DIELECTROPHORETICALLY SWITCHABLE MICROFLUIDIC WEIR STRUCTURES FOR EXCLUSION-BASED SINGLE-CELL MANIPULATION

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ABSTRACT

We offer the first known platform for parallelized single-cell manipulation that combines negative dielectrophoretic (n-DEP) sorting with the efficient loading behavior of hydrodynamic traps. Our devices provide manipulations using ejection- and/or exclusion-based techniques. In ejection operations we unload targeted sites by driving their associated electrodes and displacing held beads or cells from the hydrodynamic capture faces. In exclusion operations we prevent site loading altogether by activating selected electrodes before introducing microparticles into the system. In our work, we have formed multi-colored patterns of interwoven dyed beads and cells. This platform thus enables scalable dielectrophoretically modulated single-cell manipulation in culture media.

Keywords: Dielectrophoresis, Hydrodynamic Trap, Weir, Single Cell Manipulation

1. INTRODUCTION

DEP is regularly used for both cell patterning [1] and sorting applications [2]. Most platforms incorporate positive dielectrophoretic (p-DEP) strategies to capture cells at electrode sites, capitalizing on associated high-magnitude capture forces and a complementary design ease. Unfortunately, this approach requires operation with low-conductivity buffers, thus presenting cell health complications. N-DEP methods, which function in cell culture media, are more difficult to develop because they are better suited for pushing cells away from localized sites instead of enabling trapping. Passive microfluidic weir structures as presented by Lee [3] demonstrate excellent single-cell loading characteristics but cannot manipulate or sort cells following capture. We have created an architecture that combines the effective capture of weir geometries with active n-DEP manipulations thus enabling active cell arrays that function in standard cell culture media (Figure 1).

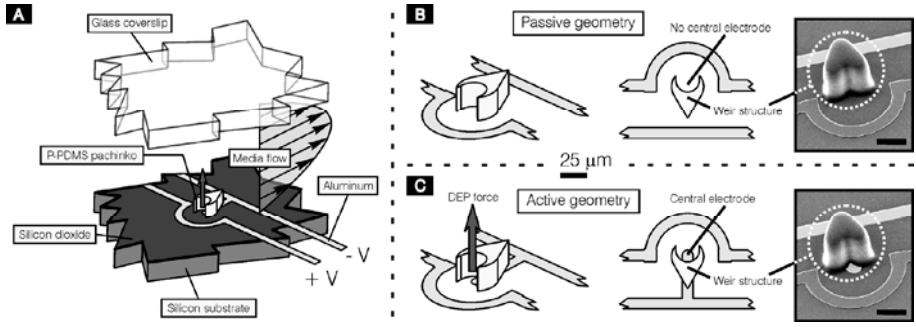

Figure 1: **(A)** provides an outline of our electrically active hydrodynamic weir platform. We use patterned electrodes to dielectrophoretically modulate site loading. **(B)** and **(C)** show passive and active weir architectures. The central electrode in the active geometries enables the DEP exclusion force (arrows). Scale bar = 25 µm.

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2. DEVICE OPERATION AND FUNCTIONALITY

Our active traps prevent weir site loading by using n-DEP to push cells away from the device capture crevices such that passing fluid flow sweeps ejected cells out of the device. This capability demanded a revised approach where weir structures are well-separated from the flow chamber ceiling. We thus implemented the structures using free-standing photopatternable silicone [4], taking advantage of its low autofluorescence as compared to SU-8. As shown in Figure 2, this revised approach still enables effective single-particle capture.

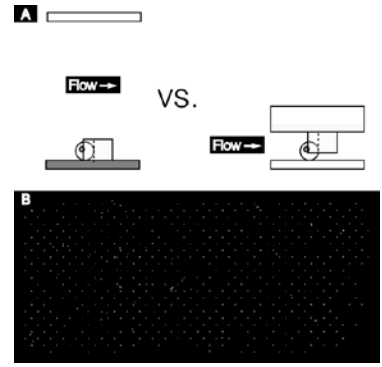

Figure 2: (A) compares our strategy (left) to the approach by Lee [3] (right). **(B)** presents the loading response of our designs, showing effective single-bead capture in a large array.

