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Review

Microfluidic technology for cell hydrodynamic manipulation

Stefania Torino *, Mario Iodice, Ivo Rendina and Giuseppe Coppola

Institute for Microelectronics and Microsystems, National Research Council, Naples 80131, Italy

* **Correspondence:** Email: stefania.torino@na.imm.cnr.it; Tel: +39-081-6132-488;
Fax: +39-081-6132-598.

Abstract: In the recent years microfluidic technology has affirmed itself as a powerful tool in medical and biological research. Among the different applications, cell manipulation has been widely investigated. Micro-flowcytometers, micromixers, cell sorters and analyzers are only few examples of the developed devices. Various methods for cell manipulation have been proposed, such as hydrodynamic, magnetic, optical, mechanical, and electrical, in this way categorized according to the manipulating force employed. In particular, when cells are manipulated by hydrodynamic effects, there is no needing of applying external forces. This brings to a simplification in the design and fabrication phase, and at the same time undesired effects on the biological sample are limited. In this paper, we will discuss the physics of the relevant hydrodynamic effects in microfluidics, and how they are exploited for cell manipulation.

Keywords: microfluidics; fluid dynamics; hydrodynamic forces; cell manipulation; cell analysis

1. Introduction

Microfluidics is a research field which is spreading faster and faster. The possibility to realize hand-held devices, that can substitute traditional instrumentations, has kept the interest of a wide scientific community [1,2]. The improvements achieved in the microfabrication techniques have deeply contributed to the diffusion of this technology [3,4,5]. Microfluidics is nowadays applied in several fields, and promises to bring innovation in particular in cell biological research [6,7,8]. Fluidic channels with a size in the micrometers range well match the cells scale, by also allowing manipulation of small quantities of fluids (nanoliters to picoliters). The characteristics of these micro-systems give the opportunity to create new methods and approaches for cell manipulation [9,10],

replacing expensive laboratory instrumentations. In the last twenty-years several micro-devices for cell manipulation, based on different physical principles, have been proposed.

1.1. Active manipulation by external forces

Among the methods that imply the use external forces, one of the most adopted is based on dielectrophoresis (DEP) [11,12,13]. When an alternating electric (AC) field is applied, the motion of a dielectric particle, such as a cell, can be controlled. Therefore, devices that integrate both fluidic channels and electrodes allow to translate, trap and rotate cells, according to the characteristic of the generated electric field. Electrodes differently oriented respect to the fluid flow direction allow to move and rotate cells or particles along multiple axes. One drawback in electrical manipulation approach is the needing of an additional technological step during the fabrication of the devices. Moreover, several scientists agree on the possibility that these fields could alter the biological sample under analysis. Optical forces are commonly employed for manipulation at the single cell level. In 1970 Ashkin showed how was possible capture biological particles in a stable manner by using a focused laser beam [14]. This approach is known as optical tweezer (OT) or optical trapping. Both the single-beam and two-beams configuration have been successfully used for generating a stable trap for manipulation and stretching of biological cells [15,16,17]. Furthermore, several researchers propone acoustic waves as manipulating forces [18,19]. The term acoustofluidics refers to the use of acoustophoresis, the motion of objects by acoustic waves, in microfluidics. Magnetic fields have been also investigated as a possible approach for manipulation of biological particles [20]. However, this method requires both the integration of magnetic elements into the device, and, in most of the cases, the pre-treatment of the biological sample.

1.2. Passive manipulation by hydrodynamic forces

Although all the approaches based on active manipulation have shown high potentiality, they have two main critical issues: first, there is the needing of integrating additional elements (such as electrodes) into the micro-device, by increasing the complexity of the fabrication process; secondly, the applied forces or fields could generate un-desired effects on the biological sample, by voiding the results. These two issues do not concern approaches based on hydrodynamic manipulation. The devices based on this method exploit the fluid forces for manipulating the biological particles. In this paper, we first present the basic fluid dynamics equations that have to be considered in the design of a new device for cell manipulation based on hydrodynamic effects [21]. Then, we discuss the most relevant applications exploiting cell manipulation by means of hydrodynamic forces.

2. Theory of Hydrodynamic Effects in Microfluidics

The behavior of fluids at the micro and micro scale is different. In fact, in order to characterize the fluidic behavior at the microscale, the equations from the classical fluid dynamics are used, but some assumptions and simplifications are introduced due to the small size of the systems.

