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Abstract

In microfluidics, the typical sample volume is in the order of nL, which is incompatible with the common biosample volume in biochemistry and clinical diagnostics (usually ranging from 1 μ L to approximately 1 mL). The recently emerged inertial microfluidic technology offers the possibility to process large volume ($\sim$ mL) of biosample by well-defined micro-structures. In contrast to conventional microfluidic technologies, where fluid inertia is negligible and flow remains almost within Stokes flow region with very low Reynolds number $Re \ll 1$ ($Re = \rho f \bar{U} H / \mu$, where ρ , f , $\bar{U}$ and μ are fluid density, average velocity and dynamic viscosity, respectively, and H is channel hydraulic diameter), inertial microfluidic devices work within an intermediate Reynolds number range ($\sim 1 < Re < \sim 100$) between Stokes and turbulent regimes. In this intermediate range, both inertia and fluid viscosity are finite, and several intriguing effects appear and form the basis of inertial microfluidics, including (i) inertial migration and (ii) secondary flow. Due to the superior features of high-throughput, simplicity, precise manipulation and low-cost, inertial microfluidics has attracted significant attention from the microfluidic community. Meanwhile, a number of channel designs that focus, concentrate and separate particles and fluids have been explored and demonstrated. In this chapter, we discuss this fascinating technology from three crucial aspects: (1) fundamental mechanism, (2) microchannel designs and (3) applications. From this chapter, we hope that readers can have a clear understanding on the concept of inertial microfluidics, its working mechanism and potential applications.

Keywords

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Chapter 25 Inertial Microfluidics: mechanisms and applications

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Abstract

In microfluidics, the typical sample volume is in the order of nL, which is incompatible with the common biosample volume in biochemistry and clinical diagnostics (usually ranging from 1 μ L to approximately 1 mL). The recently emerged inertial microfluidic technology offers the possibility to process large volume ($\sim$ ml) of biosample by well-defined microstructures. In contrast to conventional microfluidic technologies, where fluid inertia is negligible and flow remains almost within Stokes flow region with very low Reynolds number $Re \ll 1$ ($Re = \rho_f \bar{U}_f H / \mu$, where ρ_f , $\bar{U}_f$ and μ are fluid density, average velocity and dynamic viscosity respectively, and H is channel hydraulic diameter), inertial microfluidic devices work within an intermediate Reynolds number range ($\sim 1 < Re < \sim 100$) between Stokes and turbulent regimes. In this intermediate range, both inertia and fluid viscosity are finite, and several intriguing effects appear and form the basis of inertial microfluidics, including (i) inertial migration and (ii) secondary flow. Due to the superior features of high-throughput, simplicity, precise manipulation and low-cost, inertial microfluidics has attracted significant attention from the microfluidic community. Meanwhile, a number of channel designs that focus, concentrate and separate particles and fluids have been explored and demonstrated. In this chapter, we discuss this fascinating technology from three crucial aspects: 1) fundamental mechanism, 2) microchannel designs, and 3) applications. From this chapter, we hope that readers can have a clear understanding on the concept of inertial microfluidics, its working mechanism and potential applications.

1.1 Introduction

The inertial migration (or the tubular pinch effect) was first observed by Segre & Silberberg in 1961 [1, 2]. In their experiments, spherical particles ($\sim$ mm in diameter) migrated to an annulus located about 0.6 times of pipe radius between centreline and pipe wall in a cylindrical pipe ($\sim$ cm in diameter). After that, scientists have been spending decades

to understand the underlying physics of this intriguing phenomenon through experimental studies, theoretical analyses and numerical simulations [3-10]. Although the exact mechanism is still unclear, it has been widely accepted that the two opposing lateral lift forces are responsible for the phenomenon: 1) the wall lift force, F_{LW} , a result of the flow field interaction between the suspended particles and the adjacent walls, which repels the particles away from the wall; 2) the shear gradient lift force F_{LS} , due to the curvature of the fluid velocity profile and its interaction with the particles, which directs particles away from channel centre. The final balance between these inertial lift forces results in a set of dynamic equilibrium positions within the cross section of channels dependent on the cross-sectional shape [11-13], Reynolds number [14], particle shape [15] and deformability [16] etc. It should be noted that there are actually two additional lateral forces acting on the particles in a wall-bounded Poiseuille flow: 1) rotation-induced lift force (or Magnus force); and 2) slip-shear-induced lift force (or Saffman force). However, their magnitudes are generally at least one order less than that of the shear gradient lift force [17, 18], which are, therefore, negligible in the common inertial microfluidic analysis.

Since the first observation of inertial migration, all the investigation was focused on the understanding of its fundamental mechanism. Until the recent emergence of microfluidics, where the size of patterned micro-channel is comparable to that of the suspended particles (so that inertial migration can be more obvious within a short channel length), it has finally found its application in biomedicine and industry. Then, inertial microfluidics, an emerging field in microfluidics, that utilizes inertial migration and other inertial effects (secondary flow and centrifugal force) to realize the manipulation of fluid and suspended particles, was defined by its characteristics of finite inertial flow [19-23].

In contrast to the common sense that, in microfluidics, fluid inertia is negligible (Stokes flow regime, $Re \rightarrow 0$), inertial microfluidics works in an intermediate range ($\sim 1 < Re < \sim 100$) between Stokes regime ($Re \ll 1$) and turbulent regime ($Re \sim 2000$), where both inertia and viscosity of the fluid are finite [18]. Besides the intriguing phenomenon of inertial migration, there are additional inertial effects due to the finite inertia of fluid (secondary flow) and particle (centrifugal force). And these inertial effects together constitute inertial microfluidics.

