Microfluidic bio-particle manipulation for biotechnology

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ABSTRACT

Microfluidics and lab-on-a-chip technology offers unique advantages for the next generation devices for diagnostic therapeutic applications. For chemical, biological and biomedical analysis in microfluidic systems, there are some fundamental operations such as separation, focusing, filtering, concentration, trapping, detection, sorting, counting, washing, lysis of bio-particles, and PCR-like reactions. The combination of these operations led to the complete analysis systems for specific applications. Manipulation of the bio-particles is the key ingredient for these applications. Therefore, microfluidic bio-particle manipulation has attracted a significant attention from the academic community. Considering the size of the bio-particles and the throughput of the practical applications, manipulation of the bio-particles is a challenging problem. Different techniques are available for the manipulation of bio-particles in microfluidic systems. In this review, some of the techniques for the manipulation of bio-particles; namely hydrodynamic based, electrokinetic-based, acoustic-based, magnetic-based and optical-based methods have been discussed. The comparison of different techniques and the recent applications regarding the microfluidic bio-particle manipulation for different biotechnology applications are presented. Finally, challenges and the future research directions for microfluidic bio-particle manipulation are addressed.

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1. Introduction

The miniaturization trend of integrated circuits since 1970s, and the development of advanced fabrication techniques for micro and nano-scale devices [1] since 1980s led to the usage of devices having the dimensions of micrometers and nanometers in many fields. This trend has helped microfluidics, which is the flow physics at micro scale, become an active research area at the intersection of chemistry, physics, biology and engineering. This intersection eliminated the boundaries between these disciplines. The elimination of these boundaries has posed many challenges and new directions for organizations of education and research. One of the important challenges is the rapid development of biochips, miniaturized analysis systems or lab-on-a-chip (LOC) devices which are microfluidic platforms on which one can handle chemical and biological analyses, point-of-care testing, clinical and forensic analysis, molecular and medical diagnostics for biological, biomedical and

chemical applications. LOC devices can perform the same specialized functions as their bench-top counterparts. They can also perform clinical diagnoses, scan DNA, run electrophoretic separations, act as microreactors, detect cancer cells and identify bacteria and viruses [2]. On a single chip, hundreds of different reactions and/or analyses can be performed at the same time through hundreds of parallel microchannels. Originally it was thought that the most significant benefit of these LOC devices would have been the analytical improvements associated with the scaling down of the size. Further developments revealed other significant advantages such as: (i) small amount of sample (in the nano to picoliter range, opening the door to the possibility of analyzing components from single cells), (ii) small amount of reagents, (iii) very short reaction and analysis time compared to bench-top counterparts, (iv) reduced manufacturing costs, (v) increased automation, (vi) high portability, and (vii) opportunity for massively parallel chemical analyses either on the same or multiple samples [3].

For chemical, biological and biomedical analyses in microfluidic systems, there are some fundamental operations such as separation, focusing, filtering, concentration, trapping, sorting, detection, counting, washing, lysis of bio-particles, and PCR-like reactions. The combination of these operations led to the complete analysis system or LOC system for a certain application.

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Manipulation of the bio-particles is the key ingredient for the aforementioned operations. Therefore, microfluidic bio-particle manipulation has attracted significant attention from the academic community. Considering the size of the bio-particles and the required throughput for the practical applications, manipulation of the bio-particles is a challenging problem. Many research groups and scientists have proposed different techniques to manipulate bio-particles such as hydrodynamic-based, electrokinetic-based, acoustic-based, magnetic-based, optical-based etc. In this review, these different techniques are discussed. Moreover, the comparison of different techniques and the recent biotechnology applications regarding the microfluidic bio-particle manipulation are presented. Finally, challenges and the future research directions are also addressed.

2. Manipulation methods

Manipulation methods can be categorized as passive or active methods depending on the presence of an external force field. Passive systems utilize the flow field together with the channel geometry or topology changes to manipulate the motion of particles. On the other hand, active systems utilize an external force field such as electric, acoustic, magnetic and optic to manipulate the motion of particles. These methods can also be categorized as label-based or label-free methods depending on the need for any labeling (or tags) for the bio-particles. The label-free methods utilize the intrinsic properties of the bio-particles such as size, shape, density, dielectric properties, acoustic properties and refractive index. On the other hand, the label-based techniques require additional labels to manipulate bio-particles. As an example, two conventional cell sorting technique namely fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting (MACS) require cell-specific labeling through fluorophore-conjugated antibodies and magnetic beads conjugated with antibodies, respectively [4].