2.1. Modelling the fluid flow

The well-known *Navier-Stokes equations*, for a non-compressible fluid, continue to hold in the microfluidic world [22,23]:

$$\rho\left(\frac{dv}{dt} + v \cdot \nabla v\right) = -\nabla \mathrm{p} + \mu\nabla^2 v + f \tag{1}$$

where ρ refers to the fluid density, v the velocity field, p the pressure drop across the channel, μ the fluid viscosity, and f the volume forces. Conceptually, the equations can be considered as a balance of the forces acting on each single fluid element:

$$\overrightarrow{net\ inertial\ force} = \overrightarrow{net\ pressure\ force} + \overrightarrow{net\ viscous\ force} \tag{2}$$

In most of the microfluidic devices, the inertial forces are negligible. This means that the previous equation can be simplified as a balance between pressure forces and viscous forces:

$$\overrightarrow{net\ pressure\ force} = -\overrightarrow{net\ viscous\ force} \tag{3}$$

Or in another form:

$$\nabla p = \mu\nabla^2 v \tag{4}$$

The ratio between the inertial and viscous forces defines a dimensionless number that is used in fluid-dynamics to characterize the fluid behavior:

$$Re = \frac{inertial\ forces}{viscous\ forces} = \frac{\rho v L}{\mu} \tag{5}$$

Re is known as *Reynolds number*, an adimensional number that is used to classify a fluid flow as laminar or turbulent. In a laminar flow all the fluid elements remain parallel to each other. No vortices can generate as usually happens in turbulent flows. If Re < 2000 laminar regime dominates, whilst for Re > 2000 the fluid is in a turbulent regime. In microfluidics, due to the small length (*L*) of the system, the Reynolds number assumes really low values.

2.2. Forces on a particle in a fluid flow

A small particle or cell suspended in a fluid is subjected to hydrodynamic forces. The first force to consider is the drag force, defined as the force that acts on an object in the direction of the fluid flow:

$$F_D = 3\pi\mu v\, d_p \tag{6}$$

where d_p is the particle or cell diameter. The equation can be written again as follows:

$$C_D = \frac{F_D}{\frac{1}{2}\rho v^2 A} \tag{7}$$

where C_D defines the drag coefficient, and *A* is the cross-sectional area of the cell or particle.

The previous expression is applicable in the case of a Stokes flow (or creeping flow), namely when inertial forces are negligible compared to viscous forces, and Re < 0.5 (condition typically satisfied in microfluidics). At higher values of Re, inertial effects become significant, and therefore a correction is introduced in equation (6). In evaluating the total force acting on a particle or cell in a fluid flow, the contribute F_I due to the inertial effects is also taken into account:

$$F_t = F_D + F_I \tag{8}$$

It has to be underlined that the previous formulation for the drag force is valid for spherical objects. For ellipsoidal objects, equation (6) is transformed as follows:

$$F_D = 6\pi\mu vaK(\beta) \tag{9}$$

where a is the equatorial semi-axis of the ellipsoid, and K a factor that depends upon the characteristics of the ellipsoid (i.e., if we are in presence of a prolate or an oblate ellipsoid). In particular, K is a function of $\beta = b/a$, the ratio between the major and the minor semi-axis of the ellipsoid. These theoretical aspects have to be analyzed in order to design a microfluidic chip for cell manipulation, by taking advantage of the hydrodynamic effects.

2.3. Velocity profile in a microfluidic flow

Another important aspect is to consider the velocity profile of the fluid flow. At low Re the flow regime is known as *Hagen-Poisuelle* flow. In this case the Navier Stokes equations can be solved to reveal that the flow profile is parabolic with the velocity at the center being the highest and the velocity at the boundary being zero. For a given mass flow rate Q, the pressure drop is:

$$\Delta p = R_F\, Q \tag{10}$$

with R_F the fluidic resistance of the system, that is function of the channel cross-section. For a channel with a rectangular cross-section, that is the typical condition for the standard microfluidic devices, the proportionality, to the first order, is wh^3:

$$R_F = \frac{12\mu L}{w\,h^3}\left[1 - \frac{h}{w}\left(\frac{192}{\pi^5}\sum_{n=1,3,5}^{\infty}\frac{1}{h^5}tanh\frac{n\pi w}{2h}\right)\right] \tag{11}$$

