VOL. 23, NO. 3, 2024, 19-29
elektrika.utm.my
ISSN 0128-4428

ELEKTRIKA
Journal of Electrical Engineering

Recent Advancements in Microfluidic Circulating Tumor Cell Sorting Devices

Muhammad Asyraf Jamrus[1] and **Mohd Ridzuan Ahmad**[1*]

[1]Department of Control and Mechatronics Engineering, Faculty of Electrical Engineering, Universiti Teknologi Malaysia, 81310 UTM Skudai, Johor, Malaysia.

[*]Corresponding author: mdridzuan@utm.my

Abstract: In recent years, there has been significant advancement in the creation of microfluidic devices for sorting circulating tumor cells (CTCs), which has transformed the field of cancer diagnosis. This study offers a thorough examination of the most recent developments in microfluidic technology created for accurate and effective isolation of CTCs from intricate biological materials. The integration of active and passive techniques on microfluidic systems has resulted in advancements in sensitivity, specificity, and therapeutic relevance. Advanced methods like acoustofluidic and microfluidic dielectrophoresis can be used for specific capture of circulating tumor cells (CTCs), while simpler approaches such as size-based filtering and deterministic lateral displacement are suitable for various sample types. Hybrid methods, which blend the advantages of active and passive principles, have become a potential strategy for enhancing CTC isolation efficiency. These advancements have far-reaching implications for liquid biopsy applications, making it easier to monitor cancer progression, detect it early, and evaluate responses to treatment without intrusive procedures.

Keywords: microfluidic, advancement, circulating tumor cell

Article History: received 28 March 2024; accepted 12 November 2024; published 30 December 2024.

1. INTRODUCTION

Cell sorting is an essential method for isolating and separating circulating tumor cells (CTCs) from samples of peripheral blood. Circulating tumor cells (CTCs) are infrequent cells that are released from primary or metastatic tumors. They are of great importance in cancer studies because they have the ability to contribute to the spread of disease and can be used as a non-invasive method for diagnosing and monitoring cancer [1]. Several strategies have been devised to effectively and accurately sort circulating tumor cells (CTCs) with high efficiency and purity. These technologies include microfluidic-based approaches, filter chips coupled with antibody-functional microspheres, and noninvasive optical isolation [2][3][4]. These strategies are designed to address the difficulties related to the infrequency and diversity of CTCs, as well as the requirement for high levels of sensitivity and specificity in their separation [5][6].

The utilization of microfluidic-based methods for cell sorting has been prominent because of its capacity to combine physical and biological principles to achieve effective cell separation [7]. For example, researchers have developed multifunctional microfluidic setups that can efficiently capture and sort individual circulating tumor cells (CTCs). These setups incorporate separation units and hydrodynamic filtration to purify the CTCs [8]. Furthermore, the utilization of inertial microflow and antibody-functional microspheres on microfluidic chips has demonstrated potential in trapping and detecting circulating tumor cells (CTCs) regardless of their size [3]. These methods not only allow for the separation of CTCs with a high level of purity but also expedite the process of identifying and studying the sorted cells [2].

Microfluidics can be divided into two groups: passive and active separation. Moreover, the advancement of innovative sorting technologies, such as cell size-based deterministic lateral displacement (DLD) and magnetophoretic separation, has significantly increased the recovery of viable circulating tumor cells (CTCs), overcoming limitations associated with conventional methods that rely on specific cell surface indicators, including epithelial cell adhesion molecule (EpCAM). This becomes particularly crucial in circumstances where EpCAM expression might be diminished in certain subgroups of circulating tumor cells (CTCs) [9][4].

In summary, cell sorting plays a vital role in the isolation and characterization of CTCs, delivering valuable insights into cancer biology, metastasis, and customized cancer therapy. The development of sophisticated microfluidic-based approaches, multifunctional configurations, and novel sorting technologies has considerably enhanced the efficiency, purity, and quick identification of CTCs, overcoming the issues associated with their scarcity and heterogeneity. Hence, this paper will address the recent advancement of CTC separation microfluidic devices.

2. MICROFLUIDIC SORTING METHODS

Active and passive microfluidic techniques play pivotal roles in the manipulation and control of fluids within

microchannels, each offering distinct advantages and applications. Passive microfluidics relies on intrinsic forces such as capillary action or gravitational forces to drive fluid flow, while active microfluidics involves the use of external forces or energy sources to manipulate fluid flow within microchannels. These techniques have been extensively employed in the isolation and separation of circulating tumor cells (CTCs) from blood samples, offering distinct approaches for achieving efficient and high-purity CTC isolation.

Passive microfluidic techniques, such as label-free methods, have been used to separate circulating tumor cells (CTCs) by using their inherent physical characteristics, such as size, deformability, and density. Passive microfluidic-based approaches and droplet-based microfluidic methods have been used to detect circulating tumor cells (CTCs) without the need for labeling. This detection is based on the aberrant metabolism of cancer cells, as described by Rivello et al. [10]. In addition, passive approaches utilize the intrinsic physical characteristics of CTCs to selectively capture or move them within the microfluidic device, without the need for external forces [11]. Moreover, inertial approaches, being a passive strategy, have been recognized as effective and established techniques for separating circulating tumor cells (CTCs) within microfluidic devices [12].

Conversely, active microfluidic techniques involve various manipulation methods such as magnetic, acoustic, dielectrophoresis, and electric-based approaches. These methods have been integrated into microfluidic platforms to isolate circulating tumor cells (CTCs). An example of active approaches used for the separation of circulating tumor cells (CTCs) is the development of magnetically driven microfluidics, as demonstrated in previous research [13]. Furthermore, there have been reports on the incorporation of active separation strategies into microfluidic platforms, which emphasize the application of active microfluidic techniques for the isolation of circulating tumor cells (CTCs) [14]. Furthermore, researchers have investigated the application of a hybrid spiral microfluidic platform in conjunction with surface acoustic waves to sort and separate circulating tumor cells. This study highlights the dynamic character of the technique [15]. The paper will discuss various active and passive microfluidic systems, as depicted in Figure 1. In summary, both passive and active microfluidic techniques have been instrumental in the isolation and separation of CTCs from blood samples. Passive methods rely on the inherent physical properties of CTCs, while active techniques involve the application of external forces or energy sources for precise manipulation and isolation of CTCs within microfluidic devices.

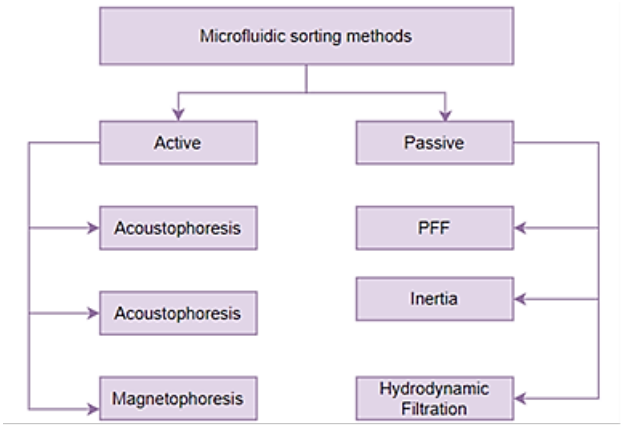

Figure 1. Cell sorting methods on microfluidic

2.1 Active Separation

2.1.1 Acoustophoresis Methods

Acoustophoresis is a highly effective method employed in diverse biological and therapeutic contexts to manipulate and separate cells and particles. Acoustic manipulation is the utilization of sound waves to exert authority on the motion and arrangement of particles in a liquid medium. The concept of acoustophoresis has been applied in various fields including bioprinting, clinical research, blood plasma separation, detection of circulating tumor cells (CTCs), and isolation of fetal nucleated red blood cells (fNRBCs) [16] [17].