The particle centrifugal force, which is proportional to the density difference between particle and medium [24-26], is normally negligible in inertial microfluidics for biomedical

applications, where the density of cells or particles is very close to that of the medium [27, 28]. Meanwhile, secondary flow usually appears in a curved channel [29] or a straight channel with disturbance structures [30-32]. In a curved channel, secondary flow is induced by a pressure gradient in the radial direction, because of fluid momentum mismatch in the centre and near-wall region within the cross section [20]. The fluid elements near the channel centreline have a higher momentum than that near the wall, therefore flow outwards, and drive relatively stagnant fluid elements near the channel wall inwards along the circumference, forming two counter-rotating streams, well known as Dean vortices [29]. Introducing secondary flow in inertial focusing brings several benefits. For example, Dean flow can modify the inertial equilibrium positions by imposing an additional viscous drag force on particles perpendicular to the main stream. Also, size-dependent differential focusing of particles dependent on the ratio of inertial lift force and secondary flow drag (F_L/F_D) promises a complete particle separation. In addition, Dean flow could reduce the channel length/footprint, due to the mixing effects of secondary flow, assisting particles to reach stable equilibrium positions more quickly [20].

Inertial microfluidics has attracted a great attention during the last decade due to its advantages of precise manipulation, simple structure and high throughput. In contrast to numerous active microfluidic manipulation technologies [33-40] where one or more external force fields are supplied to control the motion of target particles or cells, inertial microfluidics is a passive manipulation technology, and it manipulates and separates bioparticles by the intrinsic hydrodynamic force [41]. Therefore, the operation of inertial microfluidics is very simple and robust, and the cost of inertial microfluidic device is relatively low. Current investigation in the area of inertial microfluidics is mainly focused on three aspects: 1) designing novel micro-channel structures, 2) uncovering the fundamental mechanisms of inertial focusing within them, and 3) exploring and expanding their applications in biomedicine and industry. This chapter is organised as following: first, we will discuss the fundamental theory behind the inertial migration and particle focusing in microfluidics, so that readers can have a clear understanding why the inertial focusing happens, and how its focusing pattern can be altered. Second, the current design of functional micro-channels in inertial microfluidics will be presented. After that, we will summarize the current developments of inertial microfluidic technology in biomedicine, disease diagnosis and industry. Finally, conclusions and perspectives of inertial microfluidics will be proposed.

1.2 Fundamental Mechanism

In inertial microfluidics, when the particle suspension is infused into a microfluidic channel, there are several forces acting on the suspended particles, and they determine particles' motion along the mainstream (axial) and lateral direction. Along the mainstream, the viscous drag force, arising due to the velocity difference between particles and fluid, accelerates particles close to the velocity of its surrounding fluid elements. When particles are near a channel wall, the wall has an effect to slow down the motion of particles, so that particles are actually lagging the fluid flow slightly. On lateral direction that is perpendicular to the fluid mainstream, there are also a number of lateral lift forces, such as rotation-induced lift force, slip-shear induced lift force, wall lift force, shear gradient lift force, deformability induced lift force, and secondary flow drag force [42-45]. In the real inertial microfluidic analyses and applications, not all of these forces need to be taken into account. Some of them are actually negligible, depending on the property of medium and particles and structure of channels.

Figure 1 Mainstream and lateral forces exert on particles in a microfluidic channel.

1.2.1 Viscous drag force

Drag force arises when an object moves through a fluid or, relatively, when the fluid flows toward an object. The origin of the drag force lies in the need to remove the elements of fluid out of the way of a moving object. The drag force on a moving spherical particle can be expressed as:

$$F_{drag} = S * f_{drag} = \pi a^2 f_{drag} / 4 \quad (1)$$

where S is the cross-sectional area of the particle, and a is the diameter of the particle. f_{drag} is viscous drag coefficient which is always determined by the particle Reynolds number $Re' = v_t \rho_f a / \mu$, here v_t is the relative velocity of fluid to particle [46].

Although the viscous drag coefficient f_{drag} has different expressions according to the range of particle Reynolds number Re' , the most widely used is the Stokes drag due to its simplicity, especially when relative velocity of fluid to particle v_t is very small [46].

$$f_{drag} = 12 \frac{\mu v_t}{a} \quad (2a)$$

Then

$$F_{drag} = 3\pi\mu a v_t \quad (2b)$$

In inertial microfluidics, viscous drag force consists of two components respectively along 1) mainstream direction, due to the axial velocity difference between fluid and the suspended particles; and 2) lateral direction, due to the secondary flow induced by the channel curvature, or disturbance structure.

1.2.2 Magnus force--rotation-induced lift force

In an in-viscous flow with uniform velocity U_f , a stationary cylinder is rotating with constant angular velocity Ω , see figure 2. Assuming no slip velocity at the surface of the cylinder, the fluid velocity at the bottom part is lower than that at the upper part. According to the Bernoulli principle, fluid pressure is higher at the lower part than that in the upper part. As a result, a lift force F_{LR} is developed to lift the cylinder. The magnitude of this lift force, per unit length of the cylinder is [42]:

$$\vec{F}_{LR} = \pi \rho_f^2 a \vec{U}_f \times \vec{\Omega} \quad (3)$$

Similarly for a rigid sphere rotating in a fluid, a lateral lift force appears due to the transverse pressure difference, and this force is called ‘‘Magnus force’’ [47]:

$$\vec{F}_{LR} = \frac{1}{8} \pi a^3 \rho_f \vec{U}_f \times \vec{\Omega} \quad (4)$$

If the sphere is not stationary, but simultaneously translating through the fluid with a velocity $\vec{U}_p$, replacing the fluid velocity vector $\vec{U}_f$ with the relative velocity $(\vec{U}_f - \vec{U}_p)$.

The direction of Magnus force is perpendicular to the plane defined by the vectors of the relative velocity and the axis of rotation. In the case of a sphere rotating with an angular velocity $\vec{\Omega}_p$ in a rotational flow field, the vector $\vec{\Omega}$ ($= \vec{\Omega}_p - 0.5\nabla \times \vec{U}_f$) represents the relative rotation between fluid and sphere.

