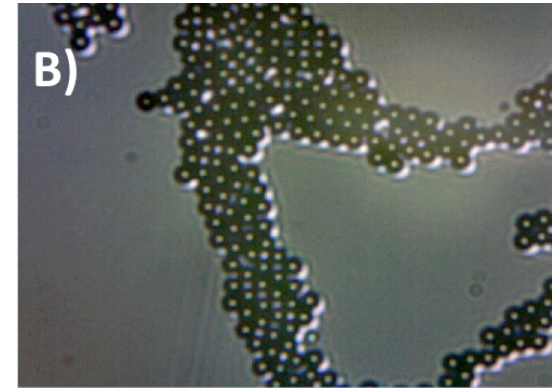
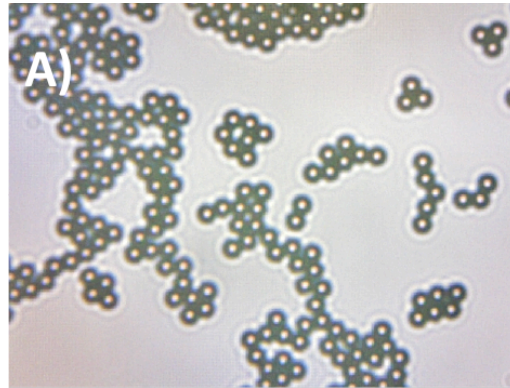
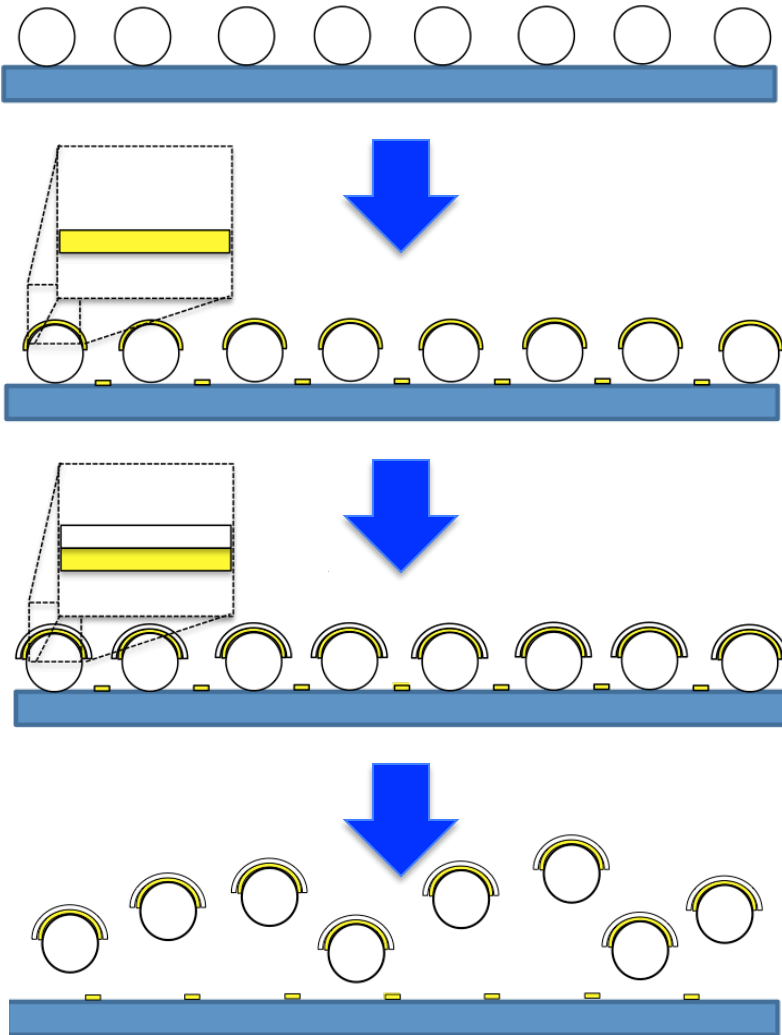
Dependent on  
Frequency/Permittivity/  
Conductivity

$$Z = \frac{\kappa}{j\omega\tilde{\epsilon}_m} (1 - 3 \cdot \phi \cdot f_{CM})$$

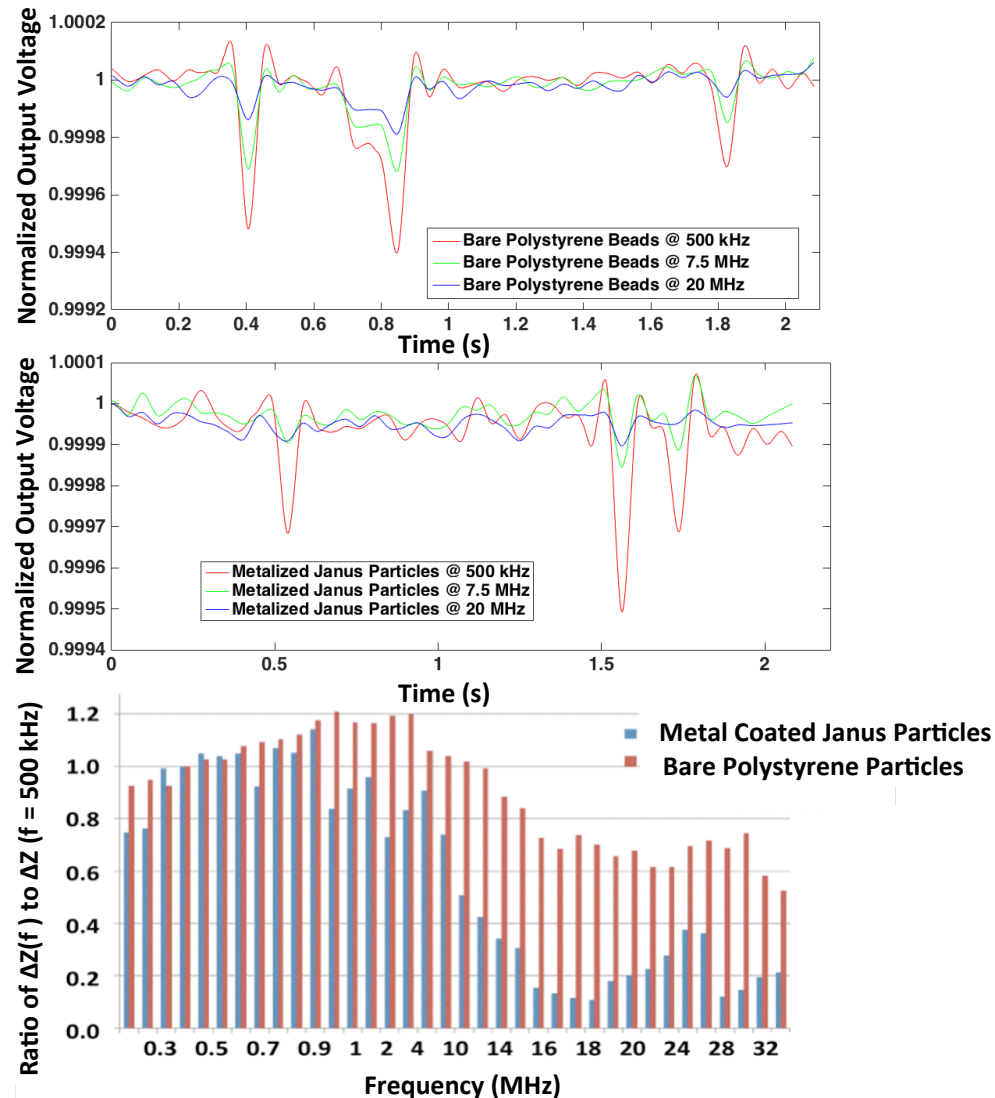




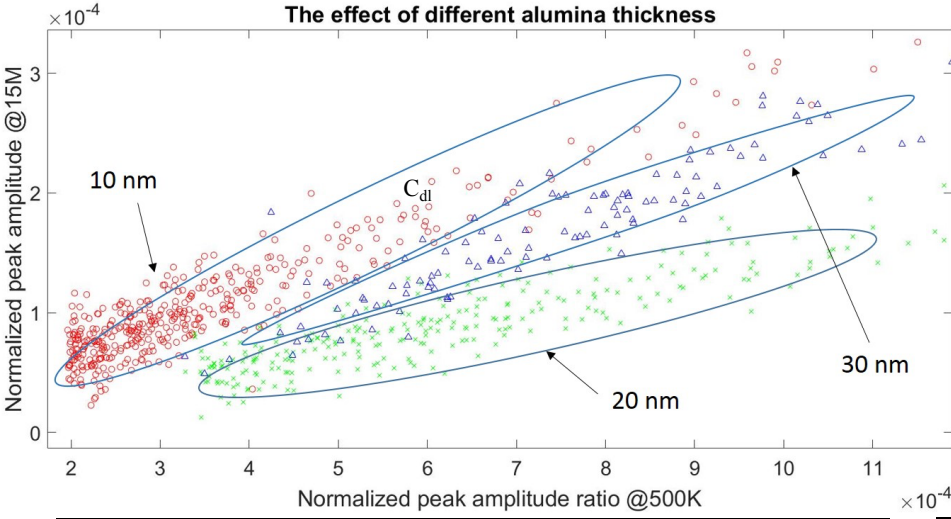
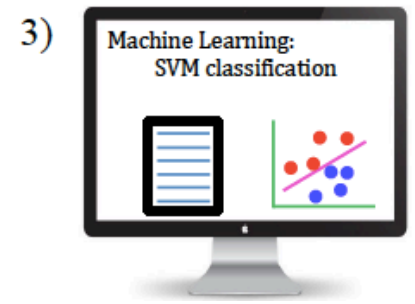
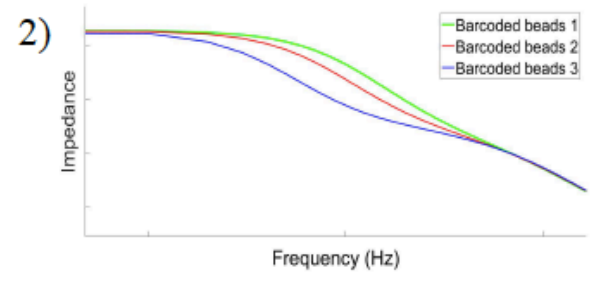
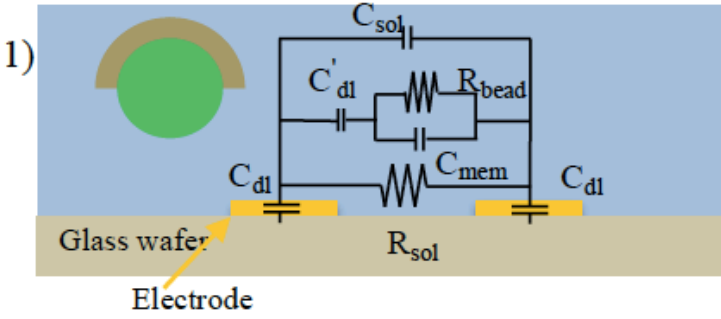
# Barcoded Particle Fabrication



