Integrative Computational Modeling

for Developing Means to Manipulate Biological Particulates and for Solving Complex Problems

Yu Zhao and Guigen Zhang

F. Joseph Halcomb III, M.D. Department of Biomedical Engineering

University of Kentucky

Overview

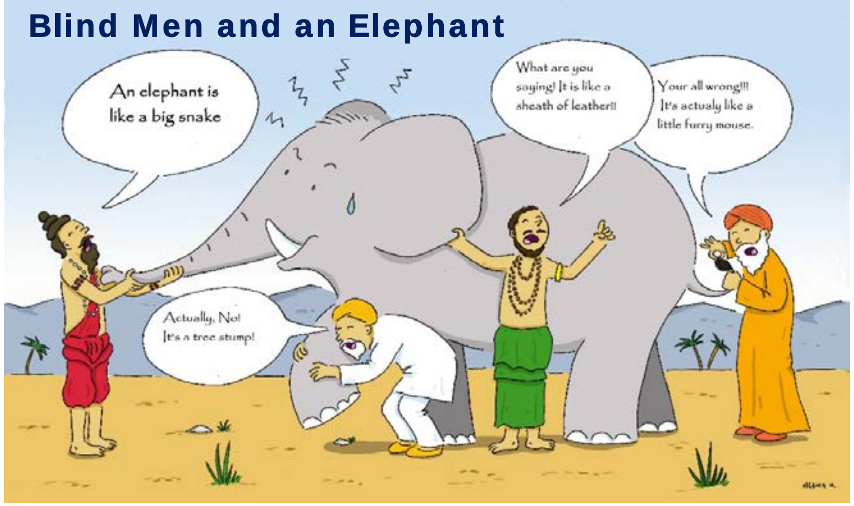
- A brief discussion on reductive vs integrative investigation

- A case study: how integrative computational modeling helps advance the understanding and application of dielectrophoresis (DEP) in various situations

- Other applications in advancing the design and development of nanopore, medical devices, novel materials, actuation devices, and coupled spectroscopic techniques, etc.

Reductive Investigation

- Reductive Engineering: reducing complex issues to small independent pieces by neglecting/discarding factors we don't know about for simplicity and clarity



DNA is:

AN INSULATOR

Dunlap et al. ***PNAS*** *90, 7652, 1993*

A CONDUCTOR

Fink and Schoenberger, ***Nature*** *398, 407, 1999*

A SEMICONDUCTOR

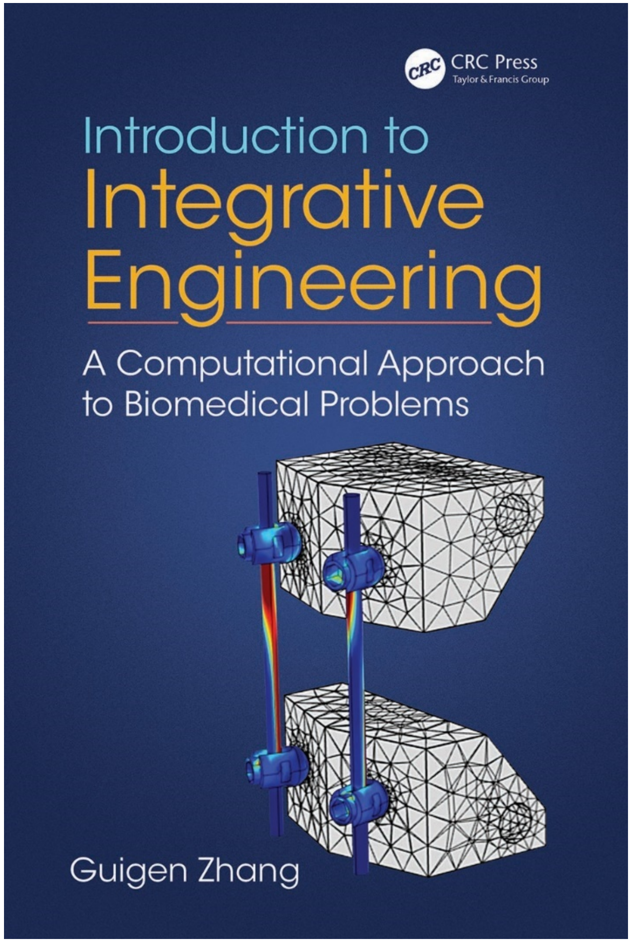
Porath et al, ***Nature*** *403, 635, 2000*

A SUPERCONDUCTOR

Kasumov et al. ***Science*** *291, 280, 2001*

- While we have been laughing at it since childhood, we are still victims of this 'Blind Men' exploratory approach in our scientific endeavors.

Integrative Investigation

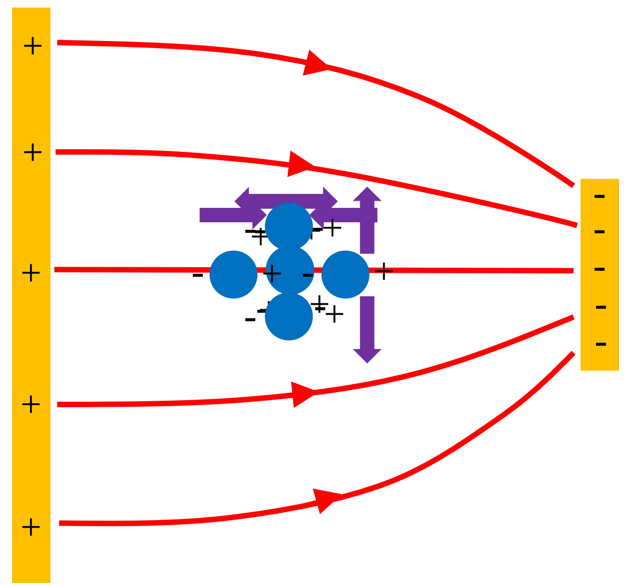


Zen Master D. Suzuki (1870 -1966):
The Zen's way of knowing a flower should not be analytically reductive, in which one would pluck the flower, bring it to a laboratory, and dissect it, because once the flower is plucked it is no longer the flower one intends to know. … Instead, one is to leave it where it is, let it be in its living state and environment, and *contemplate* it.

An integrative way uses non-reductive, yet analytical and investigative means to interact with the world based on computational modeling supported by experimental validation and realization.

Advancing dielectrophoresis (DEP) and expanding its application

- What is Dielectrophoresis (DEP)

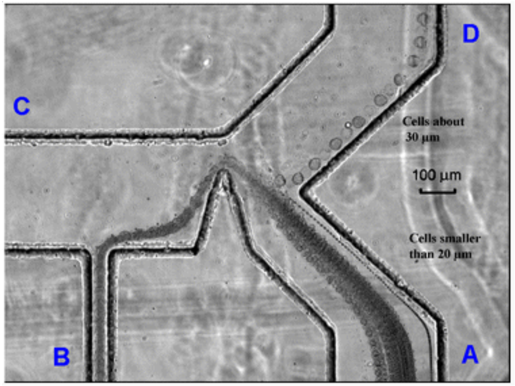


Move particles with no restrictions on particle property → Cell separation; Cell capture

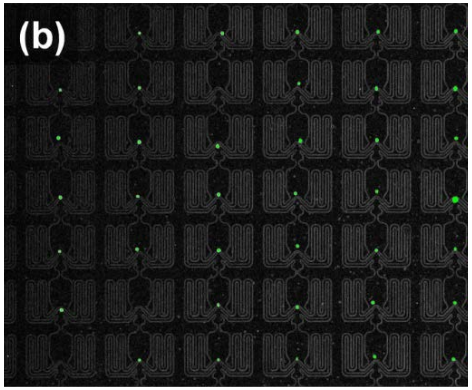
Orientation dependent interaction → Tissue engineering; Biofabrication

Useful DEP applications

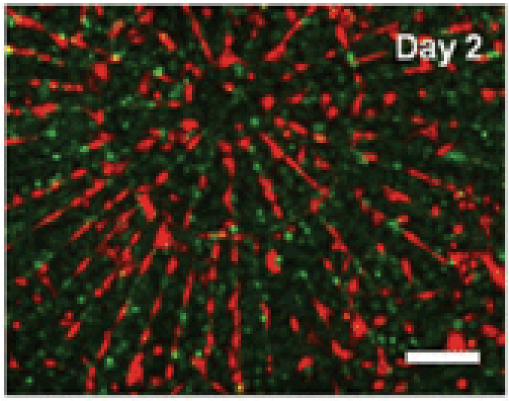
Separation of cells based on size difference