Magnus force can be considered as a result of pressure difference induced by the streamline asymmetry, due to the rotation of sphere. Although above particular expressions (3-4) are only valid for low Reynolds numbers, this kind of lift force due to the rotation of a body is also present in more strongly inertial flow [42, 48].

Figure 2 Rotation induced lift force for a rigid cylinder and sphere in a uniform flow.

1.2.3 Saffman force--slip-shear-induced lift force

Using the matched asymptotic expansion method, Saffman [43] calculated the lateral lift force on a sphere in a simple unbounded shear flow. The magnitude of this force is:

$$F_S = \frac{K}{4} V_t a^2 (\gamma v^{-1})^{1/2} \quad (5)$$

where K is a numerical constant ($K \sim 81.2$), γ is shear rate, v is the kinetic viscosity and V_t is the relative velocity between particle and fluid at the streamline through the centre of particle. It should be noted that this force is the only effect of shear rate, independent of rotation of particle. In the real situation of force-free spheres, a relative rotation will be induced by the fluid shear. Consequently, a Magnus-type force may appear on the spheres. In most practical flows, the effects of rotation and shear cannot be considered as independent, and a simple superposition of the two lift forces would inevitably bring errors [42]. Unless the rotation speed is much greater than the shear rate, for a freely rotating particle $\Omega_p = \frac{1}{2}\gamma$, Saffman force F_S , caused by the interaction of slip velocity (Stokeslet flow field) and shear, will generally be at least one order of magnitude larger than Magnus force F_{LR} caused by the interaction of slip and particle rotation at low Reynolds numbers [48].

The direction of Saffman force is always towards the side where the magnitude of relative velocity V_t is maximum. If the particles are leading the flow, Saffman force directs to the stagnant wall in a simple shear flow; Figure 3(a); if the particles are lagging the flow, Saffman force points to the moving wall, see Figure 3(b). Saffman force is more relevant in the case of non-neutrally buoyant particles in a vertical flow, or additional outer force (electrical or magnetic) [18, 49] acting on the particle to lag or lead fluid flow. In these cases, the Saffman force will direct to the channel centreline when particles lag the flow, or direct toward the channel walls when particles lead the flow in Poiseuille flow.

Figure 3 Saffman force on a sphere in a simple shear flow. V_t is the relative velocity of particle to fluid. (a) $V_t > 0$ indicates that particle moves faster than the corresponding fluid element, leading the flow. (b) $V_t < 0$ means that particle moves slower than the fluid element, lagging the flow. The direction of lateral lift force always directs toward the side where the magnitude of relative velocity V_t is maximum.

1.2.4 Wall lift force

The existence of walls creates a velocity gradient (shear rate) of fluid, and causes the rotation of spherical particles due to the fluid shear. Thus, transverse Magnus force and

Saffman force may act on the particles to migrate particles laterally. In addition, the secondary part of wall effects is the variation of the flow field around particles due to the presence of the physical walls. In order to eliminate effects of shear rate to the lateral lift force, one possible scheme is to investigate the motion of dense particles near a vertical wall in a stagnant fluid. In general, the effect of wall on the motion of immersed objects is to retard the motion of the object in both parallel and perpendicular directions, as well as exerting a transverse migration motion. Two distinct interactions between an immersed object and walls exist: (i) The motion of the immersed object is primarily influenced by a single wall on one side of the object. Any other walls are too far from the immersed object to influence significantly its motion. In this case, the main effect of wall is decelerating the particle and driving the immersed object away from the wall by a wall lift force F_{LW} [50], Figure 4(a). It applies to the situation where the characteristic dimension of immersed particle is much less than that of the channel. (ii) The immersed object is surrounded by the boundaries (walls) of the flow domain. Thus, the boundaries decelerate significantly the motion of object, and move particles to the centreline of channel. It happens if the characteristic dimension of the immersed particle is of the same order of the dimension of flow channel, e.g. small bubbles moving in capillaries [42].

Figure 4 (a) Boundaries retard the motion of the particle, and lateral wall lift force F_{LW} directing perpendicularly to the main flow direction repels particles away from the wall. (b) Shear gradient lift force F_{LS} on a particle in a Poiseuille flow. In the moving frame with the immersed particle, the relative velocity of fluid to particle v_t is larger on the wall side due to the parabolic velocity profile of fluid. Therefore, shear gradient lift force F_{LS} directs toward the wall.

1.2.5 Shear gradient lift force

As discussed above, the particle will lag the flow due to the effects of wall. If the curvature of the undisturbed fluid velocity profile is zero, it becomes a simple shear flow. Then the pressure will be higher on the left, pushing particles to the centreline of channel, as shown in Figure 3(b). However, in the Poiseuille flow, the magnitude of relative velocity of fluid to particle v_t is much higher on the left side of particle than that on the right side, due to the parabolic nature of velocity profile, as shown in Figure 4(b). And it even overwhelms the asymmetry caused by lag velocity. Similar to Saffman force, the dissymmetry of relative velocity causes a low pressure on the left/wall side, generating a shear gradient lift force F_{LS} that's opposite to the wall lift force F_{LW} . The shear gradient lift force leads particles toward the wall until the wall lift force repels and balances it [48, 51].

