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Numerical investigation of microfluidic sorting of microtissues

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ABSTRACT

We characterize through simulation a microfluidic-based particle sorting approach instrumental in flow cytometry for quantifying microtissue features. The microtissues are represented herein as rigid spheres. The numerical solution employed draws on a Lagrangian–Lagrangian (LL), Smoothed Particle Hydrodynamics (SPH) approach for the simulation of the coupled fluid–rigid-body dynamics. The study sets out to first quantify the influence of the discretization resolution, numerical integration step size, and SPH marker spacing on the accuracy of the numerical solution. By considering the particle motion through the microfluidic device, we report particle surface stresses in the range of $\sigma = [0.1, 1.0]$ Pa; i.e., significantly lower than the critical value of 100 Pa that would affect cell viability. Lift-off of non-neutrally buoyant particles in a rectangular channel flow at the target flow regime is investigated to gauge whether the particle shear stress is magnified as a result of dragging on the wall. Several channel designs are considered to assess the effect of channel shape on the performance of the particle sorting device. Moreover, it is shown that a deviation in flow rate does not influence the focusing of the particles at the channel outlet.

1. Introduction

Biomedical research and clinical applications rely on accurate devices for sorting and separating of cells. For decades, single cells have been successfully purified using fluidic sorting techniques. Those techniques were mostly limited to purification of small cells with diameters $d < 10$ μm. On the contrary, many of the conventional cell sorting techniques have been inefficient for the purification of cell aggregates or 3D microtissues; i.e., spheroids with diameter $d > 100$ μm. For instance, cell separation techniques such as Magnetic Activated Cell Sorting (MACS) and affinity chromatography rely on capture molecules that adhere to the cell surface. Their success rate decreases when handling large particles as they rely only on the surface properties of the aggregates. Alternatively, in charge based techniques, such as Fluorescence Activated Cell Sorting (FACS), the particle is deflected in an external electric field. Large inertia of cell aggregates decreases the deflection induced by the electric field thus requiring a larger travel distance for successful particles separation. The approach is highly sensitive since slight perturbations in particle trajectory can magnify over long distances and negatively impact the controlled particle motion.

Large particles have traditionally been sorted manually, i.e. under a microscope. This approach, however, is less desirable owing to its low throughput and issues related to repeatability, sensitivity, and quantification of experiments. A successful automated physical separation based on optical parameters; i.e., a FACS methodology, was implemented in the COPAS Bio-Sorter [1]. The sorting mechanism is pneumatic and consists of a microvalve actuated in response to particular optical

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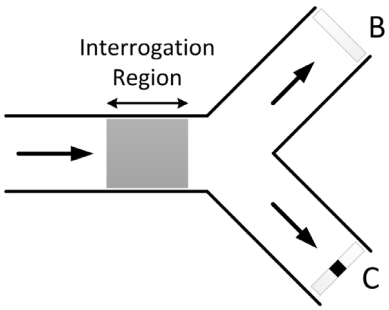

Fig. 1. Schematic illustration of the device used for sorting of large particles and 3D microtissues. At the normal condition, branches *B* and *C* are respectively open and closed, letting the desired particles move freely through branch *B*. Upon the detection of a desired property in the interrogation region, the solenoid valves switch the status of *B* and *C* to direct undesired particles to the waste container.

features. Unwanted particles are diverted into a waste tank, while desired particles take the default flow path and pass through. The system, which provided significant efficiency gains for sorting of large particles ranging from 10 μm to 1500 μm, is limited in that it employs single photon optics, which cannot analyze the interior of aggregate cells deeper than 50 μm. Buschke and collaborators developed a multiphoton flow cytometry system capable of deep optical penetration of large aggregates [2], and designed a microchannel for particle sorting [3]. The electromechanical sorting apparatus is shown schematically in Fig. 1. The device relies on an interrogation zone to identify particles displaying certain optical features, and two branches controlled by microvalves used to divert particles based on the identified optical features. Upon detection of a certain feature in the interrogation region, an open/close command signal is sent to the microvalves. The valves operation is delayed to account for the particle travel time. The device was shown to improve the efficiency of large particles sorting.

Herein, we consider the sorting solution in [2,3] to demonstrate how numerical simulation can be used to analyze the particle sorting attributes for different device designs and flow regimes. The simulation framework can predict particle stresses and lift-off and thus ensures that the apparatus will not damage the cells and microtissues due to impact or large fluid-induced stress. Direct numerical simulation can also be used at different Reynolds (*Re*) numbers to predict the particles' location and velocity, thus predicting how certain design attributes control the aggregate dynamics in the interrogation region.

2. Simulation framework

The approach adopted here is based on a Lagrangian–Lagrangian formulation of the fluid and solid phases. The SPH method is used to represent the dynamics of fluid flow and maintain the two-way coupling with rigid body dynamics by regarding body geometries as moving boundaries. The 3D rigid body rotation is characterized by means of a set of three translational coordinates and four Euler parameters [4].

2.1. The smoothed particle hydrodynamics method

SPH [5,6] is a meshless numerical discretization approach that has been used in problems involving celestial dynamics, fluid dynamics, elastic deformations, etc. [7–9]. At its core, SPH introduces a *smoothing* scheme for any space dependent field value as well as a discretization scheme using Lagrangian *particles*. For the mathematical identity given as

$$f(\mathbf{x}) = \int_S f(\mathbf{x}')\delta(\mathbf{x}-\mathbf{x}')\mathrm{d}\mathbb{V}, \tag{1}$$

the smoothing attribute is formulated as

$$f(\mathbf{x}) = \int_S f(\mathbf{x}')W(\mathbf{x}-\mathbf{x}', h)\mathrm{d}\mathbb{V} + O(h^2), \tag{2}$$

where W is a smoothing kernel function whose smoothness is controlled by the characteristic length h. The kernel function is a symmetric, $W(\mathbf{r}, h) = W(-\mathbf{r}, h)$, and normalized, $\int_S W(\mathbf{r}, h)\mathrm{d}\mathbb{V} = 1$, function of distance $\mathbf{r}$. Additionally, it approaches the Dirac delta function as the size of the support domain tends to zero; i.e., $\lim_{h\to 0} W(\mathbf{r}, h) = \delta(\mathbf{r})$. An example kernel function, and the choice used in this study, is the cubic spline function [10]

$$W(q, h) = \frac{1}{4\pi h^3} \times \begin{cases} (2-q)^3 - 4(1-q)^3, & 0 \le q < 1 \\ (2-q)^3, & 1 \le q < 2 \\ 0, & q \ge 2, \end{cases} \tag{3}$$

where $q \equiv |\mathbf{r}|/h$. This cubic spline has a support domain with radius $2h$.