If w << h or h << w, the previous expression can be simplified as follows:

$$R_h = \frac{12\,\mu\,L}{w\,h^3} \tag{12}$$

From equation (10) the analytic solution for the velocity can be derived by fixing the channel cross-section. For a typical microfluidic channel with a rectangular cross-section the expression for the velocity is:

$$u(y,z) = \frac{16h^3}{\mu\pi^3}\left(-\frac{dp}{dx}\right)\sum_{i=1,3,5...}^{\infty}(-1)^{(i-1)/2}\left[1 - \frac{cosh(\frac{i\pi z}{2h})}{cosh(\frac{i\pi w}{2h})}\right]\frac{cos(\frac{i\pi y}{2h})}{i^3} \tag{13}$$

As we already mentioned, the *Hagen-Poiseuille* flow is characterized by a parabolic velocity profile, in which the velocity of flow in the center of the channel is greater than that toward the outer walls. This means that according to the position across the channel a particle experiences different velocity values, and therefore different hydrodynamic forces. This is an important aspect that has been exploited in several examples of microfluidic devices manipulating cells by hydrodynamic forces.

3. Hydrodynamic Manipulation

In this section we will discuss the applications of hydrodynamic forces to cell *focusing*, *separation*, *trapping* and *rotation* in microfluidics.

3.1. Hydrodynamic focusing

Hydrodynamic focusing can be defined as the confinement of a flow containing target objects (cells or particles), known as *sample fluid*, by another flow, known as sheath *fluid* [24]. Hence, the principle of hydrodynamic focusing is simple: a central sample solution with a low flow rate flows within an outer fluid sheath traveling at a higher flow rate. The operation of flow-cytometry is based on this method. Generally, the term cytometry refers to a process in which the physical and chemical characteristics of a single cell are measured. In flow-cytometry, cells are analyzed as they are transported by the sample fluid stream. The flow stream brings cells one by one through an interrogation point, where they are illuminated by a light beam. The illuminated cell scatters the light with a characteristic directional intensity distribution. Further, fluorescently tagged antibodies are often used to mark and identify cells. Both scattered and fluorescent light is measured, providing a number of parameters to yield statistics about sample sub-populations. Flow cytometry is routinely used in the diagnosis of health disorders, and it has applications in a large number of fields, including molecular biology, pathology and immunology. In this wide range of fields, there is the need of developing devices that can substitute the traditional flow cytometry instrumentation, reducing costs and increasing portability. Lab-on-chip and microfluidic technology allow to automating into a hand-held microfluidic chip the complex diagnostic procedures that are normally performed in a centralized laboratory. The low *Reynolds* numbers that characterizes the microfluidic regime, and the laminar regime that derives, ensure a good control on the sheath and sample fluid stream. In fact, thanks to the laminar flow properties, the two fluids will flow parallel to each other, without mixing. This is a key point, since the correct operation of flow-cytometry depends upon a precise control of the focused sample stream. In a microfluidic flow-cytometer, this is achieved not only by controlling the velocities of the fluids at the inlets, but also by choosing a proper geometry for the microchannels. In microfluidics, the biggest effort is required for achieving a three-dimensional hydrodynamic focusing, since these novel devices are based on two-dimensional patterns. Therefore, it could result not easy to replicate the tree-dimensionality traditionally achieved in standard bench-top instrumentations. Several applications of two-dimensional hydrodynamic focusing for cells or particles analysis in planar micro-flow cytometers have been proposed [25–28]. The first prototypes were based on the configuration in Figure 1b, that is the simplest one to design in the attempt of replicating the traditional macro-chamber for hydrodynamic focusing at the micro-scale. In these devices, it could happen that cells or particles may not pass the focused stream one by one at the