1.2.6 Net inertial lift force

For a neutrally buoyant rigid sphere flowing in a straight wall-bounded Poiseuille flow, besides a viscous drag force along the main axis, there are four lateral forces acting on the sphere as we discussed above: Magnus force due to slip-rotation, Saffman force due to slip-shear, wall lift force due to the disturbance of flow field around particles from wall, and shear gradient lift force due to the curvature of undisturbed fluid velocity profile. Among them, shear gradient lift force is at least one order of magnitude greater than the Saffman force, and three orders of magnitude greater than Magnus force [17, 44]. Therefore, both the shear gradient lift force and the wall lift force are widely accepted as the dominant effects for the inertial migration of particles [18]. The balance of the shear gradient lift force and the wall lift force creates several equilibrium positions halfway between the walls and centreline of the channel, and this theory can explain the observation of Segre and Silberberg reasonably well [1, 2], Figure 5(a).

Through the method of matched asymptotic expansions, Asmolov [6] derived an analytical expression of the net inertial lift force acting on a small rigid sphere ($a/H \ll 1$) in a Poiseuille flow:

$$F_L = f_L \rho_f \gamma^2 a^4 \quad (6)$$

The force can be further simplified as:

$$F_L = f_L \rho_f \bar{U}_f^2 a^4 / H^2 \quad (7)$$

The hydraulic diameter H is defined as $H = D$ for a circular channel (D is the diameter of circular cross-section) or $H = 2wh/(w + h)$ for a rectangular channel (w and h correspond to the width and height of the rectangular cross-section). The lift coefficient f_L

Figure 5 (a) Balance of shear gradient lift force and wall lift force results in the inertial equilibrium positions in a Poiseuille flow. (b) The net lift coefficient is a function of particle lateral position x and Reynolds number Re . Reproduced from reference [52].

is a function of the particle lateral position x and channel Reynolds number Re [6, 53], Figure 5(b). The lateral position x_{eq} where $f_L = 0$ corresponds to the inertial equilibrium position. It should be noted that the channel centreline $x = 0$ is not a stable equilibrium position, since a little deflection from centreline will never return the particles back. In

addition, it has found that f_L decreases with increasing Re (or $\bar{U}_f$), suggesting that inertial lift force scales less strongly than $\bar{U}_f^2$ [12, 20].

The recent investigation suggested that finite size of particle impacts the inertial migration of particles. For a finite-size particle ($0.05 \leq a/H \leq 0.2$), particle would cause disturbance to the main channel flow. Near the channel centre, where the effects of the wall are weak, the lift force scales as $F_L \propto \rho_f \bar{U}_f^2 a^4 / H^2$. While near the channel wall, where the wall effects dominate, it can be scaled as $F_L \propto \rho_f \bar{U}_f^2 a^6 / H^4$ [45].

1.2.7 Secondary flow drag

If particle suspension is not flowing in a straight channel, but a channel with curvatures, e.g. spiral or serpentine, a secondary flow arises due to the velocity mismatch in the downstream direction between fluid in the central and near-wall regions. The fluid elements near channel centreline have higher inertia and would tend to flow outward around a curve due to the centrifugal effect, creating a pressure gradient in the radial direction within the channel. In a fully-bounded channel, due to the centrifugal pressure gradient, relatively stagnant fluid near the walls re-circulates inward, finally forming two symmetric circulating vortices [20], called

Figure 6 Dean flow with two counter-rotating vortices appears in a curved channel. Reproduced from Ref [20].

Dean vortices, as shown in Figure 6. The parameters that influences the distribution and strength of the secondary flow in a curved channel includes Dean number De (=

$(H/2R)^{1/2}Re$), Reynolds number Re , aspect ratio of the channel $AR (=h/w)$ as well as the shape of cross section [29, 54].

Following Squires and Quake [55], the secondary flow velocity scales as

$$U_D \sim De^2 \mu / (\rho H) \quad (8)$$

Furthermore, the magnitude of secondary flow U_D can be approximated as [56, 57]:

$$U_D = 1.8 \times 10^{-4} \times De^{1.63} \quad (9)$$

Besides curved channels, secondary flow also appears in straight channels with disturbance structures (e.g. expansion-contraction arrays, pillar array) due to the similar mechanism. Moreover, Dean-like vortices can even be observed in specific positions of these channels [31]. Here, secondary flow drag is used to represent the viscous drag force due to the effects of Dean vortices in curved channels and other kinds of flows (Dean-like vortices) in the cross section of microchannel.

1.2.8 Other effects: particle shape, deformability, density and fluid viscoelasticity

Although solid rigid particles can be used as a simple model in the study of hydrodynamic behaviour of particles in a microchannel, the practical bioparticles such as cells and vesicles are not rigid but deformable. The deformability will induce additional lift force on the particles. The deformability-induced lift force is perpendicular to the main streamline, which is believed to be the effects of shape-change of particle and nonlinearities caused by the matching of velocities and stresses at the deformable particle interface [18]. In inertial microfluidics, centre-directed deformability-induced lift force shifts inertial equilibrium positions a little closer to the channel centreline than that of rigid particles [16].

Generally, for the applications of inertial microfluidics in biomedicine, the density of particle is often assumed to be equal to that of the medium, and the centrifuge force is ignored in the analysis and application. However, under certain circumstances where particle density is significantly greater than that of medium, centrifugal force on particles may need to be taken into account [44]. Besides, the shape of a particle also influence particle inertial focusing, and the rotational diameter D_{max} of a particle was found to determine the final focusing position [15]. By employing the difference in shape of particles, it has demonstrated

the possibility of separating particles that have similar dimensions along one axis but that varies along another axis [58].