Acoustophoresis operates by utilizing sonic fields to generate forces on particles or cells inside a fluid media. The forces emerge as a result of the interaction between the acoustic field and the particles, causing the particles to move and be controlled within the medium. This technique has been successfully employed in several microfluidic configurations to accomplish effective separation of blood plasma and isolation of certain cell types, such as CTCs and fNRBCs [16] [17].

Several studies have investigated the use of acoustophoresis in CTC research, emphasizing its potential benefits in terms of being non-invasive, having a high processing capacity, and selectively isolating CTCs without requiring external markers. A study conducted by Wang et al. (2015) showcased the effectiveness of a microfluidic acoustophoresis device in specifically separating CTCs from whole blood samples using criteria like size and deformability [18]. This study highlighted the adaptability of acoustophoresis in manipulating various types of cells and showed its potential to enhance the accuracy of CTC identification. Researchers have also investigated the combination of acoustophoresis with other microfluidic technologies in order to improve the effectiveness of capturing CTCs.

In their 2019 study, Wu et al. conducted research on acoustofluidics for the purpose of separating circulating tumor cells. They achieved this by utilizing transparent niobate transducers, which not only provide better performance but also minimize heat production [23]. The device has an estimated capture rate of 91.5% ± 4.5% for isolating polystyrene particles and cancer cell lines (MCF7 and HeLa) that are mixed with white blood cells ((WBCs) when a flow rate of 200 μL/h is used. Smith et al. (2019) conducted a study where they integrated acoustophoresis with other microfluidic techniques to retrieve cancer cells from human blood [19]. The results emphasized the potential collaboration of acoustophoresis with complementary approaches, providing a comprehensive strategy to tackle the difficulties related to CTC heterogeneity.

In addition, Anand et al. (2021) proposed a two-step acoustophoresis technique (A2) for isolating viable

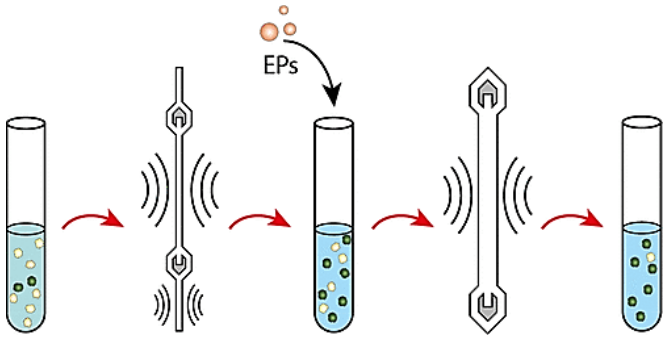

Figure 2. Overview of the two-step acoustophoresis [20]

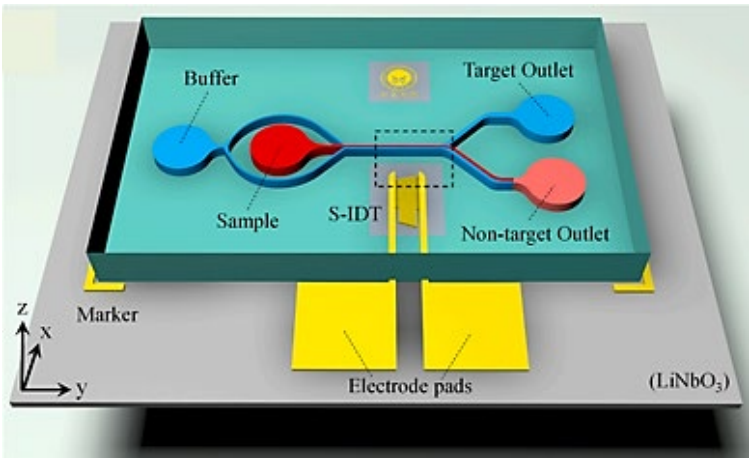

Figure 3. Schematic diagram of the concept of a label-free cell sorting device based on np-TSAW [22]

circulating tumor cells (CTCs) from whole blood [20]. This study utilizes two consecutive acoustophoresis procedures as shown in Figure 2: During primary separation, cells are sorted based on their mobility in the acoustic environment using acoustic pressures. This process facilitates the aggregation of WBCs and concentrates viable cancer cells in a localized region. In the second stage, negative selection acoustophoresis is employed, utilizing anti-CD45 particles to selectively eliminate a significant number of white blood cells, while simultaneously delicately retrieving viable cancer cells for subsequent examination and cultivation in a laboratory setting. The approach exhibited a cancer cell retrieval efficiency of 28% when 10,000 cancer cells were introduced into 1 mL samples. In studies with a reduced number of cells (1000), the A2 technique exhibited a cell recovery rate of 28.0 ± 0.5% for DU145 cells.

In a subsequent study, Karthick et al. (2018) conducted research on acoustophoresis using the principle of acoustic impedance contrast. They found that by aligning the acoustic impedance of peripheral blood mononuclear cells (PBMCs) with that of the sample medium, the migration of PBMCs can be halted [21]. This enables the migration and isolation of CTC, which possess distinct acoustic impedance in comparison to peripheral blood mononuclear cells (PBMCs). The work showcases the effective separation of HeLa and MDA-MB-231 cells from PBMCs, resulting in a retrieval rate of 86% and a more than 50-fold increase in concentration within a span of one hour. In addition, Geng et al. (2023) created a highly compact acoustofluidic device utilizing the narrow-path traveling surface acoustic wave (np-TSAW) (Figure 3). The work showcases the exact isolation of particles and the separation of 8 µm and 10 µm particles with high separation efficiency and purity [22]. This is achieved by utilizing polystyrene (PS) particles of varying sizes and blood cells that have been intentionally contaminated with cancer cells. The device achieved a sample purity of 98.75% with a flow rate of 1.2 ml/h.

Acoustic radiation-based cell separation is a non-invasive technology that uses sound waves to separate cells. It is a reliable and versatile technique that can be used in several domains like chemistry, biology, and engineering. It is known for its gentle approach, robustness, and compatibility with biological systems. (Zhao et al.) [24]. Acoustofluidics has shown the ability to separate circulating tumor cells (CTCs), which are typically sized between 8-20 µm, as well as exosomes, which are significantly smaller at 30-150 nm [25]. Nevertheless, the limited presence of circulating tumor cells (CTCs) in the bloodstream, usually ranging from 1 to 100 cells per milliliter, presents a considerable obstacle to their retrieval and identification [26]. In addition, the acoustofluidic techniques used for sorting circulating tumor cells (CTCs) have the difficulty of reaching a high level of purity. This is because CTCs and other blood components, especially leukocytes, have similar sizes that overlap. The similarity in size, particularly in smaller cell types like colon cancer or small-cell lung cancer, creates difficulties in achieving purity, which hampers the successful separation of CTCs (circulating tumor cells) [27]. Moreover, the scarcity and diversity of CTCs pose

considerable obstacles to their isolation and concentration, which is the primary drawback of acoustofluidic methods [28]. These limitations are worsened by the challenge of separating individual circulating tumor cells (CTCs) from the other components of blood, the short amount of time CTCs stay in the bloodstream, and the decrease in CTC-associated markers. These challenges collectively present significant technical difficulties for acoustofluidic CTC sorting [29].

