Impedance Based Microfluidic Device for Measuring Drug Response of Cancer Cells

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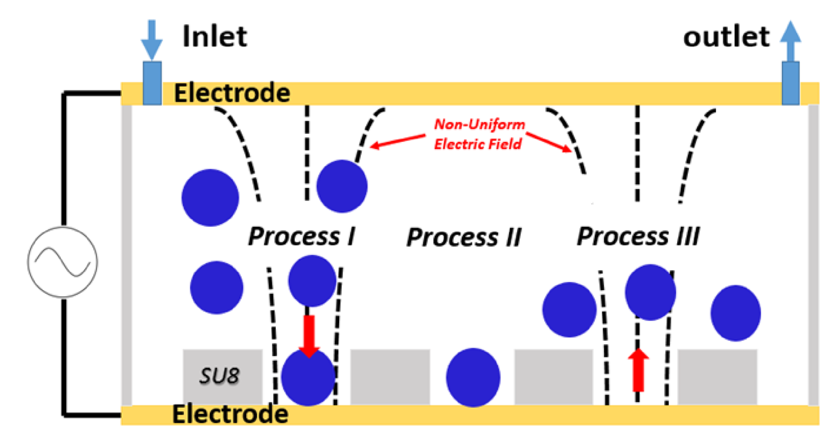
OBJECTIVES

Develop

- Microfluidic device for characterization of dielectric properties of biological cells
- Technique to decrease sample volume and increase cell volume fraction concurrently
- Microfluidic device capable of capturing cells and measuring cell responses due to external stimuli such as pH/ conductivity/ osmolarity changes as well as drug uptake



Process I : pDEP Cell Trapping
Process II : Dielectric Spectroscopy Measurement
Process III : nDEP Cell Unloading

Scan with QR code reader app to see the video

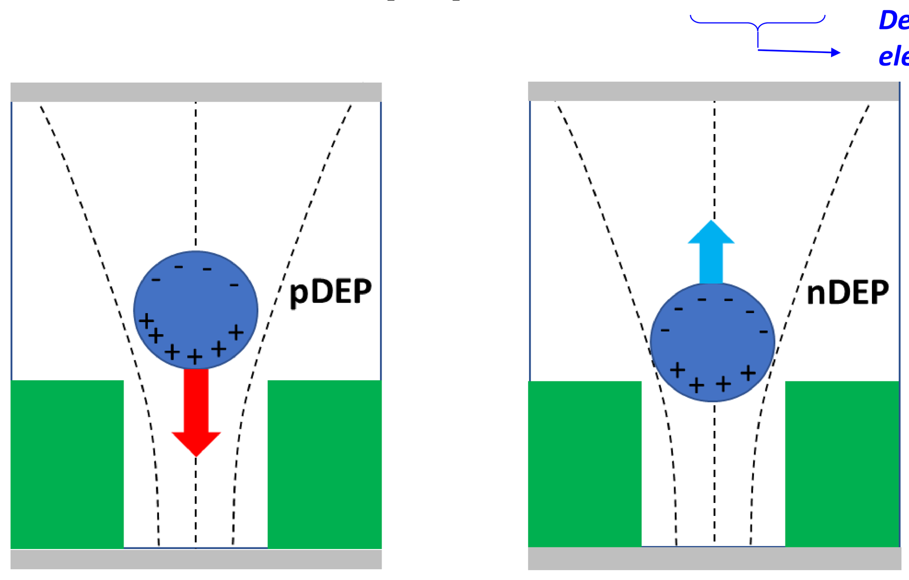
METHODOLOGY

- **Dielectrophoresis (DEP)** is the motion of polarizable particles that are suspended in an ionic solution and subjected to a spatially non-uniform electric field. Polarizability of a particle relative to the suspending medium determines the basic direction of DEP force (positive/negative DEP), which also strongly depends on the frequency of the applied electric field.

$$F_{DEP} = 2\pi r_p^3 \varepsilon_0 \varepsilon_r \, Re(CM)\nabla|E|^2$$

$$= \mathcal{F}(\varepsilon_p, \sigma_p, a, \varepsilon, \sigma, \omega, E(r))$$

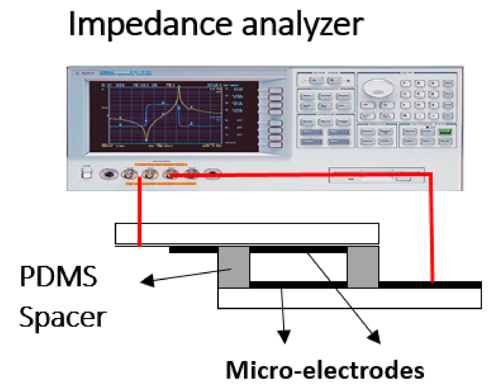
Species properties & size
Medium Properties
Device geometry & applied electric signal