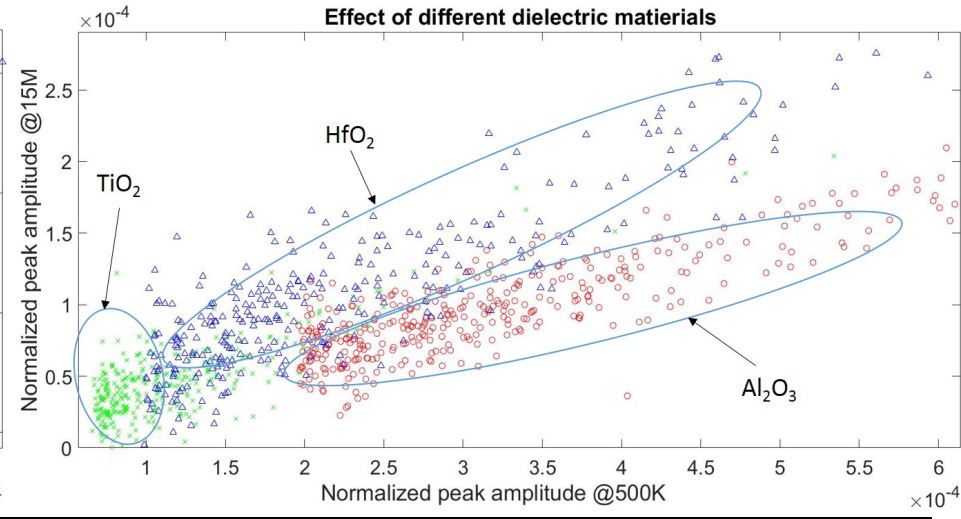
# Multi-Frequency Lock-In Amplification



# Electronic Separation of Particles



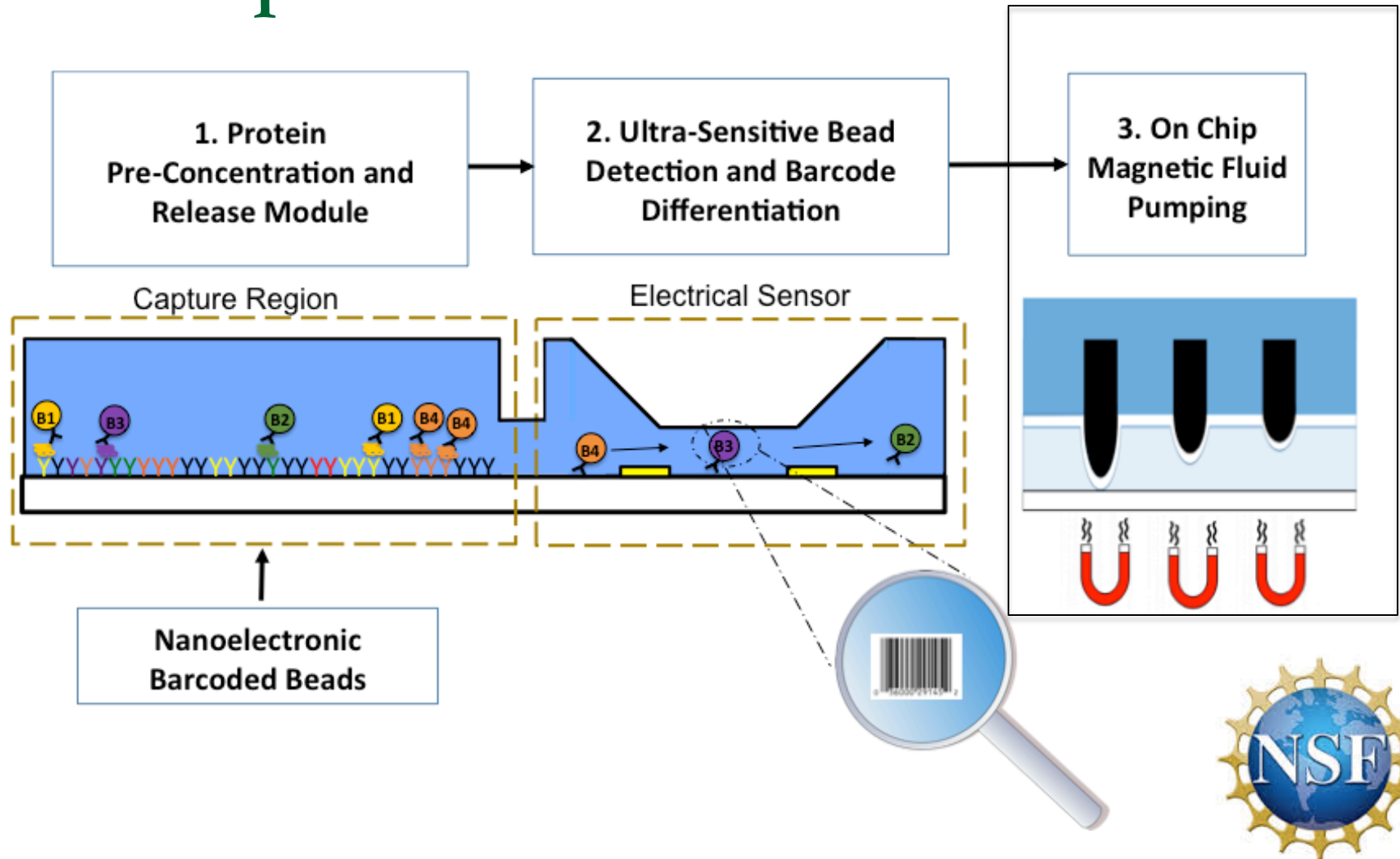
	20nm	30nm	Polystyrene
10nm	99.12%	95.44%	81.54%
20nm		98.96%	99.37%
30nm	98.96%		88.79%



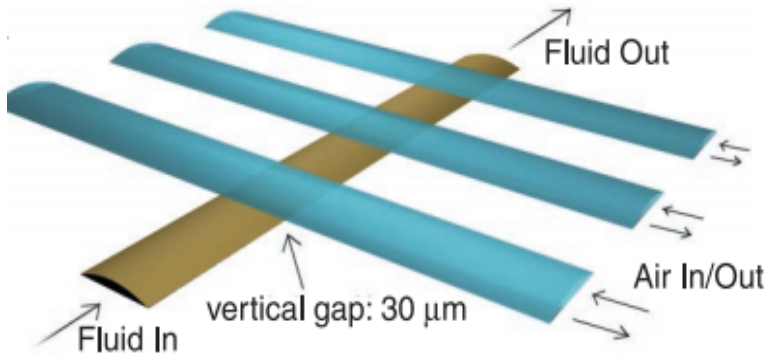
	HfO2	Al2O3	Polystyrene
TiO2	85.07%	99.05%	98.97%
HfO2		97.95%	91.72%
Al2O3	97.95%		81.54%



