

Interfacing devices with cells

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Cells are the fundamental unit of life, and as such, understanding how they function and exploiting their features has garnered intense interest. From basic biologists trying to understand how cells work to clinicians trying to detect the presence of tumor cells during cancer therapy, many communities have intense interest in manipulating and measuring cells. Cells are difficult to interrogate, however. They are soft, fragile materials, and are small ($\sim\mu\text{m}$). Further, there are many cells in the body ($\sim 10^{13}$ to 10^{14} cells/human), yet small numbers of cells can be profoundly important (~ 100 circulating tumor cells per ml of blood). Microfabrication, because it allows for the creation of systems that are size-matched to cells while enabling integration of sensing and actuation, provides a potential solution to some of these manipulation challenges.

Our lab tries to exploit beneficial features of microtechnology to manipulate and interrogate cells. One approach is to take advantage of the electrical properties of cells to enact separations (Figure 1). Cells can be modeled electrically as a series of RC-networks embodying the properties of the cell interior (the cytoplasm), the cell membrane, and the exterior of the cell (the media). If any of these electrical parameters varies in response to a biological difference, then the overall electrical properties of the cell will vary, which can be detected electrically. Many important biological differences manifest themselves as electrical differences. For instance, as cells die via apoptosis, the membrane properties change (both conductance and capacitance), which can be readily detected electrically [1].

To detect electrical properties of cells, we have developed a method called iso-dielectric separation (IDS), where cells are placed in a spatially varying electric field and a spatially varying conductivity gradient that forces them to the location in a channel where their net polarizability (p) is zero (Figure 2) [2]. At that location, the force on the cell, given by the dielectrophoretic force ($F = p \cdot \nabla E$) will go to zero [3, 4]. Cells with different polarizabilities will end up in different locations in the channel, thus separating cells based upon electrical properties. The physical implementation of the method is described in Figure 3, and consists of a glass chip with patterned electrodes to create the field, along with microfluidics to deliver cells and create the conductivity gradient. An example separation of yeast based upon membrane integrity is shown in Figure 4.

Iso-dielectric separation has a number of features that exploit the properties of microsystems for cell manipulation. First, the conductivity gradients in the system can interact with the imposed electric fields to create electrohydrodynamic instabilities. These instabilities are stabilized by the walls, so scaling down the system via microfabrication enhances performance. Second, the system is capable of manipulating $\sim\mu\text{m}$ -sized cells one-at-a-time at high throughputs ($\sim 10^4$ cells/min), enabling both single-cell resolution yet the ability to process significant numbers of cells. Third, the method is fundamentally insensitive to non-electrical variations in the cells. The most important such variation is size variation. A typical cell population will have an $\sim 2\times$ variation in size, and so avoiding spurious size-based separations is paramount. Cells in IDS migrate to their electrical equilibrium point, which is independent of cell size, and thus the separation is independent of size. Finally, because the separation is electrically based, the ability to integrate this approach with more sophisticated electronics for sensing/actuation is readily possible.

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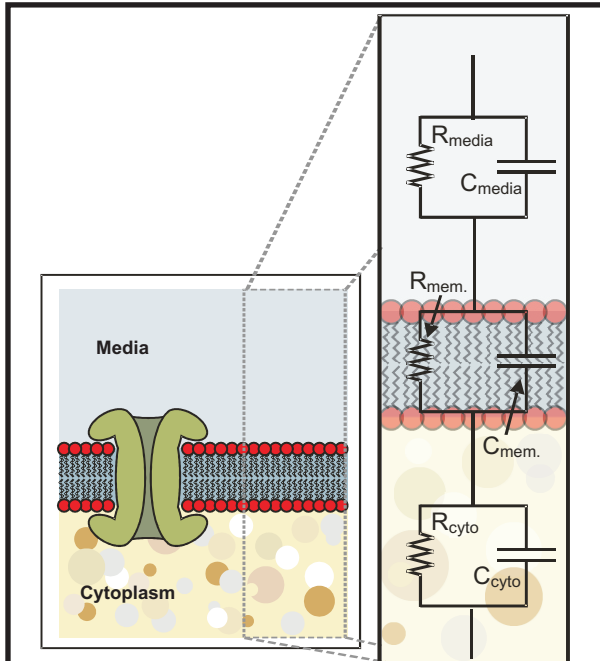


Figure 1: Electrical model of a cell. A typical biological cell consists of a conductive aqueous interior (cytoplasm) surrounded by an insulating lipid bilayer membrane. (Some cells additionally have a cell wall exterior to the cell membrane). Each of these compartments can be modeled by a resistor (representing the conductivity of the compartment) and a capacitor (representing the compartment permittivity). Biological processes that vary the properties of these compartments will result in changes to the electrical properties of cells.