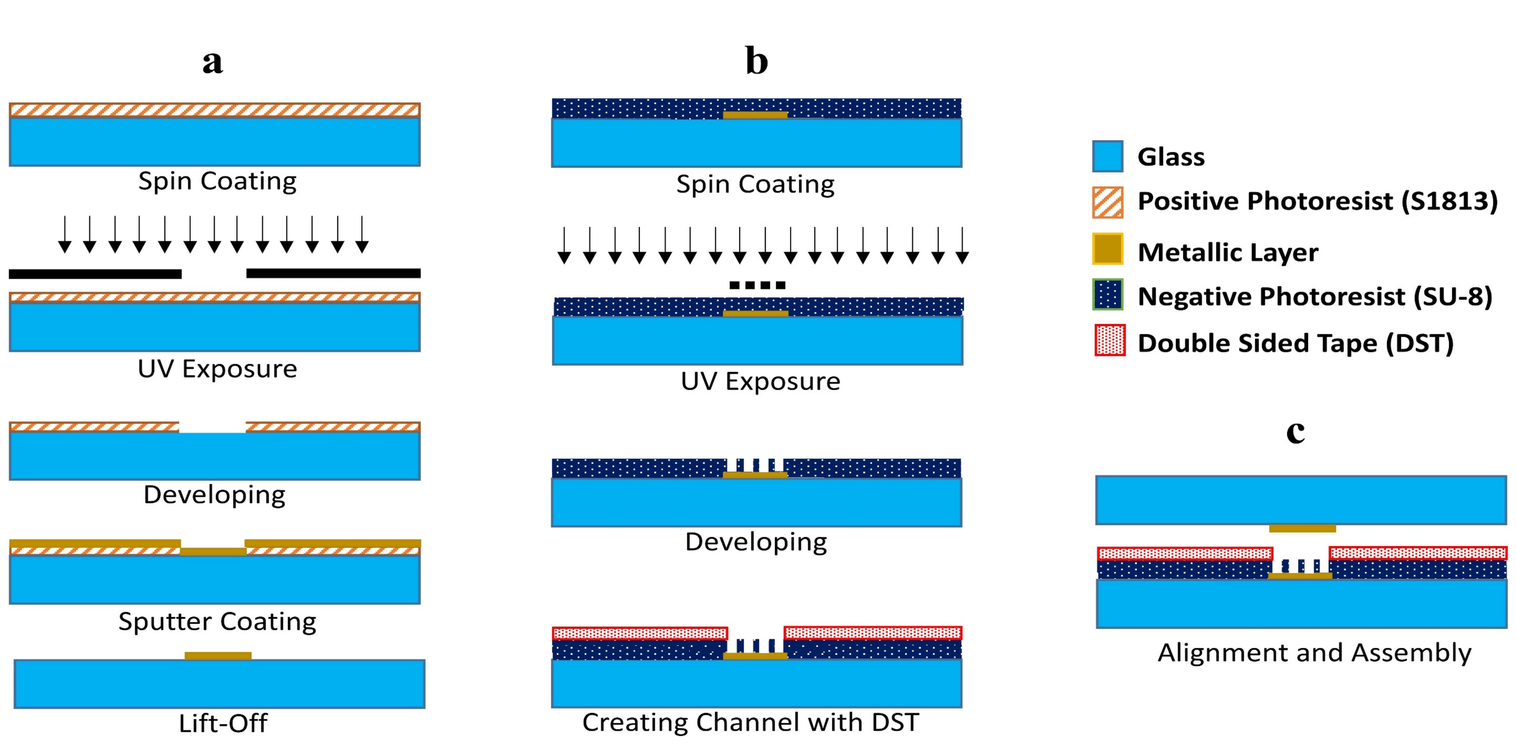
$$CM(\varepsilon_p^*, \varepsilon^*) = \frac{\varepsilon_p^* - \varepsilon^*}{\varepsilon_p^* + 2\varepsilon^*}$$