2.1.2 Magnetophoresis (MACS) Method

Magnetic-activated cell sorting (MACS) for circulating tumor cell (CTC) sorting is a technique that utilizes magnetic beads conjugated with antibodies to selectively label and isolate CTCs from blood samples. The MACS method involves the use of magnetic columns or magnetic separators to capture the labeled CTCs, enabling their separation from other blood components. This approach has been widely employed in CTC isolation due to its simplicity, efficiency, and versatility in capturing CTCs regardless of their surface epitopes [30].

The MACS technique has been integrated into various microfluidic platforms to enable high-efficiency CTC isolation. For instance, a microfluidic chip combined with MACS technology has been developed for tumor antigen-independent sorting of circulating hepatocellular carcinoma cells, demonstrating the attractiveness of this method for efficient CTC isolation [30]. Additionally, the CTC-iChip running platform, which integrates deterministic lateral displacement, inertial focusing, and magnetophoresis, has been reported to employ MACS for the removal of bead-labeled leukocytes, highlighting the versatility of MACS in CTC sorting [31,32].

Wang et al. (2019) did a study focusing on the development of a capture platform that integrates a deterministic lateral displacement (DLD) with MACS technology to separate CTCs as shown in Figure 4. This method is to enhance the efficiency of CTC separation without relying on tumor antigens [33]. Results showed that the integrated platform achieved a CTC yield of 85.1% ± 3.2% at optimal flow rates, and it demonstrated increased sensitivity to EpCAM low CTCs compared to other methods. This highlights the capacity of MACS technology for effective isolation of circulating tumor cells (CTCs). Furthermore, Vidlarova et al. [34] emphasized the remarkable sensitivity of MACS, which enables the identification of CTCs even when they are present in concentrations as low as 1 per 10^7 blood cells. In addition, Visal et al. [35] examined the utilization of a cytokeratin-based technique in the MACS system for counting CTCs, emphasizing its ability to specifically capture CTCs. In addition, Iliescu et al. [36] highlighted the presence of the MACS system as a commercially viable and relevant immunomagnetic cell sorting technology for the separation of CTCs.

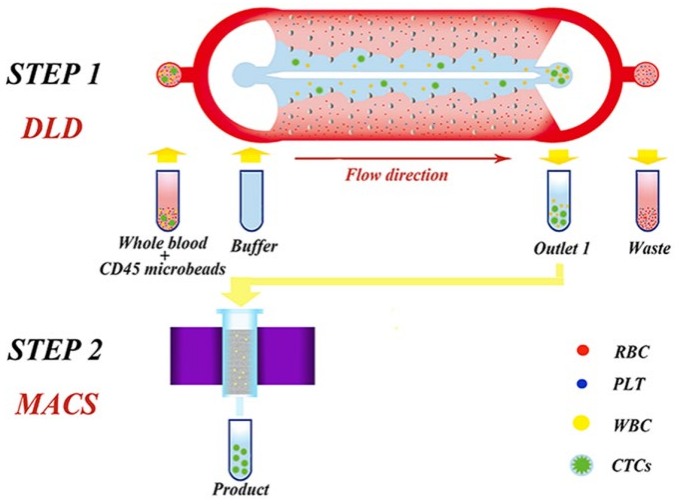

Figure 4. Steps of DLD-MACS for CTC separation [33]

On top of that, Nasiri et al. (2021) suggested the development of a hybrid MACS using an inertial microfluidic device. The first half of the device utilizes inertial forces to separate red blood cells (RBCs) and white blood cells (WBCs) from circulating tumor cells (CTCs). The following magnetic cell separation section then catches CTCs that have been tagged with magnetic nanoparticles and Ep-CAM [38]. The device demonstrates exceptional separation efficiency, reaching about 95%, and purity, reaching approximately 93%, for circulating tumor cells (CTCs) when operated at a flow rate of 1000 µL/min. The device effectively handled diluted blood samples including nanoparticle-conjugated circulating tumor cells (CTCs) without experiencing any clogging problems. Microscopic pictures verified the successful separation of CTCs from blood cells.

In summary, the integration of MACS with microfluidic devices appears to be a promising approach for efficient and precise isolation of circulating tumor cells. This advancement has the potential to enhance cancer liquid biopsy and analysis of CTCs. Nevertheless, despite its inherent capabilities, there are numerous obstacles linked to the utilization of MACS for CTC separation. An inherent limitation of MACS for CTC separation is its restricted efficacy in capturing infrequent and diverse CTC populations. The scarcity and diverse nature of circulating tumor cells (CTCs) present substantial obstacles to the utilization of CTCs in liquid biopsy (Cheng et al., 2015). Moreover, the scarcity, delicacy, and diversity of CTCs pose considerable technological obstacles to their effective isolation from blood [16]. The considerable variety of circulating tumor cells (CTCs) poses challenges in capturing and isolating distinct subpopulations, which are vital for conducting thorough research and characterization of CTCs. In addition, the device's efficacy in isolating circulating tumor cells (CTCs) from breast cancer patients was shown to be ineffective in both preclinical and clinical studies undertaken by Lozar et al. (2020) [37]. This suggests that further research is required to fully understand and improve the performance of this device.

2.1.3 Dielectrophoresis Method

Dielectrophoresis (DEP) is a technique that has gained significant attention in the field of biomedical research, particularly in the context of circulating tumor cell (CTC) separation and manipulation. DEP exploits the dielectric

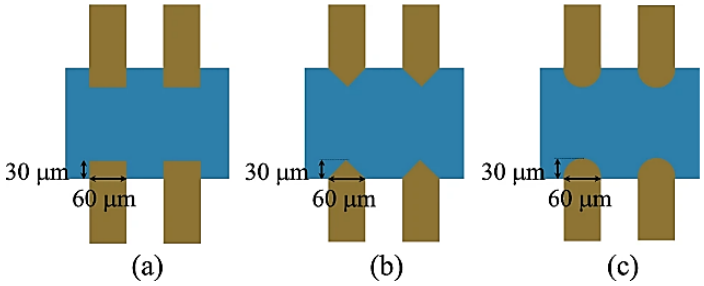

Figure 5. The configuration of investigated electrodes: (a) rectangular (b) triangular (c) semi-circular [45]

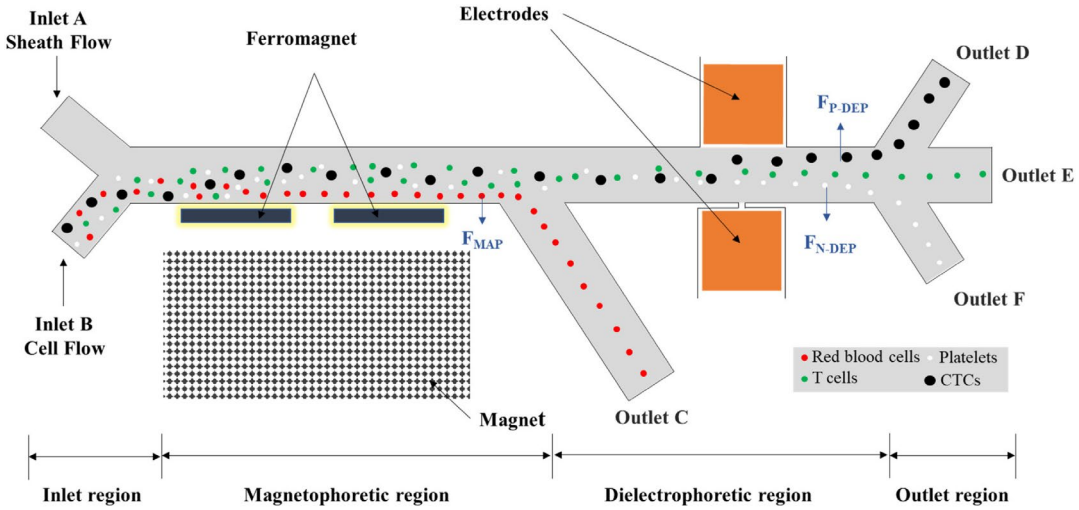

Figure 6. The schematic illustration of the microfluidic channel [47]

properties of cells to manipulate their trajectories in nonuniform electric fields, enabling the selective separation of cells based on their dielectric properties Varmazyari et al. [39].DEP has been widely utilized in the development of microfluidic devices for the isolation and characterization of CTCs. This technique has been applied to separate CTCs from blood cells based on their distinct dielectric properties, allowing for the label-free enrichment of CTCs [40]. The mechanism of DEP enables the separation of cells with different diameters based on their dielectric properties, offering a promising approach for the specific isolation of CTCs [41].