interrogation point. This is because they may be located at different depths in the microchannel, if their size is significantly smaller than the channel height. This will affect the detection performance of such flow cytometers. This problem is often solved by reducing the height of the channel to the range of the mean cell size. This approach could solve the problem, but microchannels clogging can easily occurs. A solution is the realization of a microfluidic device that allows 3D focusing. In this way, particles are focused in both the horizontal and the vertical directions. Most of the proposed solutions are realized by using a multi-layer microfluidic device [29]. Multi-step photolithography and assembly protocols have been developed for fabricating these 3D microfluidic structures. However, such methods require either tedious assembly of individual components or multiple alignments and exposures during mold fabrication, with an increase of the cost and complexity of the final devices hindering their applicability. Moreover, such configurations exploit at least two sheath fluids to pinch the sample fluid, with the main drawback of requiring multiple inlets. This undesired complication strongly limits the exploitation of parallelization [20–32], namely the possibility of having more channels working simultaneously. Parallelism is one of the main advantage of microfluidics, helping also in overcoming the clogging problems and, at the same time, increasing the device throughput. Several solutions to these problems have been proposed, by engineering microfluidic devices that allow to hydrodynamically focus cells without needing of a sheath fluid region [33].

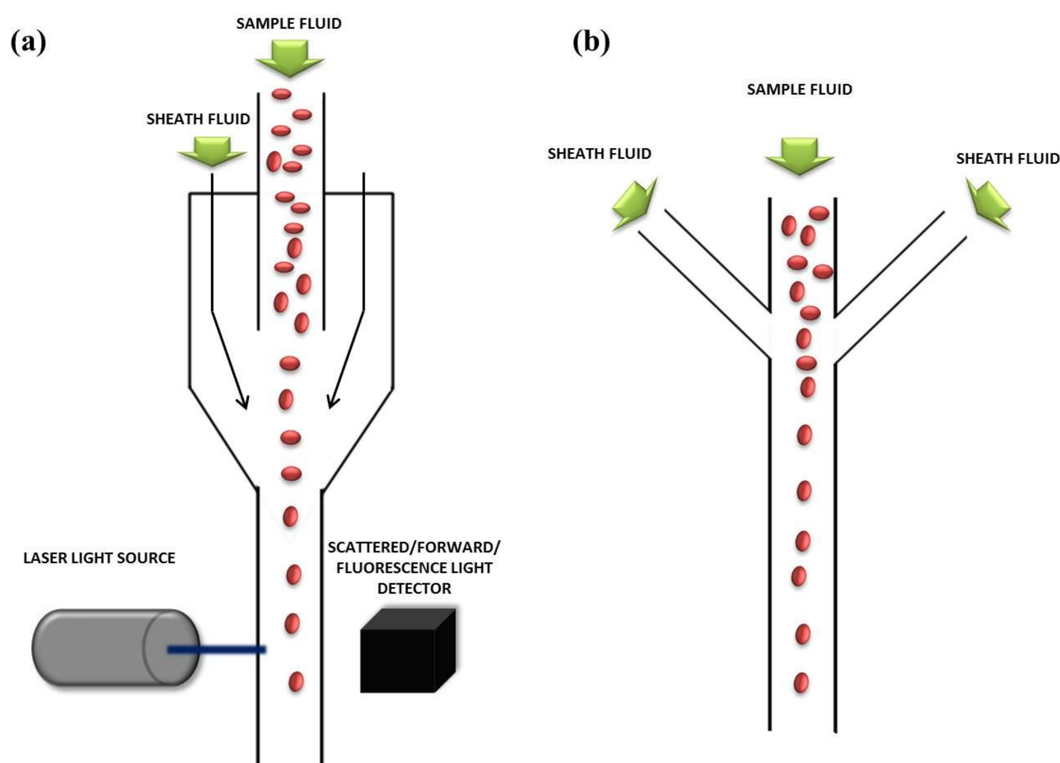

Figure 1. (a) Principle of hydrodynamic focusing in traditional flow-cytometry. (b) The most common microfluidic 2D pattern for hydrodynamic focusing.

Another sheath-less focusing method, that exploit hydrodynamic forces, is the one known as inertial focusing [34–38]. The method utilizes the cross-stream particle motion to focus particles into one or multiple streams through a microchannel. The first related experiment was performed by Segre and Silberberg (1961) [39]. Particles were observed to migrate toward a narrow annulus in a centimeter-scale circular pipe as the result of competition among the inertial lift forces acting on particles, of which the two dominant ones are the walls lift and the shear-gradient induced lift. This condition is achievable for particle motion in laminar microfluidic devices. Inertia-based particle focusing offers a very high throughput, which, on one hand, makes this method suitable for high-speed applications such as flow cytometry.