$$-0.5 < \mathrm{Re}[CM(\varepsilon_p^*, \varepsilon^*)] < 1$$

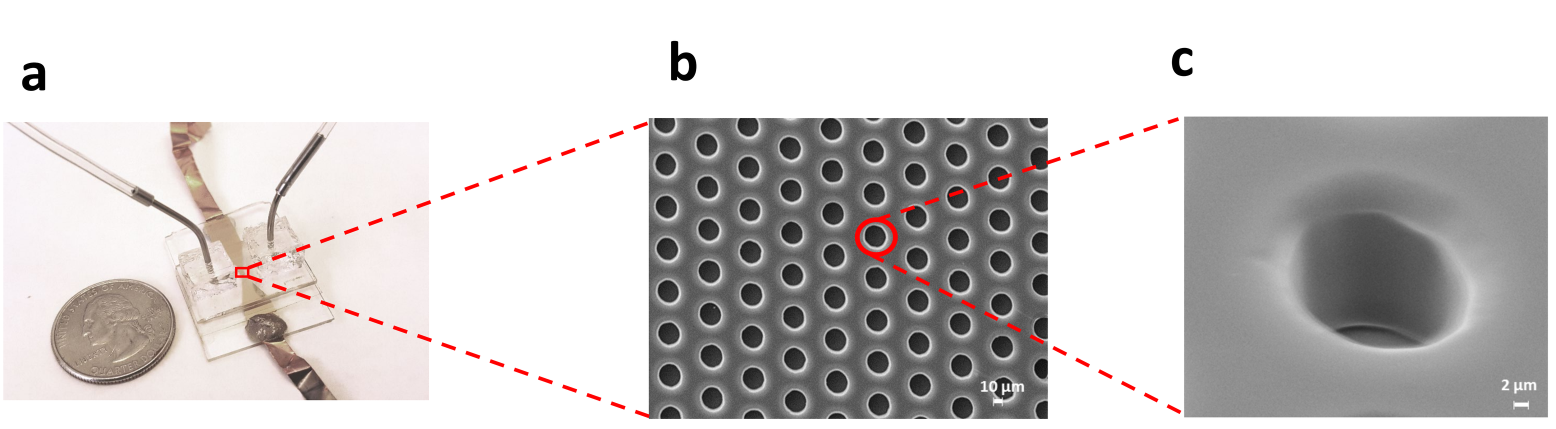
- **Dielectric Spectroscopy (DS)** is a non-invasive technique for measuring the dielectric properties of a material of interest.