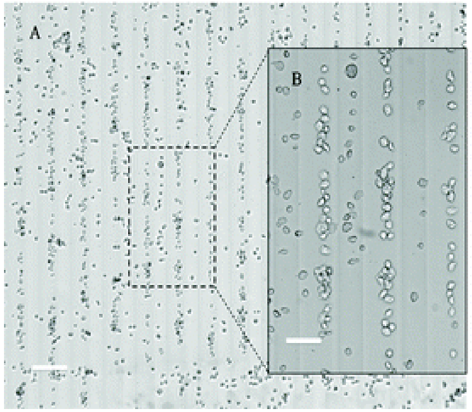
Single cell capture with specifically designed microwells



Liver organ on chip



Pattern cells in 3D hydrogel



Analytical basis for DEP

Without computational modeling, understanding of DEP phenomena heavily relies upon the analytical method

Point dipole method

Laplace Equation → Dipole Moment → DEP Force

$$\Delta\psi = 0 \qquad \vec{m} = 4\pi a^3 \varepsilon_m \frac{\varepsilon_p^* - \varepsilon_m^*}{\varepsilon_p^* + 2\varepsilon_m^*} \vec{E} \qquad \vec{F} = 2\pi a^3 \varepsilon_m \frac{\varepsilon_p^* - \varepsilon_m^*}{\varepsilon_p^* + 2\varepsilon_m^*} \nabla E_{rms}^2$$

Advantages:

1. It is convenient to be used to determine the magnitude and direction of DEP force
2. It can be easily implemented to study the movement of a single particle

Limitations:

1. The estimated DEP force is not accurate when the field is highly non-uniform
2. Particle-particle interaction and non-homogeneity of particle are not considered

Validity of other numerical methods

Maxwell Stress Tensor (MST) method

Lorentz Force law → Volume Integration → Intermediate DEP force → Divergence Theorem → DEP force

$$\vec{f} = \rho\vec{E} + \vec{J}\times\vec{B}$$

$$\vec{F} = \iiint_V \varepsilon_p \left(\left(\nabla\cdot\vec{E}\right)\vec{E} + (\vec{E}\cdot\nabla)\vec{E} - \frac{1}{2}\nabla E^2\right) dV$$

$$\vec{F} = \oiint \frac{1}{4}\varepsilon_m \left[\left(\vec{E}\vec{E}^* + \vec{E}^*\vec{E}\right) - |E|^2\,\overleftrightarrow{U}\right]\cdot\vec{n}\,dA$$

The MST method has been treated as providing the most robust and accurate solution to DEP force

Some concerns are raised about the validity of MST method, including:

- Misconception of essence of force
- Misuse of torque expression
- Validity for non-homogeneous particle

Developing and implementing a new DEP theory

A new volumetric polarization and integration method is developed to overcome deficiencies of MST method and elucidate underlying mechanism of complicated DEP phenomena

Induced electric field → Polarization → Force density, Torque density, Energy density

$$\vec{E}_{particle} - \vec{E} = -\frac{1}{4\pi\varepsilon_m}\frac{Q\vec{d}}{(d/2)^3}$$

$$\vec{P} = 3\varepsilon_m\left(\vec{E} - \vec{E}_{particle}\right)$$

$$\vec{f} = (3\varepsilon_m(\vec{E} - \vec{E}_{particle}) \cdot \nabla)\vec{E}$$

$$\vec{t} = 3\varepsilon_m(\vec{E} - \vec{E}_{particle}) \times \vec{E}$$

$$w = 3\varepsilon_m(\vec{E}_{particle} - \vec{E}) \cdot \vec{E}$$

Volume Integration → Force, Torque, Energy

$$\vec{F} = \oiiint \left(3\varepsilon_m(\vec{E} - \vec{E}_{particle}) \cdot \nabla\right)\vec{E}\,dV$$

$$\vec{T} = \oiiint 3\varepsilon_m(\vec{E} - \vec{E}_{particle}) \times \vec{E}\,dV$$

$$W = \oiiint 3\varepsilon_m(\vec{E}_{particle} - \vec{E}) \cdot \vec{E}\,dV$$

Some comparisons

Both the volumetric polarization and integration method and MST method are used to calculate DEP force on non-homogeneous particle

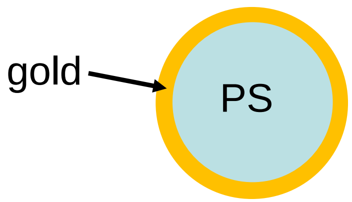


TABLE II. DEP force on gold coated particles.

	10^4 Hz	$10^{4.5}$ Hz	10^5 Hz
Volumetric-integration method (nN)	80.04	80.04	80.04
MST method (nN)	-4.24×10^4	-4.24×10^4	-4.23×10^4

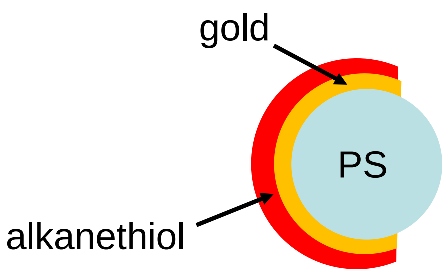


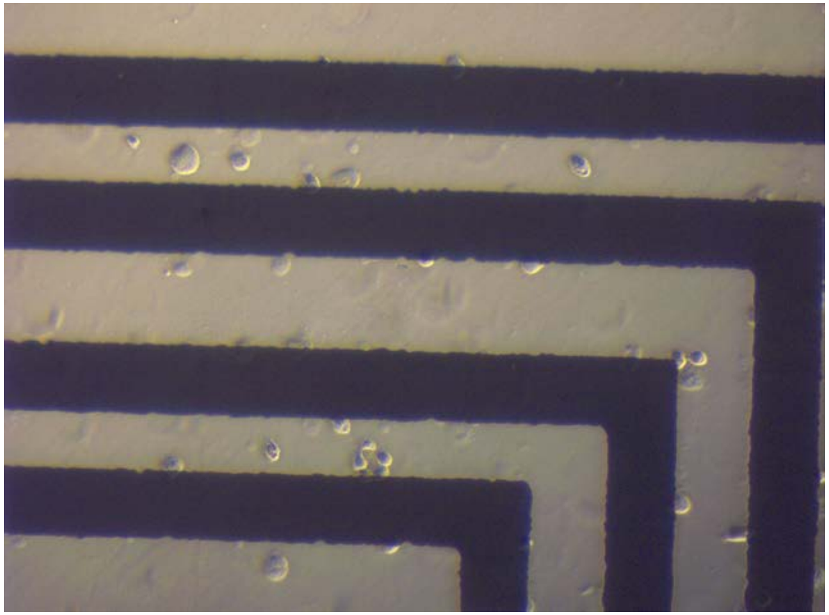
TABLE III. DEP force on Janus particles

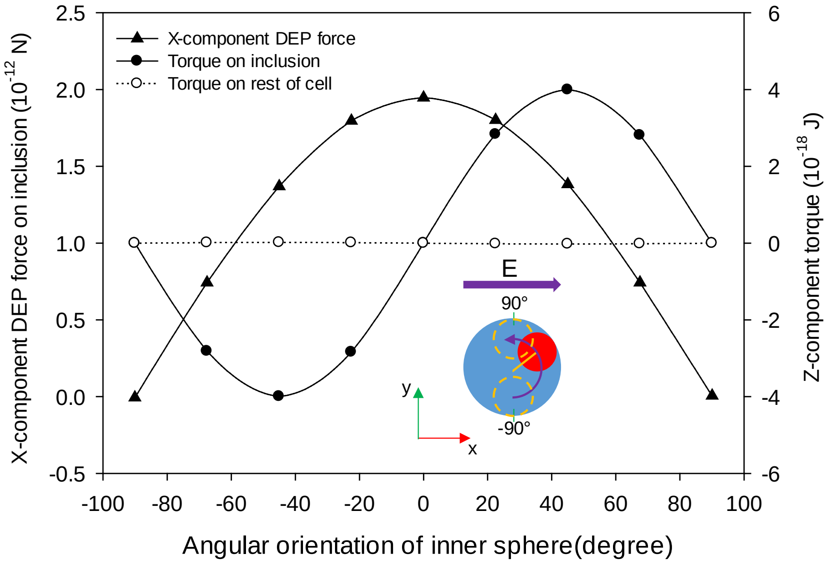
	Volumetric-integration method						
	25 kHz	50 kHz	75 kHz	100 kHz	1 MHz	5 MHz	20 MHz
Janus particle (nN)	27.4	27.4	27.6	27.8	51.7	105	114
Janus particle with alkanethiol layer (nN)	−77.2	−17.3	2.1	10.2	32.1	77.0	97.4
	MST method						
	25 kHz	50 kHz	75 kHz	100 kHz	1 MHz	5 MHz	20 MHz
Janus particle (nN)	-1.23×10^4	-3.40×10^4	-5.08×10^4	-6.04×10^4	-8.02×10^4	-2.76×10^4	-2.95×10^3
Janus particle with alkanethiol layer (nN)	-9.63×10^4	-9.63×10^4	-9.62×10^4	-9.61×10^4	-7.32×10^4	-1.06×10^4	−667

Use of MST method for non-homogeneous particle will lead to incorrect results!