In addition, previous investigations were restricted within the regime of Newtonian fluid. Recently, by addition of polymers, e.g. poly(ethylene oxide) (PEO) [59], polyvinylpyrrolidone, (PVP) [60], hyaluronic acid [61] etc., or long chain DNA [62] into the Newtonian base fluid, non-Newtonian medium with elastic property can be formed. Additional normal stress difference could be introduced to exert on the suspended particles in these viscoelastic fluid. Generally, the elastic force on particles directs to the positions where the shear rate is minimum, so that three-dimensional (3D) particle focusing along channel centreline is achieved [63, 64]. Three-dimensional focusing is of great importance in on-chip flow cytometry, where particles or cells need to be aligned and spaced precisely along a single line for one-by-one detection and analysis. More recently, by combining the elastic force and inertial lift forces in a viscoelastic medium, an inertial-elastic focusing concept was introduced [59], and three-dimensional focusing of particles by employing viscoelasticity was even achieved for Reynolds number up to $Re \approx 10,000$ [61]. The mechanism of this amazing phenomenon is still unclear, which deserves further investigation. In the following sections, without specific notations, the medium is assumed to be Newtonian fluid, thus elastic force is ignored in the analysis.

1.3 Different structures of micro-channels in inertial microfluidics

The straight channel is often employed as a basic model to investigate the fundamental mechanism of inertial migration due to its simplicity [7, 12, 45, 65-67]. However, for applications in particle separation or sorting, the position differences for particles with different properties (size, shape, deformability) are normally not distinct enough for sufficient separation. Introduction of secondary flow by curvature or disturbance structure may amplify this difference, promoting the separation of particles by differential lateral positions. Meanwhile, the characteristics of applied secondary flow are varying for differently structured microchannels, as well as inertial lift forces. Therefore, the number and location of final equilibrium positions of particles are highly dependent on the structure of microchannel. The characteristics of inertial forces in channels with different structures are summarized in Table 1.

1.3.1 Straight channels

In a straight channel with circular cross-section, inertial equilibrium positions are located within a narrow annulus at about 0.6 times of the channel radii from the channel centreline [1, 52]. However, in a straight channel with a rectangular cross-section, the situation becomes more complex. In a square straight channel ($AR=1$), particles normally focus into four symmetric equilibrium positions [68], facing the centre of each wall. Interestingly, a further reduction to two equilibrium positions happens in a low aspect ratio ($AR \approx 0.5$) channel, located near the long faces of the channel [12, 69, 70].

In a straight channel, particles' lateral migration velocity (U_L) and the minimum channel length (L_{min}), which is the minimum length that is required for particles to migrate to their inertial equilibrium positions, can be evaluated by balancing the net inertial lift force with the Stokes drag [53]:

$$U_L = \frac{F_L}{3\pi\mu a} = \frac{\rho_f \bar{U}_f^2 a^3}{6\pi\mu H^2} \quad (10)$$

$$L_{min} \approx \frac{H}{2U_L} * \bar{U}_f = \frac{3\pi\mu_f H^3}{\rho_f \bar{U}_f a^3} \quad (11)$$

Two dimensionless Reynolds numbers can characterize the lateral migration of particles in straight channels: 1) channel Reynolds number Re describing the ratio between inertial force and viscous force of fluid; and 2) particle Reynolds number $R_p (= Re \frac{a^2}{H^2})$ additionally considers the size ratio of particle to channel. When $R_p \gg 1$, inertial migration of particles across the fluid streamlines becomes obvious [19].

Generally, straight channels are not good at particle separation. Most of the applications on particle separation by straight channels are actually based on the filtration concept, that is, larger particles are focused after a certain length due to the sufficient inertial lift forces, while their smaller counterparts remain uniformly distributed, then larger target particles can be removed from the mixture and concentrated [8, 13, 71, 72]. In order to achieve a complete separation, cascaded straight channels were applied to separate particles based on the size-dependent lateral migration speed [11].

Table 1 The magnitude variation of forces in microchannels with different structures [44, 73]. Note: CE indicates contraction-expansion.

	Straight	Spiral	Asymmetric serpentine	Symmetric serpentine	CE array	Pillar array
Wall lift force						
Shear gradient lift force						
Secondary flow drag						
Equilibrium positions	2-4	1-4	1-4	1-4	1-4	1-2
Theoretical separation scaling	$> a$	a^2	a^2	a^2	$\geq a^3$	NA
References	[11-14, 45, 67, 68, 71]	[22, 23, 74-78]	[19, 79-82]	[19, 24, 41, 83]	[31, 69, 70, 84-89]	[32, 90-93]

1.3.2 Spiral channels

Particles flowing in a curved channel with finite inertia experience both inertial lift forces and secondary flow drag. When the channel curvature is along a single constant

direction, the curved channel forms a spiral channel. And the direction of secondary flow within each cross-section is almost constant, even though there may be a little variation on its magnitude due to the change of channel curvature. By a first order approximation, one can make an assumption that the effects of inertial lift force and secondary flow drag act in superposition on a particle in a spiral channel. A particle held stationary at an inertial equilibrium position experiences a secondary flow drag whose magnitude is directly proportional to the local secondary flow velocity [20]. This secondary flow drag force acts to entrain particles within the streamline of symmetrically rotating vortices, which is primarily an effect of mixing. In contrast, inertial lift forces tend to keep particles at specific equilibrium positions within channel cross section. The order of magnitude scaling between inertial lift forces and Dean drag $R_f = a^3 R/H^3$ determines the final behaviour of the suspended particles. This dimensionless parameter is useful for the prediction of particle focusing in curved channels.

At limiting conditions where (i) $R_f \rightarrow 0$, Dean drag force dominates the behaviour of particles, particles neglect inertial equilibrium positions, and remain entrained within the secondary flow streamlines; and (ii) $R_f \rightarrow \infty$, inertial lift force is dominant, particles migrate to the inertial equilibrium positions independent of the secondary flow [20]. For most cases, in the intermediate range of R_f , inertial equilibrium positions can be modified by the secondary flow, leading to new intriguing focusing phenomenon. It has been noted that R_f is dependent on particle size, so that different-sized particles may occupy distinct equilibrium positions in a spiral channel. These size-dependent behaviours have been widely applied on particle separation in spiral channels [22, 23, 54, 75-78, 94-96].

