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Deformability- and size-based microcapsule sorting

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ABSTRACT

Biomedical applications often require to sort cells according to their physical properties, such as size, density or deformability. In recent years, microfluidics has provided a variety of tools to sort micro-objects. We present here a simple microfluidic device consisting of a channel containing a semi-cylindrical obstacle against which capsules are squeezed by the flow, followed by a diverging chamber where streamlines separate. We demonstrate that this basic system is capable of sorting elastic microcapsules according to their size at low flow strength, and according to the stiffness of their membrane at high flow strength. Contrary to most existing sorting devices, we show that the present one is very sensitive and capable of discriminating between capsules with differences in membrane elasticity of order unity.

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1. Introduction

The shape and mechanical properties of blood cells govern many important phenomena, such as margination [1], adhesion [2], and extravasation [3]. Pathologies such as cancer [4] or infections [5] may alter cell size and stiffness. Abnormal stiffness can be used as a sorting parameter in the detection and isolation of pathological cells [6].

Microfluidics presents many advantages for cancer diagnosis applications, such as small reaction volumes, high sensitivity, and ability to sort micro-objects (particles, capsules, and cells) as described in [7]. Among label-free separation techniques, the most studied are size-based sorting devices: deterministic lateral displacement [8,9], dielectrophoresis [10], hydrophoresis [11], acoustic waves [12,13], and inertia [14]. Other methods, such as immunocapture [15] or fluorescence-activated sorting [16] involve labels, i.e. specific markers located at the surface of the micro-objects. Finally, other techniques such as optical stretchers [17] and stiffness-dependent separation [18] can sort heterogeneous populations based on their mechanical properties. While size-based microfluidic sorting has already been studied extensively [19], the concept of sorting based on deformability has emerged more recently and proves very promising [18,20].

In bioengineering, particles, capsules and vesicles are considered as simplified models for cells [21–23]. Capsules are biomimetic micro-objects consisting of a thin elastic membrane reticulated around a liquid core. The membrane can be made of natural components such as proteins: human serum albumin (HSA) [24], or ovalbumin [25]. The behavior of capsules is studied under conditions mimicking physiological situations, such as flowing through a constriction [26], and in the context of drug encapsulation and delivery [27].

The influence of confinement has been extensively studied for millimetric and micrometric capsules flowing through cylindrical [25], square [28], or rectangular channels [29].

In a recent numerical study, Zhu et al. [30] proposed to sort elastic capsules based on their deformability by flowing them around an obstacle through a straight channel followed by a diverging chamber. The experimental validation of deformability-based sorting techniques is not trivial because of the lack of homogeneous populations of micro-objects with well-controlled stiffness. We have created a microfluidic device with such a geometry. We use spherical albumin microcapsules whose mechanical properties depend on the production conditions.

In this article, we evaluate the feasibility of experimentally sorting heterogeneous populations of microcapsules depending on their stiffness.

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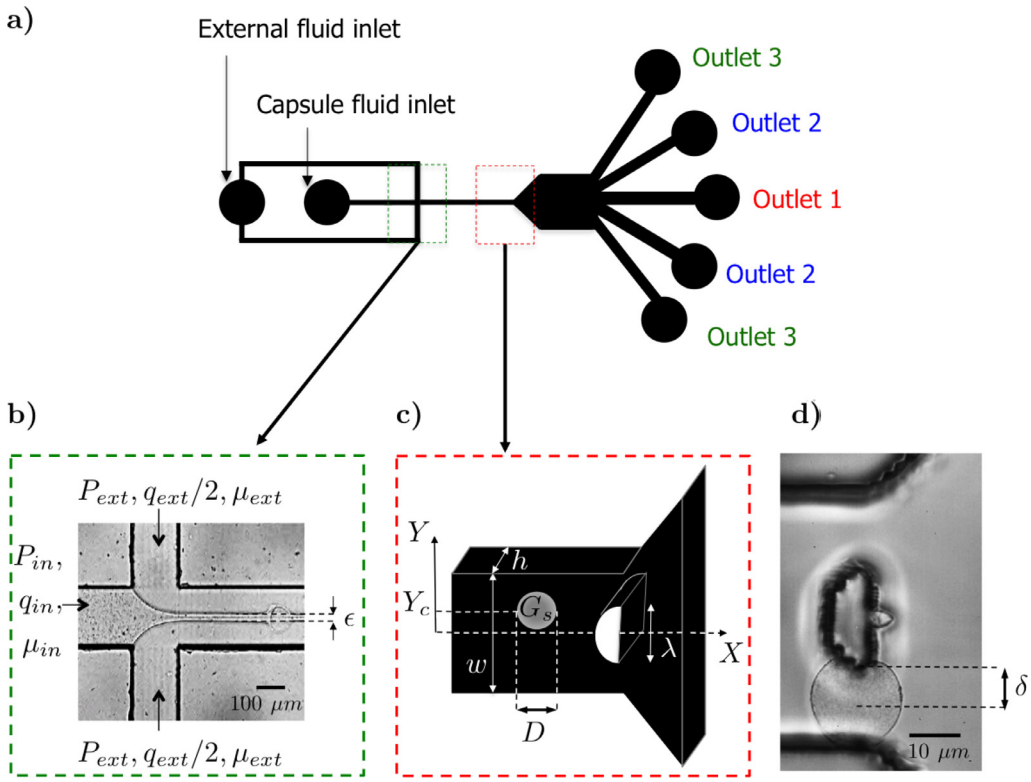