Considering the manipulation of a bio-particle in a microfluidic system, depending on the methods there may exist multiple forces on a bio-particle, some of which can be dominant or negligible. Therefore, the order of magnitude estimate of the various forces experienced by a bio-particle is crucial for microfluidic applications to predict the resultant motion of bio-particles. As an example, Brownian motion is the random movement of particles due to the thermal effects; however, Brownian motion is negligible for the particles with a size larger than 1 μm for microfluidic applications [5].

There are several techniques to manipulate bio-particles in microfluidic systems. Several of those methods are reviewed within this paper. Stand-alone review papers are present for each of these methods [6–14] since there has been a vast amount of research effort on these techniques for microfluidic platforms for the last two decades. In this review, our objective is to give the basics of each method. More work is dedicated for the comparison of the techniques in terms of associated sample preparation, throughput, channel geometry, material and fabrication, and the required hardware. We believe that such a comparison will provide valuable help for the researchers from many disciplines who would like to apply microfluidic technology to bio-particle related biotechnology applications.

2.1. Hydrodynamic-based (HD)

In microfluidic applications, the flow can be induced by pressure difference (pressure-driven flow) and/or by electrical field (electro-osmotic flow). Since electric field is introduced for electro-osmotic flow, other forces (which will be discussed in the following subsection) other than drag force generated on the particle come into

picture. In the case of pressure-driven flow, pressure difference is the main parameter which control the incompressible fluid flow in microchannels. The drag force is the only force generated on the particles as a result of the interaction of the particle with the flow field. Hydrodynamic-based methods are passive methods in which the bio-particle manipulation is performed by use of the drag force generated on the particles through specially designed channel geometries and topologies. The dimensionless numbers which characterize the particle flow in a microchannel are the channel Reynolds number (Re) and the particle Reynolds number (Re_p) [15]:

$$Re = \frac{\rho U_{\max} D_h}{\mu}, \quad Re_p = \frac{\rho U_{\max} d^2}{\mu D_h} = Re\left(\frac{d}{D_h}\right)^2, \quad (1)$$

where $U_{\max}$ is the maximum velocity in the microchannel, ρ is the fluid density, μ is the dynamic fluid viscosity, d is the particle diameter, and D_h is the hydraulic diameter of the channel. Typically, flows within microchannels are in Stoke's flow regime (low Re flows) which means the flow follows the boundaries of the domain. When particles are present within the channel, they also follow the streamlines of the flow field in a deterministic manner. However, when an obstacle and/or flow contraction/expansion is presented within the channel, the particle trajectories reveal size dependence. Therefore, by specially designed channel geometries, bio-particles can be manipulated according to their size and deformability.

Introducing obstacles and posts with a critical spacing can be utilized as filter structure to capture (trap) or isolate specific bio-particle of interest with a size larger than the critical size [6]. However, pore-based filtration may be ineffective with deformable bio-particles and/or bio-particles with unique shapes. By introducing series of posts, a size dependent lateral displacement of bio-particles can also be achieved, which is known as deterministic lateral displacement (DLD) (see Fig 1a) [16–20]. DLD can be utilized for bio-particle separation, sorting and focusing. The presence of slanted or anisotropic obstacles within the microchannel can also induce size-based motion of the particles due to the particle-obstacle interaction induced rotational flows, which is known as hydrophoresis (see Fig. 1b) and can be implemented for bio-particle separation, sorting and focusing [21–26]. With the introduction of contraction/expansion (pinch segment) within the microchannel network together with the laminar flow profile, bio-particles can also be manipulated to flow at different streamlines, which is known as pinch-flow fractionation (PFF) (see Fig 1c) and can be implemented for bio-particle separation, sorting and focusing [27–31].

The Stoke's flow regime is valid up to $Re \sim 1$. When Re reaches unity and beyond, the inertial effects become significant and modify the flow characteristics, which is known as inertial microfluidics. In this regime, particles do not follow the streamlines of the flow field. When the inertial effects come into picture, two inertial lift forces are induced on the particle: (i) a shear gradient lift force and (ii) a wall-effect lift force [15]. A wall-effect lift force induces a repelling force away form the wall. On the other hand, shear-gradient lift force induces an attractive force towards the wall [15]. When the channel geometry becomes curved, a secondary rotational flow begins to be observed due to the inertia of the fluid which is known as Dean flow. The dimensionless numbers which characterizes this secondary flow are the Dean number (De) and the curvature ratio (δ) [15,32]:

$$De = Re\left(\frac{D_h}{2r}\right)^{1/2}, \quad \delta = \frac{D_h}{2r}, \quad (2)$$

where r is the radius of curvature of the channel. De and δ are two important parameters which affect the motion of the particles within curved channels. Inertial microfluidics can be utilized for separation, sorting, focusing, and isolation of bio-particles [33–39].