A Review of Inertial Microfluidics: From Fundamental Theories to Biomedical Applications

A Term Project Report Submitted

by

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Abstract

Inertial microfluidics is an area of study that combines inertial and viscous phenomena to manipulate fluids and particulates at micrometric levels. Research is still ongoing but now includes applications in healthcare, biological and chemical diagnostics, and even in materials science. The unique physics, automation, and scalability of these systems make them useful in various domains. This report attempts to highlight the primary constituents of inertial microfluidics, more specifically, the basic interactions of forces, particles movements and the alignment of particles into stable positions within channels of varying designs. It pursues the participation of suspended particles in the dynamics of a fluid motion, the phenomenon of Dean flows in curved channels and how some geometric changes in the structure can affect the secondary flow field generated for particle rearrangement and mixing. Also, important notable cases are shown and discussed for their use in diagnosis and clinical research, the active problems, and progress in the field. While the study addresses the theoretical concern, this report is expected to provide insight on the practical concern of inertial microfluidics for biomedicine, chemical control systems, and materials synthesis.

***Keywords**: Inertial microfluidics, Particle migration, Secondary flows, Dean flow, Biomedical applications.*

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Chapter 1

Introduction

The world of microfluidics is often associated with flows in which the Reynolds number is very low (Re < 1); inertia is often neglected because of the dominance of viscosity. As a result, streamlining assumptions with Stokes flow was considered sufficient in microfluidic systems because the channels were so small [1], [2]. More recent work, however, has emphasized the presence of inertial effects in microchannels, especially at intermediate Reynolds numbers (1 < Re < 100), where there is an active balance between the effects of viscosity and inertia on particle motion [1], [3]. These scenarios introduce the potential for inertial and secondary flows, so that particles can be suspended in microfluidic systems with a high degree of control [1], [4].

In the 1960s, Segre and Silberberg made one of the first examples of timid migration, when they reported that in the case of cylindrical pipes, particles of a fixed size are capable of being focused about an equilibrium position [5]. This effect, which is now studied in microfluidic systems, has provided impetus to the development of methods of particle focusing, separation and manipulation [3], [6]. The ability to control particles through hydrodynamic means to eliminate external fields enable inertial microfluidics to be a forceful candidate for many applications [1], [3]. The newest developments have contributed a new scope for inertial microfluidics to be applied in synthesis of material, chemical analysis, and biomedical diagnosis [1], [3], [6]. There are two ways of differentiating flow that are hydrophoresis and field-flow fractionation, which passively and actively separate and thus provide that efficient separation while dealing with cells [3], [6]. Besides that, there are other channel design improvements dealing with the management of fluid and the dynamics of the particle phenomenon, for instance, through curved geometry and structured microchannels [3], [6]. The report then presents the fundamental ideas, experimental work, as well as technological innovations regarding inertial microfluidics. Afterward, the report provides future perspectives on the many sciences and industries that may be affected [1], [3].

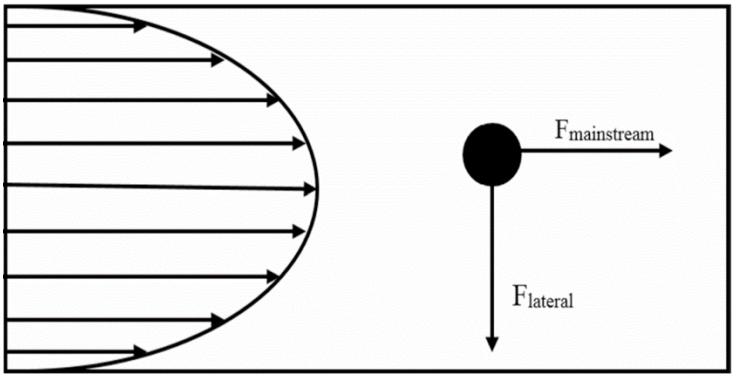


Fig. 1 *Drag and lift forces on particle in a fluid*

Chapter 2

Objective

This report explores the motivations and advancements in inertial microfluidics as they pertain to fluid mechanics at the micro level, with a focus on the interplay of inertial and viscous forces. This paper addresses the behavior of particles under microchannel flow and the equilibrium positions of particles in microchannels as special instances of secondary flows in microstructures, such as Dean vortices in curved microchannels. The application of inertial microfluidics for biomedical applications, isolation of cancer cells, rapid enumeration of malaria, and separation of bacteria from human blood cells, is a significant aspect of this report. The applications illustrate the high throughput efficacy of the technology in high-throughput and label-free diagnostics. Lastly, the report discusses the effect of microchannel geometry on particle transport and flow behavior. It also discusses challenges, advancements, and prospects of inertial microfluidics, to highlight the impact the technology can have on medical diagnostics and biotechnologies.

Chapter 3

Literature Review

Inertial microfluidics is a new way to control small particles movement in liquids. In contrary to other methods, it does not need extra forces like electricity or magnets [3], [8]. Instead, it uses the natural movement of fluids. This makes it simple, efficient, and useful in many fields, such as medicine and environmental science [7], [9].

The two main forces in inertial microfluidics are shear-induced lift and wall-induced lift. These forces push particles into certain positions inside a fluid channel. This process is called inertial focusing [3], [4]. Unlike traditional microfluidics, which works at low fluid speeds, inertial microfluidics functions at a medium speed [9]. The shape of the channel, the speed of the fluid, and the size of the particles all affect how it works [8]. A key factor in inertial microfluidics is secondary flow. When liquid moves through curved or spiral channels, it creates swirling movements called Dean vortices. These help to separate particles, which is useful for sorting cells and detecting diseases [7].

Numerical Methods has played a big role in improving inertial microfluidics. Scientists are now use numerical based models to predict how fluids will behave under certain conditions. The methods like the Lattice Boltzmann Method (LBM) and finite element analysis (FEA) are helping in designing better devices [4] based on inertial microfluidics. These tools are reducing the need for expensive experiments. Artificial intelligence (AI) is also being used to create better designs. It makes more accurate predictions [8] than previously available techniques.

One important use of inertial microfluidics is in medicine. For example, it helps find cancer cells in the blood. Since these cells are rare, early detection is important for treatment [3]. This method is better than traditional chemical-based methods because it is faster and simpler. It is also useful for studying single cells, separating tiny particles called exosomes, and analyzing genes. It can also tell apart white and red blood cells, improving the accuracy of blood tests [7], [4]. Since it can process large amounts of samples quickly, it is useful for hospitals and research labs. Inertial microfluidics is also helpful in detecting diseases. It can separate bacteria and viruses from body fluids, making it easier to diagnose illnesses [9]. This is especially important during pandemics, when quick testing is needed.

Besides healthcare, inertial microfluidics is used in industries and environmental work. One industrial use is in biofuel production. Microalgae are being separated using it. Microalgae are separated using it. The production of biofuels requires microalgae [4]. In the field of environmental science, it is being is used to assess the quality of water. By eliminating dangerous materials like heavy metals and microplastics. These devices help to maintain clean water [8]. Since they work quickly and can be used in the field, they are useful for environmental agencies and researchers.