1.3.3 Straight channels with disturbance structures

Besides curvature, the introduction of disturbance structures (contraction-expansion cavities [86], micro-pillar obstacles [32]) into straight channels will also induce convective secondary flow within the cross section. In the contraction-expansion array (CEA) channel, the shape of this convective secondary flow is very similar to the Dean flow in the curved/spiral channels, therefore, it was termed as Dean-like flow [31]. In contrast to the Dean flow whose magnitude is proportional to $Re^{1.63 \text{ or } 2}$ [20, 55], the magnitude of Dean-like flow was found to be linear with Re [31]. Meanwhile, the secondary flow in CEA channel only appears within the narrow contraction regions [70], and its effect on particle inertial

focusing is intermittent. Furthermore, due to a suddenly increased channel width during the expansion area, the shear gradient lift force drops sharply, and the wall lift force even vanishes during this area because particles are too far from the two sided walls.

In addition to the secondary counter-rotating flow within the cross-section of the main channel around the contraction-expansion region, a horizontal micro-vortex within the contraction-expansion chamber can also be generated due to the detachment of boundary layer under a high flow speed [97]. This horizontal micro-vortex has been intensively investigated for particle selective trapping, especially for circulating tumour cells (CTCs) isolation [26, 98-100].

Besides expansion-contraction cavity, micro-pillar obstacles embedded within a micro-channel can also induce irreversible twisted flows at a finite inertial flow. Furthermore, the lateral position of the pillar can be used to tune the position and shape of the net recirculating flows. It has shown precise control of fluid transformation by programming the positions of sequenced cylindrical pillars [32, 90]. Similar to the secondary flow induced by the contraction-expansion chamber or channel curvature, the locally induced secondary flows by sequenced pillars could also be used to modify particle inertial focusing process [91, 93].

1.3.4 Serpentine channels

As we know, in spiral channels, the curvature is along a single direction, therefore the secondary flow can reach steady state after a given channel length, and almost consistent within different cross-sections. In a serpentine channel with alternating curves, the situation becomes more sophisticated. For example, with alternating curves, secondary flow will vary along the channel length, and particles' movement within the alternating curves may not approach steady state after each turn, and accumulation of this unsteady may cause unpredictable and non-intuitive behaviours of particles. Therefore, analysis of particle behaviour with a simple superposition method cannot always be effective.

Di Carlo et al. [19] investigated the particle inertial focusing in serpentine channels. In their study, original four equilibrium positions in a straight channel with square cross section were reduced to two in a symmetric serpentine channel. Above a critical Dean number, particle focusing was perturbed. Furthermore, in an asymmetric serpentine channel, the number of equilibrium positions could be further reduced to one. From their understanding, the balance between the inertial lift forces (F_L) and the Dean drag force (F_D) determines the

preferred location of focusing positions. Dean flow does not create particle focusing, but it acts in superposition with inertial lift forces to reduce the number of inertial equilibrium positions. If $F_D \gg F_L$, no focusing will be observed; if $F_D \ll F_L$, focusing due to inertial lift forces alone will be observed. In symmetric serpentine channels, the effects of curvature-induced secondary flow will be counteracted by its corresponding opposite segments, thus secondary-flow-modified single focusing may only be achieved in the asymmetric serpentine channels [19]. However, our recent experimental and analytical study found some discrepancies [24, 41, 83], which demand a further exploration.

1.4 Applications of inertial microfluidics

Due to the superior advantages of simplicity, high-throughput, precise manipulation and low cost etc., inertial microfluidics has broad applications in biomedicine (e.g. bio-fluid sample preparation and disease diagnosis) and industry (e.g. waste water purification and micro-fibre fabrication), and the application area is still expanding rapidly. Generally, its applications include but not limited to: 1) sheathless alignment; 2) particle filtration and separation; 3) solution exchange; 4) microfiber fabrication; and 5) hydrodynamic phenotyping of single cell.

1.4.1 Sheathless alignment

Particle alignment is essential for many biological detection systems, especially On-chip flow cytometry [101], where particles/cells are precisely positioned near an optical or electrical detector and aligned along a specific path one-by-one to achieve accurate results. In contrast to the conventional techniques utilizing sheath flow surround the sample flow to achieve 3D particle focusing in flow cytometry, sheath-less inertial focusing is simple and easy to handle, without reduction in sample flow rate [44]. It has been widely explored and demonstrated in on-chip flow cytometry [56, 80, 82, 102], as shown in Figure 7(a). On chip flow cytometry can also be integrated with a cell-sorting module to actively separate and purify sample subpopulations [81, 103, 104], as shown in Figure 7(b).

1.4.2 Particle filtration and separation

Particle filtration and separation are widely used in industry and biomedicine, such as wastewater purification, blood sample preparation and disease diagnosis. In microfluidics, continuous flow separation and sorting of particles are generally based on two principles: 1)

equilibrium separation, where particles occupy different property-dependent equilibrium positions, see (I) in Figure 8 (a); and 2) kinetic separation, where various particles possess different transport speeds perpendicular to primary flow direction under an applied force field [105, 106], as shown (II) in Figure 8(a). In these two separation principles, different particles occupy distinct final positions at the outlet, and complete separation can then be realized. In addition, there is another kind of mechanism depending on the forces parallel to primary flow, but it is not common in inertial microfluidics.

Particle filtration is based on the principle that target particles are focused, and the rest particles are randomly distributed, so that target particles can be get rid of particle mixtures, as shown (I) in Figure 8(b). However, the collected target particles are still not perfectly pure, containing partial unwanted ones. Theoretically, by

Figure 7 (a) Schematic of On-chip flow cytometry setup. Inertial focusing in straight and asymmetric serpentine microchannels was employed to align particle along a single path one-by-one for single cell level detection downstream. Reproduced from [82]. (b) Inertial particle focusing in a low-aspect-ratio straight channel with a

series of constrictions in height is integrated with a pulsed laser activated cell sorter (PLACS) to realize active real-time cell sorting. Reproduced from [104].