Elucidating cell rotation behavior

By taking interior components of cell into consideration, volumetric polarization and integration method can successfully explain rotational behavior of cell

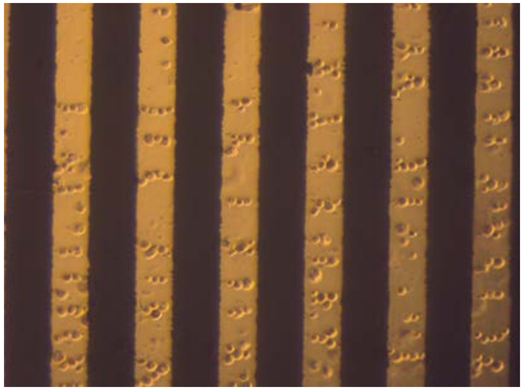




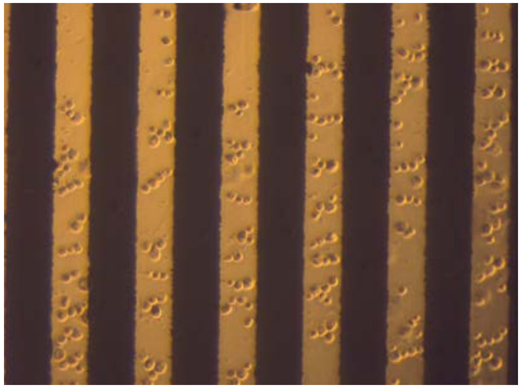
Direction of rotation is determined by location of inclusion

Elucidating cell rotation behavior

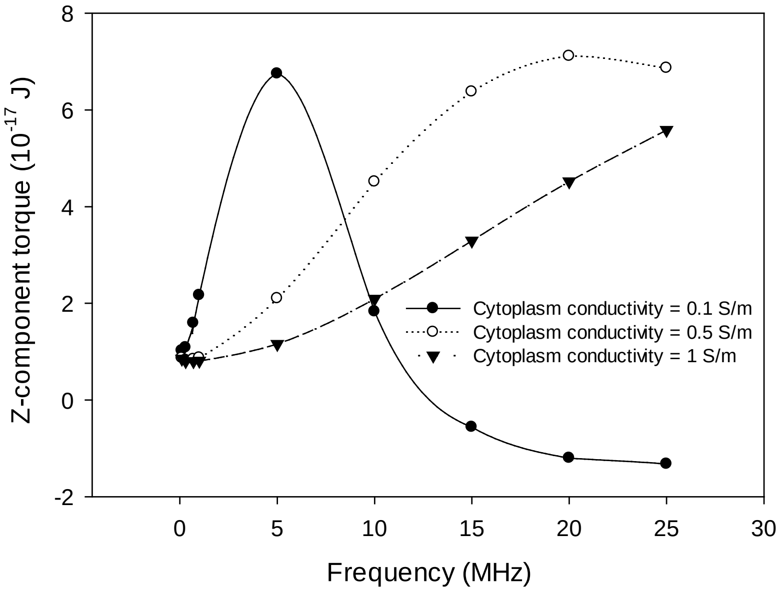
By taking interior components of cell into consideration, volumetric polarization and integration method can successfully explain rotational behavior of cell



5 MHz



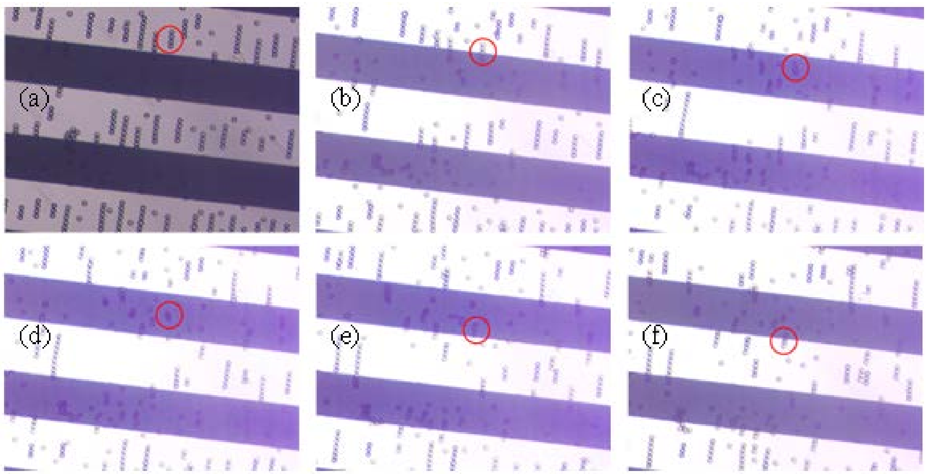
20 MHz

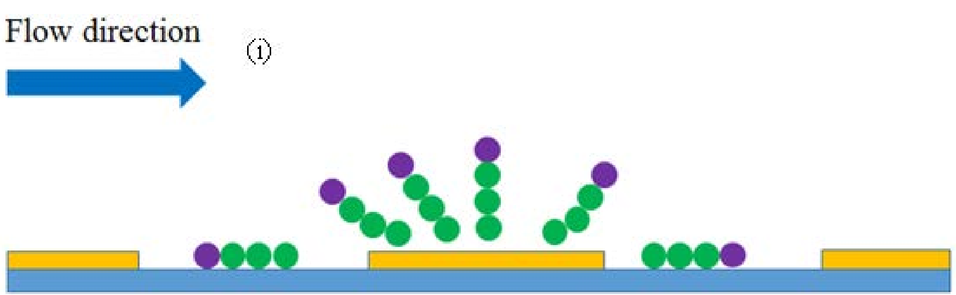


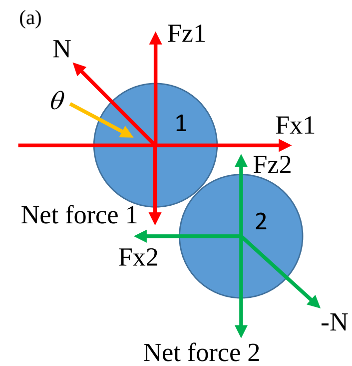
Cytoplasm conductivity affects the response of rotational speed to frequency

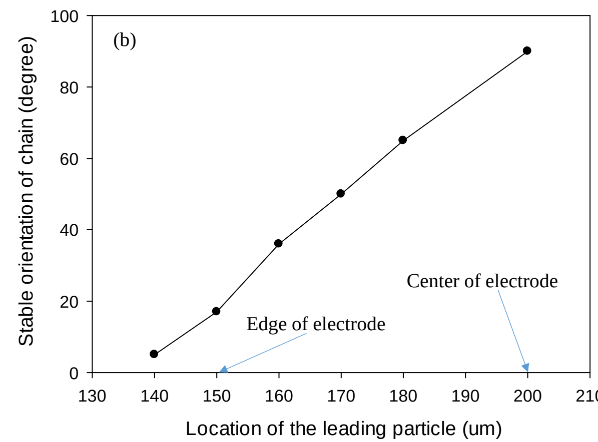
Pearl-chain tumbling behavior

The unique tumbling movement of pearl chains can also be explained by using the volumetric polarization and integration method

