INTEGRATED MICROBIOREACTOR WITH PIEZOELECTRIC TRANSDUCER ARRAY FOR CELLULAR DIAGNOSTICS

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ABSTRACT

This paper reports a perfusion microbioreactor that can be integrated with a piezoelectric transducer array for rapid disease diagnosis, such as identifications of cancer cells and infection-induced cell abnormality. By using the gap between suspended transducers as the high-aspect-ratio barriers to establish high flow resistance into the culture chamber, a very low shear flow region is achieved on the transducer surfaces. This design offers minimal influences of mechanical forces on cellular detection and cells cultured on the surface of transducers. Detailed design, simulation results and experimental verifications of the microbioreactor are discussed.

KEYWORDS: Microbioreactor, Cell culture

INTRODUCTION

Perfusion-based bioreactors with isolated culture chamber from bulk fluid flow had provided a means to create a micro-culturing chamber that mimics *in vivo* environment [1, 2]. The key novelties of these pioneer works included microfluidic structures with high flow resistance from perfusion channels to the culture chamber, such as shallow 2 μm openings [1] or micropillar arrays [2]. These geometrical barriers suppress direct convective flow to minimize shear stress on the living cells. Diffusion mass transport is the main mechanism for exchanging media between the culture chamber and perfusion channels. The chamber size is usually limited to 100 μm to resemble capillary system with short diffusion paths. This type of microbioreactors is best suited for studying the biomechanics of living cells particularly because of the minimal fluid flow around the immediate vicinity of the cell. In this paper, we describe a microbioreactor that can be integrated with a large array of piezoelectric transducers that bypasses the limitation of diffusion length. Detailed discussions of the piezoelectric transducer have been reported in another paper [Fig. 1(B)] [3]. By monitoring the tractions exerted by cells anchored on the surface of the transducer, quantitative mechanical cues of diseased cells could be deduced from the real-time cell-traction-modulated impedance responses of the transducer. This approach is particularly amenable to rapid diagnosis of cancer cells, malaria-infected red blood cells, and other cell types that respond mechanically to diseases.

THEORY

Using high-aspect-ratio geometrical barriers, a microfluidic bioreactor was designed to maximize mechanical signal-to-noise ratio, where mechanical perturbations from fluid flow are minimized to (1) suppress fluidic shear force on the cells and (2) avoid mechanical influence from the surrounding fluid on the transducer.

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Figure 1(A) shows a cut-out drawing of the microfluidic chamber design. One of the key design features is the 40 to 50 μm gaps between transducers forming the barriers with high flow resistance into the culture chamber. The convective media flow takes place largely underneath the culture chamber, resulting in minimal influence on the transducers and the cells. Another key design feature is that, by using the transducers as the flow barriers, the volume of the culture chamber can be large enough to contain the entire transducer array, in millimeter range, without being limited by the diffusion length consideration. Furthermore, a large culture chamber allows for scaling up with multiple detections in one microbioreactor. Finally, the large feature sizes result in relaxed alignment tolerance between the PDMS microbioreactor and the transducer array.

EXPERIMENTAL

To verify the design concept of the microbioreactor, both finite-element analysis and microfluidic experiments were performed. Figure 1(B) shows the SEM micrograph of the microfabricated piezo-transducer array, where the cross section of the perfusion channel was 500 μm square, and the transducer width ranged from 20 to 40 μm with gap ranging from 40 to 50 μm. The simulation results with COMSOL® 3.5a indicated that this configuration results in a very low shear flow region on the surface of the transducer, in the range of several nm/s when the volume flow rate is 0.03 μL/min [Fig. 1(C)]. Figure 2(A) shows that the simulated shear stress on the surface of the transducer has been suppressed to 15 to 30 μPa for two different chamber depths. Figure 2(B) shows the distribution of concentrations in three different chamber sizes at 1 s, 20 s, and 120 s from bottom to top. The sizes are T=100 μm with D=1 mm (black lines), T=50 μm with D=1 mm (gray lines), and T=50 μm with D=0.75 mm (dot lines), where T and D are depth and diameter respectively. Note that the concentrations at the edge of transducers quickly reach more than 40% concentration in 1 second, and the turn-over time is around 20 seconds. Figure 2(C) is the concentration distribution of the cross-section of a microbioreactor with T=50 μm and D=0.75 mm at 120 s. This shows that the concentration distribution of the scaled-up microchamber in the beginning is determined by the distance between the chamber wall and transducer gaps.