3.2. Hydrodynamic separation

As discussed in previous sub-section, hydrodynamic focusing has the aim of aligning cells in a single stream in order to allow analysis at the single-cell level. However, for some purposes, the sample analysis is not sufficient. Indeed, cell separation is a mandatory preliminary step for many biological and medical procedures [40]. For examples, in surgery only purified platelets are used for transfusion [41]. Similarly, some therapies implies blood treatments for removing bacteria from the blood before returning it to the patient. Another important application is related to the isolation of stem cells, in order to use them for tissue engineering and disease treatment. Moreover, scientists have recently started to focus on the isolation of *circulating tumor cells*—CTCs. The possibility to separate and collect CTCs plays an important role in the study of the biology of the cancer. In fact, it is well known that tumor metastasis are the major cause of death in cancer patients. Tumor cells first develop in the tissue of the primary tumor, then they can move into the blood and diffuse to other parts of the body. Isolation of CTCs could help in understanding the way in which tumor metastasis spread through the body. All the wide range of medical applications requiring separation approach have brought to the development of several micro-devices for cells or particles separation. The conventional label-free approaches for cell separation employ filter-membranes. The efficiency of the method is strongly limited by pores clogging [42]. Microfluidics gives the possibility of thinking to novel functional tools for cell separation, by reducing the analysis time, increasing the sensitivity, and at the same time, reducing the sample volumes. Moreover, the hydrodynamic characteristics of the fluid flow at the microscale, and the high flexibility in the channel design offered by micro-fabrication techniques, allow to obtain high efficient separations by only exploiting hydrodynamic effects. A separation method is based on the principle known as *deterministic lateral displacement* (DLD) [43,44]. The method employs arrays of pillars placed in a microchannel. The distance among the pillars is tailored according to the size of the cells or particles that have to be sorted. The pattern of the array determines the displacement of cells or particles. Indeed, in the design phase, according to the pillars position, the pathway that will be followed by cells or particles can be predicted. However, the pillars configuration brings to the creation of narrow areas, by increasing the possibility of channel obstructions. Several works showed the capability of the approach in selecting cells by their size both with rigid and deformable cells [45]. Other proposed devices are based on the *field-flow fractionation* (FFF) technique [46,47,48]. As we reported in the theoretical section, in a microfluidic devices, with a pressure driven flow, the velocity has a parabolic profile. This means that the velocity reaches the highest value at the center of the channel, and the minimum ones close to the channel walls. The velocity gradient implies that according to the particle

or cell size, they will experience different velocities and, therefore different retention time. Hence, FFF is like an elution technique, where separation is obtained thanks to different retention achieved in microchannels (similar to the principle of the most common chromatography techniques). Beside this method, *pinched flow fractionation* (PFF) is another hydrodynamic separation technique which exploits the effect of the flow on cells or particles having different sizes [49,50]. A micro-device for PFF has two inlets, one for the sample fluid, and the other for the sheath fluid. The two inlets merge into a narrow channel that then opens into a broader one. The width of the narrow channel is in the cells or particles size range, whilst the broader one can be even 100 times wider. The separation effect is achieved by controlling the ratio between the sheath and the sample flow rate in order to get cells at one of the sidewall of the narrow channel. As for FFF, smaller cells will get closer to the channel walls with respect to bigger cells. In this way, as cells pass from the narrow to the broader channel, they will follow different pathways according to their size, and therefore they could be directed to different outlets to achieve separation.