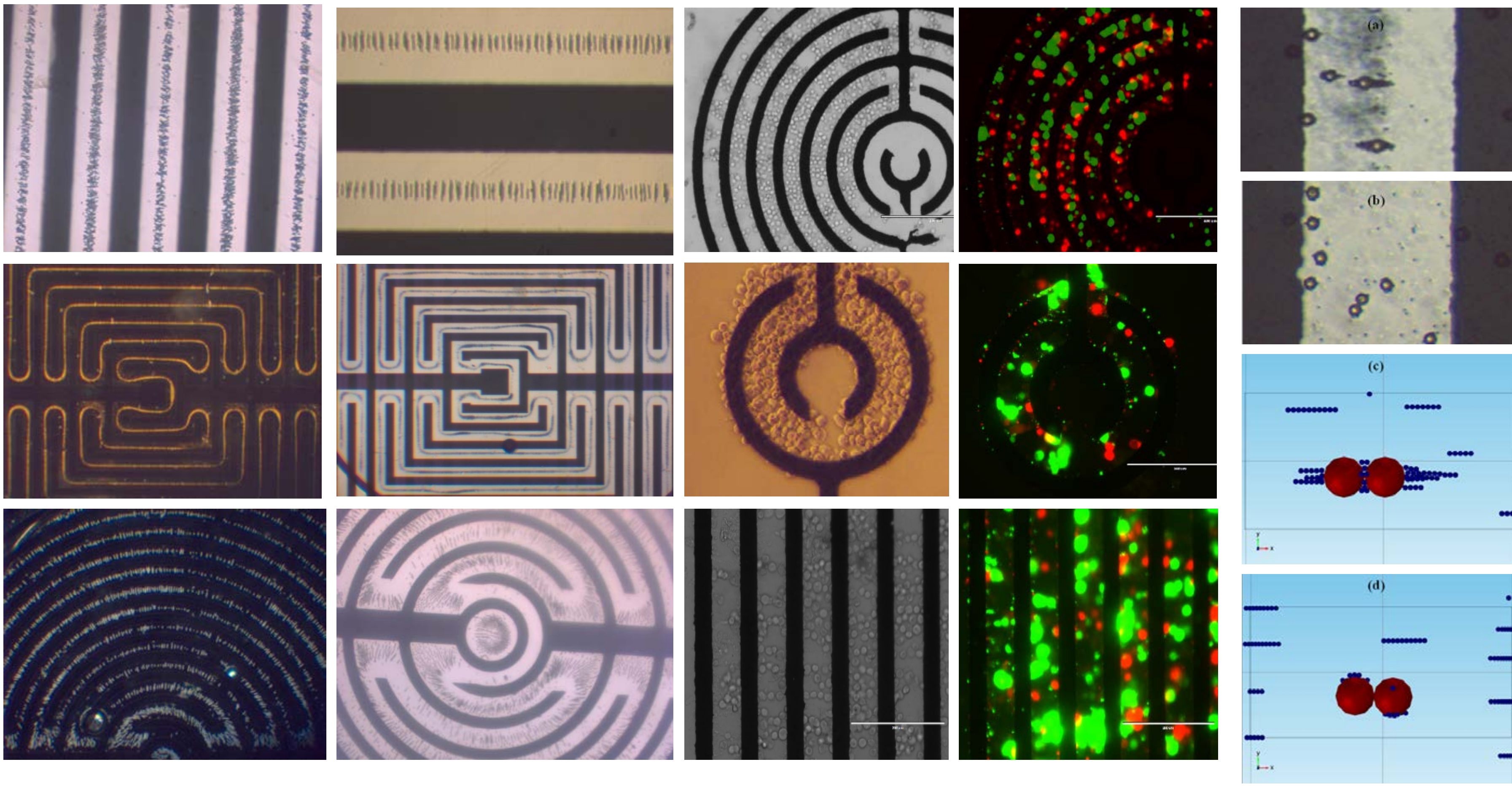








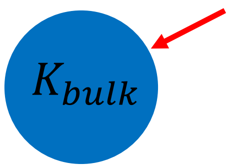
Rapid biomanufacturing



Considering the double layer effect

Electric double layer (EDL) will affect the dielectric property of particle, but its effect is not fully understood due to lack of physical relevance in current analytical theory

Conventional approach



$K_s = \sigma\mu$

Point dipole assumption →

$$K_{total} = K_{bulk} + \frac{2K_s}{a}$$

(Unable to explain experimental observation)

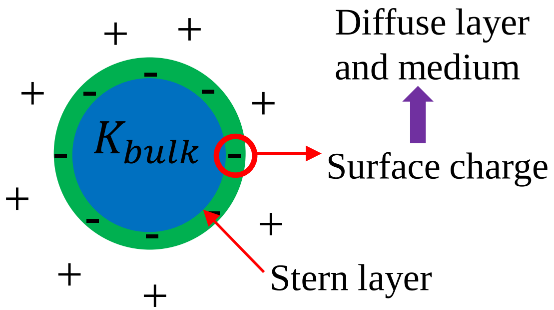
↓ Add correction term

$$K_{total} = K_{bulk} + (A_1 + A_2\kappa a)\frac{2\sigma\mu}{a}$$

$$K_{total} = K_{bulk} + \frac{2\sigma\mu}{a} + \frac{2\sigma_m}{\sqrt{\kappa a}}$$

} Lack physical relevance

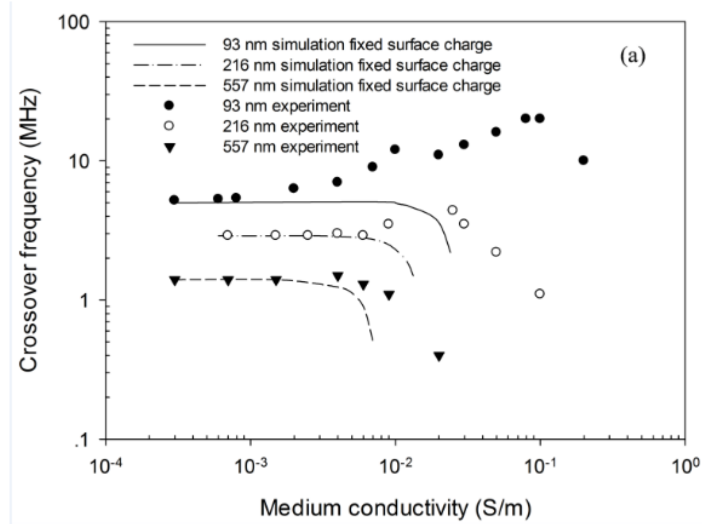
Considering the double layer effect

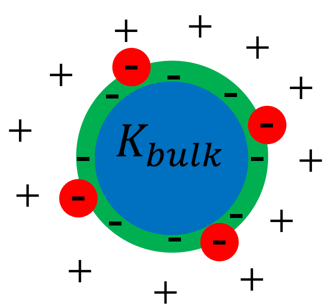


$$-\nabla^2\phi = \frac{F\left(c\cdot e^{\left(-\frac{q\phi}{kT}\right)} - c\cdot e^{\left(\frac{q\phi}{kT}\right)}\right)}{\varepsilon_m}$$

$$\vec{\boldsymbol{n}}\cdot\nabla\phi = \frac{\sigma}{\varepsilon_m}$$

The disagreement between experimental and modeling results indicate something is missing

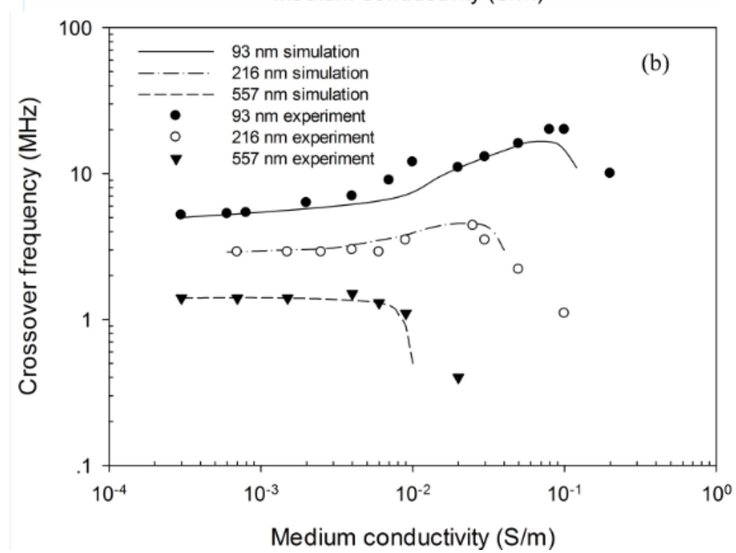




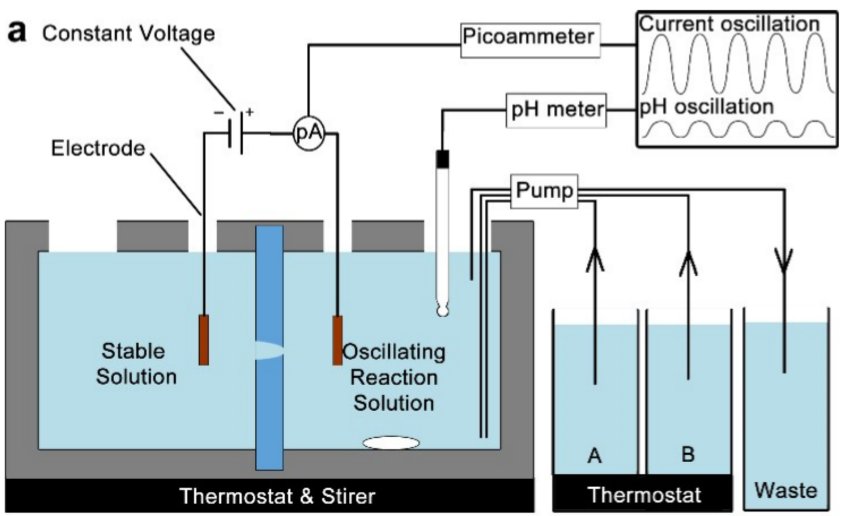
Langmuir adsorption is used to describe the specific adsorption behavior