Even though inertial microfluidics has many benefits, there are still some challenges. Clogging is a major issue, particularly when the fluid contains an excessive number of particles. Another major problem is biofouling, that is slowing down of the process due to accumulation of biological

material inside the channels [3]. For the devices to function better and last longer, scientists must figure out how to address these issues. These systems are costly as well as complex in design. Although methods like soft lithography and 3D printing are being used but prices are still high [8]. Fitting microfluidic devices into already-existing factories and labs presents another difficulty. This new technology was not intended for usage in the majority of traditional systems. Creating hybrid systems that combine conventional and contemporary methods is one approach to resolving this issue [9].

Inertial microfluidics appears to have a promising future. New materials are being tested by scientists to strengthen and improve gadgets. Special polymers and blended materials can help prevent clogging and biofouling [4]. Automation and robotics may also improve processing speed and accuracy. One interesting area is personalized medicine. This technology could help doctors create more effective treatment plans by offering quick and accurate medical analysis [7]. When combined with AI, it has the potential to revolutionize healthcare. In environmental science, inertial microfluidics can aid in the development of clean water supply devices. Real-time water quality testing portable devices are being developed by researchers [8]. These could be useful in places with clean water scarcity.

In conclusion, inertial microfluidics is growing quickly and has many uses. It is helpful in medicine, industry, and environmental protection. However, some challenges still need to be solved, such as clogging, biofouling, and high production costs. With continued research and better designs, these issues can be fixed. As manufacturing becomes cheaper and easier, this technology will become more common. It has the potential to change healthcare, industry, and environmental science in the future.

Chapter 4

The fundamentals of inertial microfluidics

In inertial microfluidics, suspended particles move through channels under viscous drag and lateral lift forces, including shear gradient and secondary flow drag. Velocity differences create pressure gradients, influencing particle migration. Depending on fluid properties, particle shape, and channel design, some forces may be negligible. This section examines key forces in particle motion.

4.1 Viscous Drag Force

The viscous drag force arises from the relative motion between suspended particles and the surrounding fluid. It is primarily influenced by:

1. *Wall Shear Stress*: This tangential force acts on the particle surface due to frictional interactions caused by fluid viscosity. It is commonly referred to as skin or friction drag.
2. *Pressure Stresses*: These normal forces arise from pressure distribution around the particle due to fluid movement, also known as form drag.

The significance of skin drags increases with enhanced surface alignment with flow direction. The total viscous resistance (drag) acting on a spherical particle in a fluid is given by Eq. (1) as

$$F_{drag} = S \times f_{drag} = \frac{\pi a^2 f_{drag}}{4} \tag{1}$$

Where,

F_{drag} = viscous drag force (N)

S = area of cross-section of the particle (m^2)

f_{drag} = viscous drag coefficient

a = particle diameter (m)

The viscous drag coefficient varies with the Reynolds number but is commonly expressed using the Stokes drag equation when relative velocity is low by Eq. (2) and (3) as

$$f_{drag} = \frac{12\mu v_t}{a} \tag{2}$$

$$F_{drag} = 3\,\mu v_t a \tag{3}$$

Where,

μ = dynamic viscosity (Pa·s)

v_t= relative velocity between fluid and particle (m/s)

Components of Drag Force in Inertial Microfluidics

1. *Axial Drag Force*: Arises from velocity differences between the particle and the surrounding fluid along the main flow direction.

2. *Lateral Drag Force*: Induced by secondary flows due to microchannel curvature or structural flow disturbances.

4.2 Magnus force: rotation-induced lift force

The Magnus force, a lift force generated by particle rotation, occurs when a rotating cylinder is placed in a uniform viscous fluid flow. Due to the no-slip boundary condition, The flow velocity over the top surface of the cylinder is greater than that at bottom surface, creating a pressure difference according to Bernoulli's principle. This pressure imbalance generates a lift force, $\overrightarrow{F_{LR}}$, which acts on the cylinder's surface, as expressed in Eq. (4).

$$\vec{F}_{LR} = \pi \rho_f a \vec{U}_f \times \vec{\Omega} \tag{4}$$

Where,

$\vec{F}_{LR}$= lift force generated by particle rotation (N)

ρ_f= fluid density (kg/m^3)

a= cylinder diameter (m)

$\vec{U}_f$= fluid average velocity (m/s)

$\vec{\Omega}$ = angular velocity

The Magnus force, or lift force generated by particle rotation, acts on a rotating rigid sphere in a fluid. It arises from the pressure difference between the upper and lower sides of the sphere caused by its rotation. The Magnus force is given by Eq. (5) as

$$\vec{F}_{LR} = \frac{1}{8} \pi \rho_f a^3 \vec{U}_f \times \vec{\Omega'} \tag{5}$$

Where,

$\overrightarrow{\Omega'}$= relative rotation between fluid and the sphere (rad/s)

$\overrightarrow{\Omega'}$= ($\vec{\Omega}$ – 0.5$\nabla \times \vec{U}_f$)

4.3 Saffman force: slip-shear-induced lift force

The Saffman force is a lift force that affects particles moving through a fluid. It happens because the particle's speed differs from the fluid's speed, creating a pressure difference. This force is generally stronger than the Magnus force. In simple terms, if the fluid moves slowly than the particle, it creates higher pressure above the particle, leading its movement toward the wall. If it moves slower, the force pushes the particle in the direction of the fluid's flow.

In a channel, if the particle lags behind the fluid, it gets pushed toward the center. If it leads, it gets pushed toward the wall. The particle's movement depends on how fast it moves compared to the fluid: faster slip speeds push it away from the wall, while slower speeds push it toward it. So, the Saffman force can lead to the movement of a particle either toward the wall or the center of the flow, depending on how it moves through the fluid. Saffman lift force magnitude determined by the matched asymptotic expansion method, is given by Eq. (6) as,

$$F_s = \frac{KV_t a^2 (\gamma v^{-1})^{\frac{1}{2}}}{4} \tag{6}$$

Where,

K = a constant value (~ 81.2)

V_t = relative velocity between fluid and particle at the Center of particle (m/s)

a = diameter of the sphere

γ = shear rate $(1/s)$

v = kinematic viscosity (m^2/s)

4.4 Wall lift force

In a fluid flow through a channel, the walls create a velocity difference, causing particles to move at different speeds. This leads to forces like the Magnus and Saffman forces, which push particles sideways.

There are two main effects from the channel walls:

1. *Single Wall Effect*: If the particle is near one wall, it slows down and is pushed away by the wall lift force. This happens when the particle is much smaller than the channel.
2. *Two Wall Effect*: If the particle is between two walls, it slows down more and is pushed toward the center of the channel. This occurs when the particle is about the same size as the channel.