Figure 8 (a) Two different particle separation principles in inertial microfluidics by (I) equilibrium separation and (II) kinetic separation. (b) Particle filtration in inertial microfluidics, (I) target particles are focused, and other particles remain random distributed; (II) all particles are focused and concentrated along one streak, and removed from one branch, leaving particle-free medium.

cascaded processes, target particles can be purified continuously. Another particle filtration principle is that all particles are focused along one specific path, and depleted from the medium, as shown (II) in Figure 8b. It is mostly applied in the situations where the liquid phase is the target in the filtration process, such as waste water purification [107] and blood plasma separation [108] etc.

Due to the superior advantages of simplicity, label-free and high throughput, inertial microfluidics has great potential in routine bio-fluid preparation and disease diagnosis, especially for target cells in low abundance, e.g. circulating tumour cells (CTCs). Cancer, also known as a malignant tumour, is a group of diseases involving abnormal cell growth with the potential to invade or proliferate in other organs of the body. Metastases from primary tumours are the leading causes (~90%) of death for nonhematological cancers [95]. During the progression of metastasis, cancer cells escaped from solid tumours and enter the bloodstream, becoming CTCs, which hold a great potential to serve as important biomarkers

for early diagnosis of cancer metastases, cancer prognosis, and therapy monitoring. CTCs analyses are considered as a real-time “liquid biopsy”, which is much less invasive than the current method for cancer diagnosis requiring invasive biopsy followed by molecular analyses. However, CTCs are extremely rare, comprising only a few out of one billion haematological cells in blood, making their isolation and characterization an extreme technological challenge. Due to the high-throughput feature of inertial microfluidics, it can process a larger volume of blood samples in a much shorter time than other techniques. A large number of inertial microfluidic systems for CTCs separation and isolation has been proposed and reported [77, 84, 100, 109, 110], and have shown very promising capacity in CTCs isolation.

Figure 9 (f) Rapid inertial solution exchange in a straight channel for controlled interaction of reagents with cells and particles. Reproduced from Ref [111].

1.4.3 Solution exchange

Manual concentration, staining and washing procedures for the cellular sample are routinely conducted by cytopathologists as a means of diagnosing malignancies and other diseases. However, current approaches for chemical treatments of cells and chemical reactions typically operate on slow time scales (~seconds to minutes), limiting the realm of fast molecular events. Inertial lateral migration has been subtly employed as a helpful tool to mediate millisecond reaction time around particles and cells [111], as shown in Figure 9. The main transfer channel is designed with low AR , so that particles will migrate to the lateral

centre of the channel regardless of their initial positions in the inlet. The channel is designed with three inlets. Particles suspension is infused from the two-sided inlets, while the reagent is delivered from the central inlet. Lateral migration of particles from original medium to the middle stream area initiates the contact of particles/cells with the chemical reagent, and duration of particles within middle stream mediates the reaction time. The proposed microfluidic system can perform several functions in the sample preparation for cytopathology that (i) automates colorimetric staining on-chip; (ii) images cells in flow; and (iii) provides additional quantitative analyses of captured images [112].

1.4.4 Microfiber fabrication

In the conventional fibre fabrication technology, circular cross section is the most prevalent. Although non-circular cross-sectional fibres can be produced by the standard spinning process through the non-circular hole of a spinneret, it is still challenging to form complex cross-sectional shapes in some materials because of die

Figure 10 Schematic illustration of the synthesis of shaped polymeric microfibers through sequenced micro-pillars in a programmable inertial microfluidic system. Reproduced from [90].

swelling, the rate of solidification, and polymer relaxation [90, 113]. Programmable flow deformation by sequenced micro-pillars in inertial microfluidics provides a possible solution.

A micro-pillar within a micro-channel induces irreversibly twisted flows at a finite inertial flow. Furthermore, the lateral position of the pillar can be used to tune the position and shape of the net recirculating flows within the cross section. Therefore, it may enable precise control of the net fluid transformation by programming the positions of sequenced cylindrical pillars. Through a computer-aided design (CAD) tool uFlow which has a stored library of pre-computed fluid deformation of the individual pillar in the flow channel, one can design and predict the net flow deformation, without requirement of significant design iteration and experimental verification [32, 92]. Nunes et al. [90] utilized this microfluidic technique to fabricate polymeric microfibers with noncircular cross-sectional shape, as shown in Figure 10. The cross-sectional shapes of various fabricated microfibers agreed reasonably well with that predicted using the uFlow code.

1.4.5 Hydrodynamic stretching

The mechanical properties of cells have become promising biomarkers of cell state and disease, such as metastatic potential [114], cell cycle stage [115], degree of differentiation [116], and leukocyte activation [117]. Through a unique combination of inertial focusing, hydrodynamic stretching and automated image analysis, an automated microfluidic technology was developed to screen single cell deformability at approximately 2,000 cells/s [118]. Sheathless inertial focusing by the

Figure 11 Deformability cytometry to characterise mechanical morphology of single cells in a large population. Inertial focusing of cells in a serpentine channel orders cells along a single stream for downstream hydrodynamic pinching. Reproduced from Ref [118].

asymmetric serpentine channel delivers suspended cells uniformly to an extensional flow region, and two sheath flows pinch the cells in the downstream, as shown in Figure 11. Uniform delivery leads to uniformity in the hydrodynamic stress and corresponding deformation of individual cells. This microfluidic technology has been applied in the identification of inflammation and malignancy in pleural fluids and stem cell state [118]. By modification of extensional flow by self-feeding manner, the deformability cytometry can enable a much higher throughput (65, 000cells/s) [119].