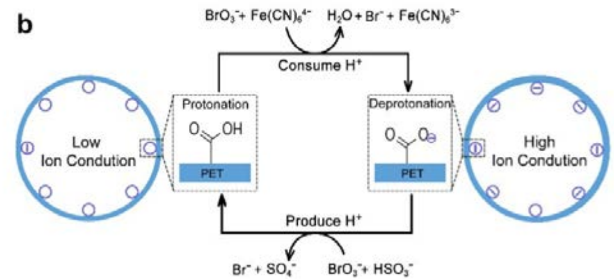
$$\sigma_s = \frac{\sigma_{max}\cdot c^*\cdot\gamma\cdot e^{\left(\frac{q\phi_i}{kT}\right)}}{1 + c^*\cdot\gamma\cdot e^{\left(\frac{q\phi_i}{kT}\right)}}$$

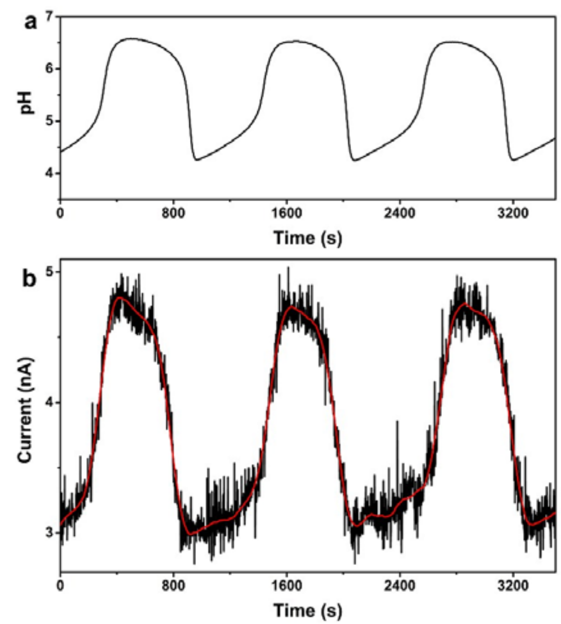
Surface adsorption plays a vital role in determining the crossover frequency