DEVICE FABRICATION

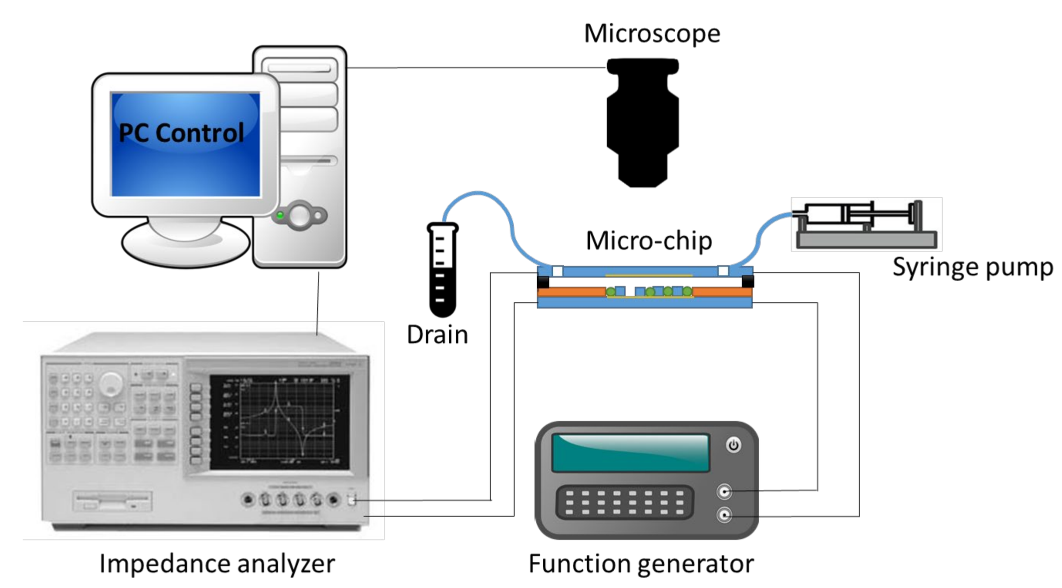


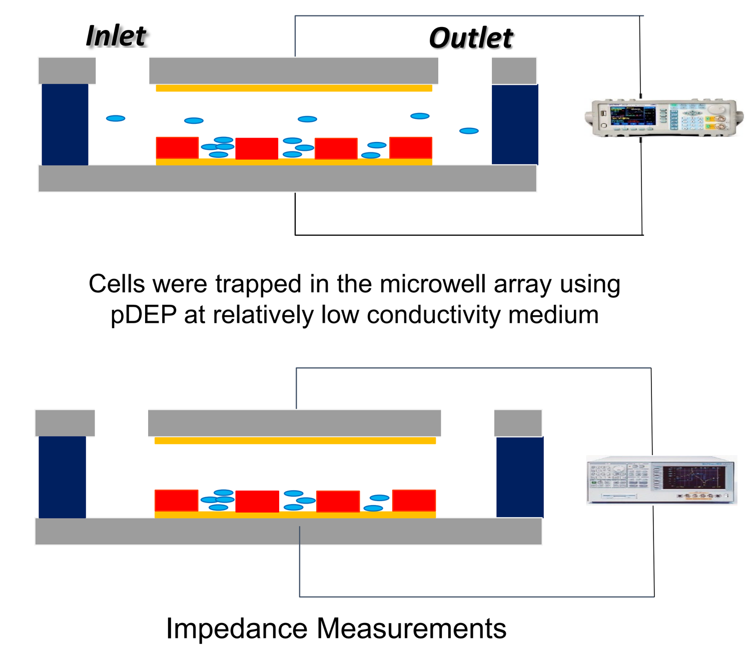
Microfabrication process of DEP chip using two-step photolithography process. a) Electrode fabrication, b) micro-wells and micro-channel fabrication, and c) electrode alignment and device assembly.

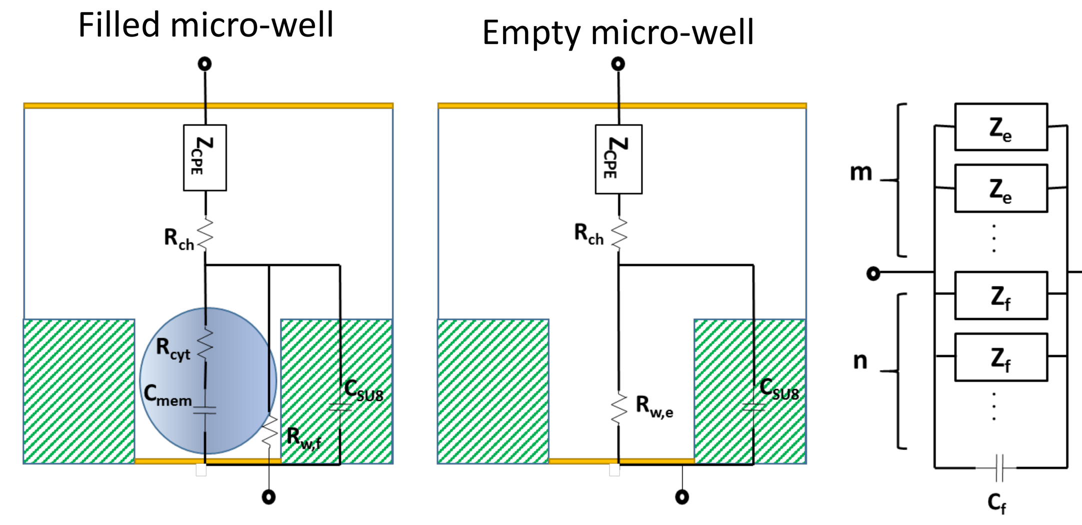


a) Assembled microfluidic chip, b) a microscopy picture of gold electrode and micro-wells, c) SEM image of one micro-well