These forces determine whether the particle moves toward the center or away from the walls.

4.5 Shear gradient lift force

In channel flow, particles tend to lag behind the flow due to the wall's influence. If the flow is undisturbed, the pressure is higher near the wall, pushing the particle toward the center. In Poiseuille flow, the faster fluid on the left side of the particle creates a low-pressure zone near the wall, pushing the particle toward it, unless the lift force at the wall pushes it away. The shear gradient lift force acts against the wall lift force.

4.6 Net inertial lift force

Among all the four lateral lift forces discussed above, the shear gradient lift force is much stronger than the Saffman force-about ten times stronger-and roughly 1,000 times stronger than the Magnus force. In microfluidic channels with slow flow and highly viscous fluids, the wall lift force and shear gradient lift force are the main forces acting on small particles.

A balance between these two forces creates several equilibrium positions near the center of the channel, as explained by Segre and Silberberg. Using matched asymptotic expansions, Asmolov derived an equation to understand the net inertial lift force on micrometric particles, where the particle diameter is much smaller than the channel diameter. This force can be expressed using the formula in Eq. (7) as,

$$F_L = f_L \rho_f \gamma^2 a^4 \tag{7}$$

The net inertial lift force F_L can be modified to the following Eq. (8) as,

$$F_L = \frac{f_L \rho_f {U_f}^2 a^4}{H^2} \tag{8}$$

Where,

f_L = lift coefficient

ρ_f = fluid density (kg/m^3)

U_f = velocity of the fluid flow (m/s)

a = particle radius (m)

H = $\frac{cross-secion\ area \times 4}{perimeter}$, hydraulic diameter of the channel

For a circular channel, H is the diameter D, for a rectangular channel, H = $\frac{2wh}{w+h}$, w is the width and h are the height of the rectangular cross-section.

The lift coefficient f_L depends on the Reynolds number (Re) and the position of the particle within the channel, represented by x. The equilibrium position of the particle occurs when f_L = 0, meaning the particle is stable. If a particle is placed exactly at the centerline (x = 0), even a small deflection from this position prevents it from returning to the center. The size of the particle also affects its migration in the flow. When the particle size is between 0.05 and 0.2 times the channel size (measured as the a/H ratio), the flow near the particle is disrupted. When the particle is near the center of the channel, the lift force behaves as,

$$F_L \alpha \frac{\rho_f \overrightarrow{U_f}^2 a^2}{H^4}$$

But when the particle is closer to the channel wall, where the wall's effects become stronger, the lift force behaves as,

$$F_L \alpha \frac{\rho_f \overrightarrow{U_f}^2 a^6}{H^4}$$

4.7 Inertial migration and focusing

Drag and lift forces help in moving the particles to their equilibrium positions along the channel cross sectional area, a process known as inertial migration and focusing. The particles flowing through a channel tend to settle into specific, stable positions because of the forces acting on them. Segré and Silberberg first observed that particles in cylindrical pipes accumulated in a ring-like region [5]. Later research confirmed similar behavior in various microchannel designs [10], [11] and with single rigid spheres in laminar flow [12].

Two main forces are responsible for this behavior. The drag force moves the particles along with the flow, while the lift force pushes them sideways. The lift force consists of two parts, one resulting from the effect of nearby walls while, the other from the shear forces in the fluid [10], [1]. The particles are either directed toward the center of the channel or toward its walls depending on the balance of these forces. Finally, they settle at a distance of about 20% of the channel

diameter from the wall [6]. The speed at which this equilibrium is reached depends on factors like fluid velocity and channel size [13], [14], [10] as reflected from Eq. (9).

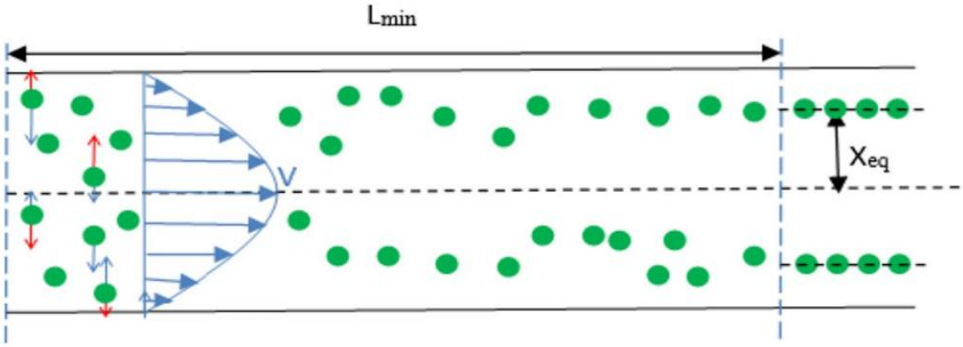


Fig. 2 Focusing dynamics (lateral migration Speed and minimum channel length) Adapted from Bhagat et al. (2009), Zhang et al. (2016)

$$F_L = \frac{f_L(Re, \frac{x}{h})\rho {U_f}^2 a^4}{H^2} \quad (9)$$

Where, f_L is lift coefficient is a function of Reynolds number and , $\frac{x}{h}$ ratio, U_f is average velocity of fluid (m/s). $f_L$increases with the decreases in Reynolds number.

4.7.1 Motion of particles in Newtonian fluid

Newtonian fluids have a constant dynamic viscosity, regardless of the applied shear force, as long as the temperature remains unchanged. Their shear stress and strain rate follow a linear relationship, with viscosity acting as the proportional factor.

i. Straight tubes and square channels inertial particle focusing:

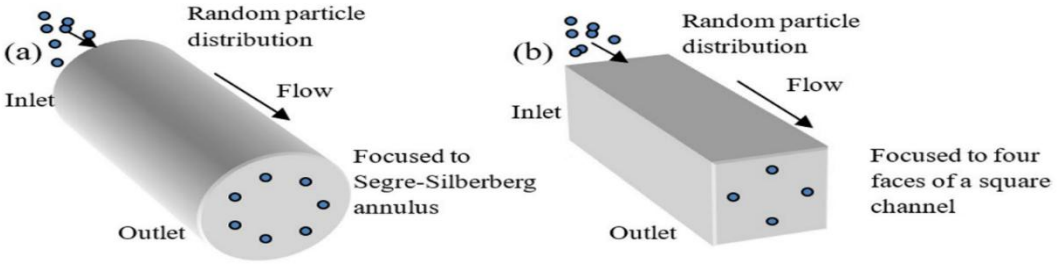


Fig. 3 a Cylindrical microchannel particle focusing.

b Square microchannel particle focusing. Adapted from Di Carlo (2009)

ii. Rectangular microchannels particle focusing:

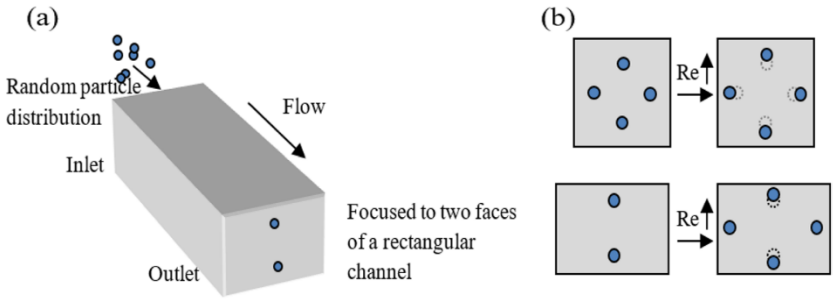


Fig. 4 a Rectangular microchannel particle focusing Adapted from Gossett et al. (**2012a**).

b Reynolds number effect on square and rectangular channels focusing Adapted from Zhang et al. (2017)

iii. Particle focusing in non-straight non-planar microchannels: Spiral microchannels are commonly used as they enhance inertial effects while reducing channel length and device size. In these channels, particles experience both inertial lift and Dean drag forces. The Dean drag moves particles along circulating vortices, while inertial lift stabilizes them at specific equilibrium points within the channel.

4.7.2 Lateral migration in a non-Newtonian fluid

Suspended particles in laminar duct flow at low Reynolds number execute lateral migration across streamlines to achieve equilibrium positions [14]. Particles within pressure-driven microchannels move laterally towards either the center or the walls. Fluid properties such as shear-thickening or shear-thinning behavior together with the particle blockage ratio affect their behavior.

In Non-Newtonian fluids, viscosity is not constant. Under shear stress they demonstrate either thickening or thinning behavior. Biological fluids such as blood alongside synthetic materials like polymers and paints serve as examples. This report examines viscoelastic fluids that demonstrate both viscosity and elasticity characteristics. The viscosity of these fluids reduces as shear rate rises because their macromolecular structure alters under stress. In viscoelastic flow conditions particles move outward as shown in research by Phan-Thein [15], Jefri and Zahed [16], and Huang and Joseph [17].

In order to analyze the flow behavior of non-Newtonian fluids, it is necessary to solve the equations of continuity and momentum conservation in the same way as for Newtonian fluids. However, given the additional complexity on non-Newtonian fluids, such as viscoelasticity, a further an extra stress tensor is added. This term captures the elastic and other time-dependent effects of the fluid and alters the total stress tensor [18].

$$\nabla \boldsymbol{u} = 0 \qquad (10)$$

$$\rho_f \left(\frac{\partial \boldsymbol{u}}{\partial t} + (\boldsymbol{u} \cdot \nabla) \right) \boldsymbol{u} = \nabla \cdot \boldsymbol{\sigma} \tag{11}$$

$$\boldsymbol{\sigma} = -\mathrm{p}\boldsymbol{I} + 2\mu e(\boldsymbol{u}) + \boldsymbol{\tau} \tag{12}$$

Where, u: velocity field, t: time, p: pressure σ: deviatoric stress tensor.

The constitutive relation for the numerical solution of the equations (Eqs. 10 and 11), is defined as,

$$\boldsymbol{\tau} + \boldsymbol{\lambda} \left(\frac{\partial \boldsymbol{\tau}}{\partial t} + \boldsymbol{u} \cdot \nabla \boldsymbol{\tau} - \nabla \boldsymbol{u}^{\boldsymbol{T}} \cdot \boldsymbol{\tau} - \boldsymbol{\tau} \cdot \nabla \boldsymbol{u} + \frac{\alpha}{\eta_p} (\boldsymbol{\tau} \cdot \boldsymbol{\tau}) \right) = \eta_p (\nabla \boldsymbol{u} + \nabla \boldsymbol{u}^{\boldsymbol{T}}) \tag{13}$$

where λ is relaxation time of the fluid (s) and η_p is viscosity of the polymer (Pa.s).

4.8 Factors affecting the focusing of particles in different channels

The internal dynamics of a microchannel are dictated by different parameters, also with channel geometry, the Reynolds number of the particles, how large the particles are in relation to the channel size, and the concentration of particles. For instance, in microchannels, a fluid-dense particle tends to occupy a position nearer to midplane between the channel wall and the axis of the channel. On the other hand, a particle of lesser density is positioned nearer to the walls, while a particle of greater density is found towards the middle of the channel.

All these parameters are related in a more complex way concerning particles focusing in microchannels. Research conducted indicates that in microchannels with a square geometry, the focusing of particles along the channel depends on the distance from the inlet and the shape of the particles. If both of these parameters are sufficiently large, particles can still migrate when the Reynolds number is low. To use the phenomenon of particle focusing in practical applications, it is important.

4.9 Secondary flow in microchannels

Secondary flow occurs when fluid moves with different velocities moving close to the walls and the center of a channel. It occurs in curved channels (Dean flow) and channels with obstacles, such as grooves or pillar formations. These flows are important because they influence transportation of particle, dispersion, and mixing in microchannels. Controlling these variables enhances lab-on-a-chip devices, drug delivery systems, and medical diagnostics, thus increasing the accuracy and also efficiency of microfluidic systems.

4.9.1 Microstructure effect

Microchannel's shape can be modified to induce secondary flow to manage the motion of the fluid and the particles within it. Deviations like curvatures, grooves in the channel walls, or other internal obstructions are known to affect the motion of a fluid. However, the Navier-Stokes

equations can hardly be solved analytically because of very complex boundary conditions. These systems and their solutions will be presented in more detail in the following sections.

i. Curving channels: Dean flow

In bent channels such as spirals or serpentines, secondary flow is caused by differences in velocity between the fluid at the center and towards the walls. The central faster-moving fluid is deflected from the center by centrifugal force, and this forces a pressure gradient. To counteract this, fluid towards the walls flows towards the center, and they create two circulating vortices referred to as Dean vortices [1]. Normally, two vortices occur, but additional ones may occur at high Reynolds numbers. The intensity of this flow is quantified by the Dean number (De) [1].

$$De = Re\sqrt{\frac{H}{2R}} \tag{14}$$

Here, R represents the radius of curvature (m). Re is the channel's Reynolds number. H is height (m).