# On-Chip Fluid Control

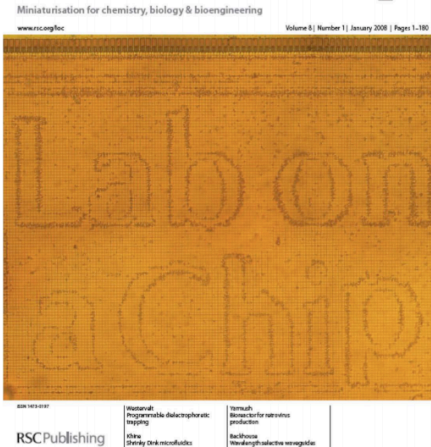


# Microfluidic Control/Valve Solutions

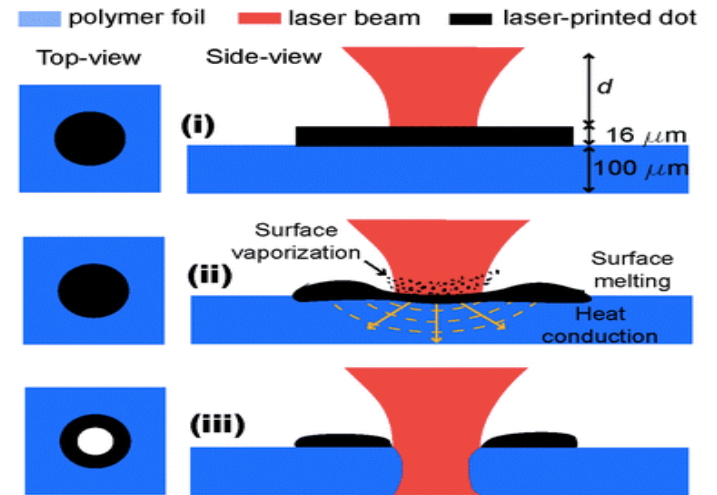


Unger et. al Science 2000

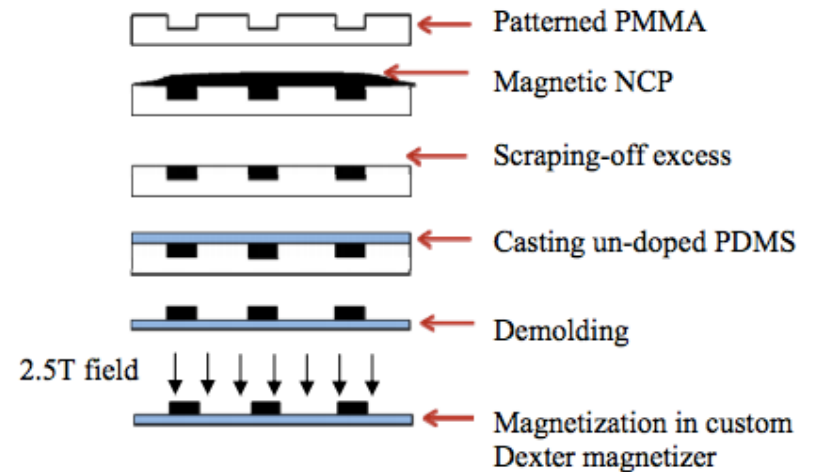
## Lab on a Chip



Westervelt et. al. Lab on Chip. 2008

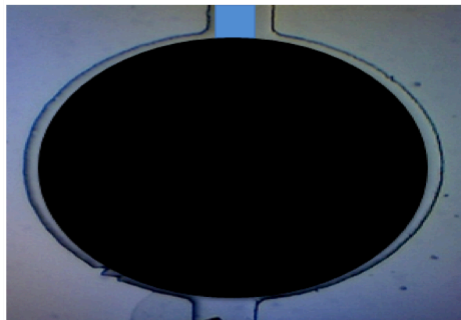
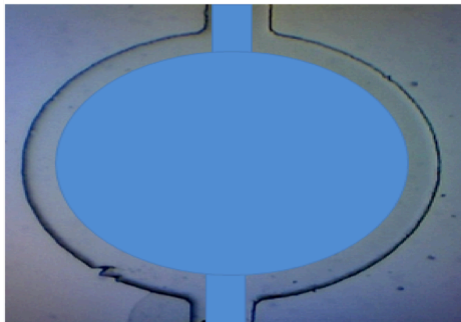
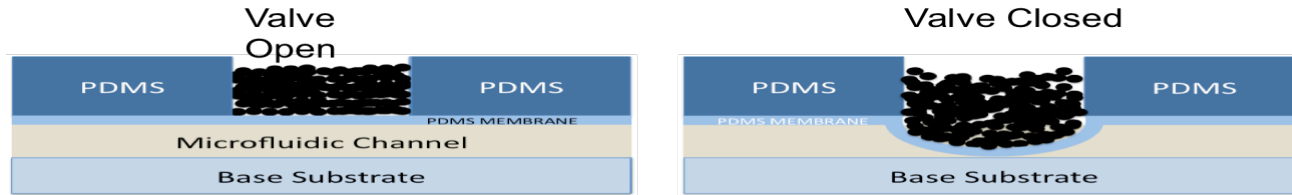


Garcia-Cordero et. al. Lab on a Chip 2010

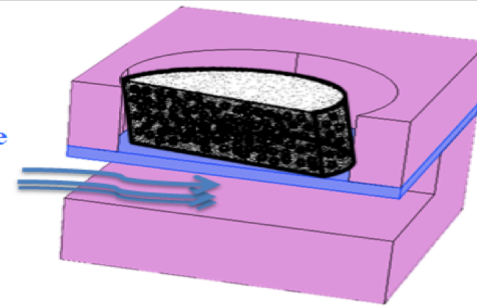


Rahbar et. al. ECST. 2012

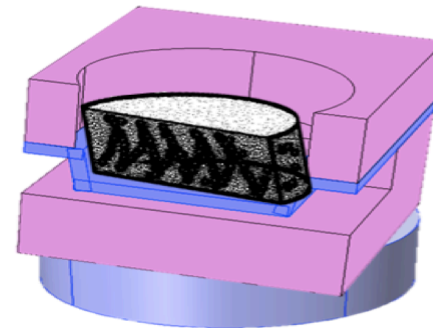
# Zero-Static Power Magnetic Actuated Fluidic Transistor



MR fluid  
Valve membrane  
Flow in channel



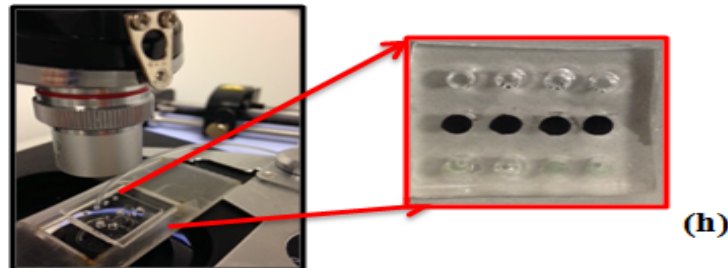
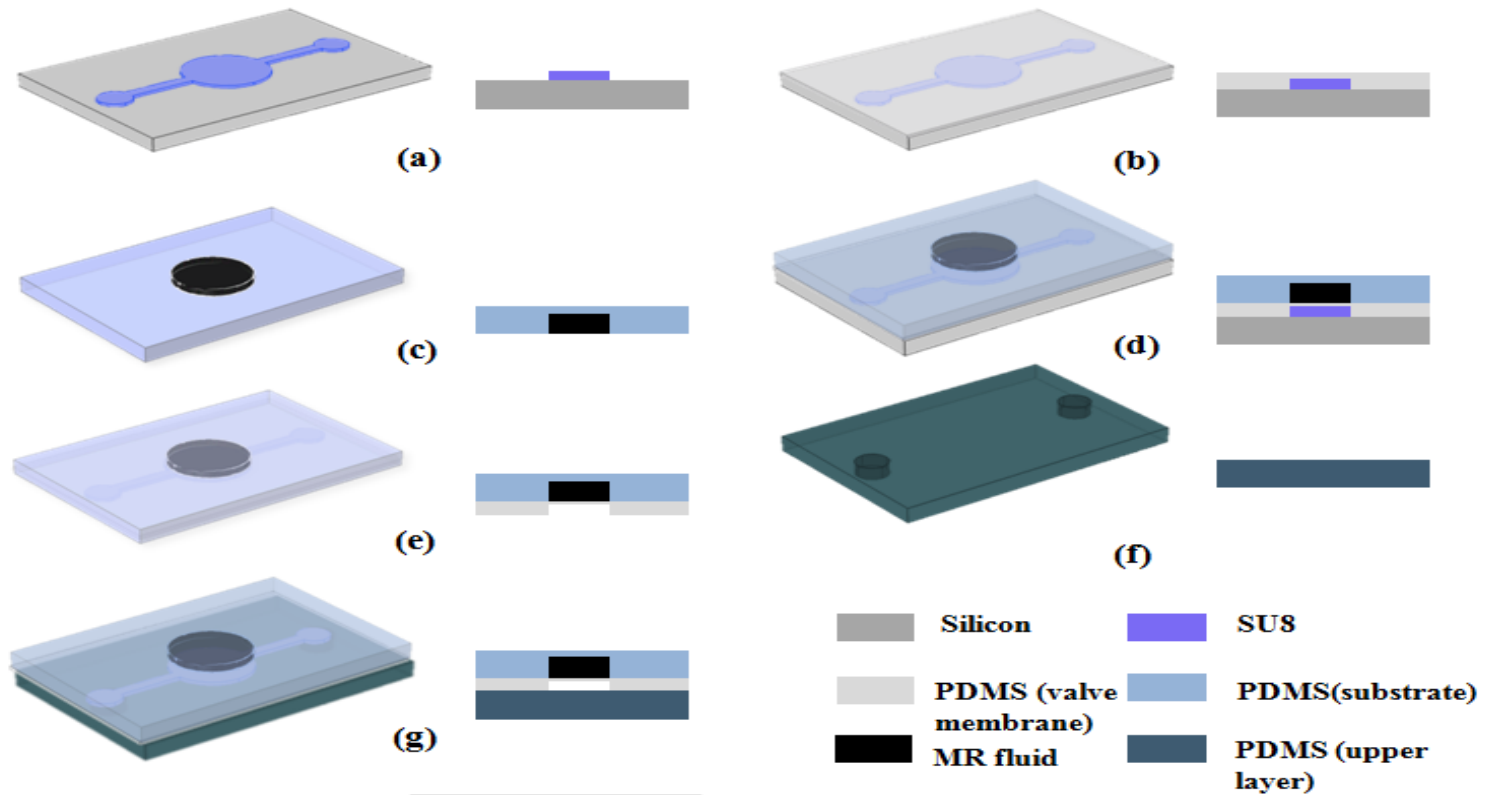
Valve off



Magnet

Valve on

# Fabrication of Magnetic Valves

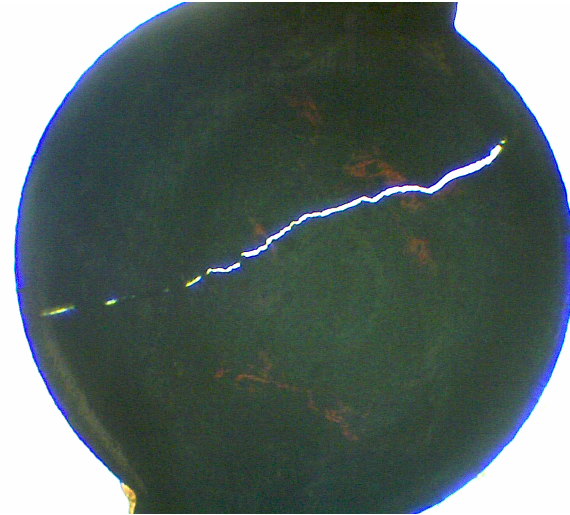


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# Microfluidic Patterning of Magnetic Layer