Our manipulation architecture provides two methods for loading. In one approach, we initially load all sites (Figure 3) by deactivating the electrodes and flushing microparticle-laced fluid through our devices. We then turn on active array sites (Figure 1C) by applying voltages to their affiliated electrodes. This procedure exerts vertical n-DEP forces on particles held in active cell-capture sites causing them to levitate above the capture surface where they cascade out of the array. Alternatively (Figure 4) we can prevent loading at active sites altogether by injecting particles into the chamber and repelling them from the capture surfaces while electrodes are ON. This approach offers benefits for cell-based assays by minimizing the potential for cells to non-specifically attach to active sites. Both approaches use n-DEP to *exclude* cells from sites, retaining for examination cells that nominally witness no DEP forces.

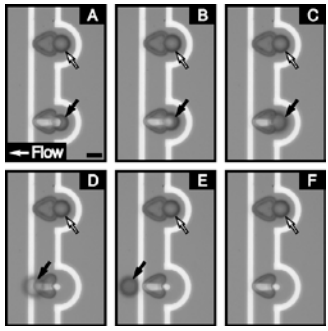

Figure 3: (A-F) show images detailing the site-specific ejection response of an active weir geometry (black arrow) as compared to a passive structure (white arrow). This approach enables the unloading of specific filled sites. Scale bar = 25 μm.

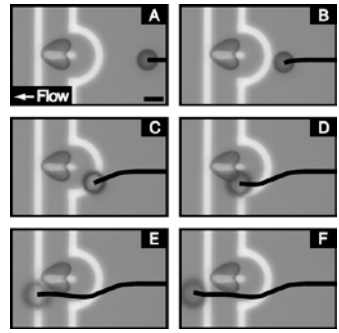

Figure 4: Instead of unloading specific sites after the fact, as shown in Figure 3, **(A-F)** demonstrate a method for preventing site loading by means of electrode activation. Throughout this sequence the electrodes are ON. Scale bar = 25 μm.

3. RESULTS AND DISCUSSION

In Figure 5 we show a checkerboard pattern formed from two different particle types. This demonstration advertises the key functionalities that our *active* array adds to prior mechanically based *passive* manipulation strategies. In scaled implementations we can approach the placement of multiple cell types at distinct locations across the chip and we can utilize the row/column site addressing schemes detailed earlier [2] for sorting operations. With BA/F3 cells we further examine device operation (Figure

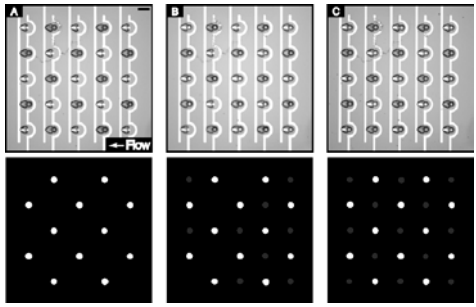

Figure 5: In **(A)** we selectively load the passive weir structures with orange beads (shown in white) using the loading approach demonstrated in Figure 4, where we apply voltages to prevent beads from loading in active sites (top – merged with bright field, bottom – fluorescent signal alone). In **(B)** we inject green fluorescent beads (shown in grey) and begin backfilling the remaining sites by turning off all applied voltages. **(C)** shows a 5×5 "checkerboard" pattern of fluorescent beads. Scale bar = 50 μm.

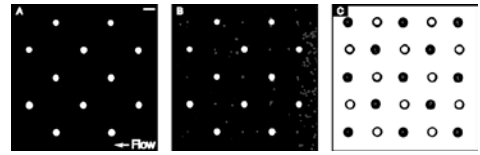

Figure 6: We first load the passive sites with green beads (shown in white) **(A)** and then backfill the grounded active sites with DsRED-expressing BA/F3 cells (shown in grey) **(B)**. In **(C)** we more closely examine the data provided in **(B)** by combining it with a post-processing screening layer showing that all target sights are loaded despite the fact that non-specific surface binding leaves residual cells in other locations. Future work will take advantage of the wide variety of published methods available for effectively managing binding interactions between cells and device surfaces. Scale bar = 50 μm.

6). Though non-specific binding hindered perfect loading in initial tests, individual cells did load into every prescribed array site (6C). In continuing work, known strategies should alleviate this binding effect. We thus present a novel approach to single-cell manipulations enabling loading and sorting in standard cell culture media.

4. CONCLUSIONS

In our work we have introduced a novel approach to manipulating single cells that capitalizes upon the efficient trapping characteristics of weir-style hydrodynamic traps and further augments that functionality using active negative dielectrophoretic sorting. In a single platform we offer means for ejecting and/or excluding particles from targeted subsets of arrayed system traps. We thus provide a unique scalable technology for sorting and positioning groups of single cells that functions effectively in standard culture media.

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