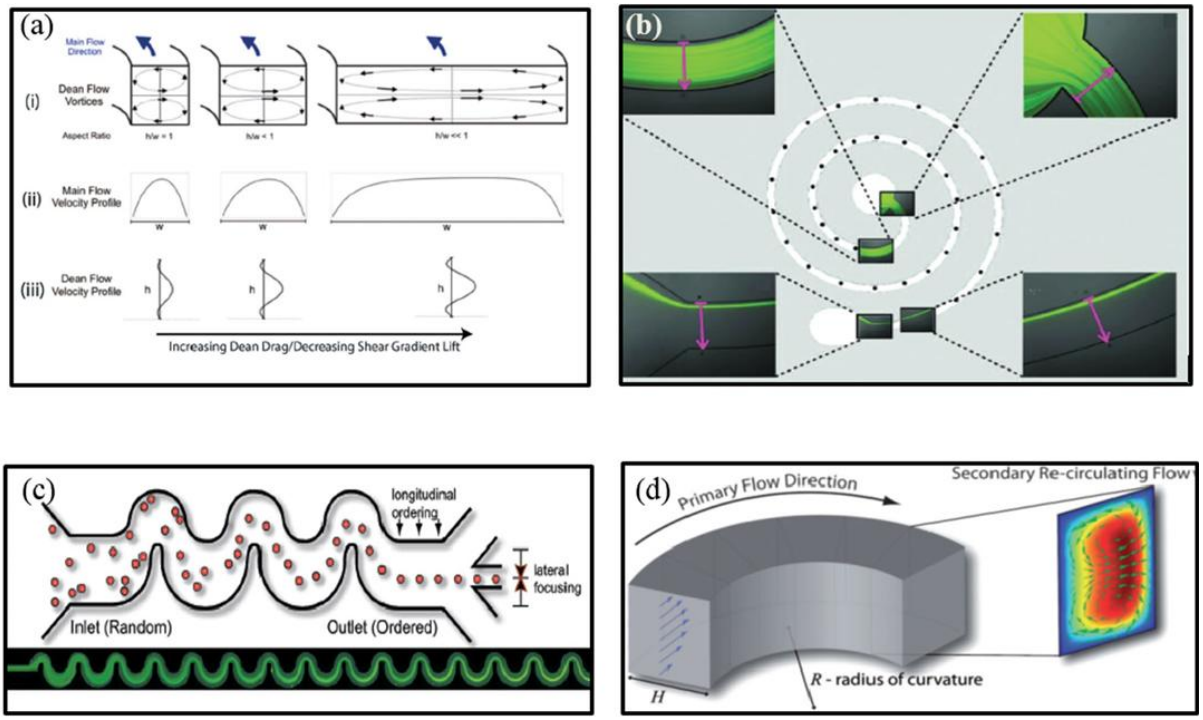


Fig. 5 a. Dean flow induced due to velocity mismatch in a curving channel (Martel and Toner, 2012) **b.** Spiraling channels, reproduced with permission from Martel and Toner (2012), AIP Publishing **c.** Alternating asymmetric curving channels (Di Carlo et al., 2007; Di Carlo, 2009), Copyright National Academy of Sciences, U.S.A. **d.** Dean flow in a curved channel (Di Carlo, 2009).

ii. Microgrooves on channel walls

Grooves are added to the channel walls, which disturb the flow of fluid to make secondary flows in microchannels. Due to which the larger particles to move toward the corners, while the smaller particles stay in the center. These secondary flows can take the place of Dean flow, which is usually used to control particle movement in fluids. This technique helps focus particles based on their size [19].

Most research has been done in conditions with low Reynolds numbers, where inertia doesn't play a big role. For secondary flows to work well in Stokes flow, the grooves need to be uneven. If the grooves are symmetrical, the fluid won't deform as needed. Simulations show that these systems can sort particles by size using the grooves and the flow's forces. This method is also used in flow cytometry, where particles are focused near the top and bottom of the channel. Smaller particles stay close to the walls, while larger particles move toward the center, creating a separation by size. The secondary flows, made by ridges on the channel walls, help achieve this. These techniques are often used to mix fluids more efficiently.

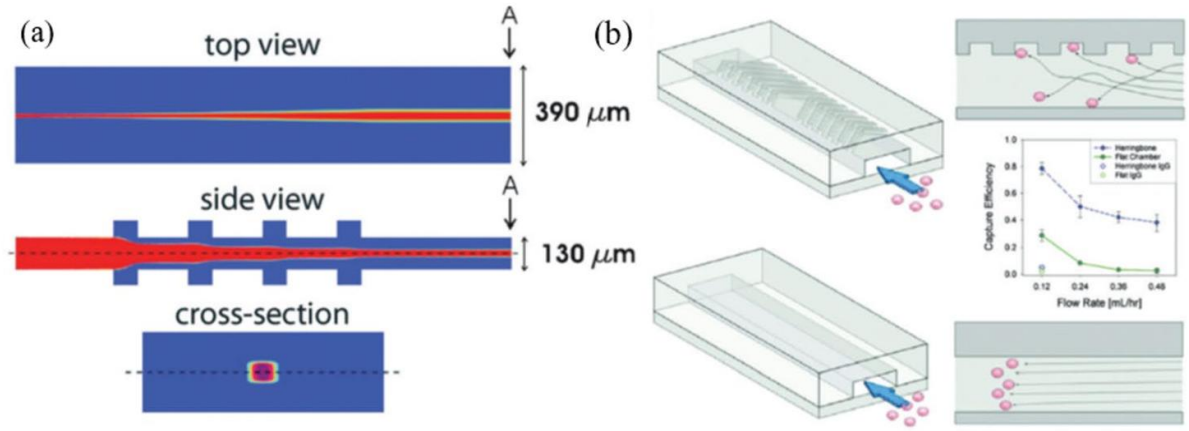


Fig 6 a Formation of the hydrodynamic sheath as described by Howell Jr. et al. (2008). **b** Particle manipulation techniques used to enhance interactions and capture cells on surfaces, as outlined by Stott et al. (2010). Reprinted with permission from Stott et al. (2010).

4.10 Effect of particles on fluid flow

In the secondary fluid stream, the interaction among particles plays a vital role. Suspended particles disturb the surrounding fluid, causing effects like reversed streamlines and secondary flows. As a result, these particles actively influence microchannel systems rather than behaving as passive elements.

4.10.1 Reversing streamlines

Reversing streamlines show how fluid travels toward a particle in its own frame of reference before it flows away. This is a crucial characteristic of the flow field around a freely rotating particle in shear flow, particularly at a finite Reynolds number. The particle's movement diverts the fluid, but when it returns to its original spot, the fluid tends to follow a similar route.

4.10.2 Particle-induced convection

In addition to the reversing streamlines, flowing particles also create secondary flow in the channel's cross-section. This process, referred to as "particle-induced convection," results in fluid circulating throughout the channel, moving around its upper and lower sections while ensuring mass conservation.

4.11 Applications of secondary flow in microfluidic systems

In fluid and particle manipulation, including mixing, trapping, focusing, and separation, Secondary flows are widely used. Dean flows are employed for three-dimensional hydrodynamic focusing and creating adjustable focal lengths. Mixing is the most common application, with methods like wavy walls and grooves increasing the interfacial area for diffusive mixing.

Curved microchannels enhance mixing by using chaotic advection, where fluid interfaces are stretched and folded. Twisted microchannels complete mixing even at low Reynolds numbers ($Re < 25$), unlike planar serpentine channels that do not induce chaotic advection.

Secondary flows help in particle sorting, as larger particles move differently than smaller ones due to varying secondary flow velocities, aiding in separation. These techniques are used to simple designs, enhanced mixing at higher flow rates, and applicability to a range of fluids.