Square Patterned Valves

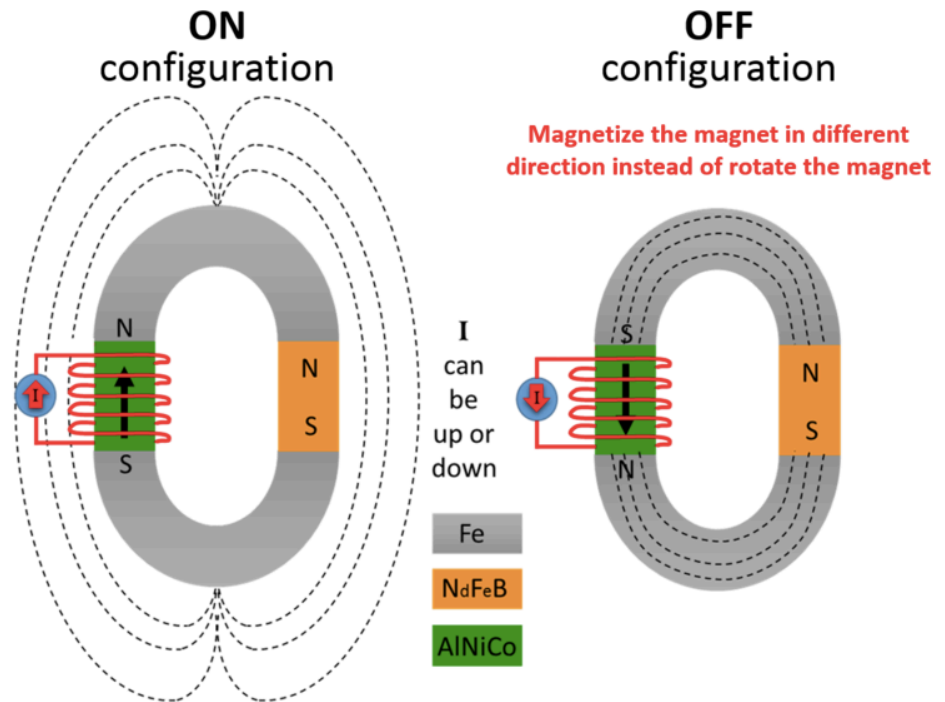


Circular Patterned Valves



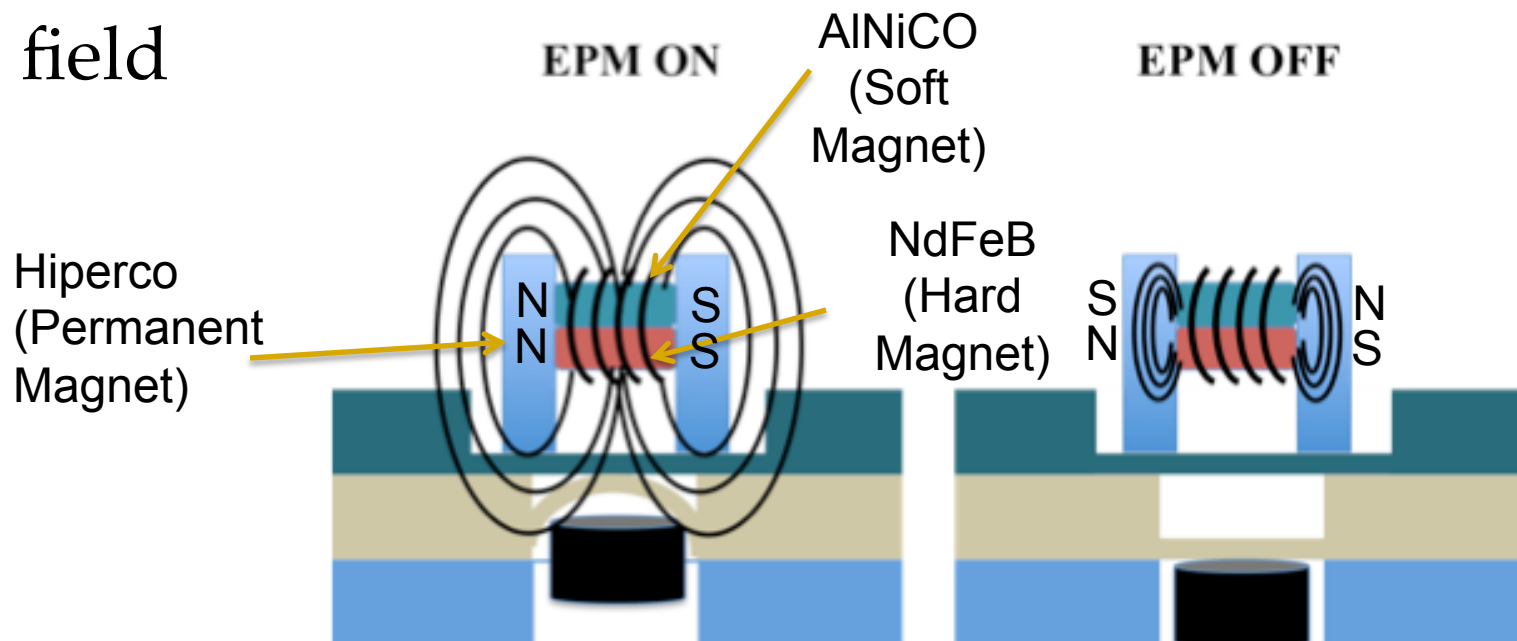
# Electropermanent Magnets

- Zero Static Power Consumption
- Electrical pulse can magnetize the soft permanent magnet in the opposite direction.
- Hard magnet (NdFeB)
- Soft magnet (AlNiCo)
- Hiperco (FeCoV)
- Electromagnetic Coil



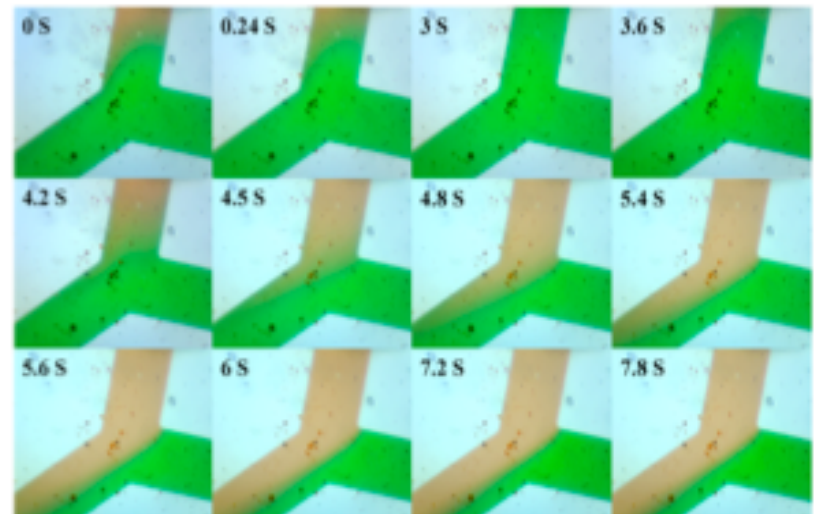
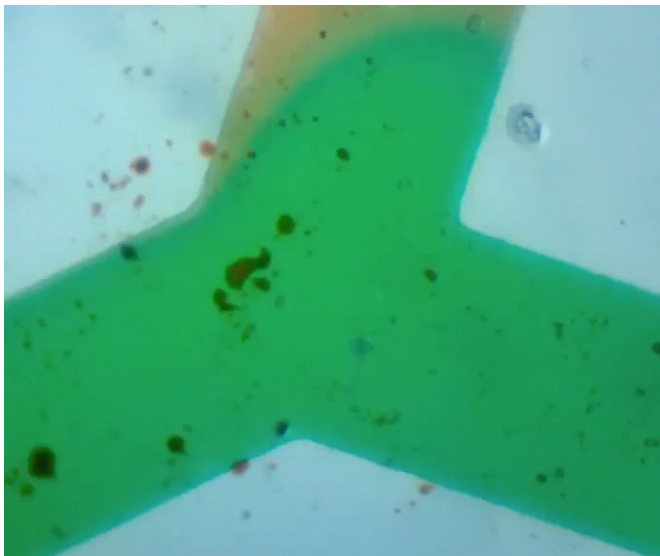
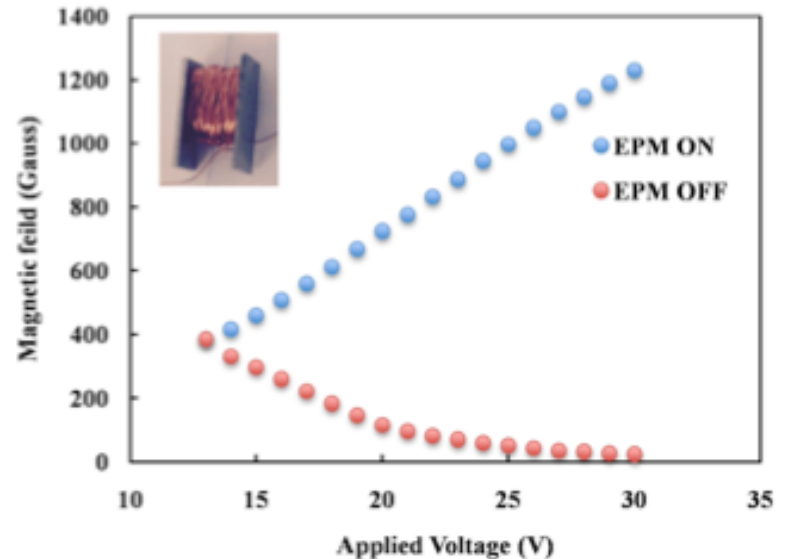
# Principle of Valve Design

- Schematic of EPM-PDMS membrane valve
- EPM in ON situation create magnetic field outside EPM and close valve
- EPM in OFF situation does not have external field



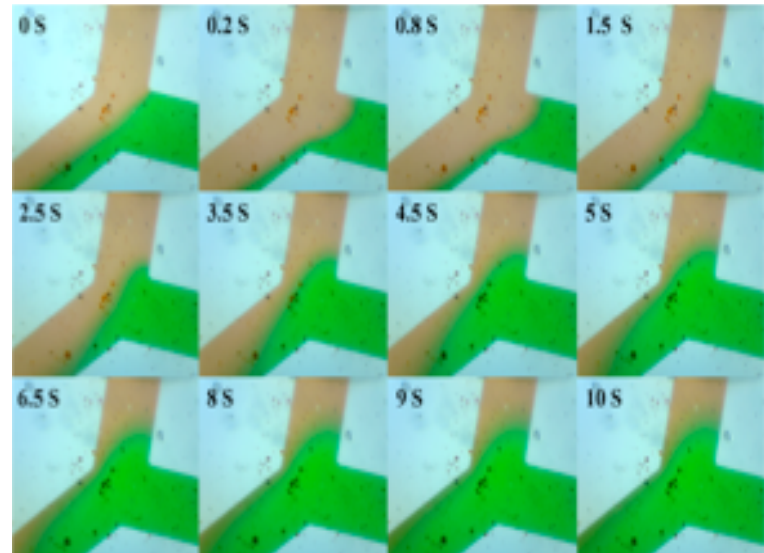
# Electronic Channel Actuation

- Hiperco poles, 120 turn coil, 30 Volts, 1.84 A current with 120  $\mu$ s applied pulse.
- Valve opens top branch at  $t = 0$ s



# Electronic Channel Actuation

- Open valve in top branch channel closes at  $t = 0$  s



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# **Technologies for Environmental Monitoring and Effects of the Environment on Physiology**

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# Asthma: Inflammation of the Airway

- Inflammation
  - Lining of airways inflamed
  - Air passage becomes sensitive to irritants and asthma triggers
- Constriction of Airways
  - Muscles around airways tighten
  - Airways become narrower
- Heterogeneous disease characterized by different disease phenotypes and involvement of multiple inflammatory pathways.