1.4.6 Summary

Inertial microfluidic technology has demonstrated broad applications in biomedicine and industry, and the functionality is largely dependent on the structure of micro-channel. Table 2 summarizes the applications of differently structured

Table 2 Applications of differently structured microchannels in inertial microfluidics. Notes: particles here specifically indicate polystyrene beads

Channel types	Applications	Sample	References
Straight	Flow cytometry	Particles, Diluted whole blood, 1% or 5% v/v RBCs	[102]
	Filtration or separation	Digestions of murine adrenal glands, 0.5% (v/v) blood, 0.5% (w/w) particles, E. coli spiked in blood Particle mixture, CTCs spiked in diluted blood (0.8% v/v) CTCs spiked in blood at 1:100, total concentration (2×10^6 cells/mL)	[71] [72] [11] [16]
	Solution exchange	MCF7 and MCF10A breast cancer cell lines, HeLa cell line	[111, 112]
Spiral	Flow cytometry	Particles (0.05% v/v), SH-SY5Y neuroblastoma cells (0.05% v/v),	[56]
	Filtration or separation	Particles Particles, SH-SY5Y neuroblastoma, glioma cells (0.05% v/v) Particles, CTCs spiked in leukocytes Different cell cycle human mesenchymal stem cells CTCs spiked in whole blood, clinical cancer patient blood sample Leukocytes from the whole blood (0.5-2% v/v)	[22, 74, 120, 121] [23] [122] [94] [75-77, 96, 110, 123] [78]
	Cell encapsulation	HL60, K562 (1-2.2% v/v)	[57]
Serpentine	Flow cytometry	10.2 μ m particles budding yeast and MCF7 cells in blood	[82] [80]
	Filtration or separation	Particles, diluted blood (2% v/v) CTCs spiked in blood, clinical samples from metastatic cancer patients Diluted whole blood, MEL cells spiked in whole blood	[79] [81] [41, 83]
	Hydrodynamic phenotyping	Mouse and human embryonic stem cells (ESCs) Jurkat leukemia and HeLa cells	[118] [119]
Contraction-Expansion array (CEA)	Flow cytometry with pulsed laser activated cell sorter	Particles, Ramos human Burkitt lymphoma Cells	[104]
	Filtration or separation	Parasites spiked in RBCs (2.5% v/v) Particles Undiluted whole blood MCF-7 cancer cells spiked in the whole blood (~45% v/v) at 1:1000 CTCs spiked in the whole blood and pleural effusions, clinical blood sample from cancer patient	[124] [70, 88, 89, 125, 126] [85] [84] [26, 99, 100]
	Solution exchange	MCF7 cells	[26]
Pillar array	Microfiber fabrication	PEG-DA	[90]
	Solution exchange	Particles, WBCS after blood lysis	[91]

microchannels in inertial microfluidics. Due to the superior advantages of high-throughput, simplicity, precise manipulation and low cost, inertial microfluidics is very promising in bio-fluid preparation and particle separation, especially for the rare target cells isolation (e.g. circulating tumour cells or CTCs). Since target cells are low in abundance, particle suspension with large volume needs to be processed within reasonably short time. Under such situation, the advantages of inertial microfluidics are obvious.

1.5 Conclusions

In this chapter, we discussed three important aspects of inertial microfluidics: fundamental mechanism, microchannel designs, and applications. We hope that readers can have a brief idea what the inertial microfluidics is, why the inertial focusing happens, and how the inertial focusing can be applied in biomedicine and industry. It should be noted that, although extensive investigations on the mechanism of particle inertial focusing have been conducted, and a variety of applications on particle/cell separation have been demonstrated, quantitative design rules are still lacking for particle inertial manipulation in differently shaped channels. Therefore, more dedicated work is needed to uncover the detailed underlying mechanism, and provide explicit rules to the end users even without specialized knowledge and experience about inertial microfluidics. In addition, more efforts are required to improve the separation resolution and processing speed through optimization of channel structure and scale up scheme.

Inertial microfluidics, as an unconventional microfluidic technology, provides more possibilities and opportunities on dealing with macroscale biofluid samples within well-defined microscale channels, and would be a promising replacement of conventional macroscale platform (flow cytometry, centrifuge and membrane filter) for bioparticle precise processing and separation. We believe that in the near future inertial microfluidics remains a hot research topic with expanding applications, due to the incredible advantages of high throughput, simple structure and low cost.

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Lists of notation

a : Particle diameter

AR : Aspect ratio of channel ($=h/w$)

D_{max} : Rotational diameter of non-spherical particle

De : Dean number

F_D : Secondary flow drag or Dean drag

F_{drag} : Viscous drag force

F_L : Net inertial lift force

F_{LS} : Shear gradient lift force

F_{LW} : Wall lift force

F_{LR} : Magnus force or rotation induced lift force

F_S : Saffman force or slip-shear-induced lift force

f_{drag} : Viscous drag coefficient

f_L : Coefficient of net inertial lift force

H : Channel hydraulic diameter

h : Channel height

L_{min} : Minimum channel length for particles to migrate to the inertial equilibrium position

R : Radius of curvature of curving channel

Re : Reynolds number

Re' : Particle Reynolds number based on relative velocity of fluid and particle

R_p : Particle Reynolds number based on the size ratio of particle to channel

R_f : Ratio of inertial lift force to Dean drag

S : Cross-sectional area of particle

U_f : Fluid velocity

U_p : Particle velocity

U_D : Secondary flow velocity or Dean flow velocity

U_L : Lateral migration velocity of particle

v_t : Relative velocity of fluid to particle

V_t : Relative velocity of particle to fluid ($=-v_t$)

w : Channel width

x : Lateral position of particle

ρ_f : Fluid density

Ω_p : Angular velocity of particle

γ : Fluid shear rate

μ : Dynamic viscosity

ν : Kinetic viscosity