4.12 Inertial microfluidics in biomedical applications

The conventional cell sorting methods using FACS, magnetic sorting, filtration and centrifugation need longer processing time, complex layout, and large space with considerable cell loss contamination or low yield. PCR methods suffer also deficiencies as they are generally poor in primer quality and DNA contamination. Microfluidics is receiving a great deal of attention for its portability and efficiency.

Microfluidics has also been applied in the context of drug delivery, a chitosan-based device for controlled release of drug and regeneration of bone was reported. This line of research is being applied to malaria diagnosis, migration of cancer cell, isolation of bacterial cell, fractionation of blood and regeneration of guided bone.

Chapter 5

Experimental Methodology in biomedical applications

5.1 Rapid Malaria Detection via Inertial Microfluidic Separation

Polymerase chain reaction (PCR) is a highly sensitive molecular method capable of detecting even minimal concentrations of malaria parasites. It also enables differentiation between various malaria species and strains [19]. Despite its sensitivity, the reliability of PCR can be compromised by several factors, including non-specific primer binding, the presence of inhibitory substances in blood serum, and DNA contamination from nucleated cells [20]. To enhance the precision of malaria detection via PCR, a novel label-free shear-modulated inertial microfluidic platform has been employed to concentrate malaria parasites from blood samples. This approach leverages the distinct characteristics of inertial focusing, which are influenced by the aspect ratio of microchannels and pinched-flow behavior. Typically, the microfluidic system incorporates a high-aspect-ratio rectangular channel equipped with contraction-expansion arrays and three outlets two lateral and one central. The operational sequence for malaria diagnosis using this technique is illustrated in Fig. 7a.

The key mechanism is involved adjusting the balance between the forces acting on particles suspended in the fluid. As the particle size becomes smaller relative to the microchannel's diameter, it disrupts the equilibrium between shear-modulated lift forces and wall-induced lift forces. This results in a shift in the lateral position of the particles. White blood cells (WBCs), which are similar in size to the microchannel's dimensions, are more affected by the inertial lift forces and therefore tend to move toward the peripheral outlets. On the other hand, most malaria parasites, which are not as affected by the forces, move toward the central outlet (in Fig. 7b).

To further enhance parasite concentration and minimize WBC contamination, a two-cycle enrichment process was developed. This cascaded method increases the purity of the malaria parasite sample, as demonstrated in Fig. 7c [21].

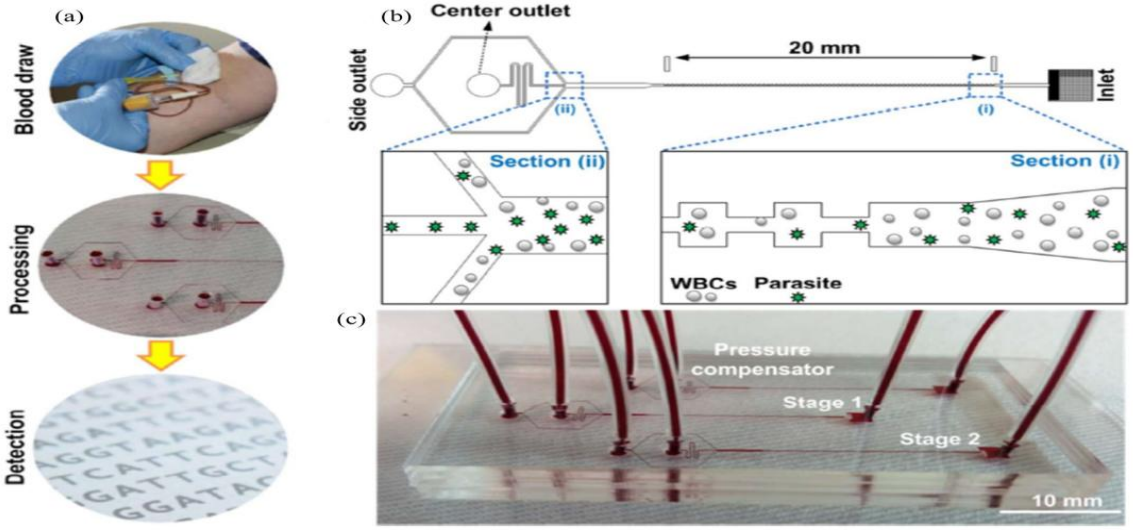


Fig. 7 a. Overview of the sample processing steps. **b.** Diagram illustrating the configuration and functional operation of the microfluidic chip. **c.** Photographs showing the real-world implementation of the cascading device designed for enriching malarial parasites. This figure is reproduced with permission from the Royal Society of Chemistry, as originally published by Warkiani et al. (2015).

5.2 Isolation of Circulating Cancer Cells Using Inertial Microfluidics

Breast cancer progression can be assessed through circulating tumor cell (CTC) based testing. In this test the cancer cells are counted in blood samples [19]. For accurate results, a reliable separation method is required. Microfluidic systems use hydrodynamic forces to separate the cells efficiently. High hematocrit blood samples are preferred for sharp separation, but the interaction of red blood cells (RBC) can affect cancer cell migration [20], [21]. An experiment studied cancer cell migration using a passive microfluidic device. This included a high-speed camera and an inverted microscope [19].

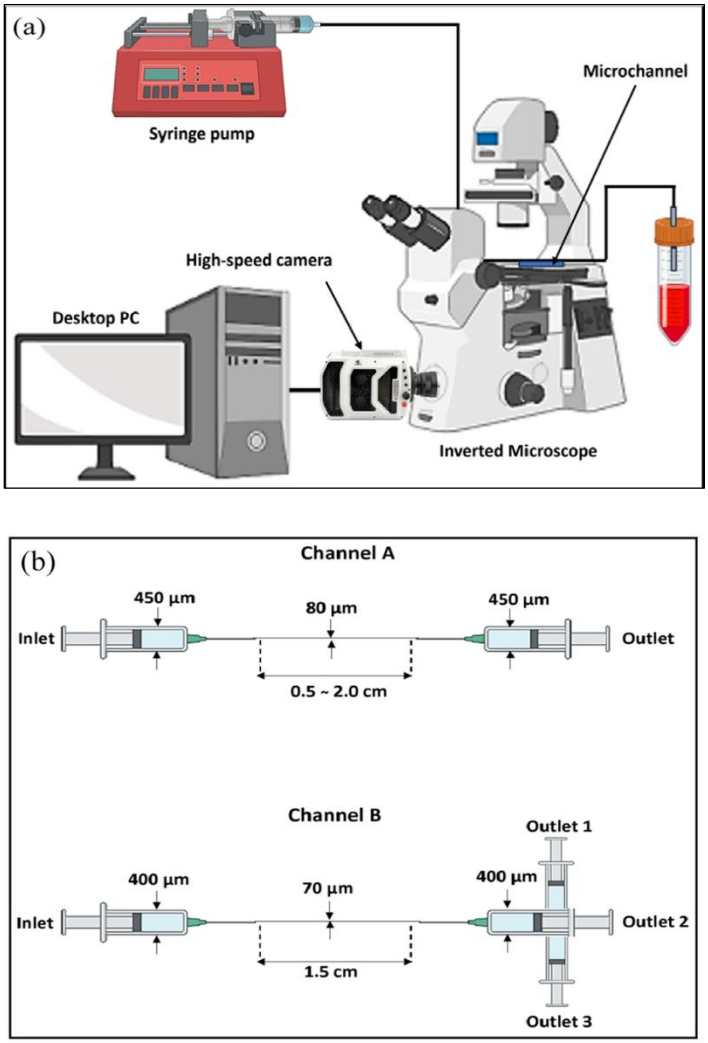


Fig. 8 a. Showing the experimental setup, highlighting where the cancer cell migration occurs.
b. Showing two different designs of PDMS microchannel systems used in the experiment. These designs are based on the work by Tanaka et al. (2012).

