RAPID AND PRECISE PARTICLE MANIPULATION IN MICROFLUIDIC DEVICES

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Summary In recent years, several hydrodynamic methods have been proposed for continuous particle classification not utilizing any other outer fields such as electrical, magnetic, or gravitational force etc. Our group also proposed a novel method for continuous, rapid and precise particle separation, named Pinched Flow Fractionation (PFF) and Hydrodynamic Filtration (HDF). Here, we present the mechanistic features of those separation schemes and some applications based on the both methods.

INTRODUCTION

Microfluidic devices have several advantages over conventional fluidic systems due to their small dimensions, stable laminar flow patterns, the easiness in duplicating the specific structures to make a large-scale array, and the flexibility in design. In this decade, therefore, a number of microfluidic systems have been developed researches for various applications such as biopolymer analysis, biological or environmental sensors, cell manipulation systems including analysis, sorting, treatments, and cultivation, and precise synthesis of novel materials. The purposes of the microfluidic research are classified mainly into three categories including (1) the quantitative analysis of ultra-small-volume samples in the studies relating functional microarrays, single-cell analysis, POC devices, or next-generation sequencers, (2) the precise manipulation of small objects in the research of cell separation and sorting, and (3) the precise preparation of small and functional materials such as emulsions, micro/nano-particles, microcapsules, and microfibers. According to the second application mentioned above, several hydrodynamic methods have been proposed for continuous particle sorting without employing outer fields such as electrical, magnetic, and gravitational forces. Our group also has proposed a technique for continuous, rapid and precise particle separation as follows.

1. Pinched Flow Fractionation

We have proposed a concept of 'Pinched Flow Fractionation (PFF) [1], and achieved the successful separation of various types of sub-micron to micron-size structures including polymer beads, cells, droplets and macromolecules. In this method, particles can be separated according to their diameters simply by introducing liquid flows with and without particles into a microchannel (see Fig.1), i.e., no outer field controls are needed. Also, in PFF method, separated particles can be continuously collected using multiple branch channels connected to the pinched segment.

If the multiple collection channels are uniformly arranged in the PFF method, all branch channels are not effectively used since the liquid flow in the pinched segment is equally distributed to branch channels. To overcome this disadvantage, "asymmetric pinched flow fractionation (AsPFF)" [2] was proposed. The microfluidic device for AsPFF has a short drain channel, and a large portion of the liquid flow goes through the drain channel. Liquid flow containing particles is then efficiently distributed to other branch channels. Therefore, almost all branch channels can be effectively used for particle collection.

The effluent positions of particles in PFF are determined by the microchannel structure designed beforehand and it is difficult to change the size range of the separated particles after fabrication. Therefore, we proposed "tunable pinched flow fractionation (tunable PFF)" [3], in which the effluent positions of the particles can be precisely tuned by

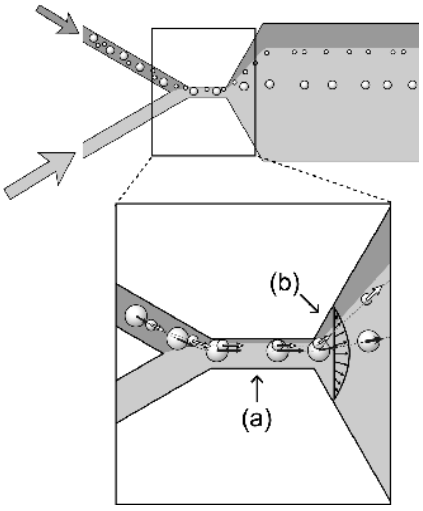

Figure1. Principle of PFF method: (a) First, particles are aligned on the sidewall of the pinched micro-channel by controlling the ratio of the flow rate from the two inlets, (b) and then, particles are separated based on their sizes in the broadened stream [1].

controlling the flow rates distributed to each outlet using microvalves. And alternative method of precise tuning of PFF liquid flow using electroosmosis made a prompt change of flow distribution in the microchannel [4]. Using PFF microchannel systems, micro-droplets were also separated based on their sizes only by introducing the emulsion from the inlet of the devices [5].

