between the activatable cell and cell activator on the surface of the carriers. The complexes formed may be just few percent larger than the uncomplexed cell or many times the size of the uncomplexed cell. In order to facilitate separations, an increase of at least 20% is desirable with higher percentages (40, 50 100 1000 or more) being preferred.

[0077] D. Separating Cells from Toxic Material

[0078] DLD can also be used in purifications designed to remove compounds that may be toxic to a cell or to keep the cells free from contamination by a toxic compound. Examples include an antibiotic, a cryopreservative, an antifungal, a toxic metabolite, sodium azide, a metal ion, a metal ion chelator, an endotoxin, a plasticizer, a pesticide, and any combination thereof. The device can be used to remove toxic compounds from cells to ensure consistent production of material from the cells. In some instances, the cell can be a log phase cell. The term "log phase cell" refers to an actively dividing cell at a stage of growth characterized by exponential logarithmic growth. In log phase, a cell population can double at a constant rate such that plotting the natural logarithm of cell number against time produces a straight line.

[0079] The ability to separate toxic material may be important for a wide variety of cells including: bacterial strains such as BL21, Tuner, Origami, Origami B, Rosetta, C41, C43, DH5α, DH10β, or XL1Blue; yeast strains such as those of genera Saccharomyces, Pichia, Kluyveromyces, Hansenula and Yarrowia; algae; and mammalian cell cultures, including cultures of MRC-5 cells; HeLa cells; Vero cells; NIH 3T3 cells; L929 cells; Sf21 cells; Sf9 cells; A549 cells; A9 cells; AtT-20 cells; BALB/3T3 cells; BHK-21 cells; BHL-100 cells; BT cells; Caco-2 cells; Chang cells; Clone 9 cells; Clone M-3 cells; COS-1 cells; COS-3 cells; COS-7 cells; CRFK cells; CV-1 cells; D-17 cells; Daudi cells; GH1 cells; GH3 cells; HaK cells; HCT-15 cells; HL-60 cells; HT-1080 cells; HT-29 cells; HUVEC cells; I-10 cells; IM-9 cells; JEG-2 cells; Jensen cells; Jurkat cells; K-562 cells; KB cells; KG-1 cells; L2 cells; LLC-WRC 256 cells; McCoy cells; MCF7 cells; WI-38 cells; WISH cells; XC cells; Y-1 cells; CHO cells; Raw 264.7; BHK-21 cells; HEK 293 cells to include 293A, 293T and the like; HEP G2 cells; BAE-1 cells; SH-SY5Y cells; stem cells and any derivative thereof to include engineered and recombinant strains.

V. Technological Background

[0080] Without being held to any particular theory, a general discussion of some technical aspects of microfluidics may help in understanding factors that affect separations carried out in this field. A variety of microfabricated sieving matrices have been disclosed for separating particles (Chou, et. al., *Proc. Natl. Acad. Sci.* 96:13762 (1999); Han, et al., *Science* 288:1026 (2000); Huang, et al., *Nat. Biotechnol.* 20:1048 (2002); Turner et al., *Phys. Rev. Lett.* 88(12): 128103 (2002); Huang, et al., *Phys. Rev. Lett.* 89:178301 (2002); U.S. Pat. Nos. 5,427,663; 7,150,812; 6,881,317). Bump array (also known as "obstacle array") devices have been described, and their basic operation is explained, for example in U.S. Pat. No. 7,150,812, which is incorporated herein by reference in its entirety. A bump array operates essentially by segregating particles passing through an array (generally, a periodically-ordered array) of obstacles, with segregation occurring between particles that follow an "array direction" that is offset from the direction of bulk fluid flow or from the direction of an applied field (U.S. Pat. No. 7,150,812).

[0081] A. Bump Arrays

[0082] In some arrays, the geometry of adjacent obstacles is such that the portions of the obstacles defining the gap are symmetrical about the axis of the gap that extends in the direction of bulk fluid flow. The velocity or volumetric profile of fluid flow through such gaps is approximately parabolic across the gap, with fluid velocity and flux being zero at the surface of each obstacle defining the gap (assuming no-slip flow conditions) and reaching a maximum value at the center point of the gap. The profile being parabolic, a fluid layer of a given width adjacent to one of the obstacles defining the gap contains an equal proportion of fluid flux as a fluid layer of the same width adjacent to the other obstacle that defines the gap, meaning that the critical size of particles that are 'bumped' during passage through the gap is equal regardless of which obstacle the particle travels near.

[0083] In some cases, particle size-segregating performance of an obstacle array can be improved by shaping and disposing the obstacles such that the portions of adjacent obstacles that deflect fluid flow into a gap between obstacles are not symmetrical about the axis of the gap that extends in the direction of bulk fluid flow. Such lack of flow symmetry into the gap can lead to a non-symmetrical fluid flow profile within the gap. Concentration of fluid flow toward one side of a gap (i.e., a consequence of the non-symmetrical fluid flow profile through the gap) can reduce the critical size of particles that are induced to travel in the array direction, rather than in the direction of bulk fluid flow. This is because the non-symmetry of the flow profile causes differences between the width of the flow layer adjacent to one obstacle that contains a selected proportion of fluid flux through the gap and the width of the flow layer that contains the same proportion of fluid flux and that is adjacent the other obstacle that defines the gap. The different widths of the fluid layers adjacent to obstacles define a gap that exhibits two different critical particle sizes. A particle traversing the gap can be bumped (i.e., travel in the array direction, rather than the bulk fluid flow direction) if it exceeds the critical size of the fluid layer in which it is carried. Thus, it is possible for a particle traversing a gap having a non-symmetrical flow profile to be bumped if the particle travels in the fluid layer adjacent to one obstacle, but to be not-bumped if it travels in the fluid layer adjacent to the other obstacle defining the gap.

[0084] In another aspect, decreasing the roundness of edges of obstacles that define gaps can improve the particle size-segregating performance of an obstacle array. By way of example, arrays of obstacles having a triangular cross-section with sharp vertices can exhibit a lower critical particle size than do arrays of identically-sized and -spaced triangular obstacles having rounded vertices.

[0085] Thus, by sharpening the edges of obstacles defining gaps in an obstacle array, the critical size of particles deflected in the array direction under the influence of bulk fluid flow can be decreased without necessarily reducing the size of the obstacles. Conversely, obstacles having sharper edges can be spaced farther apart than, but still yield particle segregation properties equivalent to, identically-sized obstacles having less sharp edges.