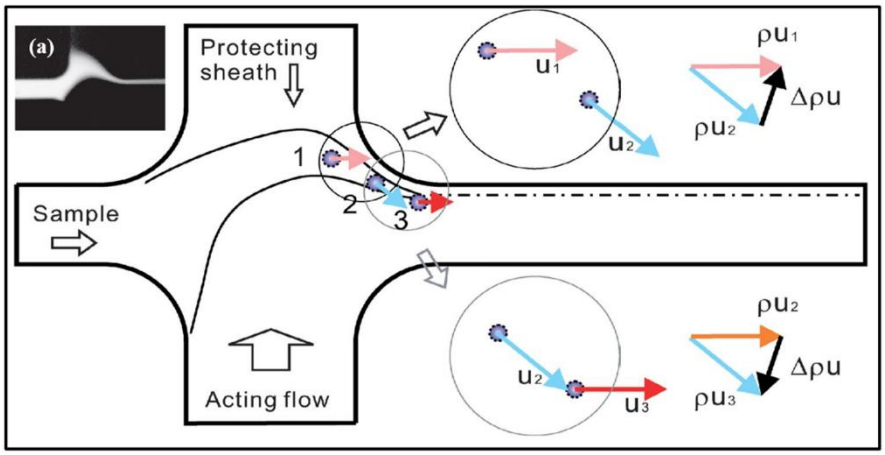
Two microchannels types were used-for high-hematocrit samples, type A for rigid particles and type B has three outlets. Fluid flow applied strong inertial forces, helping the particles transfer to specific positions. Soft lithography was used to make microchannel [22]. Cancer cells and rigid particles treated differently due to size and deformity. In PBS (phosphate buffer solution), rigid particles migrate rapidly, requiring a small channel. In RBC suspension, migration was reduced with an increase in RBC concentration. The second outlet resulted in a low sample volume in the second outlet, which proved that inertia migration has still occurred despite RBC Interaction [19]. A square concrete barrier in a high-resolution microfluidic device improved particle separation [23]. Microfluidics are used widely to separate and enrich tumor cells from blood samples. This efficient cell manipulation and enables to detect [24], [25]. CTCs, measuring 13–25 µm, are commonly separated from blood cells using size-based methods [26]. The pre-separation of CTCs is crucial for precise detection [27], [28]. Hydrodynamic microfluidic methods utilize fluid flow, unswayed by any

external forces, to carry out the separation of cells. The channels are curved, either serpentine or spirals, in order to separate cells by size [29]. A double spiral microfluidic device quickly distinguishes tumors and blood cells using the size difference, achieving high throughputs for traditional methods [18]. Many factors affect microfluidic separation, including channel geometry, flow conditions and liquid properties [30]. A hybrid system was recently simultaneous to separate the CTC from RBC and WBC [31] by mixing spiral inertial microfluidics with surface acoustic waves. This technique improves cancer detection and treatment.

5.3 Soft Inertial Microfluidics for Bacteria Separation from Human Blood Cells

Isolating bacteria from human cells in limited sample volumes presents multiple difficulties. The method should not affect mRNA or protein expression. It must allow high-throughput analysis. It should also be effective at low bacterial levels. Additionally, it should separate a heterogeneous bacterial population from human epithelial and blood cells. RBCs, with a similar size to bacteria in one dimension (2–3 μm), make separation difficult by reducing the effective size difference. At high particle Reynolds numbers, particles gain momentum and deviate from the flow path during sudden flow changes. In a microfluidic system, a sample flow merges with a stronger flow in a narrow channel, accelerating particle movement. A low-rate sheath flow prevents particle-wall interaction. As particles move, they lose momentum, causing separation from the fluid axis. The size gap between RBCs (6–8 μm) and bacteria (1–2 μm) enhances separation. Larger cells shift from the main flow, while smaller ones stay within it [11], [12], [18].

The device features curved channels, a focused flow region, and particle collection units. Three inlets deliver fluids: sample, protective sheath, and acting flow. These merge in the main channels. Downstream, outlets collect small particles, large particles, and waste. A separate control channel, managed by an extra pump, adjusts separation and offsets fabrication inconsistencies. Adjusting fluid input alters particle distribution, directing them to the appropriate collectors [11], [13], [30].



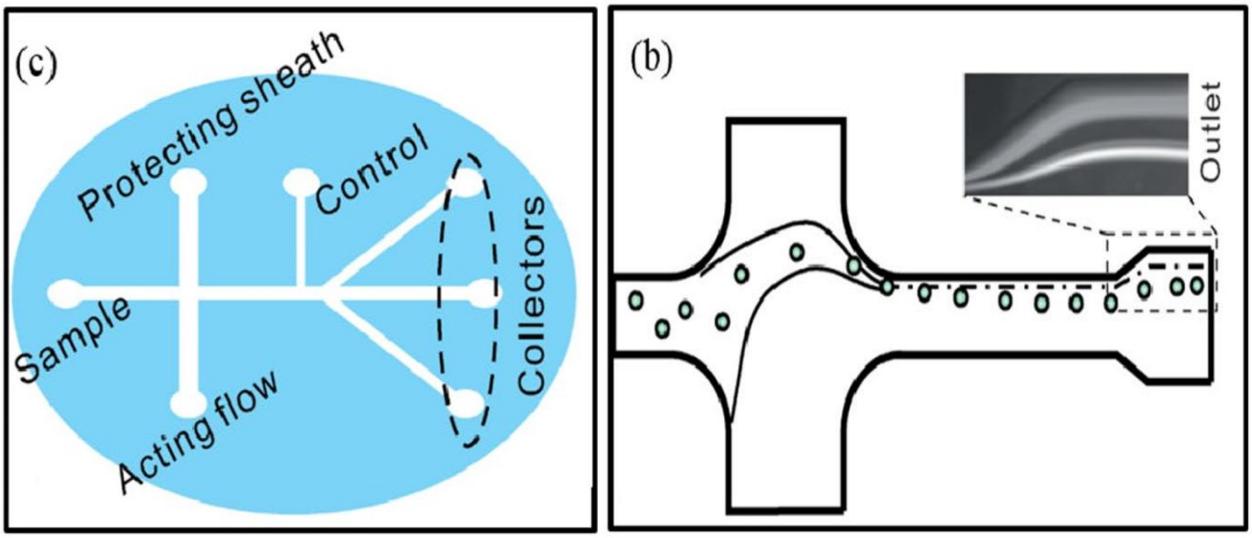


Fig. 9 a. The formation of a curved, focused sample flow and the inertial force on fluid elements **b.** particle separation, with larger particles deflecting at the expanded outlet **c.** the device design schematic. Adapted from Wu et al. (2009).

