

Capacitance Signatures for Rapid Detection of the Polarity of the Dielectrophoretic Force on Single Yeast Cells

G.A. Ferrier*, S.F. Romanuk*, D.J. Thomson*, G.E. Bridges*, and M.R. Freeman**

*Department of Electrical and Computer Engineering, University of Manitoba, Winnipeg, Canada, gferrier@ee.umanitoba.ca

**Department of Physics and NINT, University of Alberta, Edmonton, Canada

ABSTRACT

In this paper, we present capacitance signatures that can be used to detect the polarity of the dielectrophoretic force on single yeast cells in less than 2 s. There is good agreement between the capacitance changes caused by continuous repositioning of yeast cells by interdigitated electrodes and simple maps of electric field squared. Yeast cells were repelled from the electrodes using 10 kHz signals and attracted to the electrodes using 1 MHz signals. These capacitance signatures can also potentially verify the viability of yeast cells. For example, non-viable yeast cells would have experienced attractive forces rather than repulsive forces at low frequencies (10 kHz).

Keywords: capacitance, dielectrophoresis, microfluidics, electromanipulation, cell diagnostics

1 INTRODUCTION

There is currently great interest in developing techniques for manipulating and detecting biological cells for cell diagnostics. Optical tweezers and fibers have been successfully used to stretch single cells and to even identify their force constants [1]. One group has shown that cancerous breast cells stretch up to five times more than healthy breast cells [2]. This technology has mainly been limited to the study of single cells and is difficult to integrate on chip due to cost and the large equipment required for experiments.

For electrical detection, Cleland *et al.* have adapted the Coulter Counter technology to microfluidic systems for counting large numbers of polystyrene spheres (5000 spheres per second) [3]. Sohn *et al.* successfully used capacitance measurements to count mouse myeloma cells achieving a resolution of a few fF [4]. Manaresi *et al.* have implemented an integrated microelectronic approach using electrode arrays where individual cells are manipulated from one electrode to the next with binary detection [5]. However, these detection systems generally work with frequencies around 100 MHz or less. In this range, the dielectric properties of biological cells are highly variable and large potential drops across the nanometer-sized cell membranes are likely to occur. In cases where very low frequencies are used (kHz range or less), the generation of

electrical double layers near the fluid-electrode interface can greatly influence the electrical readings.

Previously, we demonstrated a system that could detect the presence of yeast cells using capacitance measurements from a cavity resonator [6]. In this system, a resonator is coupled to a set of electrodes, which are aligned 90 degrees relative to the flow direction of a microfluidic channel that is 25 μm in height and 80 μm in width. Using these electrodes, we can manipulate cells using low frequencies (up to MHz) and simultaneously perform capacitive detection using high frequencies (GHz). By implementing interdigitated electrode designs in this system (Fig. 1), we can gain insight into the dynamic position of yeast cells relative to the electrodes.

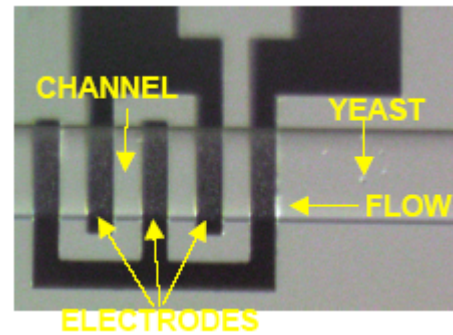


Figure 1: Interdigitated electrodes (dark) aligned at 90 degrees to the channel flow direction. The flow of yeast cells generated from an automatic syringe pump is from right to left.