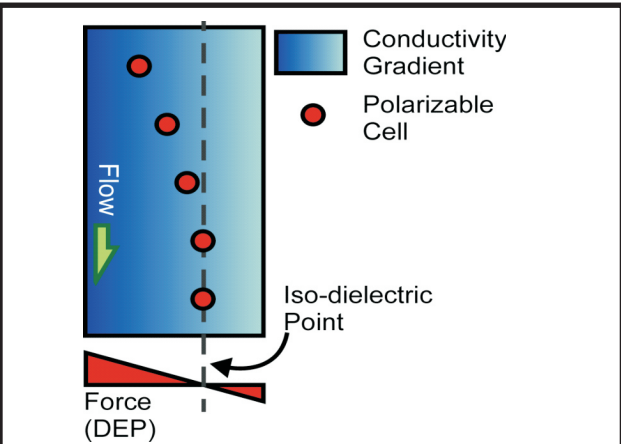
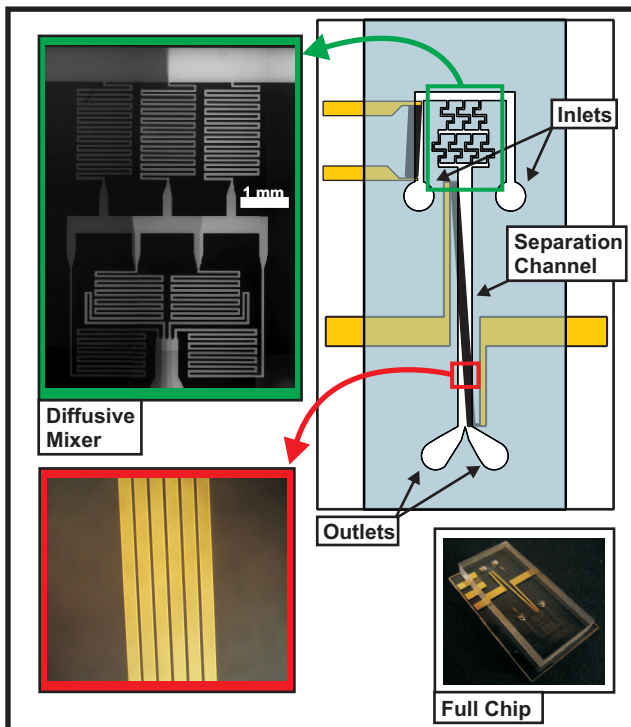


Figure 2: Overview of IDS. A polarizable cell is placed in a liquid conductivity gradient with a non-uniform electric field, causing the cell to experience a dielectrophoretic (DEP) force. In IDS, the cell is initially placed in a region of high liquid conductivity (higher than the cell), causing the DEP force to push the cell toward lower solution conductivity (i.e., to the right). Once the cell reaches the location where its effective conductivity matches that of the liquid, the DEP force goes to zero and the cell attains equilibrium.

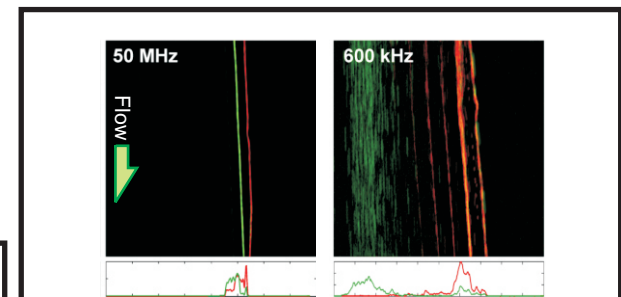


Figure 4: Example separation. Two images taken near the outlet of the separation channel, showing populations of yeast flowing downstream. The conductivity decreases from left to right. The yeast have been stained with a fluorescent stain such that live yeast with intact membranes are labeled green, while dead yeast with disrupted membranes are labeled orange. At 50 MHz, the two populations have indistinguishable electrical properties, while at 600 kHz, the differing membrane properties result in differing equilibrium locations for the two populations, allowing their separation.

Figure 3: Device architecture. Layout of the device, consisting of two inlets, a diffusive mixer to establish the electrical conductivity gradient, and a separation channel, along which diagonal pairs of electrodes are arranged. The electrodes are created by patterning gold on a glass substrate, while the microfluidic paths are made by molding PDMS from a SU-8 master. The PDMS and gold-patterned glass are aligned and bonded via oxygen plasma.