Chapter 6

Result and discussion

When looking at how particles behave inside microfluidic channels under moderate Reynolds numbers, something quite interesting happens. Instead of following the streamlines like in low-Reynolds systems, the particles actually shift across those lines due to lift forces that act laterally. These forces—originating from the flow's velocity gradients and wall interactions—basically push particles into specific spots depending on their size and shape. In straight rectangular channels, for instance, you often find that particles stabilize in symmetric positions near the channel center or walls. These locations are known as equilibrium positions. The spacing and number of these positions vary with channel geometry and flow speed, and once the particle size becomes sufficiently large relative to the channel, this focusing effect becomes more predictable and consistent [13], [14]. One big leap in performance came when curved or spiral channels were introduced. These geometries bring secondary flows into play called Dean flows that spiral within the cross-section. In simple terms, as the fluid curves around the channel, centrifugal forces pull it outward, which causes counter-rotating vortex flows to develop. These swirling currents drag small bits to the center while larger pieces push back and get forced out to the edges because of their speed. This naturally sorts the particles without needing any extra assistance. This sorting works like a charm when the flow conditions are just right: the flow needs to be quick enough to create momentum effects but not so fast that it leads to instability. Experimental studies have shown that particle focusing begins when the size ratio (particle diameter to hydraulic diameter) exceeds roughly 0.07. Below this threshold, particles don't settle well into stable paths [15], [16].

Now, when real biological samples like blood are used, things get a little more complex. The swirling currents pull small bits to the center while larger pieces, due to their weight, get pushed out to the edges. This naturally sorts the particles without needing any extra help. Cells aren't just round balls; they come in all shapes and sizes, and their stiffness and how they interact with each other can be pretty different. For instance, red blood cells are soft and can change shape when they flow, which often makes them behave differently than rigid particles. Even so, scientists have managed to use spiral microchannels to isolate specific parts from whole blood. Take circulating tumor cells (CTCs) for instance. These cells being a bit bigger than normal blood cells, can be separated out well without the need to label or tag them. One study achieved more than 90% recovery with over 80% purity, and that was using just a single-stage spiral device, which speaks to the practical value of inertial methods in diagnostics [5], [6].

We have taken step forward to some extent, yet there are still problems to solve. For example, channels can be blocked. Proteins and particles in the blood can adhere to the walls of these channels over time. This situation will mess up the flow if not dealt with. It will also affect the accuracy of the focus. Applying coatings to surfaces has improved this situation. Treatments like PEG (polyethylene glycol) and zwitterionic coatings have been applied to microchannel walls to prevent unwanted adhesion, and they've been successful in maintaining flow performance over longer sample runs [7].

Another area that's seeing growth is the integration of sensing technologies into the same microfluidic device. Some systems now combine inertial separation with electrical or optical

sensors downstream, allowing for real-time detection. In cases where bacterial detection is needed, the microfluidic platform first separates and concentrates the bacteria before feeding it directly to a sensing unit. This approach shortens the time to result and reduces the need for bulky lab equipment. It also opens the door for field applications in remote settings [8].

Interestingly, by tweaking channel dimensions, researchers have also been able to target deformable particles. Some designs introduce additional flow features—like contraction-expansion arrays—to precondition the sample, so that deformable particles like white blood cells behave more like rigid ones and can be separated with greater accuracy. These tweaks are subtle but crucial, especially for biological applications where particle behavior isn't ideal [9].

All these results underline a larger trend: inertial microfluidics is increasingly viable for real-world use. Unlike optical or magnetic sorting methods, it doesn’t rely on labels or large external equipment. That makes it compact, cost-effective, and scalable. Although challenges remain, particularly with respect to particle variability and long-term use, the field continues to push forward with new channel designs, hybrid systems, and smarter integration with electronics. Given its strengths in throughput, simplicity, and versatility, inertial microfluidics stands as one of the more promising tools in the growing field of lab-on-a-chip devices [14], [17]

Chapter 7

Conclusion

Inertial microfluidics has become a promising method in biomedical science. It started as a simple idea based on fluid dynamics. Today, it is used in real devices for sorting cells and particles. The biggest advantage is that it doesn't require external forces. There are no magnets, labels, or active components. Everything depends on how the fluid flows and how the channel is shaped. This makes the system easy to build and operate. Particles in the flow move in certain ways depending on their size, shape, and flexibility. This allows for sorting without changing or damaging them. That's very useful in medical tests. For example, separating tumor cells from blood is now possible without using chemical labels. The process is also fast and low-cost, which is important in places with fewer resources. Many devices now use spiral or curved channels. These shapes help guide particles into specific paths. Studies show good results in terms of purity and recovery rates. These devices can handle large volumes. They can also work with small, rare cells. However, biological samples are often unpredictable. Cells are soft, sticky, and change shape. That makes them harder to separate.

To deal with this, researchers have developed hybrid devices. These design combines inertial forces along with layers or extra stages of flow. Some chips also include sensors. This allows not only sorting but also real-time monitoring. As a result, the system becomes a full diagnostic tool, not just a filter. The technology is growing fast. More accurate models are helping improve design. Simulations like lattice Boltzmann methods allow better predictions. These help in understanding how particles behave in complex flows. Based on this, engineers are designing smarter channels that work better with different types of samples. Another area of development is portability. The devices are being made small and easy to use. Some full lab can conduct tests without the need for setup. It is useful for remote or emergency places. The inertia can help with the microfluidics point-of-care testing and rapid diagnosis. The goal is to create devices that anyone can use without special training.

Material choice also plays a role. New polymers and soft lithography techniques allow for cheaper and more flexible designs. This is helping reduce costs even more. At the same time, the devices are becoming more reliable. They can now be reused or made disposable, depending on the need. In the future, integration will be important. The devices may include steps for sample preparation, sorting, sensing and even data output. This will make them the entire lab-on-a-chap system. They can change how we test for diseases, detect infection, or study cells. Even with some current challenges, progress is clear. The inertia is moving in the use of the real world from the research laboratories.

With continuous innovation, it can become a standard tool in clinical and research settings. Its low cost, speed and simplicity gives it a strong advantage. As new designs are revealed, its role in diagnostics and cell biology will only increase.

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