2 DIELECTROPHORESIS

Cell manipulation is performed using dielectrophoresis [7,8], which requires non-uniform fields to direct cells away from or toward regions of maximum electric field (electrode edges) depending on the relative polarizabilities of the cell and the fluid it is immersed in. The time-averaged dielectrophoretic force on a sphere is given by

$$\langle F_{DEP} \rangle = 2\pi r^3 \epsilon_0 \epsilon_m \text{Re}[f(\omega)] \nabla E_{RMS}^2 \quad (1)$$

where r is the cell radius, $\epsilon_0 \epsilon_m$ is the absolute permittivity of the medium, E_{RMS} is the RMS electric field, and $\text{Re}[f(\omega)]$ is the real part of the Clausius-Mossotti factor:

$$f(\omega) = \frac{\epsilon_p^* - \epsilon_m^*}{\epsilon_p^* + 2\epsilon_m^*}, \quad (2)$$

which contains the frequency dependence of the cell-electrode interaction. The complex particle and medium permittivities given by ϵ_p^* and ϵ_m^* have the form $\epsilon^* = \epsilon - j\sigma/\omega$.

Based on the capacitance signatures from the interdigitated electrodes, we can determine the sign of the Clausius-Mossotti factor of yeast cells in less than 2 s. With this information, one could adjust the operating frequency to approach the crossover frequency (when the Clausius-Mossotti factor is zero), which in general can be used to identify different types of cells, their condition (are they cancerous?), and whether they are viable or not. For viable yeast, the crossover frequency is approximately 100 kHz. By applying 10 kHz and 1 MHz frequencies, we generate conditions where yeast cells are either repelled from or attracted to the electrodes.

Figs. 2a and 2b show typical capacitance signatures for the repelled and attractive cases, respectively. Fig. 2a illustrates that cells experiencing repelling forces are progressively driven away from the electrodes and thus generate progressively smaller capacitance shifts as they propagate over each electrode.

When cells experience attractive forces, they are pulled toward the electrodes. If the dielectrophoretic force is not too strong, the counteracting fluid forces lift the cell to a marginal height above the electrodes. As a result, Fig. 2b illustrates that consistently large capacitance changes are observed when cells experience an attractive dielectrophoretic force. Furthermore, there is a clear double-peaked behaviour shown in the attractive capacitance signatures, which is caused by cells propagating *near* the electrode edges and perturbing the strong fields there. Note that the double-peaked response in Fig. 2a is gradually lost over time since the yeast cell is moving further away from the electrode array.

It is also interesting to note that repelled yeast cells generally experience faster transition times across the electrode array than cells brought attracted to the electrodes. This is likely because the yeast cells are moving at a slow flow rate (the cells pass through the full electrode array - 225 μm - in about 1 s or less), which allows gravity to lower their trajectory below that of maximum fluid velocity. For laminar flow, which occurs almost exclusively in microfluidic channels, the maximum flow velocity occurs in the center of the channel (i.e., 12.5 μm above the electrode array). Consequently, the cells are actually being repelled into the elevation of highest fluid

velocity. Conversely, yeast cells that are attracted to the electrodes are lowered into elevation heights where the fluid velocity is reduced.

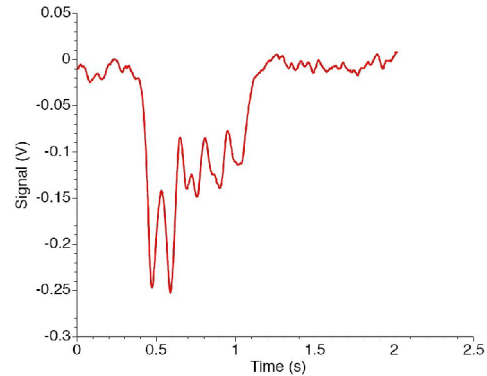


Figure 2a: At 10 kHz, a yeast cell is progressively repelled from the electrode array. Note that the double-peaks gradually reduce to single peaks as the influence of the electrode edges reduces.