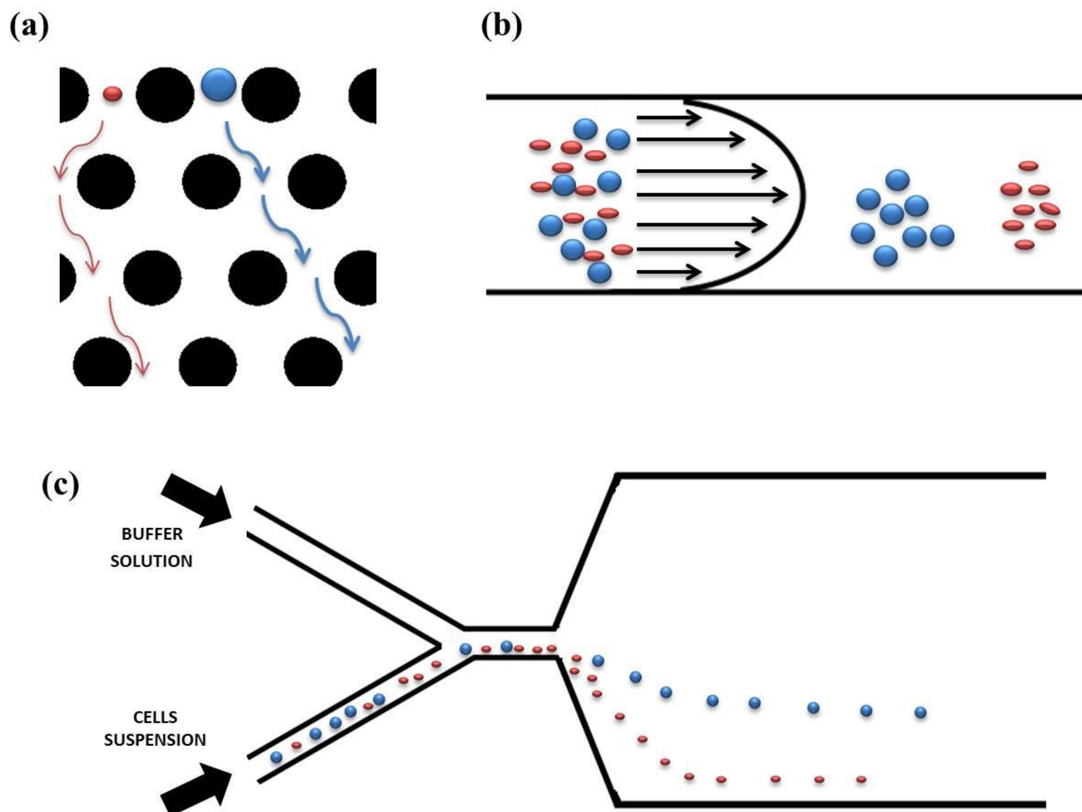

Figure 2. Operation principle for the hydrodynamic separation methods based on (a) deterministic lateral displacement (DLD), (b) flow-field fractionation (FFF), and (c) pinched flow fractionation (PFF).

As already discussed in the section dedicated to hydrodynamic focusing, inertial forces can be exploited in order to manipulate cell direction [51,52,53]. Indeed, when the velocity of the flow increases, the effect of lift forces becomes significant [54]. In particular, by choosing the right fluid flow, and the right geometry for the channel, the balance between the shear-induced force and the

wall-lift induced force can be used for inducing cell separation, since the equilibrium positions will depend upon the cells size.

3.3. Hydrodynamic trapping

In medicine and biology, traditional measurement methods are only able to provide information that are related to the average characteristics of the population under analysis, while there is an increasing interest in technologies that could perform single cell analysis. Cell trapping methods exploiting hydrodynamic forces allow in principle complete characterizations of individual cells from a suspension. The microfluidic technique, also called *hydrodynamic tweezers*, requires a complete analysis of the fluid forces that contribute to the cell motion. Microchannels have to be shaped in order to create stagnation points, in which cells tend to stop. Several solutions for trapping cells without using external forces or fields have been proposed. One of these consists in the introduction of micro-sieves into the channel [55,56]. Each micro-sieve acts as a trap for a single cell. In another approach, trapping sites are inserted laterally to the main fluidic channel. Cells or particles are moved to the trapping area thanks to the forces exerted by the fluid. This is achieved by tuning the velocity of the flow at an optimum value, and by also choosing the proper design for the channel geometry [57,58]. In another approach, an oscillating micro-tool is introduced in the fluidic channel [59], and the trapping effect is achieved thanks to the oscillation generated into the fluid. Recently, a different approach based on the investigation of the hydraulic resistances of the channels has been proposed [60]. Cells flowing through the main channel, with a resistance Rh_{main}, tends to move to the trapping site, with a resistance Rh_{trap}. The ratio between Rh_{main}/Rh_{trap} determines the efficiency of the trap.