Recently, numerous novel DEPs have been proposed, constructed, and assessed by numerical simulations. As an illustration, Alkhaiyat et al. (2023) introduced a novel DEP design to separate CTCs from white blood cells (WBCs) and platelets (PLTs) [44]. The work employs numerical simulations to optimize the geometric characteristics of the LOC, including the channel width, electrode topologies, and applied voltage values, in order to attain a high separation efficiency for the three cell types. The outcome demonstrates that CTCs can be isolated from white blood cells (WBCs) and platelets (PLTs) with an absolute purity of 100%. Subsequently, Varmazyar et al. (2022) conducted a study specifically aimed at maintaining the viability of cells in the proposed DEP architecture [45]. The study examines three different arrangements of sidewall electrodes (as shown in Figure 5) and assesses their performance by analyzing simulation data obtained through the finite-element approach. According to the study, semi-circular electrodes demonstrated superior performance, achieving a recovery rate of around 95% while maintaining an applied electric field below the threshold for cell electroporation.

Recent research has focused on integrating dielectrophoresis with microfluidic devices to improve the specificity and efficiency of CTC separation. Heredia-Soto et al. [42] emphasized the utilization of microfluidic sorting devices, such as ApoStream and DEPArray, that employ dielectrophoresis to separate circulating tumor cells (CTCs). In addition, Velmanickam et al.'s review [43] highlighted the incorporation of dielectrophoresis into microfluidics, fluorescence, and electrical impedance, leading to the development of compelling devices and procedures for disease screening and diagnosis. Furthermore, Shamloo et al. (2020) developed a MACS-DEP to separate CTCs from other blood cells highlighting the device's reliable and uncomplicated method for diagnosis purposes [46]. In addition, Zhao et al. (2022) devised a novel MAP-DEP configuration for the extraction of CTCs from blood, which exhibits promise in terms of size- and property-driven cell separation [47]. Figure 6 demonstrates the utilization of a specialized magnet design in the microfluidic chip, featuring two closely positioned segments. This configuration generates a powerful magnetic field gradient, enabling accurate particle separation. The utilization of a double-segment magnet design enhances the intensity of the magnetic field in close proximity to the boundaries, hence leading to heightened forces and enhanced precision in the process of separation.

The proposed design can sort numerous cell kinds, such as CTCs, red blood cells, platelets, and T cells, with a high degree of purity, thereby enabling the sorting of other cell types.

The combination of dielectrophoresis (DEP) and microfluidic devices offers a highly promising method for the manipulation and separation of circulating tumor cells (CTCs). The potential of DEP for label-free CTC separation has been established, providing advantages such as not relying on cell surface markers and eliminating the necessity for pre-labeling processes [48]. Furthermore, microfluidic systems based on dielectrophoresis (DEP) have demonstrated effective methods for isolating cancer cells from different subtypes of white blood cells, while maintaining their viability [45]. Moreover, DEP has been employed in ongoing separation methods for CTCs, demonstrating its capability for effective and uninterrupted CTC isolation [49]. Nevertheless, a significant limitation of DEP separation devices is their restricted capacity to process samples, impeding the purification of samples on a broad scale [50]. Furthermore, the efficiency of DEP is hindered by the infrequency, diversity, and susceptibility of CTCs, which presents difficulties in their successful isolation [51]. Additionally, the drawbacks of chip-based DEP microfluidic systems, such as low throughput and reduced separation efficiency, have been attributed to the high conductivity of blood [52].

2.2 Passive Separation

2.2.1 Pinched Flow Fractionation Methods (PFF)

Pinch Pinched Flow Fractionation (PFF) is a microfluidic technology that exhibits potential in the separation and isolation of circulating tumor cells (CTCs). This method employs laminar flow to consistently separate suspended particles according to their diameters, providing a label-free technique for the separation of circulating tumor cells (CTCs). The study was conducted by Wang and colleagues [53]. PFF has shown promise in the ongoing and effective segregation of non-spherical particles, such as CTCs, by utilizing their form and size [54]. Furthermore, PFF has been employed for the segregation of different particles, including microalgae and nanoparticles, demonstrating its adaptability and potential for a wide range of uses [55].

Recent studies have investigated innovative modifications of the standard PFF approach. For example, Timary et al. [56] showed that non-spherical bacterial cells can be sorted based on their form using PFF, with the sorting process being facilitated by shear forces. This study highlights the versatility of PFF as a method for particle separation. In addition, Wang et al. [57] developed the Inertia-Enhanced Pinched Flow Fractionation technology (iPFF) to enhance the separation efficiency of PFF and improve its ability to isolate certain cell types.

PFF employs the disparities in size and density between circulating tumor cells (CTCs) and regular blood cells to direct CTCs into a distinct flow pathway for isolation. Nevertheless, the technology faces difficulties in terms of practical adoption and widespread use for isolating circulating tumor cells (CTCs) from actual clinical samples due to the demanding criteria of an exceptionally low Reynolds number (Re < 1) and lengthy processing time [58]. Several researchers have endeavored to integrate PFF with other methodologies in order to enhance its efficacy, such as shear-modulated inertial microfluidics. However, obstacles persist in its clinical application.

2.2.2 Inertia-Based Microfluidic Methods

Inertia-based separation is a promising method for isolating circulating tumor cells (CTCs) from blood samples, offering a label-free and size-based approach to enrich and detect these rare cells. This technique utilizes the physical properties of CTCs, such as size and deformability, to separate them from other blood components. Several studies have demonstrated the effectiveness of inertia-based separation in isolating CTCs from various cancer types, including pancreatic cancer, gastric cancer, and non-small-cell lung cancer [59][[60][61][62]. The use of microfluidic devices, such as spiral channel chips and multi-flow microfluidic channels, has been shown to effectively separate CTCs based on their inertia, providing high purity and sensitivity in CTC isolation [62][63][64].

Researchers have investigated the use of both passive (inertia sorting) and active approaches to separate CTCs from diluted whole blood samples. This study shows that hybrid platforms have the ability to improve the effectiveness of CTC separation [65]. In addition, the progress in creating new microfluidic systems, like as the Labyrinth and ClearCell FX, has significantly improved the use of inertia-based separation for enriching circulating tumor cells (CTCs). This advancement has allowed for the creation of patient-derived xenografts and functional investigations, which are crucial for personalized treatment [59][66][67].