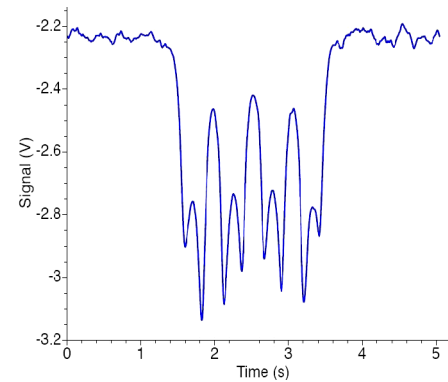


Figure 2b: At 1 MHz, the yeast cell is drawn toward the electrodes and the fluid flow carries it across the electrode array. Here, the attractive force is not strong enough to overcome the fluid flow and trap the cell onto the electrode.

3 SIMULATIONS

Figs. 3a and 3b were generated by solving the Laplace equation, $\nabla \cdot ((\sigma + j\omega\epsilon_0\epsilon_r)\nabla V) = 0$, using the electromagnetics module in the finite element analysis program, COMSOL® Multiphysics. Since the capacitance change caused by a yeast cell is approximately proportional to the electric field squared, we have plotted E^2 inside our microfluidic channel, which is 25 μm high and 80 μm wide. The permittivity and conductivity of the solution was 78 and 18 mS/m (corresponding to a NaCl concentration of 90 ppm) respectively.

For the repelling case, Fig. 3a, E^2 values are taken from a linear trajectory beginning from a point 5 μm above from the electrode (i.e., the yeast cell - 4 μm radius - would be 1

μm above from the electrode edge) and finishing at the center of the channel (i.e., $12.5 \mu\text{m}$ above the electrode array). For the attractive case, Fig. 3b, we have acquired E^2 data from a constant elevation of $5 \mu\text{m}$ above the electrode array. The capacitance signatures shown in these figures reveal very similar patterns compared with those shown in Figs. 2a and 2b. We have taken the negative of the E^2 values to show that the corresponding capacitance change is negative.

Fig. 3c shows the electric field squared profiles for various elevation heights above the electrode array. As the elevation height decreases, the electric field squared amplitude increases and the emergence of double-peaks becomes more apparent. At $10 \mu\text{m}$ above the electrodes, (just below the midpoint of the channel) the double-peaks have completely disappeared. By observing the ratio between the amplitudes of the double-peaks resulting from the presence of the electrode edges and the absolute strength of the electric field squared, one can use such curves to calibrate the position of the yeast cells.

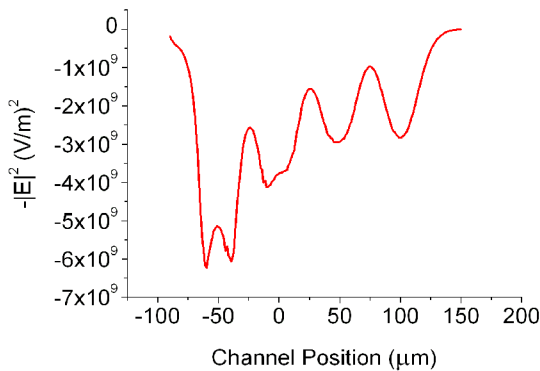


Figure 3a: The electric field squared amplitude decreases as we move further away from the electrode array.

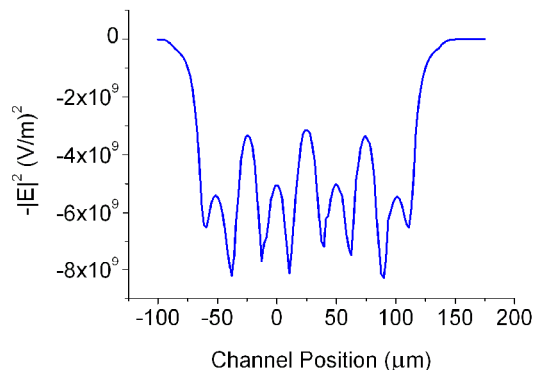


Figure 3b: The electric field squared magnitude is consistently large and reveals double-peaks, which correspond with the large electric fields existing at the electrode edges.