Normal bronchiole



Asthmatic bronchiole



# Asthma Diagnosis: Gold Standard

- Lung function test – Spirometry
  - Measures how much air you can breathe out
  - Limited clinical sensitivity with false positives
- Exhaled Nitric Oxide Test
  - High clinical sensitivity and specificity
  - Requires breathing for 10 minutes
  - Chemiluminescence
    - NO in breath sample reacts with ozone to form NO<sub>2</sub> in excited state. When returning to ground state it emits light.
  - Bulky
  - Not suitable for POC



<http://allergy-asthma-clinic.com/index.php/service/spirometry/>



<http://www.geinstruments.com/products-and-services/nitric-oxide-analyzer>

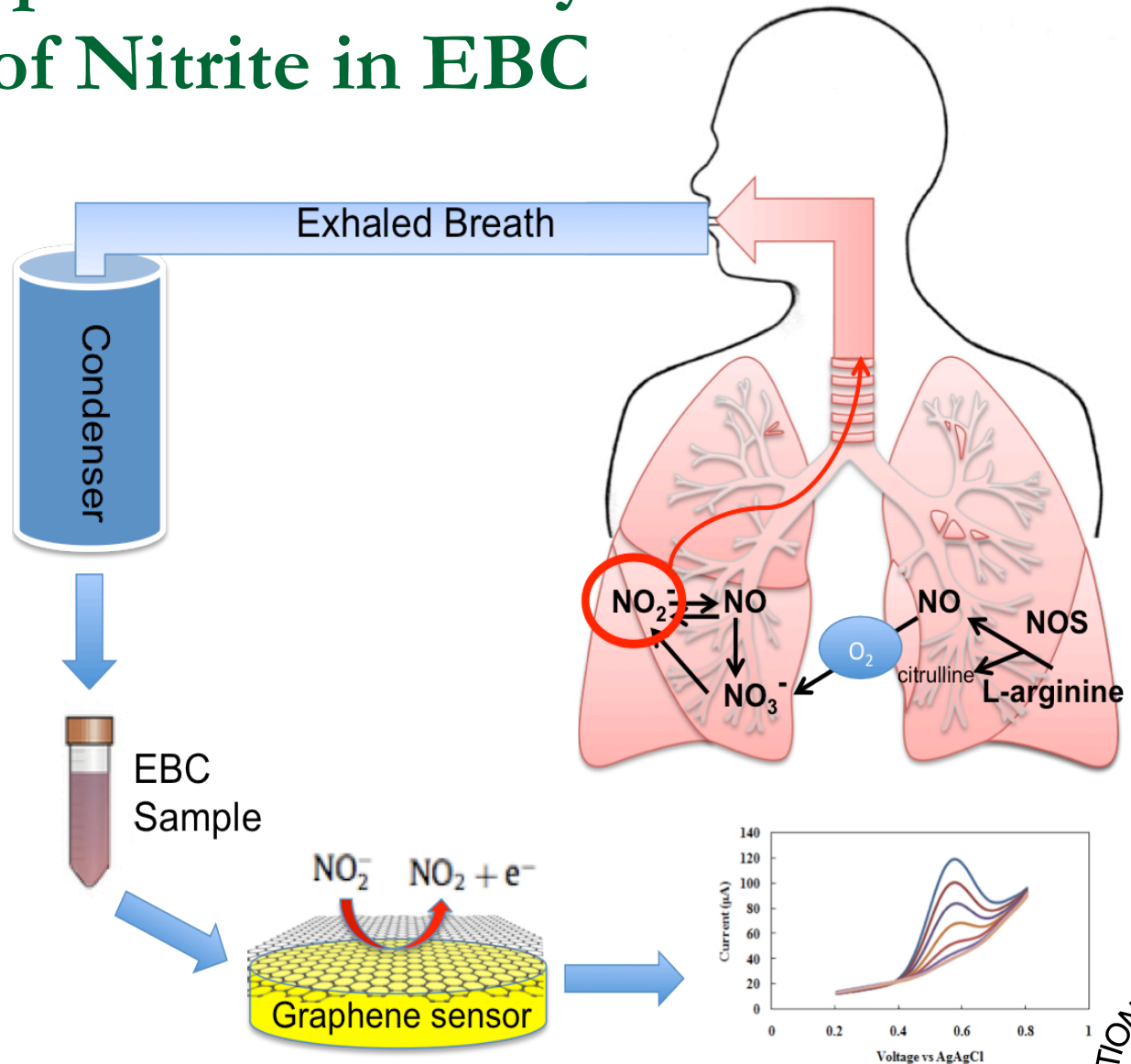
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# Motivation: Nitrite Content in Exhaled Breath Condensate

- **Objective**—Study the acute effects of diesel exhaust (DE) on asthmatics.
- The formation of reactive nitrogen and oxygen species plays a role in asthma pathogenesis.
- Nitric oxide (NO) and its metabolites in exhaled breath condensate (EBC) may be markers of oxidative/nitrosative stress, in addition to inflammation.
- After exposure to Diesel Exhausts, subjects with asthma demonstrated increased airway hyperreactivity and obstruction.
- Increased nitrite in EBC, in the absence of increased exhaled NO.



# Direct Sample to Answer System for Detection of Nitrite in EBC

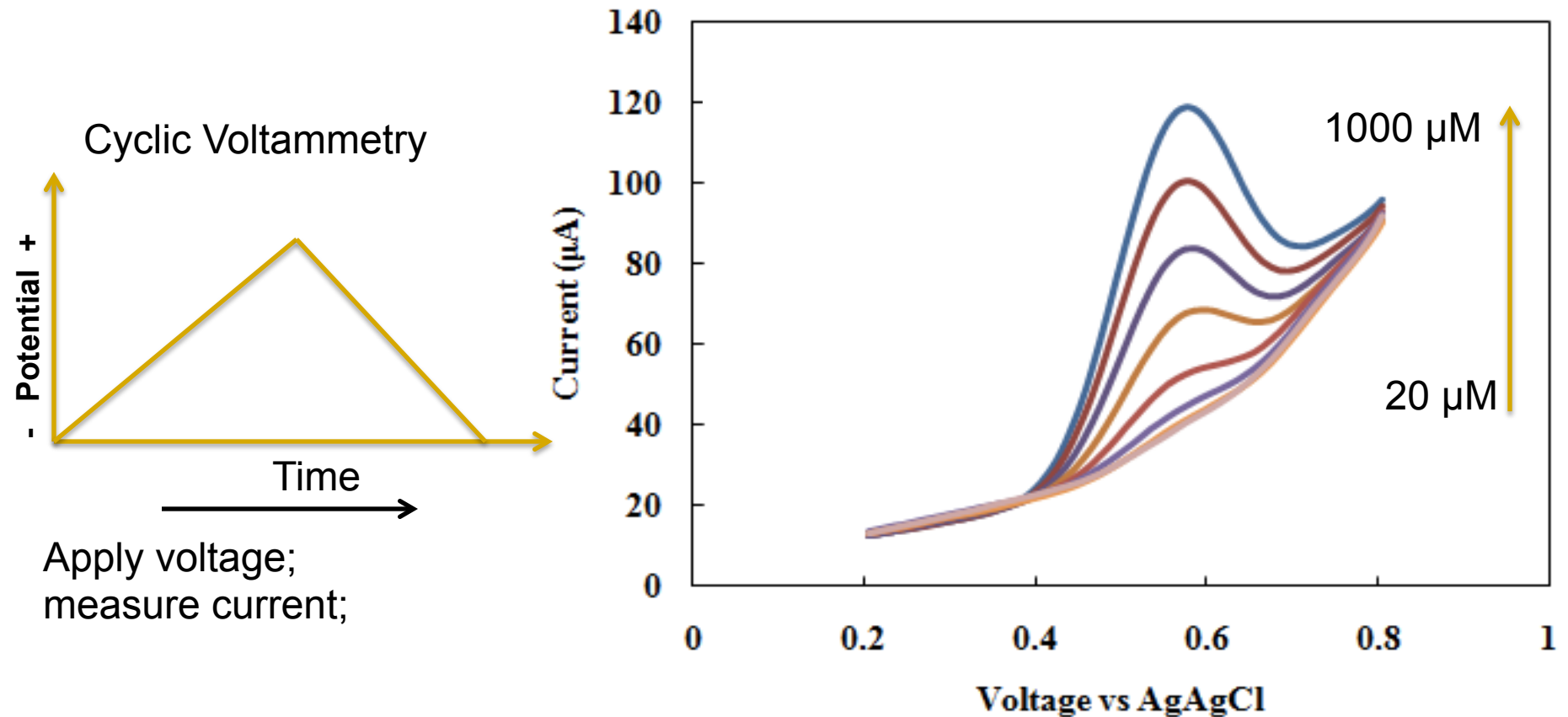


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# Reduced Graphene Oxide as a Sensing Material