A recent study has demonstrated the efficacy of hybrid microfluidic devices, specifically the spiral microfluidic platform combined with DEP, in the sorting and separation of CTCs. This indicates the possibility of therapeutic applications. The study emphasized the efficacy of a hybrid microfluidic channel in separating A549 CTCs from white blood cells, irrespective of their size, with a rapid rate of processing and a significant separation distance [70]. The results highlight the capability of hybrid microfluidic devices to improve the effectiveness of CTC isolation. Uddin et al. (2023) conducted a study on hybrid inertia-DEP microfluidic devices for the separation of CTC and WBC. The paper included Figure 7. The study examines the efficacy of the device in separating CTC and WBC by varying the electrical voltage and flow rates [71].

In addition, Altay et al. (2022) devised a method combining inertial microfluidics with surface acoustic waves (SAWs) to separate CTCs from RBCs and WBCs. The device employs the passive separation method by utilizing inertial forces in curved microchannels, while the active separation approach incorporates the utilization of SAWs to trap and concentrate cells on specific nodal lines in the microchannel, as depicted in Figure 8 [15]. The study discovered that the hybrid microfluidic platform effectively separated three distinct cell types (CTCs, RBCs, and WBCs) into separate outlets. This demonstrates the potential of high-throughput, multi-staged, and hybrid microfluidic devices for efficiently separating and isolating different cell types based on their sizes.

In addition to size-based separation, the mechanical properties of CTCs, including their deformability and mechanical interactions, have been leveraged to enhance

the efficiency of inertia-based separation [68]. The ratio of inertia lift force and Dean drag force has been identified as a key factor in focusing CTCs and larger white blood cells, while excluding red blood cells, platelets, and plasma proteins, highlighting the potential of inertia-based separation to achieve high-purity CTC isolation [69].

In general, this method has demonstrated the potential to reach a high level of purity and sensitivity in the isolation of CTCs, offering significant knowledge about the spread and advancement of tumors. Moreover, the incorporation of inertial microfluidic channels with magnetic separation and other approaches has shown promise in achieving effective and uninterrupted separation of CTCs from peripheral blood. This integration enhances the capabilities of CTC isolation platforms. Nevertheless, it is important to take into account the existing constraints. The presence of diverse antigens on the surface of CTCs presents a difficulty in their separation, as there are yet no universally recognized CTC antigens. The presence of heterogeneity can impact the effectiveness of isolating and the accuracy of capturing CTCs. Moreover, although the size-based approach is efficient for numerous CTCs, it might not encompass all subgroups of CTCs, potentially resulting in an inadequate depiction of the CTC profile.

2.2.3 Hydrodynamic Filtration

Hydrodynamic filtration is a promising technology that uses fluid dynamics to separate circulating tumor cells (CTCs) from other blood components. This method is highly beneficial since isolating circulating tumor cells (CTCs) is difficult due to their heterogeneity and rarity. Hydrodynamic filtration utilizes microfluidic devices and filters to take advantage of the variations in size, deformability, and other physical characteristics between circulating tumor cells (CTCs) and regular blood cells [72]. Studies have shown that this approach is highly effective, with some achieving capture rates of circulating tumor cells (CTCs) as high as 100%.

An approach for isolating circulating tumor cells (CTCs) involves filtration utilizing ScreenCell® devices, which separate CTCs based on size using a filter with 6.5 to 8 µm pores (Francescangeli et al.) [73]. Moreover, hydrodynamic techniques like deterministic lateral displacement (DLD) have effectively separated circulating tumor cells (CTCs) from blood with a high processing capacity, showcasing the potential of hydrodynamic filtration in isolating CTCs [74]. Moreover, the adaptability and multifunctionality of DLD as a technique for many purposes have been emphasized, suggesting its capability for CTC isolation [75]. The paper highlights the

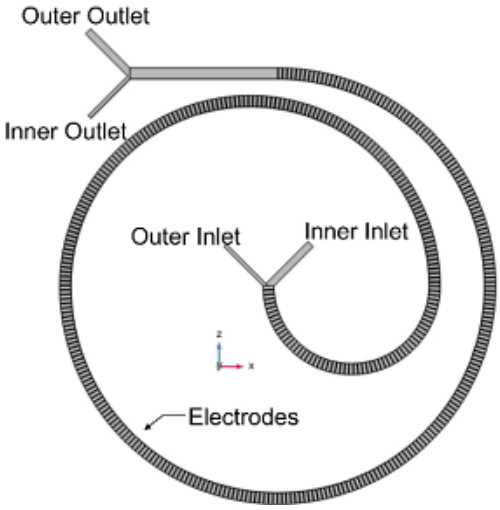

Figure 7. Schematic of the electrode-embedded spiral channel [71]

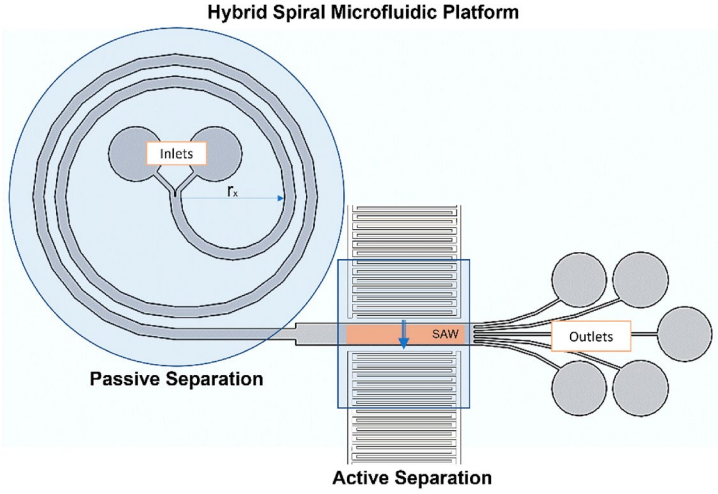

Figure 8. Schematic representation of the hybrid spiral microfluidic [15]

application of deterministic lateral displacement (DLD) in microfluidic-based technologies for isolating large CTC clusters from whole blood, emphasizing the importance of hydrodynamic filtration in CTC isolation [76].

Other than that, studies have demonstrated the effectiveness of DLD in isolating CTCs from whole blood samples with high efficiency and purity. For instance, a cascaded microfluidic device based on DLD and integrated with a filter enabled high-throughput and highly efficient isolation of CTCs from lung cancer patients, highlighting the potential of DLD in liquid biopsy for cancer detection and monitoring [77]. Additionally, recent advances in blood fractionation include the use of a novel cascaded DLD approach to isolate CTC clusters from whole blood with a high recovery yield, demonstrating the versatility of DLD in handling different CTC populations [78].

Furthermore, the integration of DLD with other microfluidic technologies, such as inertial focusing and magnetophoresis, has been explored to enhance the isolation of CTCs. This approach has shown promise in isolating CTCs from whole blood samples with high efficiency and purity, indicating the potential for DLD to be part of integrated systems for CTC isolation [79][80].

Hydrodynamic filtration has demonstrated significant promise, but issues including leukocyte contamination and the necessity for further optimization to increase capture rates and purity still need to be resolved [3]. Cell sorters utilizing hydrodynamic filtration have been emphasized for their development and uses, showcasing the continuous progress in this field [81]. Additionally, issues such as clogging while isolating CTCs from blood using the DLD approach have been noted, highlighting the necessity for additional optimization and research to overcome these constraints [76]. However, ongoing research and development are focused on exploring the potential of DLD in separating CTCs from complicated biological materials to enhance its therapeutic usefulness in cancer diagnosis and prognosis [82].

Hydrodynamic filtering for CTC isolation has tremendous potential because of its high efficiency, capacity for high-throughput processing, and compatibility with other isolation methods. Continued research and development in this field are crucial to enhance the technique and overcome current obstacles, ultimately improving its clinical effectiveness in cancer diagnosis, prognosis, and treatment.