EXPERIMENTAL SETUP





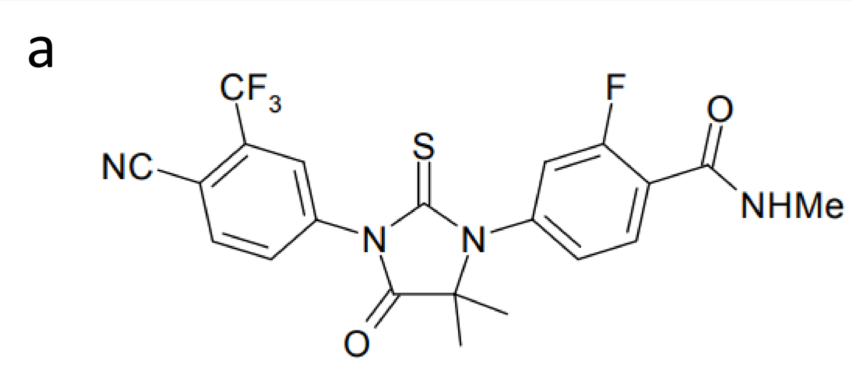


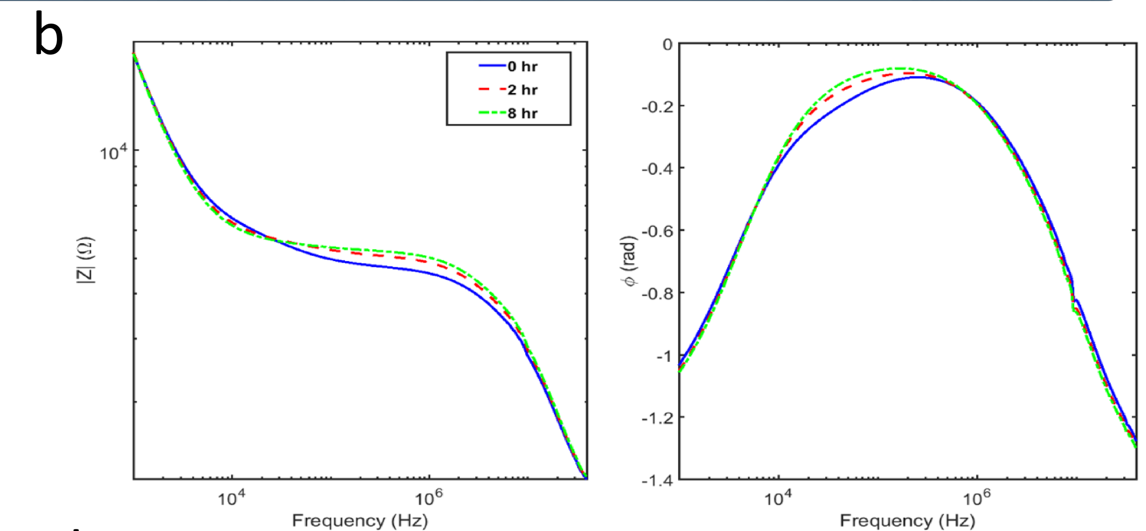
$$Z_e = Z_{CPE} + R_{ch} + \frac{1}{1/R_{sol,e} + j\omega C_{SU8}}$$

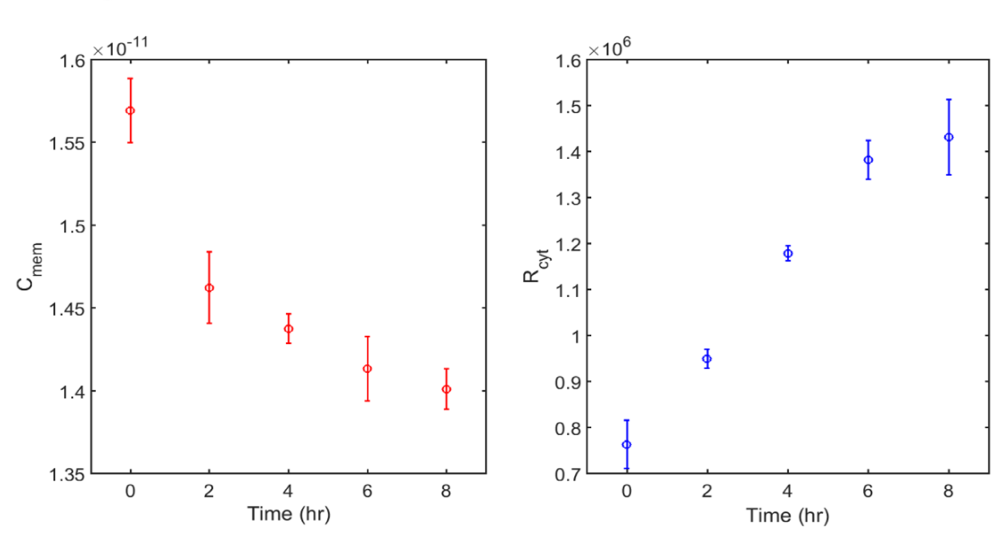
$$Z_f = Z_{CPE} + R_{ch} + \frac{1}{1/R_{sol,f} + j\omega C_{SU8} + 1/\left(R_{cyt} + 1/j\omega C_{mem}\right)}$$