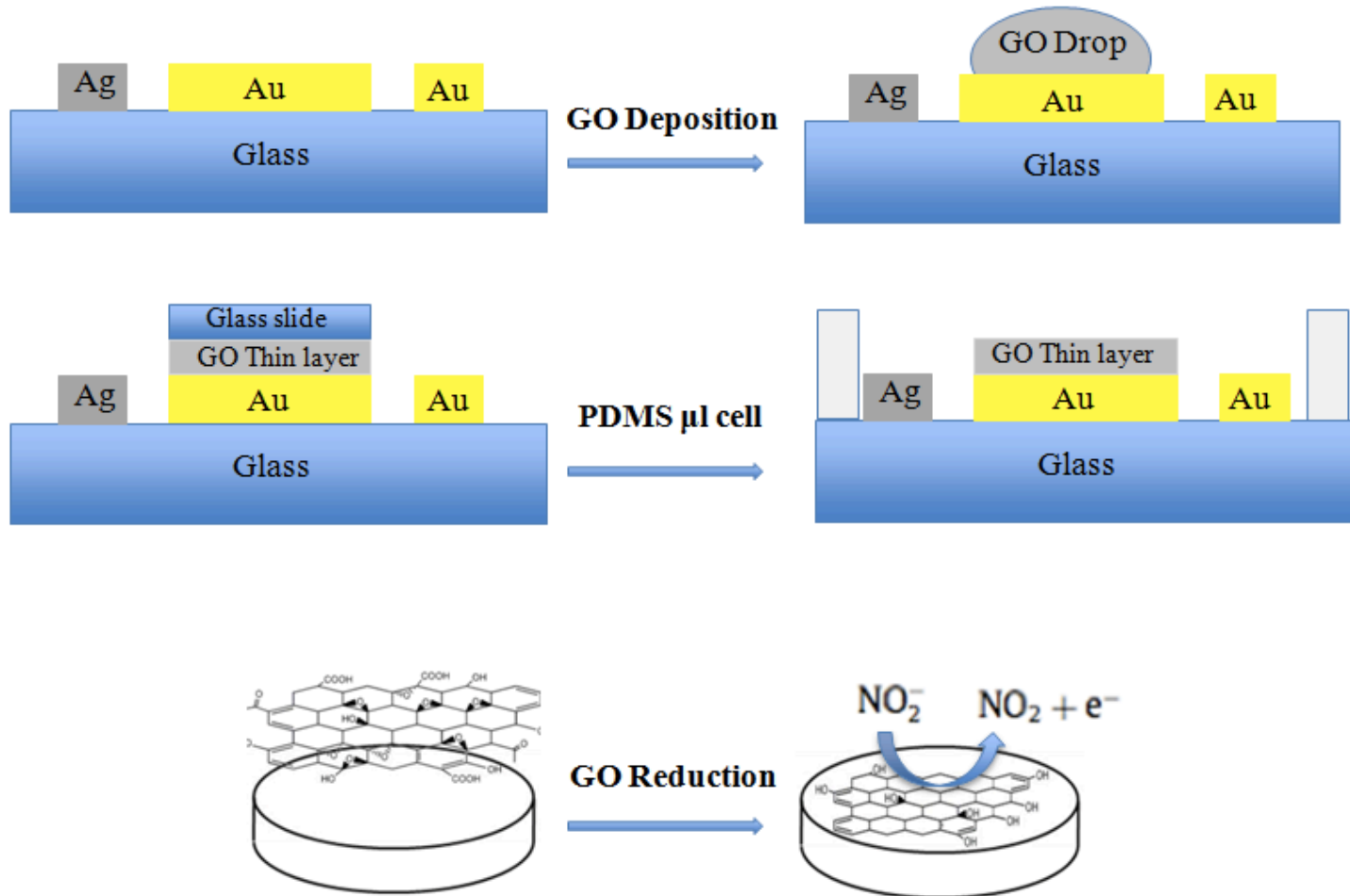
- Enhanced Sensitivity over traditional electrochemical sensing
  - Rapid Electron Transfer from electrode to electrolyte
  - Passive and anti-corrosive material
- Advantageous for sensing Nitrite in EBC
  - Results in a very specific Redox peak at 0.7 V.
  - Nitrite is the only molecule in EBC that results in redox peak at 0.7 V.
  - EBC has significantly large amount of Nitrate content, however Redox peak is at significantly higher voltage.
  - Completely label-free and probe-free: No need for any surface enzyme

# Measurement of Nitrite in Buffer

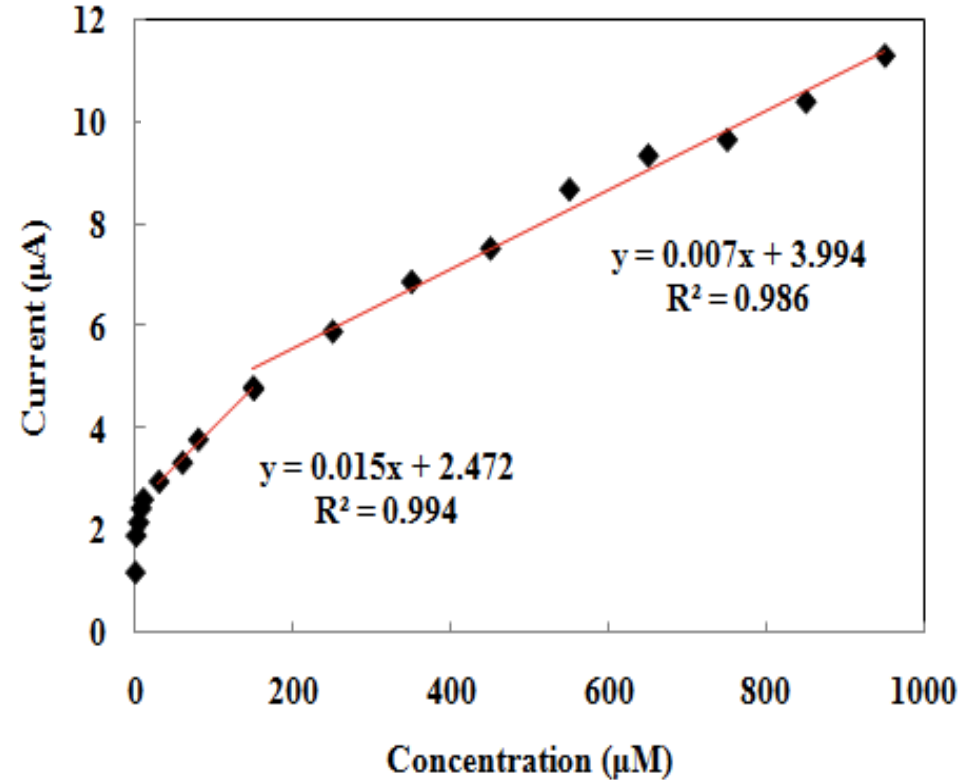
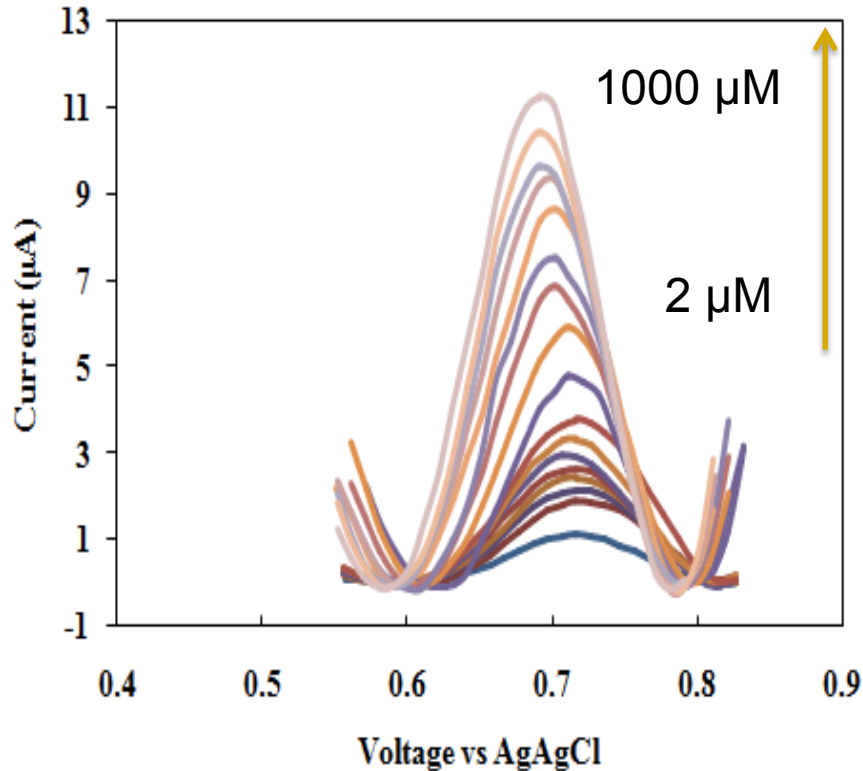


- Square wave voltammetry of different concentrations of nitrite.

# Reduced Graphene Oxide Electrode Fabrication



# Nitrite Spiked EBC Samples

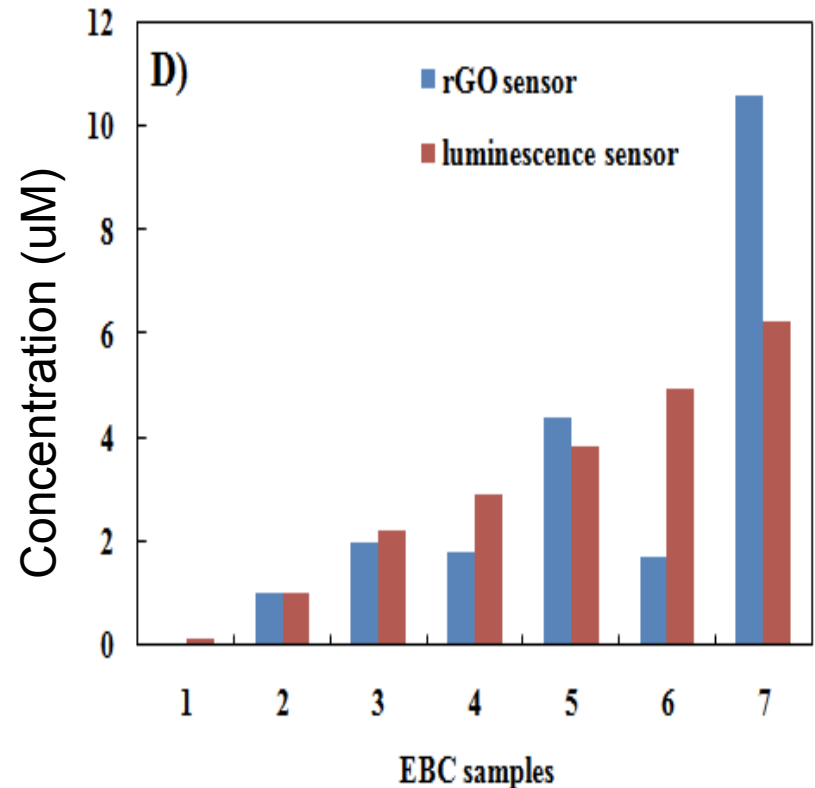
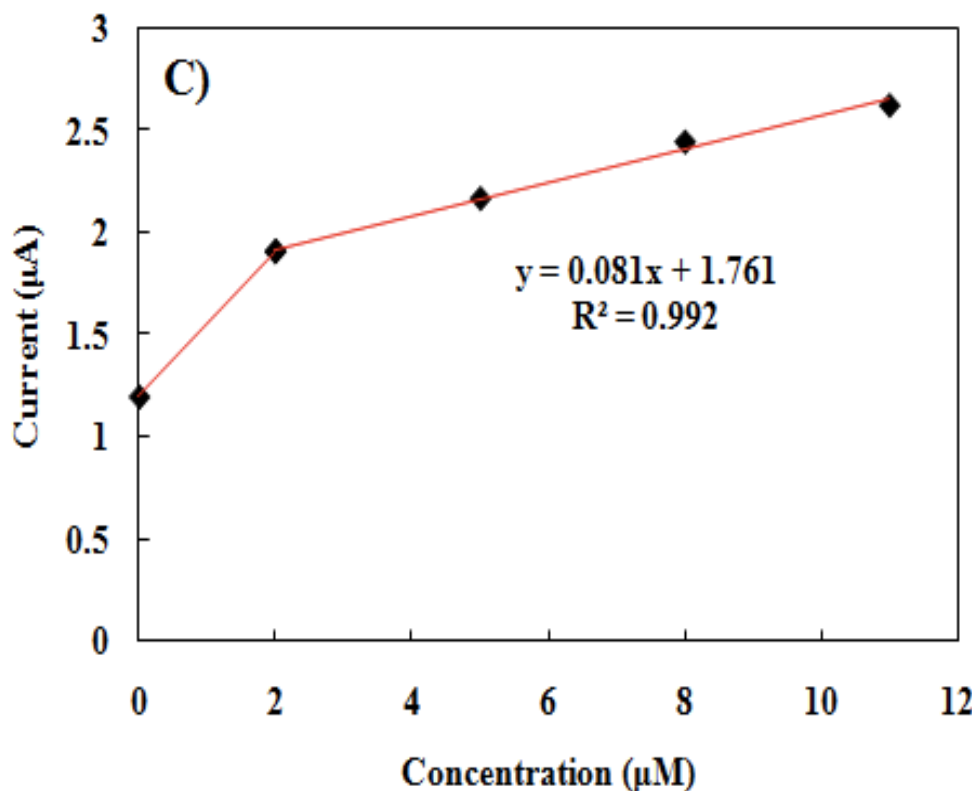