3. CONCLUSION

In recent years, significant advancements in microfluidic circulating tumor cell (CTC) sorting devices have propelled the field toward unprecedented precision and efficiency in cancer diagnostics. The convergence of active and passive techniques within microfluidic platforms has led to enhanced capabilities for CTC isolation, addressing challenges related to sensitivity, specificity, and clinical translation. Active methodologies, including immunomagnetic sorting and microfluidic dielectrophoresis, offer targeted and highly specific CTC capture, while passive strategies such as size-based filtration and deterministic lateral displacement provide simplicity and compatibility with diverse sample types. The synergy achieved through hybrid approaches, integrating the strengths of both active and passive principles, represents a promising direction for optimizing CTC isolation efficiency. These recent advancements hold immense potential for revolutionizing liquid biopsy approaches, enabling non-invasive monitoring of cancer progression, early detection, and the evaluation of therapeutic responses. As microfluidic CTC sorting devices continue to evolve, future efforts will likely focus on standardization, validation, and seamless integration into clinical workflows, ushering in a new era of personalized cancer care and diagnostics.

ACKNOWLEDGMENT

The research was supported by the Ministry of Higher Education of Malaysia and Universiti Teknologi Malaysia under the Professional Development Research University Grant [no. Q.J130000.21A2.06E67] in the project ‘Development of Microfluidic Systems in PDMS for Microalgae Detection and Separation for Renewal Energy Application’. We thank them for funding this project and for their endless support.

REFERENCES

[1] Z. Wang, N. Sun, H. Liu, C. Chen, P. Ding, X. Yueet al., "High-efficiency isolation and rapid identification of heterogeneous circulating tumor cells (CTC's) using dual-antibody-modified fluorescent-magnetic nanoparticles", ACS Applied Materials & Interfaces, vol. 11, no. 43, p. 39586-39593, 2019.

[2] B. Chen, S. Guo, X. Zhao, Y. Yang, & W. Liu, "Noninvasive optical isolation and identification of circulating tumor cells engineered by fluorescent microspheres", Acs Applied Bio Materials, vol. 5, no. 6, p. 2768-2776, 2022.

[3] Y. Su, Q. Tian, D. Pan, L. Hui, Q. Zhang, W. Tianet al., "Antibody-functional microsphere-integrated filter chip with inertial microflow for size–immune-capturing and digital detection of circulating tumor cells", ACS Applied Materials & Interfaces, vol. 11, no. 33, p. 29569-29578, 2019.

[4] D. Hu, H. Liu, Y. Tian, Z. Li, & X. Cui, "Sorting technology for circulating tumor cells based on microfluidics", ACS Combinatorial Science, vol. 22, no. 12, p. 701-711, 2020.

[5] L. Wu, M. Tang, Z. Zhang, C. Qi, J. Hu, X. Maet al., "Chip-assisted single-cell biomarker profiling of heterogeneous circulating tumor cells using multifunctional nanospheres", Analytical Chemistry, vol. 90, no. 17, p. 10518-10526, 2018.

[6] J. Myung, S. Park, A. Wang, & S. Hong, "Integration of biomimicry and nanotechnology for significantly improved detection of circulating tumor cells (CTCs)", Advanced Drug Delivery Reviews, vol. 125, p. 36-47, 2018.

[7] W. Tang, D. Jiang, Z. Li, L. Zhu, J. Shi, J. Yanget al., "Recent advances in microfluidic cell sorting techniques based on both physical and biochemical principles", Electrophoresis, vol. 40, no. 6, p. 930-954, 2018.

[8] X. Zhang, X. Wei, X. Men, C. Wu, J. Bai, W. Liet al., "Dual-multivalent-aptamer-conjugated nanoprobes for the superefficient discerning of single circulating tumor cells in a microfluidic chip with inductively coupled plasma mass spectrometry detection", ACS

Applied Materials & Interfaces, vol. 13, no. 36, p. 43668-43675, 2021.

[9] W. Zhao, L. Yang, B. Jenkins, R. Cheng, B. Harris, W. Zhang et al., "Tumor antigen-independent and cell size variation-inclusive enrichment of viable circulating tumor cells", Lab on a Chip, vol. 19, no. 10, p. 1860-1876, 2019.

[10] F. Rivello, K. Matuła, A. Piruska, M. Smits, N. Mehra, & W. Huck, "Probing single-cell metabolism reveals the prognostic value of highly metabolically active circulating stromal cells in prostate cancer", Science Advances, vol. 6, no. 40, 2020.

[11] D. Caballero, R. Reis, & S. Kundu, "Cancer traps: implantable and on-chip solutions for early cancer detection and treatment", Advanced Materials Technologies, vol. 8, no. 18, 2023.

[12] R. Nasiri, A. Shamloo, & J. Akbari, "Design of a hybrid inertial and magnetophoretic microfluidic device for CTC separation from blood", Micromachines, vol. 12, no. 8, p. 877, 2021.

[13] L. Luo and Y. He, "Magnetically driven microfluidics for isolation of circulating tumor cells", Cancer Medicine, vol. 9, no. 12, p. 4207-4231, 2020.

[14] K. Jiang, D. Jokhun, & C. Lim, "Microfluidic detection of human diseases: from liquid biopsy to COVID-19 diagnosis", Journal of Biomechanics, vol. 117, p. 110235, 2021.

[15] R. Altay, M. Yapıcı, & A. Koşar, "A hybrid spiral microfluidic platform coupled with surface acoustic waves for circulating tumor cell sorting and separation: a numerical study", Biosensors, vol. 12, no. 3, p. 171, 2022.

[16] A. Maurya, J. Murallidharan, A. Sharma, & A. Agarwal, "Microfluidics geometries involved in effective blood plasma separation", Microfluidics and Nanofluidics, vol. 26, no. 10, 2022.

[17] X. Wei, K. Chen, S. Guo, W. Liu, & X. Zhao, "Emerging microfluidic technologies for the detection of circulating tumor cells and fetal nucleated red blood cells", ACS Applied Bio Materials, vol. 4, no. 2, p. 1140-1155, 2021.

[18] Z. Wang, "Acoustic separation of circulating tumor cells," Proceedings of the National Academy of Sciences, vol. 112, no. 16, pp. 4970–4975, 2015.

[19] J. P. Smith, "Acoustophoretic recovery of cancer cells from human blood," The Journal of the Acoustical Society of America, vol. 146, no. 4, pp. 3132–3140, 2019.

[20] E. Undvall Anand, C. Magnusson, A. Lenshof, Y. Ceder, H. Lilja, and T. Laurell, "Two-step acoustophoresis separation of live tumor cells from whole blood," Anal. Chem., vol. 93, no. 51, pp. 17076–17085, 2021.

[21] S. Karthick, P. N. Pradeep, P. Kanchana, and A. K. Sen, "Acoustic impedance-based size-independent isolation of circulating tumor cells from blood using acoustophoresis," Lab Chip, vol. 18, no. 24, pp. 3802–3813, 2018.

[22] W. Geng et al., "An ultra-compact acoustofluidic device based on the narrow-path traveling surface acoustic wave (np-TSAW) for label-free isolation of living circulating tumor cells," Anal. Chim. Acta, vol. 1255, no. 341138, p. 341138, 2023.

[23] Z. Wu et al., "The acoustofluidic focusing and separation of rare tumor cells using transparent lithium niobate transducers," Lab Chip, vol. 19, no. 23, pp. 3922–3930, 2019.