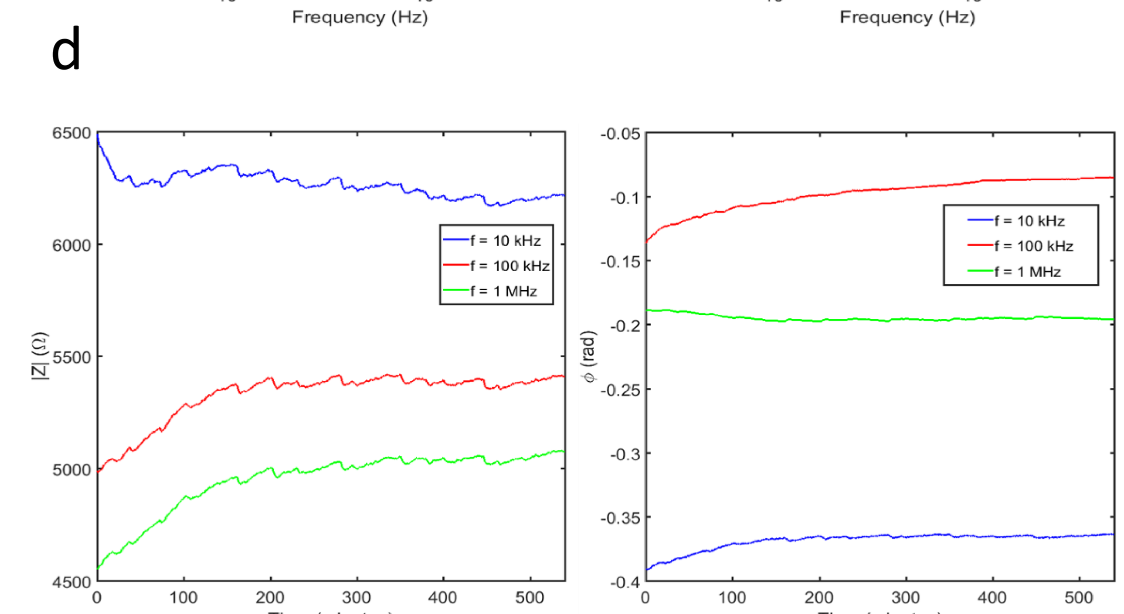
$$Y_{tot} = \frac{n}{Z_f} + \frac{m}{Z_e} + j\omega C_f, \qquad Z_{tot} = 1/Y_{tot}$$