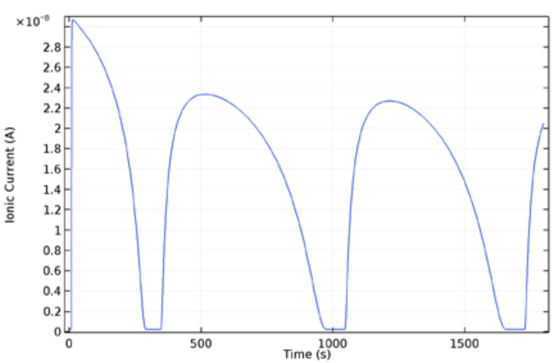


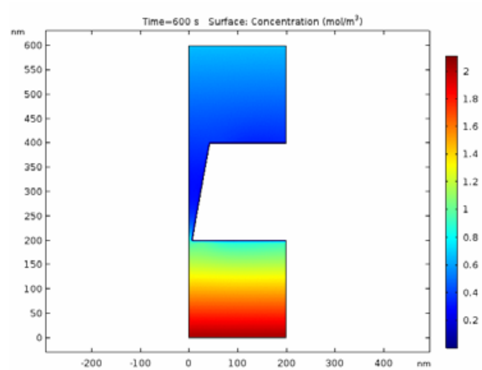
Other application: nanopore device



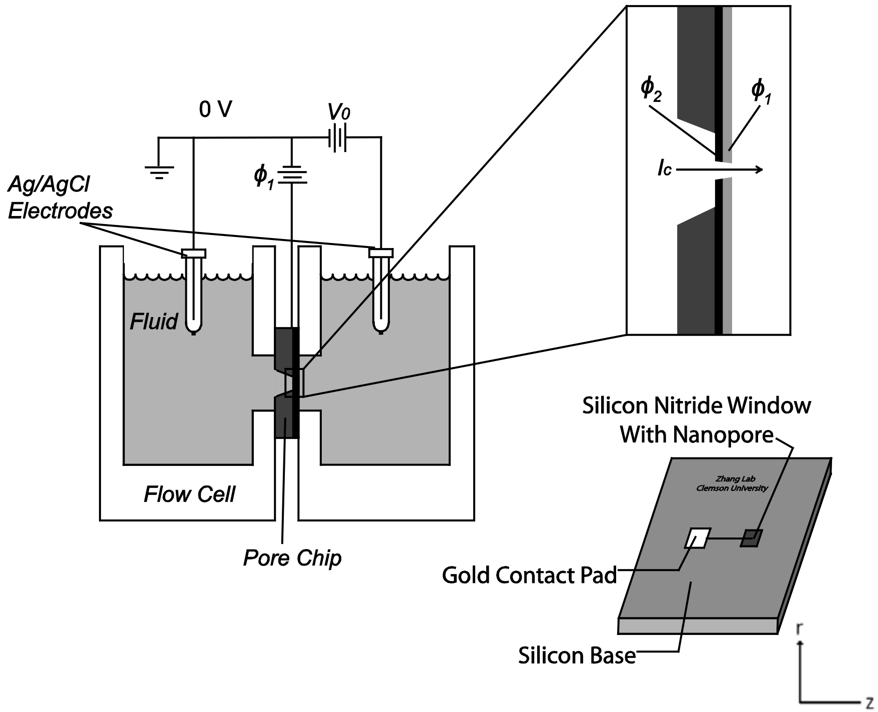


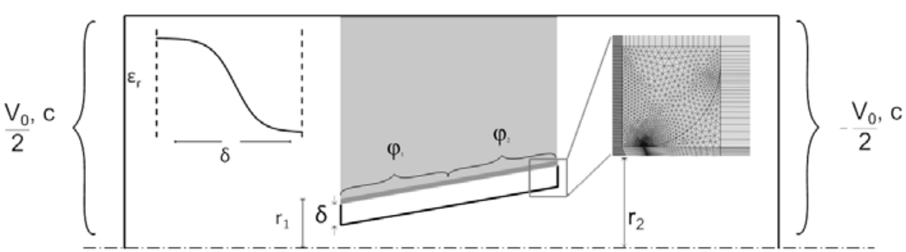


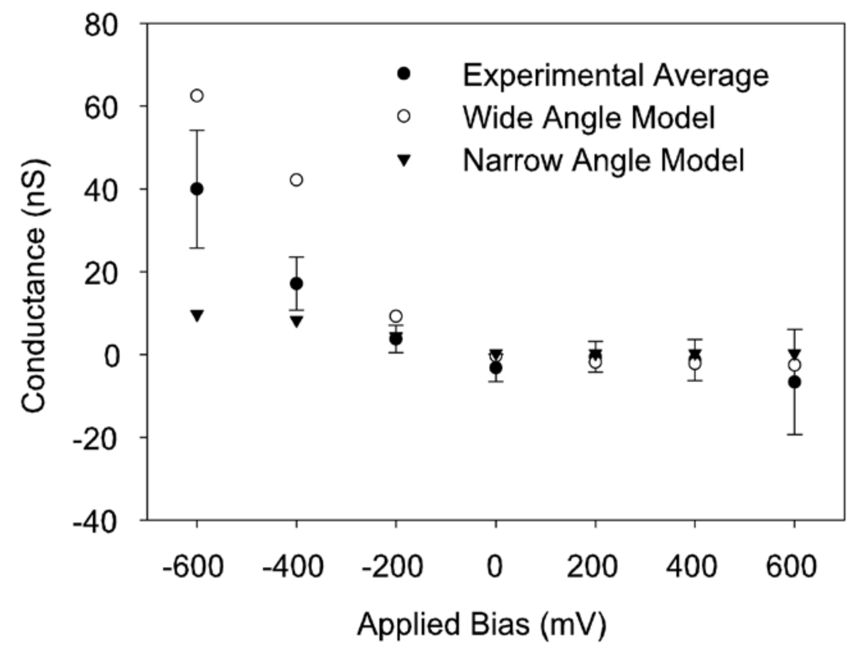




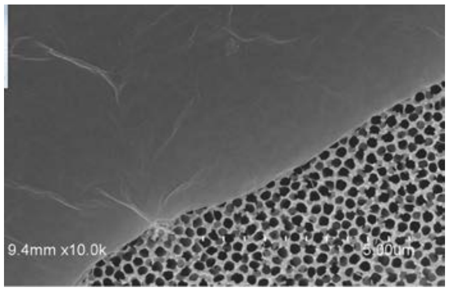
Nanopore for ionic gating

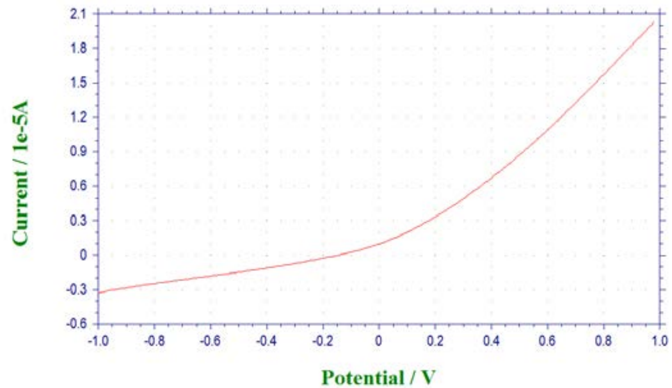


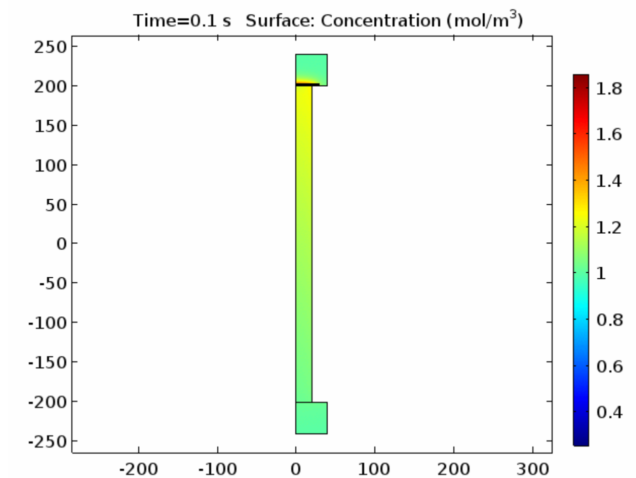


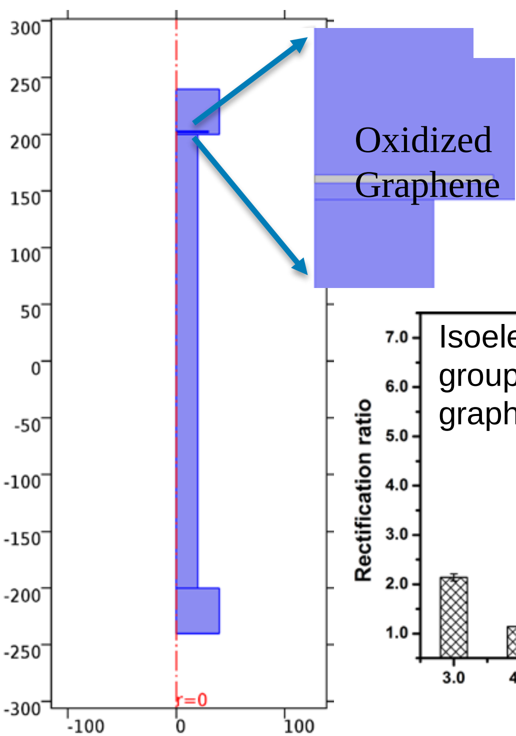


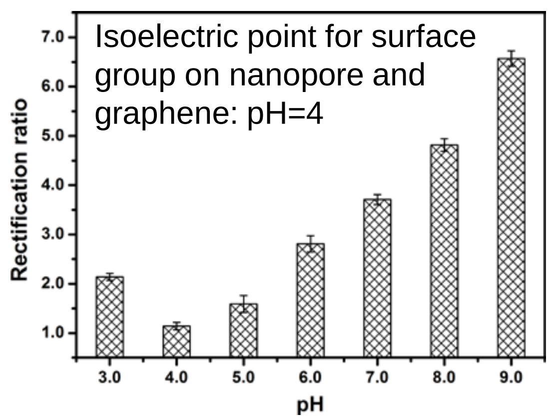
Nanopore for ionic gating

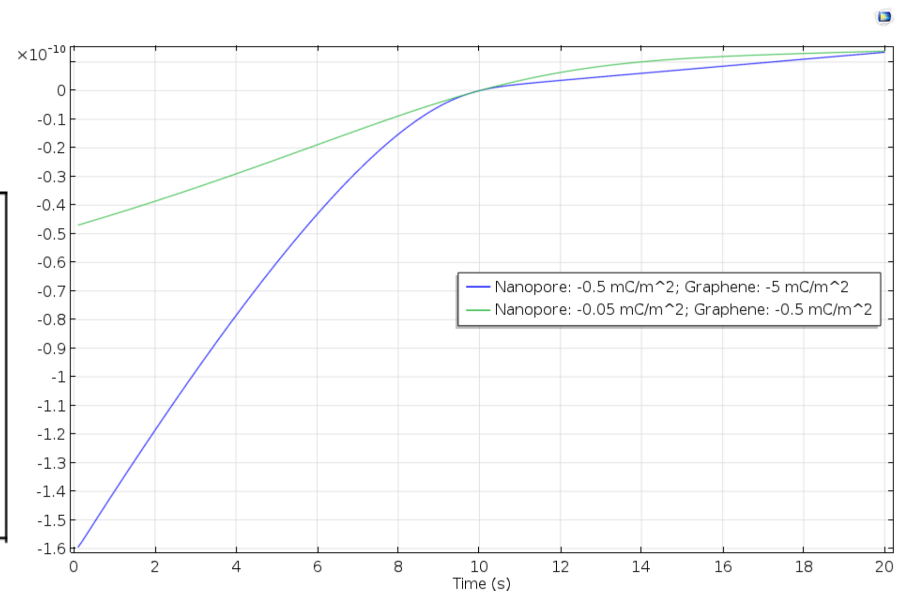




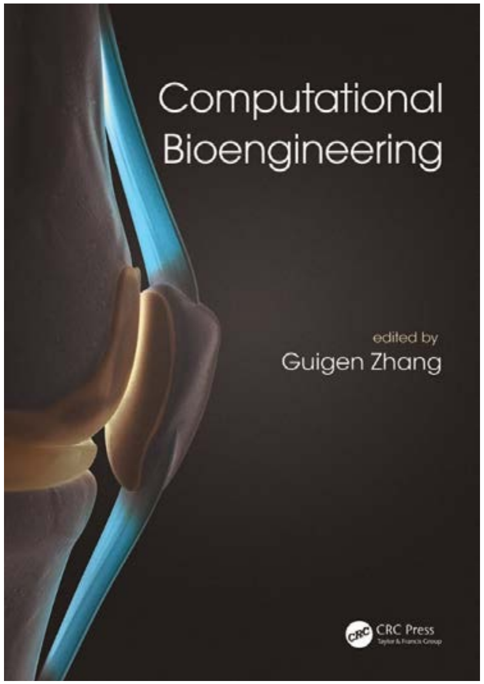


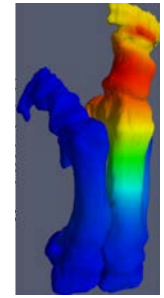


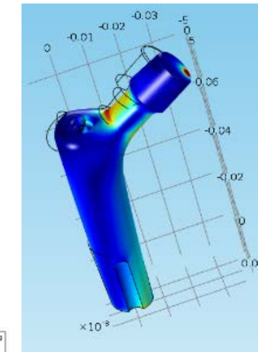


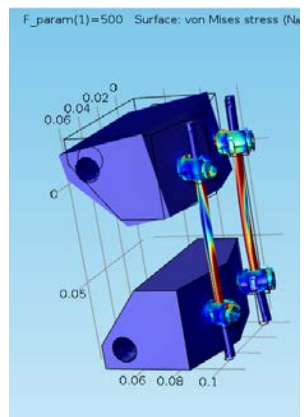


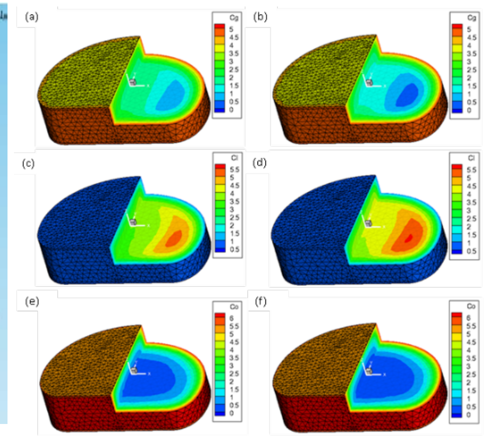
Bioengineering problems