2. Hydrodynamic Filtration (HDF)

We have proposed another scheme for continuous separation of particles or soft matters utilizing laminar flow profiles in a microchannel network with multiple branch channels, named Hydrodynamic Filtration (HDF) [6], in which both concentration and classification of particles can be performed at the same time, by simply introducing a liquid containing a particle mixture. In this method, the hydrodynamics of laminar flow is also utilized in a microchannel having multiple branch points and side channels, not necessitating any outer field controls. In addition, not the cross-sectional size of the microchannel, but the flow profile inside the channel determines the size limit of the concentrated/classified particles. Therefore, a problem of channel clogging, which is similar to the mesh clogging or membrane fouling in the case of existing filtration methods, can be avoided.
As shown in Fig.2, when the relative flow rate distributed into side channels at a branching point is low enough, only a small portion of the liquid near the sidewall is withdrawn from the main stream. In this flow state, particles whose diameter is larger than a specific value cannot enter the side channels, even if they are flowing near the sidewalls in the main channel, and even if the particle is smaller than the cross sectional area of the side channels. In addition, after passing through the branching point, particles are slightly concentrated. On the other hand, when the flow rates distributed into the side channels are increased a little larger, particles near the sidewalls can go through the side channels. Particle concentration and classification can be achieved by combining these flow states. By repeating the flow state so as that the introduced particles would never enter the side channels, a large portion of the introduced liquid can be removed from the main stream after passing through the multiple branching points, resulting in the concentrated particle alignment onto the sidewalls. Then by increasing the relative flow rates into the side channels stepwise in the downstream region, aligned particles are collected independently according to their sizes. This operation dramatically increases the collected particle concentration, since only a small portion of the liquid flow near the sidewalls is collected.

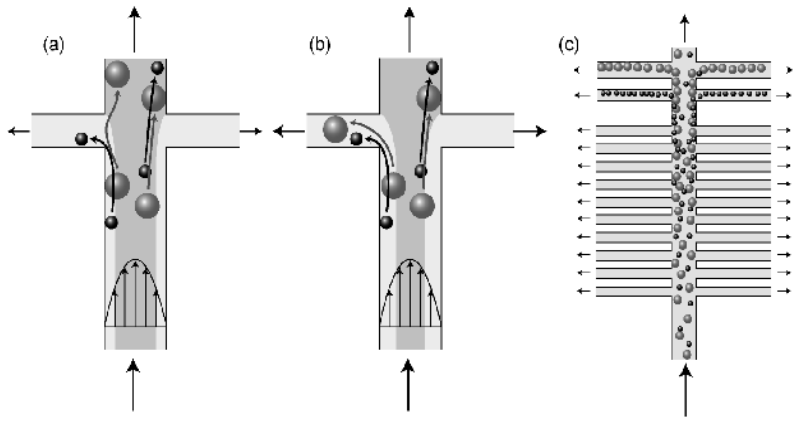

Figure 2. Principle of HDF method: Particle behavior at the bifurcation point when the flow distribution ratio of branch micro-channel to main channel is relatively (a) smaller and (b) larger. (c) Particle concentration and separation behavior in the micro-channel with multiple bifurcation points and branch channels [6].

However, the inevitable contamination of small particles into the concentrated large-particle fraction decreases the separation efficiency. To overcome these disadvantages, we proposed an improved HDF scheme [7] for particle separation, employing flow splitting and recombining. That is, by repeating liquid removal from the main channel, and recombining to the downstream, particles are perfectly aligned on one sidewall in the main channel. Then, particles can be separated according to their sizes, by increasing the relative flow rates into the outlet channels. By employing the modified HDF technique employing flow splitting and re-combining, the separation efficiency was improved. Several applications of these systems have been demonstrated for the separation of various kinds of biological materials including blood cells, hepatocytes, emulsions, bubbles and non-spherical cells/particles, and the cell treatment for a limited span of time and selective extraction of cell nuclei [8-15].

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