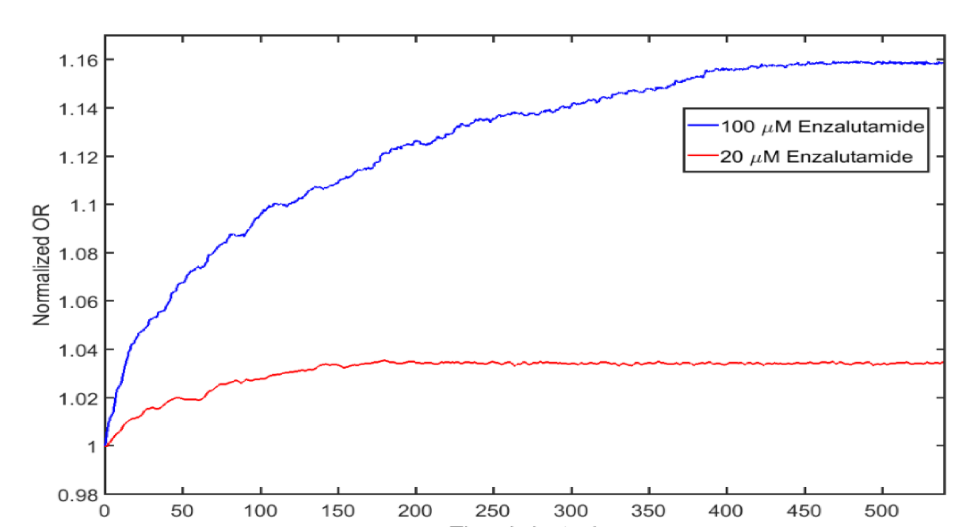
RESULTS

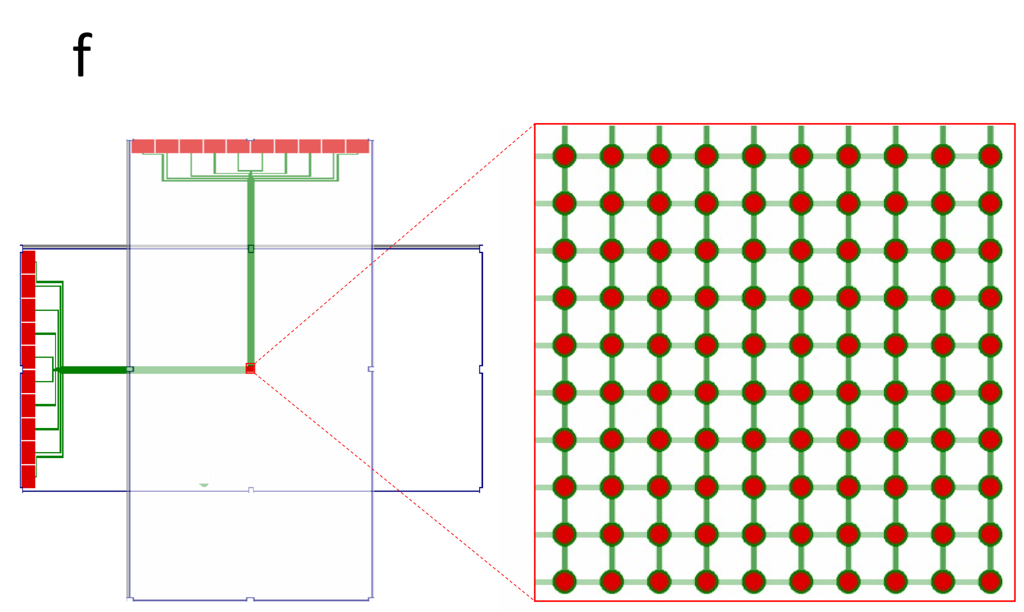












a) Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. **b)** Figure b shows the impedance value and phase angle spectra of live healthy PC-3 cells, after 2 hours, and after 8 hours. Based on impedance value spectra, the live cells show a higher impedance value at lower frequencies while they experience a lower value at higher frequencies. **c)** The equivalent circuit model was used to evaluate membrane capacitance and cytoplasmic resistance of PC-3 cells treated with 100 µM Enzalutamide for 0, 2, 4, 6, and 8 hours. **d)** Figure d shows the impedance value and phase angle changes at 10 kHz, 100 kHz, and 1 MHz frequencies. **e)** The ratio of the impedance magnitude at a high frequency to a low frequency is known as opacity ratio (OR). Figure e shows the changes in normalized opacity ratio (OR) for PC-3 cells exposed to 100 µM and 20 µM Enzalutamide drug.

f) Future Improvements : We plan to extend the current microfluidic device for single cell measurements by fabricating a three-dimensional grid electrode system to address each micro-well individually.

CONCLUSION

- We fabricated a miniaturized dielectric spectroscopy device capable of cell trapping, enrichment, and impedance measurement.
- An equivalent circuit model was proposed for system and cell cytoplasmic conductivity and membrane capacitance were extracted.
- The current platform allows real-time measurements of dielectric properties of biological cells under changing flow conditions; enabling assessment of cell response to variations in the buffer conductivity, osmolarity and pH, as well as drug uptake.

Publication: 1. *Mansoorifar, A.*, Koklu, A., Sabuncu, A. C., & Beskok, A. (2017). Dielectrophoresis assisted loading and unloading of microwells for impedance spectroscopy. Electrophoresis, 38(11), 1466-1474.
2. Mansoorifar, A., Koklu, A., Ma, S., Raj, G. V., & Beskok, A. (2018). Electrical Impedance Measurements of Biological Cells in Response to External Stimuli. Analytical chemistry, 90(7), 4320-4327.
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