Square wave voltammetry of spiked samples in concentration range of in EBC.

Calibration curve with their slope.

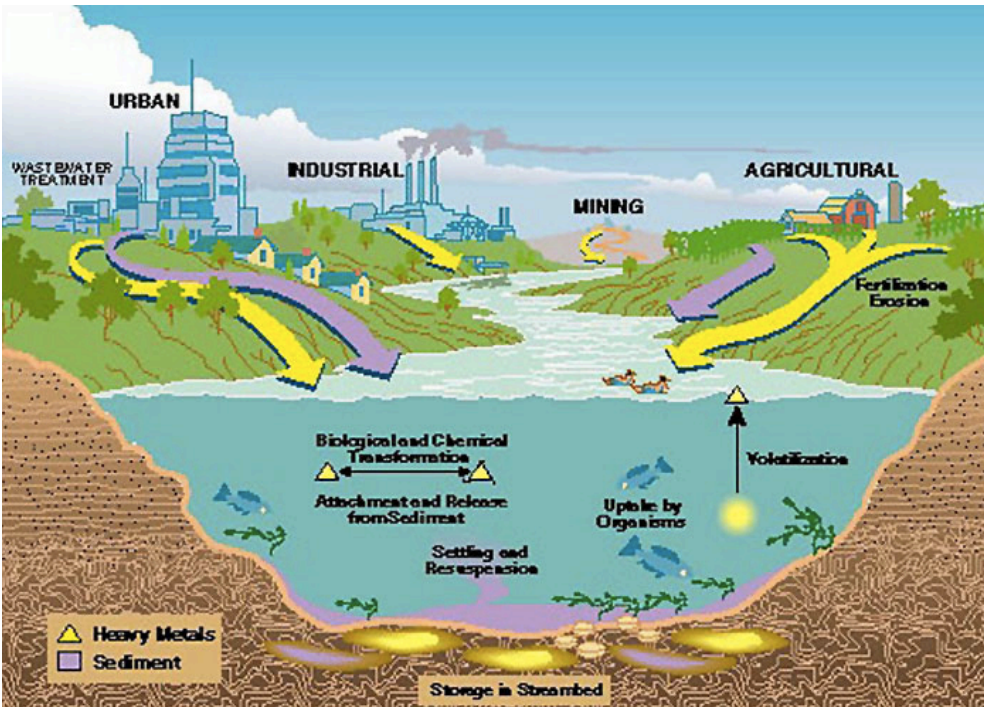
# Nitrite Measurements with Patient EBC

- Subjects were asthmatics exposed to 2 hours of driving on the New Jersey Turnpike (exposure to diesel exhaust).
- Comparison between predicted concentration and gold-standard chemiluminescence data.



# Mapping Freshwater Sediment for Toxic Compounds

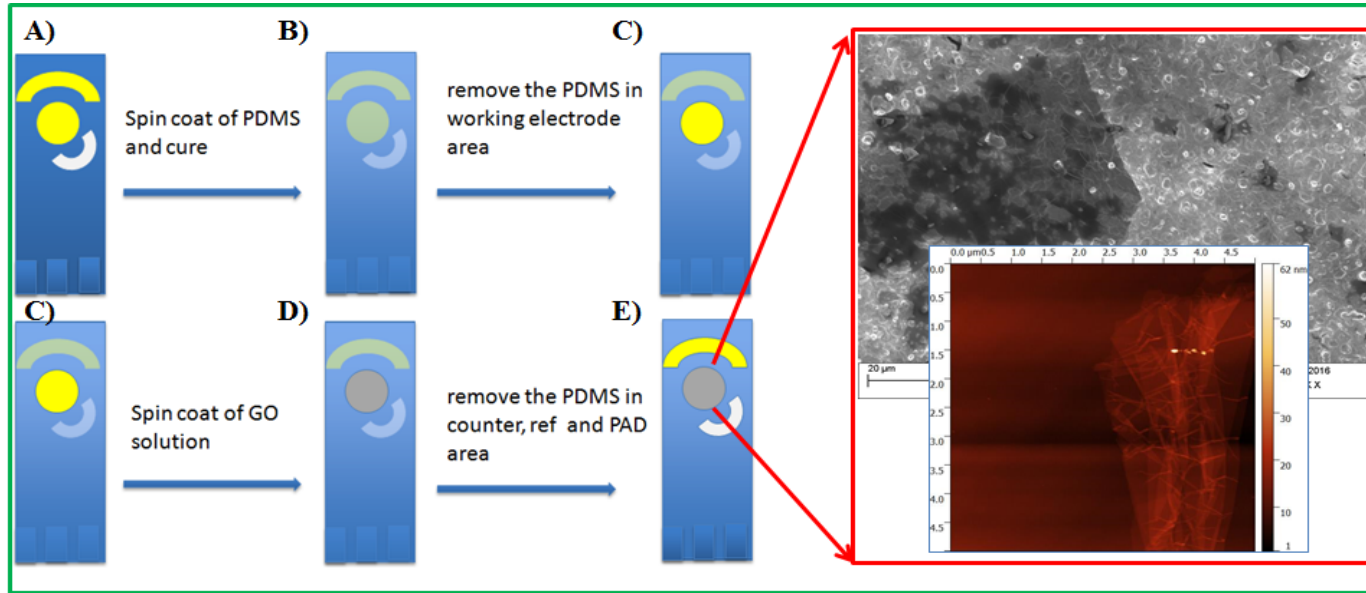
- “Persistent high concentrations of contaminants in the bottom sediments of rivers and harbors have raised considerable concern about potential risks to aquatic organisms, wildlife, and humans.” (US EPA)



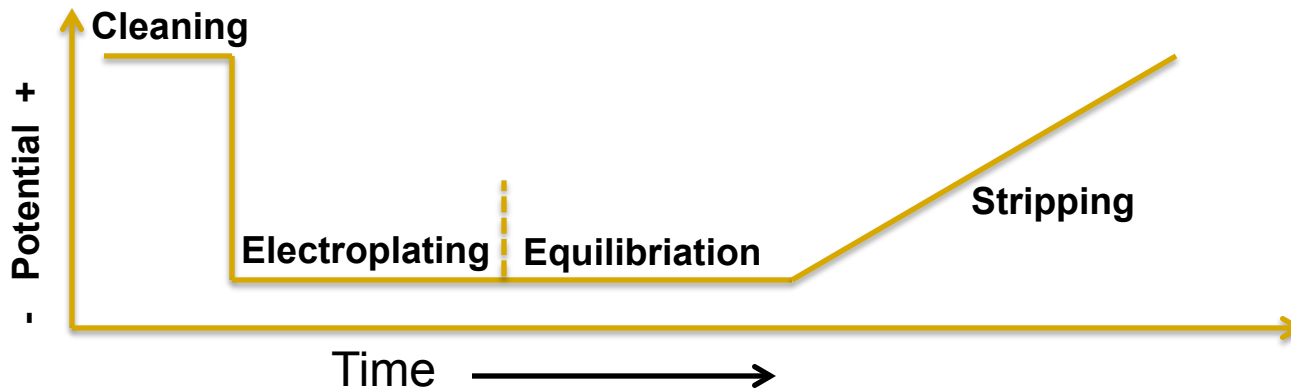
<sup>1</sup><https://www.epa.gov/greatlakes/contaminated-sediment>