3.4. Hydrodynamic rotation

Microfluidic technology has led to significant improvements in biology and medicine research. Indeed, with microfluidic systems it is possible microfluidics to image cells while they are in their three-dimensional shape. This is a great breakthrough, if we consider that traditionally cells are compressed on a glass-slide when they are analyzed at the microscope. However, in microfluidics there is still a limitation, since in some cases only one side of each cell will be facing the observation point of view. In order to avoid a lack in information, a possible solution is to investigate the possibility to induce cell rotation. This can be achieved by taking advantage of the effects induced by a shear flow on flowing cells or particles. The effect of a shear flow on spherical and asymmetrical particles has been extensively studied, and the theoretical models describing all the phenomena have been formulated [61,62,63]. In basic shear flows, such as Couette flow and Poiseuille flow, buoyant particles undergo fluid forces, and therefore rotation is observed. The type of motion depends upon the properties of the particles, of the fluid and of the flow. Indeed, the motion induced will be different in the case of symmetrical or asymmetrical particles, or for less or more viscous fluids [64,65]. Moreover, different velocities of the flow will generate different rotational effects. Several works have studied theoretically, numerically and experimentally, the phenomena in different conditions. Some of them have analyzed particle rotation in a 2D Poiseuille flow [66]. The motion of ellipsoidal particles in a shear flow has been also studied [67,68]. In addition, the motion of sub-micrometer particles has been investigated by taking in consideration the Brownian effect [69]. Microfluidic

regime is characterized by a low Reynolds number, where particle and fluid inertia are negligible. The rotation induced on a particle flowing through a microchannel will follow the so called Jeffrey orbits [61,70]. Several devices for inducing cell rotation by only exploiting hydrodynamic effects have been proposed.

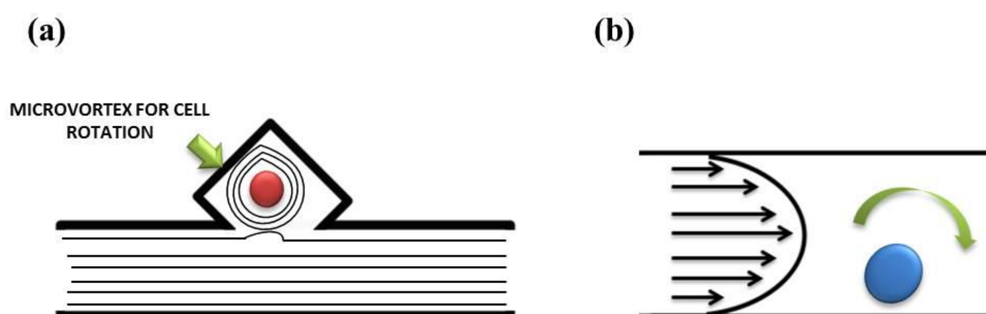

Figure 3. Principle of hydrodynamic rotation based on (a) micro-vortex and (b) velocity gradient in a Poiseuille flow.

In one of the proposed devices, single cell and micro-particle rotation have been achieved using the concept of micro-vortices, which relies on the creation of a recirculating flow profile [71]. In a similar approach micro-vortices are generated by fabricating channels with diamond-shape side chambers [72,73]. Other works focused on the possibility of inducing cell rotation in a Poiseuille flow [74,75,76]. These approaches started from the consideration that in microfluidics, for a pressure driven flow, the velocity has a parabolic profile. Therefore, particles or cells close to a channel wall will experience a velocity gradient, and a torque will be induced on them. Configurations using a multiple inlets geometry are, in particular, effective in controlling cells path and, therefore, their angular velocities.

4. Conclusions

In the last twenty years, microfluidic technology has shown high potentiality in the development of powerful devices for improving cell analysis. Microfluidics offers a set of effective tools for studying biology. It reduces the time and cost of common bioanalytical assays, and enables single-cell level studies. An important class of applications concerns cell manipulation, employing hydrodynamical, magnetical, optical, mechanical, and electrical forces. These techniques can be used for focusing, separation, trapping and rotation of biological samples. In this paper we have focused our attention on the methods that exploit only hydrodynamic forces. This approach has the advantage of simplifying the chip fabrication, since there is no need of introducing additional elements, such as electrodes or magnetic components. At the same time, undesired effects on the biological sample are avoided. In the section dedicated to the theory, we have reported the relevant equations, and the forces, that have to be taken into account in the design of a microfluidic device for cells or particles manipulationby means of hydrodynamic forces. Then, we have presented an overview on how hydrodynamic forces have been employed for focusing, separation, trapping and rotation.

Conflict of Interest

The authors declare no conflict of interest.

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