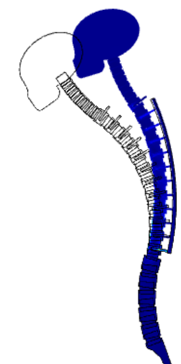


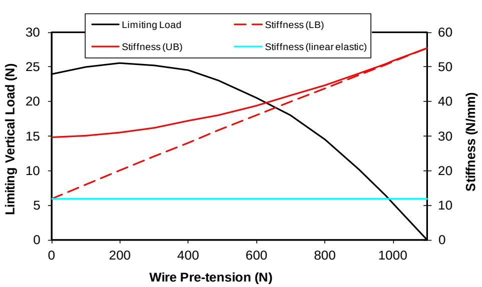


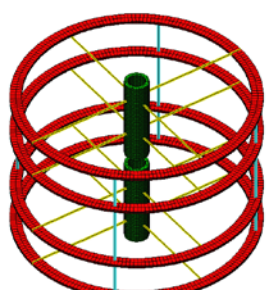


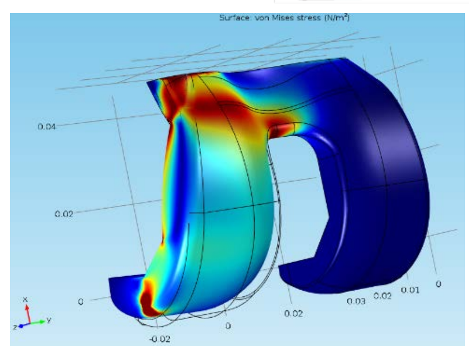


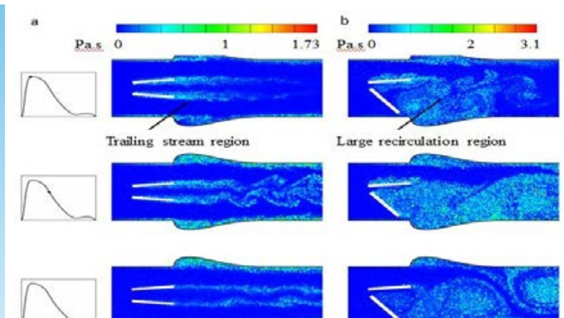












Artificial muscle: Ionic polymer - metal composites (ipmc)

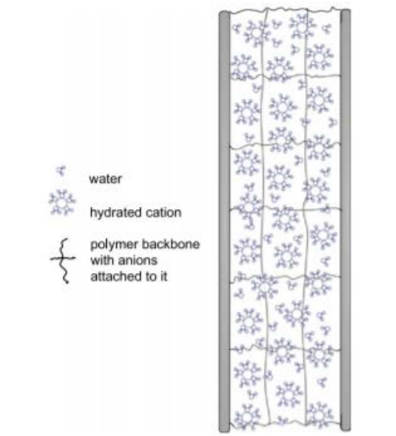
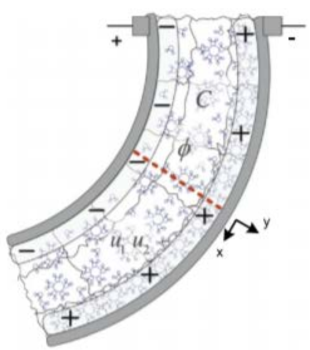
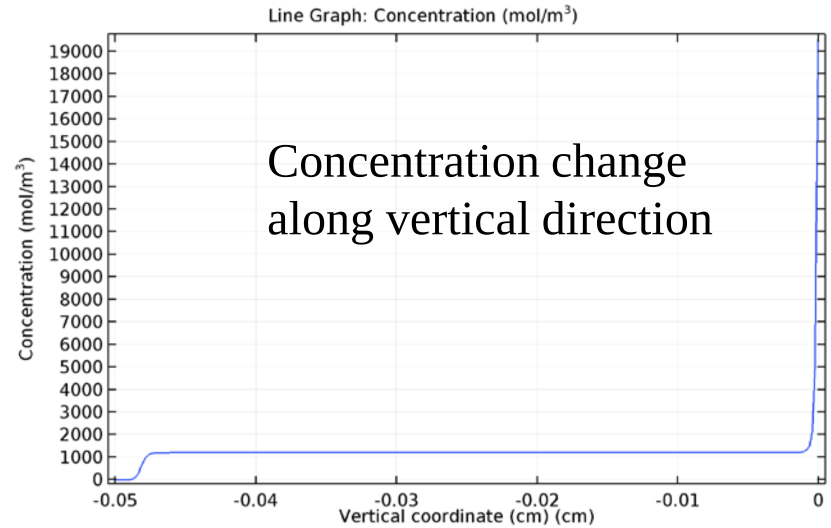
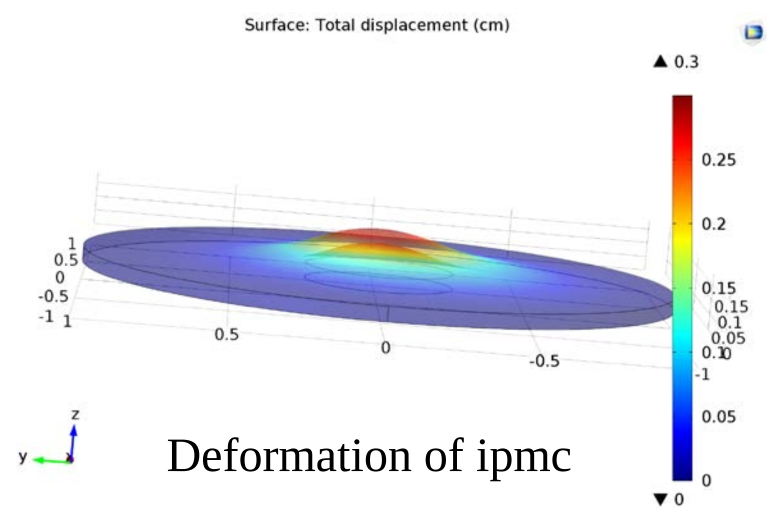


Fig. 1. IPMC model—no voltage is applied to the electrodes.

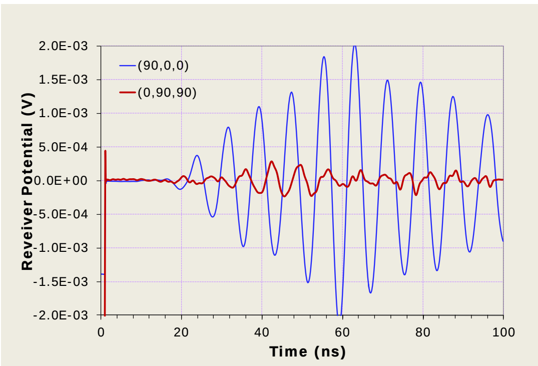


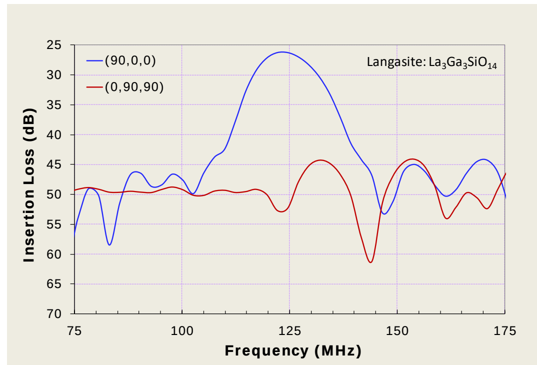


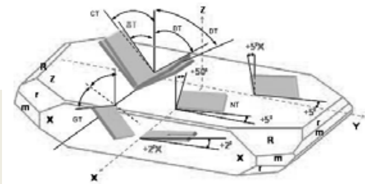


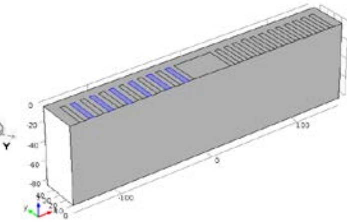
Voltage → Cation concentration gradient → Cation accumulation/depletion causes body force → bending