<https://www.pinterest.com/ervingar/water-resource-lesson-plans/>

# Reduced Graphene Oxide for Lead Detection



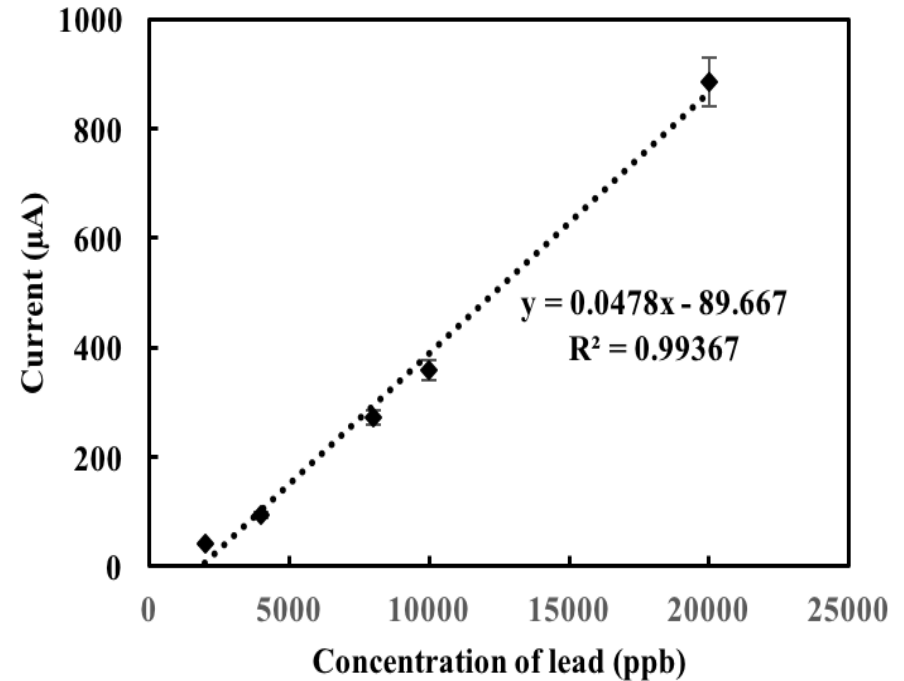
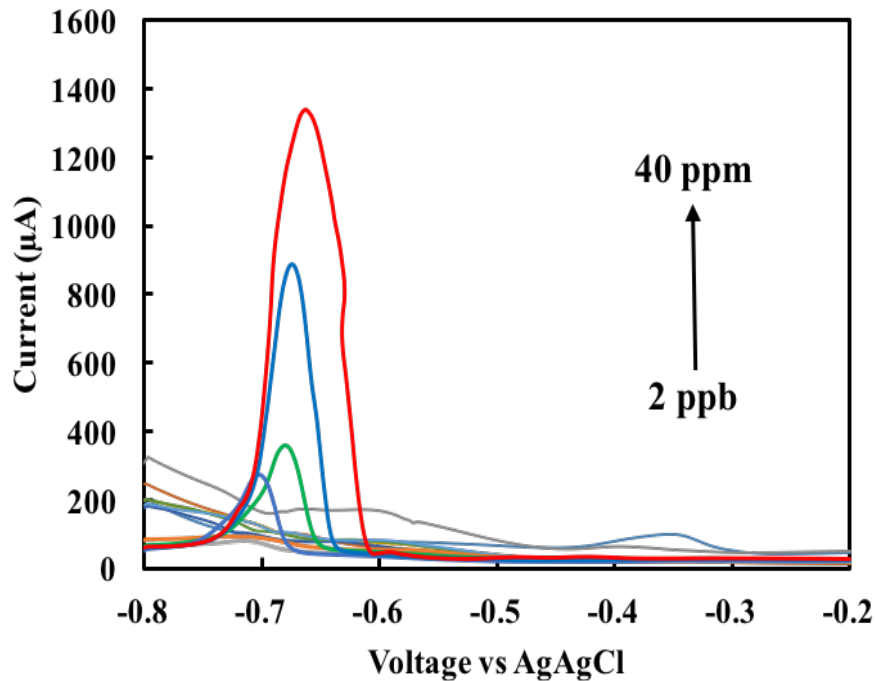
## ■ Anodic Stripping Voltammetry





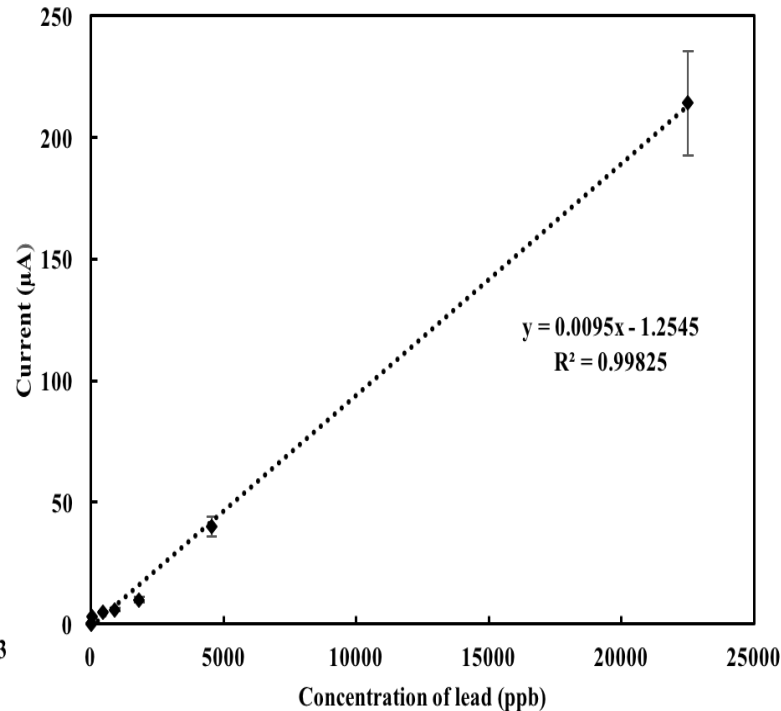
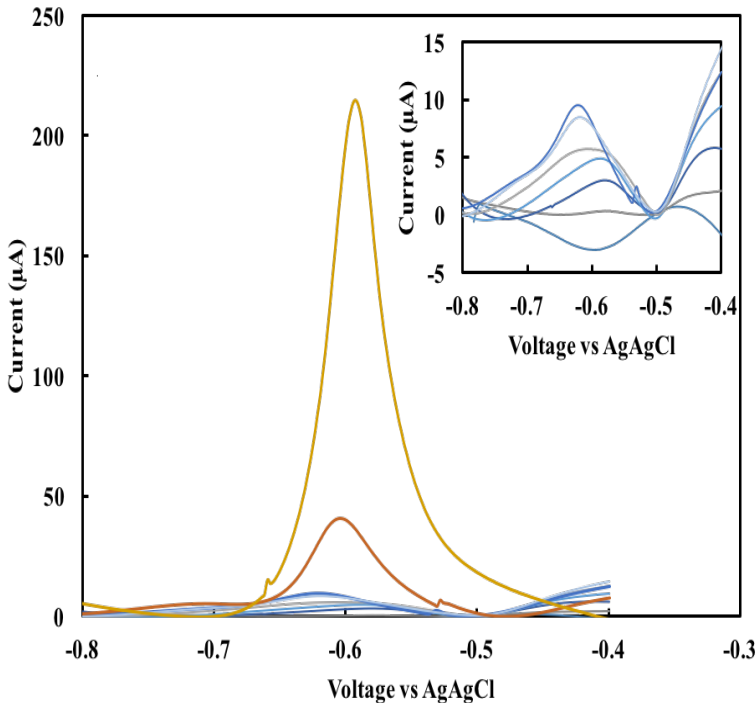
# Stripping Voltammetry Titration

- Detection limit of 2 parts per billion in buffer

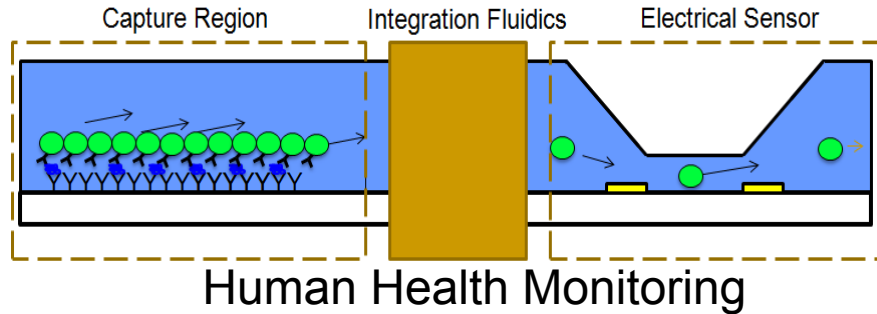


# Lead Detection in Field Samples

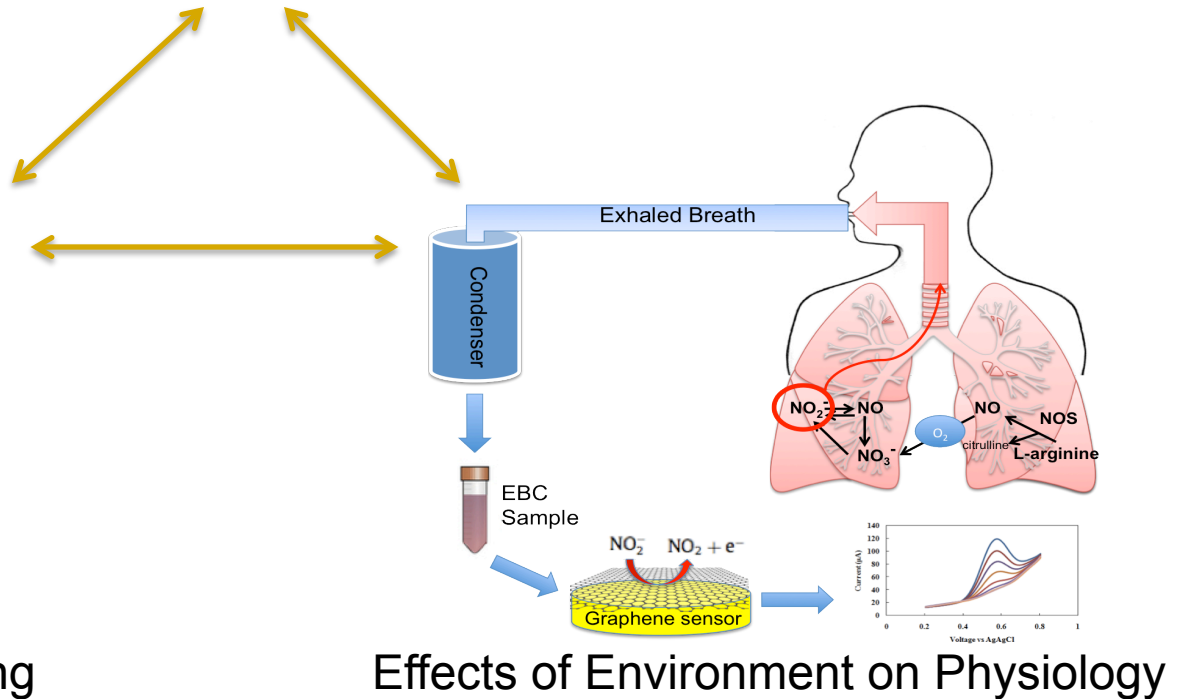
- Test in complex matrix.
- Samples obtained from the Arthur Kill
- Detection limit of 2 ppb demonstrated in sediment leachate.



# Conclusion



Environmental Monitoring



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