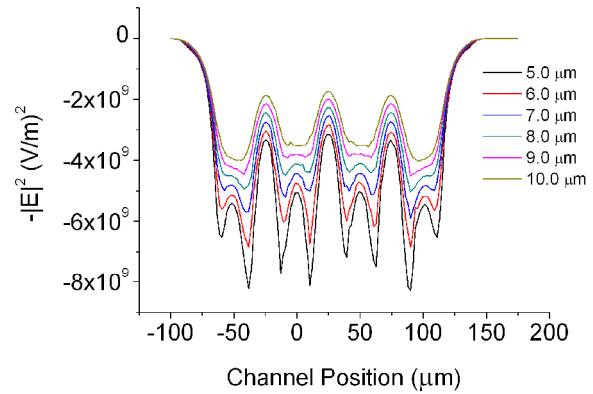


Figure 3c: Electric field squared along the electrode array length for different elevation heights above the electrode array.

4 CONCLUSIONS

We have developed a system that can dielectrophoretically manipulate yeast cells using low frequencies and detect the manipulation of those yeast cells using a high frequency (1.6 GHz) signal. An interdigitated electrode array provided a way for acquiring the dynamic signatures that occurred. We have confirmed that a 10 kHz frequency signal repels yeast cells and a 1 MHz frequency attracts them. This is consistent with the dielectric behavior of viable yeast cells. The simulated and experimental capacitance signatures are in good agreement with one another. When the capacitance signatures become weaker and the double-peak behavior fades with time, we have repulsion. If the signatures remain large as the yeast cell flows across the electrode array, we have an attractive force.

5 ACKNOWLEDGMENTS

The authors wish to thank the National Institute for Nanotechnology (NINT), the Natural Sciences and Engineering Research Council (NSERC), the Canada Foundation for Innovation (CFI), the Canadian Institute for Advanced Research (CIAR) and Canada Research Chair for financial support of this research.

6 REFERENCES

- [1] S-L. Liu, A. Karmenyan, M-T. Wei, C-C. Huang, C-H. Lin, and A. Chiou, "Optical forced oscillation for the study of lectin-glycoprotein interaction at the cellular membrane of a Chinese hamster ovary cell," *Optics Express*, 15(5), 2713, 2007.
- [2] B. Lincoln, H.M. Erickson, S. Schinkinger, F. Wottawah, D. Mitchell, S. Ulvick, C. Bilby, and J. Guck, "Deformability-based flow cytometry," *Cytometry Part A*, 59A(2), pp. 203-209, 2004.
- [3] D.K. Wood, M.V. Requa, and A.N. Cleland, "Microfabricated high-throughput electronic particle detector," *Review of Scientific Instruments*, 78, 104301, 2007.
- [4] L.L. Sohn, O.A. Saleh, G.R. Facer, A.J. Beavis, R.S. Allan, and D.A. Notterman, "Capacitance cytometry: measuring biological cells one by one," *Proc. Natl. Acad. Sci.*, 97(20), 10687-10690, 2000.
- [5] N. Manaresi, G. Medoro, A. Romani, M. Tartagni, and R. Guerrieri, "Beyond the microscope: embedded detectors for cell biology applications," *ISCAS* (3), 2911-2914, 2005.
- [6] G.A. Ferrier, A.N. Hladio, D.J. Thomson, G.E. Bridges, M. Hedayatipoor, S. Olson and M.R. Freeman, "Microfluidic electromanipulation with capacitive detection for cell diagnostic applications," *NSTI Nanotech 2007*, Santa Clara, California, Volume 2, MO22.03, pages 214-217, 2007.
- [7] H.A. Pohl, "Dielectrophoresis – the behavior of neutral matter in non-uniform electric fields," Cambridge University Press, Cambridge, 1978.
- [8] T.B. Jones, "Electromechanics of particles." Cambridge University Press, New York, 1995.