Fig. 1. Sketch of the experimental device. The fluids flow from left to right. (a) General view of our sorting device. (b) Photograph of the flow-focusing at the entrance of the straight channel. The capsule suspension is pinched by an external viscous fluid of viscosity μ_{ext}, and forms a fluid thread of viscosity μ_{in} and thickness ϵ. (c) Dimensions of the obstacle and of the rectangular straight channel. (d) The distance between the center of mass of the capsule and the obstacle is defined as δ.

2. Materials and methods

2.1. Capsule suspensions

Capsules are prepared by interfacial cross-linking as described elsewhere [31]. Briefly, a water-in-oil emulsion is formed using a 10% ovalbumin solution in a phosphate buffer pH 5.9 or pH 8, dispersed in cyclohexane added with 2% (w/v) sorbitan trioleate. Adding 2.5% (w/v) terephtaloyl chloride to the organic phase induces ovalbumin cross-linking at the interface and the formation of the membrane. This chemical reaction is stopped by dilution with chloroform:cyclohexane (1:4, v/v) after 5 min. Capsules are then rinsed with an aqueous solution of polysorbate, then with pure water, resuspended in water and stored at 4 °C. We obtain a polydisperse population of capsules of diameter D, determined with the Image J software using a circular fit, and expressed as the mean ± the standard deviation. The deformability of capsules obtained by this protocol has been shown to depend on the pH of the buffer solution containing ovalbumin. Capsules prepared at higher pH are more rigid than those prepared in more acidic conditions [25]. Capsule stiffness is characterized by the 2D elastic shear modulus of the membrane G_s.

2.2. Microfluidic device

The sorting device (Fig. 1) consists of a straight rectangular channel of width w and depth h that contains a semi-cylindrical obstacle of diameter λ at its end (Fig. 1c). Upstream of the main channel, a flow-focusing module is added to focus the capsules onto the center of the obstacle (Fig. 1). Downstream of the obstacle, the channel widens (Fig. 1a), then splits into several exits. The width of the confined zone between the side wall and the obstacle was chosen to be smaller than the capsule size (Fig. 1d). We define as δ the distance between the center of mass of the capsule and the pillar.

2.3. Production of the microfluidic device

Microfluidic chips are produced in PDMS using standard soft lithography techniques [32]. PDMS and curing agent (Sylgard) are mixed in a 10:1 ratio and cast onto the master, which consists of a silicon wafer with SU8-photoresist microstructures (Microfactory, Paris). After baking for 2 h at 70 °C, the PDMS is cross-linked and can be peeled off from the SU8 master. It is then plasma-bounded together with a glass slide using air plasma generated by a plasma-oxidizer (HARRICK, NY 14850, USA). After 2 h in a stove at 70 °C, the device is ready to be used.

2.4. Experimental setup

The sketch of our experimental setup is shown in Fig. 1. A pressure controller (MFCS, Fluigent, France) is used to impose a pressure P_{in} to the core fluid and a pressure P_{ext} to the external fluid. The chip is placed on the stage of an inverted microscope (DMIL LED, Leica Microsystems GmbH, Germany). Videos are recorded using a high-speed camera (Fastcam SA3, Photron, USA).

2.5. Coflow experiments

We carry out coflow experiments with miscible fluids. The reservoirs containing the external and internal fluids are connected to the pressure controller using PEEK tubes with an internal diameter of 0.25 mm. A fluid of viscosity μ_{in} is perfused at pressure P_{in} into another fluid of viscosity μ_{ext} moved at pressure P_{ext} ($\mu_{in} < \mu_{ext}$). The pressures applied to each entrance are adjusted, varying P_{in}/P_{ext} in order to control the core flow width ϵ

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