[24] Z. Zhao, S. Yang, F. Li, L. Zhang, J. Wang, K. Changet al., "Acoustofluidics: a versatile tool for micro/nano separation at the cellular, subcellular, and biomolecular levels", Advanced Materials Technologies, vol. 8, no. 14, 2023.

[25] B. Dou, L. Xu, B. Jiang, R. Yuan, & Y. Xiang, "Aptamer-functionalized and gold nanoparticle array-decorated magnetic graphene nanosheets enable multiplexed and sensitive electrochemical detection of rare circulating tumor cells in whole blood", Analytical Chemistry, vol. 91, no. 16, p. 10792-10799, 2019.

[26] K. Clack, N. Soda, S. Kasetsirikul, R. Mahmudunnabi, N. Nguyen, & M. Shiddiky, "Toward personalized nanomedicine: the critical evaluation of micro and nanodevices for cancer biomarker analysis in liquid biopsy", Small, vol. 19, no. 15, 2023.

[27] S. Regmi, C. Poudel, R. Adhikari, & K. Luo, "Applications of microfluidics and organ-on-a-chip in cancer research", Biosensors, vol. 12, no. 7, p. 459, 2022.

[28] E. Giunta, L. Annaratone, E. Bollito, F. Porpiglia, M. Cereda, G. Bannaet al., "Molecular characterization of prostate cancers in the precision medicine era", Cancers, vol. 13, no. 19, p. 4771, 2021.

[29] A. Raza, A. Khan, V. Inchakalody, S. Mestiri, Z. Yoosuf, T. Bedhiafiet al., "Dynamic liquid biopsy components as predictive and prognostic biomarkers in colorectal cancer", Journal of Experimental & Clinical Cancer Research, vol. 41, no. 1, 2022.

[30] X. Wang, L. Sun, H. Zhang, W. Lin, W. Qu, Z. Zenget al., "Microfluidic chip combined with magnetic-activated cell sorting technology for tumor antigen-independent sorting of circulating hepatocellular carcinoma cells", Peerj, vol. 7, p. e6681, 2019.

[31] F. Jiang and N. Xiang, "Integrated microfluidic handheld cell sorter for high-throughput label-free malignant tumor cell sorting", Analytical Chemistry, vol. 94, no. 3, p. 1859-1866, 2022.

[32] F., J., Mishra, A., Dubash, T., Herrera, S., Mohammad, R., Williams, E., … & Toner, M. (2020). Microfluidic concentration and separation of circulating tumor cell clusters from large blood volumes. Lab on a Chip, 20(3), 558-567.

[33] X. Wang, L. Sun, H. Zhang, W. Lin, W. Qu, Z. Zenget al., "Microfluidic chip combined with magnetic-activated cell sorting technology for tumor antigen-independent sorting of circulating hepatocellular carcinoma cells", PeerJ, vol. 7, p. e6681, 2019.

[34] M. Vidlarova, A. Rehulkova, P. Stejskal, A. Prokopova, H. Slavik, M. Hajduchet al., "Recent advances in methods for circulating tumor cell detection", International Journal of Molecular Sciences, vol. 24, no. 4, p. 3902, 2023.

[35] T. Visal, P. Hollander, M. Cristofanilli, & S. Mani, "Circulating tumor cells in the -omics era: how far are

we from achieving the ‘singularity’?", British Journal of Cancer, vol. 127, no. 2, p. 173-184, 2022.
[36] F. Iliescu, D. Poenar, F. Yu, M. Ni, K. Chan, I. Cimaet al., "Recent advances in microfluidic methods in cancer liquid biopsy", Biomicrofluidics, vol. 13, no. 4, 2019.
[37] T. Lozar et al., “Preclinical and clinical evaluation of magnetic-activated cell separation technology for CTC isolation in breast cancer,” Front. Oncol., vol. 10, p. 554554, 2020.
[38] R. Nasiri, A. Shamloo, and J. Akbari, “Design of a hybrid inertial and magnetophoretic microfluidic device for CTC separation from blood,” Micromachines (Basel), vol. 12, no. 8, p. 877, 2021.
[39] V. Varmazyari, H. Habibiyan, H. Ghafoorifard, M. Ebrahimi, & S. Ghafouri-Fard, "A dielectrophoresis-based microfluidic system having double-sided optimized 3d electrodes for label-free cancer cell separation with preserving cell viability", Scientific Reports, vol. 12, no. 1, 2022.
[40] L. Mathur, M. Ballinger, R. Utharala, & C. Merten, "Microfluidics as an enabling technology for personalized cancer therapy", Small, vol. 16, no. 9, 2019.
[41] Musso, N., Romano, A., Bonacci, P., Scandura, G., Pandino, C., Camarda, M., … & Cacciola, R. (2022). Label-free enrichment of circulating tumor plasma cells: future potential applications of dielectrophoresis in multiple myeloma. International Journal of Molecular Sciences, 23(19), 12052.
[42] V. Heredia-Soto, N. Rodríguez-Salas, & J. Feliu, "Liquid biopsy in pancreatic cancer: are we ready to apply it in the clinical practice?", Cancers, vol. 13, no. 8, p. 1986, 2021.
[43] L. Velmanickam, V. Jayasooriya, M. Vemuri, U. Tida, & D. Nawarathna, "Recent advances in dielectrophoresis toward biomarker detection: a summary of studies published between 2014 and 2021", Electrophoresis, vol. 43, no. 1-2, p. 212-231, 2021.
[44] A. M. Alkhaiyat and M. Badran, “Numerical simulation of a lab-on-chip for dielectrophoretic separation of circulating tumor cells,” Micromachines (Basel), vol. 14, no. 9, 2023.
[45] V. Varmazyari, H. Habibiyan, H. Ghafoorifard, M. Ebrahimi, and S. Ghafouri-Fard, “A dielectrophoresis-based microfluidic system having double-sided optimized 3D electrodes for label-free cancer cell separation with preserving cell viability,” Sci. Rep., vol. 12, no. 1, p. 12100, 2022.
[46] A. Shamloo, A. Yazdani, and F. Saghafifar, “Investigation of a two-step device implementing magnetophoresis and dielectrophoresis for separation of circulating tumor cells from blood cells,” Eng. Life Sci., vol. 20, no. 7, pp. 296–304, 2020.
[47] K. Zhao et al., “Implementation of an integrated dielectrophoretic and magnetophoretic microfluidic chip for CTC isolation,” Biosensors (Basel), vol. 12, no. 9, p. 757, 2022.
[48] Z. Çağlayan, Y. Yalçın, & H. Kulah, "Examination of the dielectrophoretic spectra of mcf7 breast cancer cells and leukocytes", Electrophoresis, vol. 41, no. 5-6, p. 345-352, 2020.
[49] M. Islam and X. Chen, "Continuous CTC separation through a dep-based contraction–expansion inertial microfluidic channel", Biotechnology Progress, vol. 39, no. 4, 2023.
[50] J. Derksen and M. Viefhues, "Parallelized continuous flow dielectrophoretic separation of DNA", Electrophoresis, vol. 44, no. 11-12, p. 968-977, 2022.
[51] X. Xu, Z. Jiang, J. Wang, Y. Ren, & A. Wu, "Microfluidic applications on circulating tumor cell isolation and biomimicking of cancer metastasis", Electrophoresis, vol. 41, no. 10-11, p. 933-951, 2020.
[52] M. Bakhshi, M. Rizwan, G. Khan, H. Duan, & K. Zhai, "Design of a novel integrated microfluidic chip for continuous separation of circulating tumor cells from peripheral blood cells", Scientific Reports, vol. 12, no. 1, 2022.
[53] Wang, S., Liu, Z., Wu, S., Sun, H., Zeng, W., Wei, J., … & Pan, X. (2021). Microalgae separation by inertia-enhanced pinched flow fractionation. Electrophoresis, 42(21-22), 2223-2229.
[54] Timary, G., Rousseau, C., Melderen, L., & Scheid, B. (2023). Shear-enhanced sorting of ovoid and filamentous bacterial cells using pinch flow fractionation. Lab on a Chip, 23(4), 659-670.
[55] Yadav, A., Tran, D., Teo, A., Dai, Y., Galogahi, F., Ooi, C., … & Nguyen, N. (2023).Core–shell particles: from fabrication methods to diverse manipulation techniques. Micromachines, 14(3), 497.
[56] G. Timary, J. Cappello, & B. Scheid, "Enhanced pinch flow fractionation using inertial streamline crossing", Microfluidics and Nanofluidics, vol. 27, no. 1, 2022.
[57] S. Wang, Z. Liu, S. Wu, H. Sun, W. Zeng, J. Weiet al., "Microalgae separation by inertia-enhanced pinched flow fractionation", Electrophoresis, vol. 42, no. 21-22, p. 2223-2229, 2021.
[58] S.-J. Hao, Y. Wan, Y.-Q. Xia, X. Zou, and S.-Y. Zheng, “Size-based separation methods of circulating tumor cells,” Adv. Drug Deliv. Rev., vol. 125, pp. 3–20, 2018.
[59] L. Rivera-Báez, E. Lin, S. Raghavan, S. Owen, R. Harouaka, K. Hermanet al., "Expansion of circulating tumor cells from patients with locally advanced pancreatic cancer enable patient-derived xenografts and functional studies for personalized medicine", Cancers, vol. 12, no. 4, p. 1011, 2020.
[60] M. Lee, G. Kim, H. Jeon, & S. Park, "Clinical application of circulating tumor cells in gastric cancer", Gut and Liver, vol. 13, no. 4, p. 394-401, 2019.
[61] D. Matsushita, T. Arigami, K. Okubo, K. Sasaki, M. Noda, Y. Kitaet al., "The diagnostic and prognostic value of a liquid biopsy for esophageal cancer: a systematic review and meta-analysis", Cancers, vol. 12, no. 10, p. 3070, 2020.
[62] J. Zhou, A. Kulasinghe, A. Bogseth, K. O'Byrne, C. Punyadeera, & I. Papautsky, "Isolation of circulating tumor cells in non-small-cell-lung-cancer patients using a multi-flow microfluidic channel", Microsystems & Nanoengineering, vol. 5, no. 1, 2019.
[63] H. Tang, J. Niu, H. Jin, S. Lin, & D. Cui, "Geometric structure design of passive label-free microfluidic