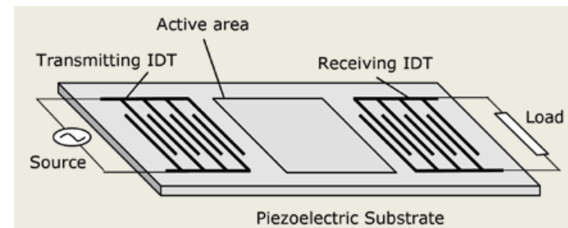
Acoustic wave actuation

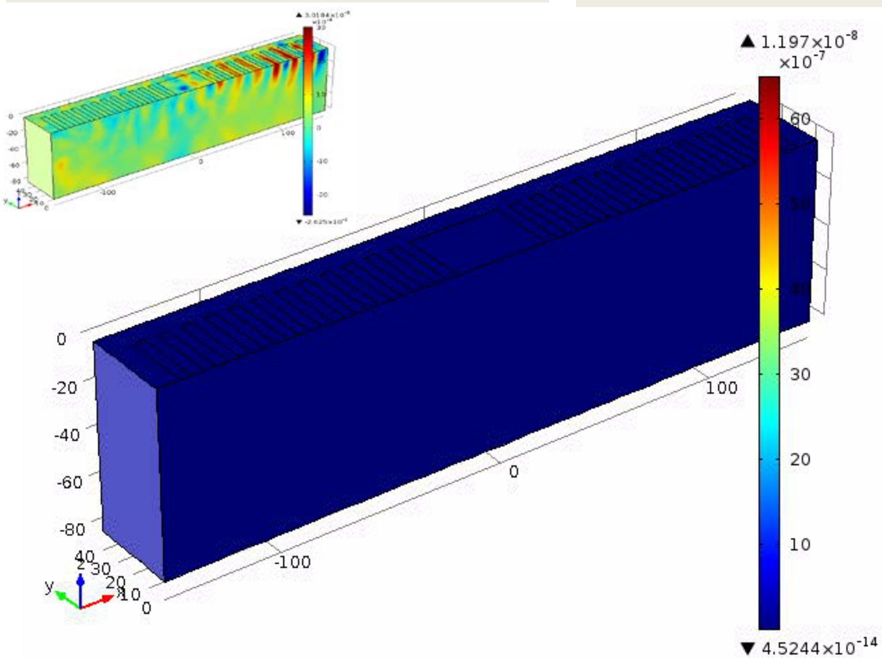


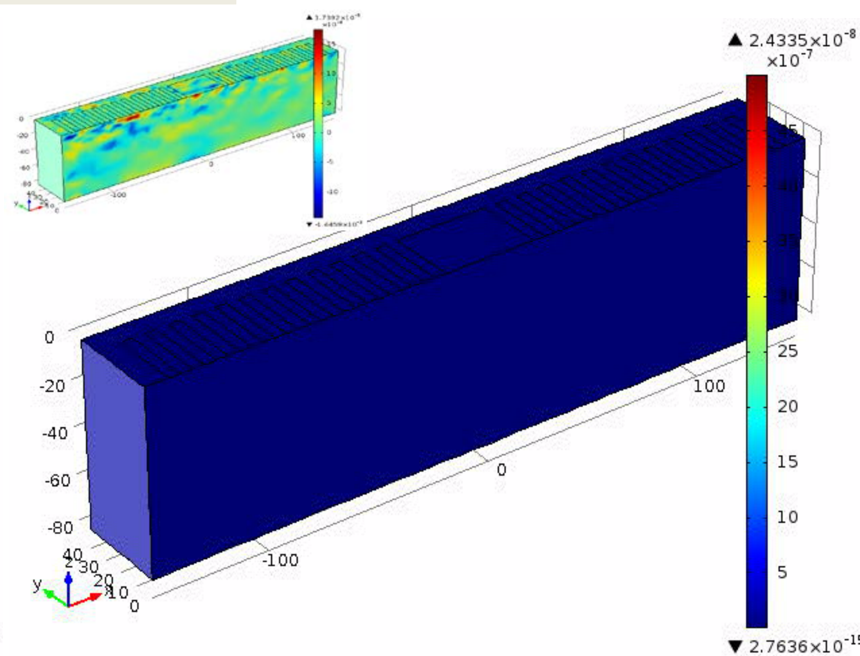








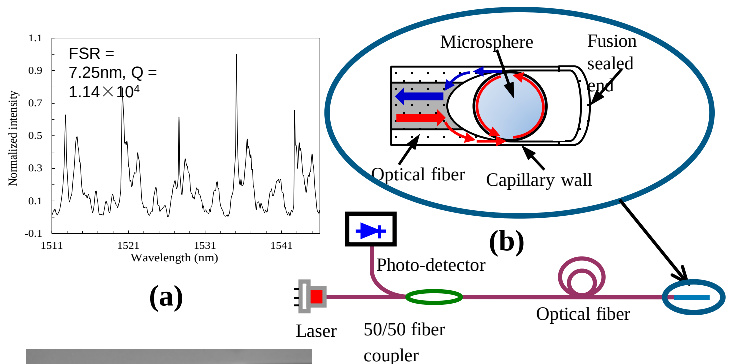


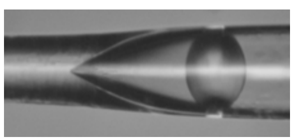


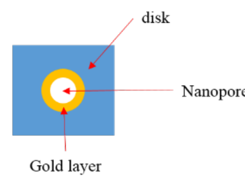
(90,0,0)

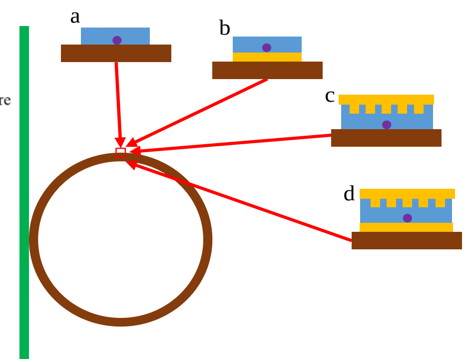
(0,90,90)

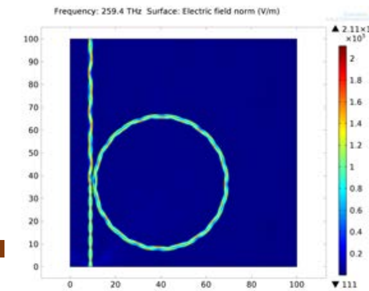
Coupled WGM/SERS/SPR Spectroscopic Technique

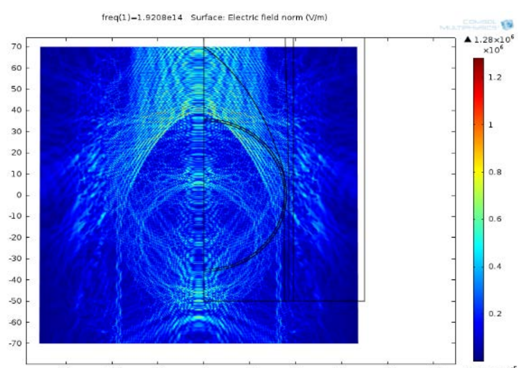


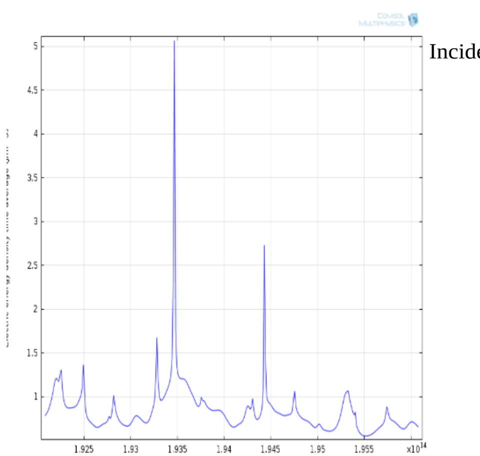


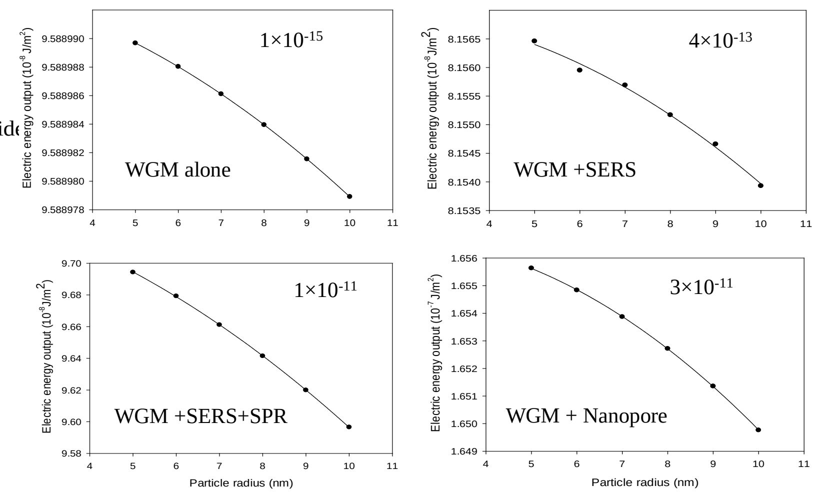












University of Kentucky
College of Engineering
F. Joseph Halcomb III, M.D.
Department of Biomedical Engineering

Questions?

- **Let us talk, explore and collaborate …**

Guigen Zhang, Ph.D., FAIMBE
Professor and Chair
F. Joseph Halcomb III, M.D. Endowed Chair

Email: guigen.bme@uky.edu
Phone: 859-323-7217
Office: 522A Robotics & Manufacturing Building