RESULTS AND DISCUSSION

Figure 3 shows the experimental results of one of the microbioreactors, where white lines are the trajectories of 1-μm polystyrene beads around the transducer surfaces [Fig. 3(A)] and maximum flow region in perfusion channel [Fig. 3(B)], and the arrows indicate the flow direction with 0.03 μL/min volume flow rate. The results show that fluid flow has been successfully suppressed on the plane of transducers, and Brownian motion dominates in this region. Figure 3(C) is a picture of HeLa cells cultured and kept viable on the transducer surfaces in the bioreactor. These results point to the potential capability of integrating with a large transducer array with the ultimate goal of massively parallel diagnoses of diseases in cells.

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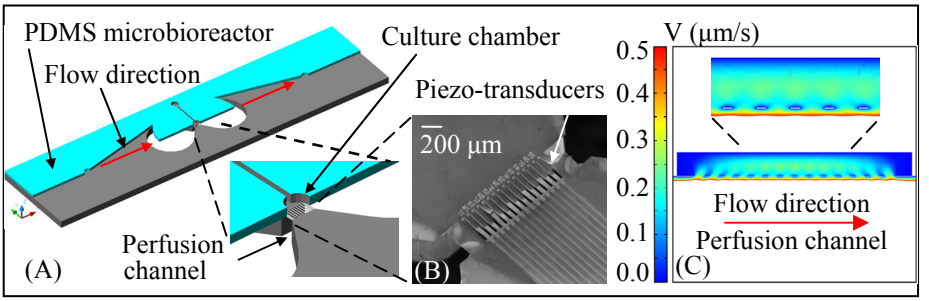

Figure 1: (A) A conceptual illustration of the bioreactor, (B)A SEM micrograph of-transducer array, and (C) FEM simulation results of velocity field.

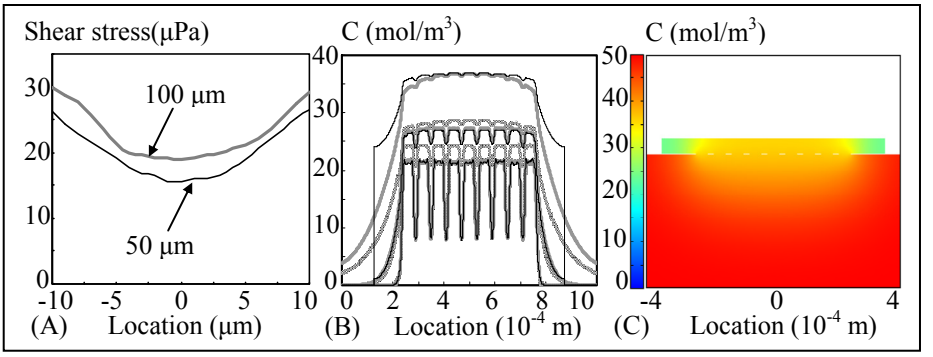

Figure 2: FEM simulation results of (A) shear stress and (B) & (C) concentration.

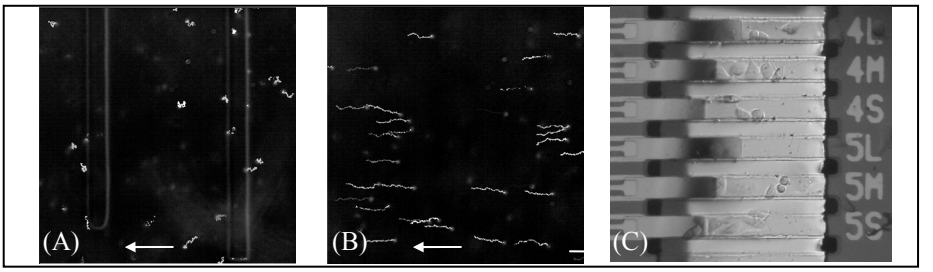

Figure 3: Flow patterns of (A) near transducer surface and (B) perfusion channel, and a micrograph of cultured HeLa cells on thin-film piezo-transducers.

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