systems for biological micro-object separation", Microsystems & Nanoengineering, vol. 8, no. 1, 2022.
[64] N. Lü, H. Tay, C. Petchakup, L. He, L. Gong, K. Mawet al., "Label-free microfluidic cell sorting and detection for rapid blood analysis", Lab on a Chip, vol. 23, no. 5, p. 1226-1257, 2023.
[65] Y. Lee, G. Guan, & A. Bhagat, "Clearcell® fx, a label-free microfluidics technology for enrichment of viable circulating tumor cells", Cytometry Part A, vol. 93, no. 12, p. 1251-1254, 2018.
[66] P. Cai, B. Hu, W. Leow, X. Wang, X. Loh, Y. Wuet al., "Biomechano-interactive materials and interfaces", Advanced Materials, vol. 30, no. 31, 2018.
[67] M. Rahman, M. Islam, R. Islam, M. Islam, M. Kaysir, M. Akteret al., "A critical review on the sensing, control, and manipulation of single molecules on optofluidic devices", Micromachines, vol. 13, no. 6, p. 968, 2022.
[68] A. Abdulla, T. Zhang, S. Li, W. Guo, A. Warden, Y. Xinet al., "Integrated microfluidic single-cell immunoblotting chip enables high-throughput isolation, enrichment and direct protein analysis of circulating tumor cells", Microsystems & Nanoengineering, vol. 8, no. 1, 2022.
[69] C. Li, W. He, N. Wang, Z. Xi, R. Deng, X. Liu et al., "Application of microfluidics in the detection of circulating tumor cells", Frontiers in Bioengineering and Biotechnology, vol. 10, 2022.
[70] M. Islam and X. Chen, "Continuous CTC separation through a dep-based contraction–expansion inertial microfluidic channel", Biotechnology Progress, vol. 39, no. 4, 2023.
[71] M. R. Uddin and X. Chen, “Design of a hybrid-inertial device for the separation of Circulating tumor cells,” in 2023 Design of Medical Devices Conference, 2023.
[72] S. Ribeiro-Samy, M. Oliveira, T. Pereira-Veiga, L. Muinelo-Romay, S. Carvalho, J. Gasparet al., "Fast and efficient microfluidic cell filter for isolation of circulating tumor cells from unprocessed whole blood of colorectal cancer patients", Scientific Reports, vol. 9, no. 1, 2019.
[73] F. Francescangeli, V. Magri, M. Angelis, G. Renzi, O. Gandini, A. Zeuneret al., "Sequential isolation and characterization of single CTCs and large CTC clusters in metastatic colorectal cancer patients", Cancers, vol. 13, no. 24, p. 6362, 2021.
[74] T. Salafi, Y. Zhang, & Y. Zhang, "A review on deterministic lateral displacement for particle separation and detection", Nano-Micro Letters, vol. 11, no. 1, 2019.
[75] M. Witek, I. Freed, & S. Soper, "Cell separations and sorting", Analytical Chemistry, vol. 92, no. 1, p. 105-131, 2019.
[76] Descamps, L., Roy, D., & Deman, A. (2022). Microfluidic-based technologies for CTC isolation: a review of 10 years of intense efforts towards liquid biopsy. International Journal of Molecular Sciences, 23(4), 1981.
[77] Y. Wang, Y. Gao, & Y. Song, "Microfluidics-based urine biopsy for cancer diagnosis: recent advances and future trends", Chemmedchem, vol. 17, no. 20, 2022.
[78] N. Lü, H. Tay, C. Petchakup, L. He, L. Gong, K. Mawet al., "Label-free microfluidic cell sorting and detection for rapid blood analysis", Lab on a Chip, vol. 23, no. 5, p. 1226-1257, 2023.
[79] W. Zhou, Y. Yan, Q. Guo, H. Ji, H. Wang, T. Xuet al., "Microfluidics applications for high-throughput single-cell sequencing", Journal of Nanobiotechnology, vol. 19, no. 1, 2021.
[80] A. Jiménez-Zenteno and A. Cerf, "Liquid biopsy based on circulating cancer-associated cells: bridging the gap from an emerging concept to a mainstream tool in precision medicine", Advanced Biosystems, vol. 4, no. 2, 2019.
[81] J. Ding, Y. Xie, Y. Zhang, & Y. Zhang, "Development and applications of cell sorters based on hydrodynamic filtration", Highlights in Science Engineering and Technology, vol. 37, p. 262-276, 2023.
[82] S. Surappa, P. Multani, U. Parlatan, P. Sinawang, J. Kaifi, D. Akinet al., "Integrated “lab-on-a-chip” microfluidic systems for isolation, enrichment, and analysis of cancer biomarkers", Lab on a Chip, vol. 23, no. 13, p. 2942-2958, 2023.