Microfluidics and Nanofluidics (2019) 23:68
https://doi.org/10.1007/s10404-019-2232-z

RESEARCH PAPER

Manipulation of bio-micro/nanoparticles in non-Newtonian microflows

Fei Tian[1,2] · Qiang Feng[2] · Qinghua Chen[2] · Chao Liu[2,3] · Tiejun Li[1] · Jiashu Sun[2,4]

Received: 18 February 2019 / Accepted: 22 March 2019 / Published online: 8 April 2019

Abstract
Most bio-micro/nanoparticles, including cells, platelets, bacteria, and extracellular vesicles, are inherently suspended in biofluids (i.e., blood) with non-Newtonian fluid characteristics. Understanding migration behaviors of bioparticles in non-Newtonian microfluidics is of significance in label-free manipulation of bioparticles, playing important roles in cell analysis and disease diagnostics. This review presents recent advances in focusing and sorting of bio-micro/nanoparticles by non-Newtonian microfluidics. Principle and examples for passive and active manipulation of bioparticles in non-Newtonian and non-Newtonian/Newtonian hybrid microflows are highlighted. Limitations and perspectives of non-Newtonian microfluidics for clinical applications are discussed.

1 Introduction

Precise manipulation of bio-micro/nanoparticles, i.e., cells, platelets, bacteria, and extracellular vesicles, is critical for cell analysis, infectious disease detection, and tumor diagnostics and prognostics (Gay and Felding-Habermann 2011; Liu et al. 2019a, b; Plaks et al. 2013; Poudineh et al. 2018; van Niel et al. 2018). In microfluidics, it is feasible to manipulate bio-micro/nanoparticles with sizes comparable to the microchannel dimension under predominantly laminar flow conditions (Ahmed et al. 2017; Sun et al. 2018; Xue et al. 2015; Zhang et al. 2018b; Zhu and Yang 2017). In particular, microfluidics enables label-free sorting of bio-micro/nanoparticles both passively and actively, relying on the physical differences in the properties of bioparticles. Passive microfluidic methods exploit solely hydrodynamic effects, such as fluid inertia effects, to focus and sort particles based on size, shape and so forth (Amini et al. 2014; Tang et al. 2017; Wunsch et al. 2016; Xiang et al. 2014, 2016, 2018; Zhang et al. 2014, 2016a). Active microfluidic methods use external forces, including electric, acoustic, and magnetic forces, to compete with hydrodynamic forces, allowing for size-, elasticity-, and polarizability-dependent separation of particles (Hejazian et al. 2015; Kale et al. 2018; Karlsen et al. 2018; Laurell et al. 2007; Li et al. 2014; Wu et al. 2017; Yan et al. 2015; Zhang et al. 2018a). In most cases, particles are suspended in a Newtonian liquid (i.e., water and PBS) prior to microfluidic manipulation. In contrast, a majority of bio-micro/nanoparticles are immersed in biofluids (i.e., blood) with non-Newtonian fluid characteristics (Campo-Deaño et al. 2013; Stickel and Powell 2005). Understanding migration behaviors of bioparticles in non-Newtonian microflows is thus of profound importance for precise focusing and sorting of particles in microfluidics.

The commonly used non-Newtonian fluids for microfluidic purposes are dilute polymer solutions and blood with

This article is part of the topical collection "Particle motion in non-Newtonian microfluidics" guest edited by Xiangchun Xuan and Gaetano D'Avino.

✉ Chao Liu
liuc@nanoctr.cn

✉ Tiejun Li
li_tiejun@hebut.edu.cn

✉ Jiashu Sun
sunjs@nanoctr.cn

1 School of Mechanical Engineering, Hebei University of Technology, Tianjin 300401, China

2 CAS Key Laboratory of Standardization and Measurement for Nanotechnology, CAS Center for Excellence in Nanoscience, National Center for Nanoscience and Technology, Beijing 100190, China

3 School of Mechanical Engineering, and Jiangsu Key Laboratory for Design and Manufacture of Micro-Nano Biomedical Instruments, Southeast University, Nanjing 211189, China

4 University of Chinese Academy of Sciences, Beijing 100049, China

intrinsic viscoelastic or shear-thinning effects (Del Giudice et al. 2015a; Kang et al. 2013; Lu et al. 2015; Yuan et al. 2018). The particles suspended in non-Newtonian microfluidics experience an elastic lift force due to the fluid viscoelasticity, which is not present in Newtonian microfluidics. This elastic lift force assists in manipulation of particles over a wide range of experimental conditions and particle sizes. In a microcapillary filled with dilute polymer solutions, elastic forces arising from non-uniform normal stress differences are exerted on suspended microparticles, driving particles toward the center of the microcapillary where the shear rate is lowest (D'Avino et al. 2012; De Santo et al. 2014; Ho and Leal 1976; Leshansky et al. 2007; Xiang et al. 2018; Yang et al. 2011). To separate microparticles of different sizes within non-Newtonian microfluidics, three strategies are outlined. The first strategy is to explore the elasticity with or without the inertia of non-Newtonian fluids in microchannels, which can lead to a size-dependent lateral migration of particles. The second one is to design a co-flow microfluidic system of non-Newtonian and Newtonian fluids that produces a stable fluid interface between two flows, allowing for a size-selective penetration of particles across the interface. The third one is to impose external force fields over non-Newtonian microfluidics, such as electric and magnetic, so that particles could be sorted by size through a combined effect of hydrodynamics and electrophoresis or magnetophoresis. These methods facilitate precise manipulation of bio-micro/nanoparticles in non-Newtonian microfluidics.

This review summarizes recent progress in manipulation of bio-micro/nanoparticles including cells, platelets, bacteria, and extracellular vesicles by non-Newtonian microfluidics. The principles of passive manipulation of bio-micro/nanoparticles in purely viscoelastic fluids are described. Microfluidic co-flow of non-Newtonian and Newtonian fluids is discussed for manipulation (including focusing, separation, isolation, and enrichment) of a variety of bioparticles with improved resolution. Active manipulation of bioparticles through applying an external force field, such as electric or magnetic, is presented. Finally, limitations and perspectives of non-Newtonian microfluidic manipulation of bioparticles for clinical applications are overviewed.

2 Passive manipulation of bioparticles in non-Newtonian microflows

Non-Newtonian microfluidics enables passive and precise particle manipulation in a continuous, label-free, and size-dependent manner, by exploiting flow-induced lift forces in a viscoelastic carrier fluid. For example, the elastic lift force F_e ($F_e \sim a^3$, in which a is the diameter of the particle) arising at non-vanishing Weissenberg number ($W_i = \lambda\gamma > 0$, in which λ is the relaxation time of a viscoelastic fluid, and γ is the characteristic shear rate) tends to drive particles toward lateral positions with minimum shear rates, i.e., the centerline and four corners of a rectangular microchannel (D'Avino et al. 2017; Liu et al. 2016b; Lu et al. 2017; Yang et al. 2012). Moreover, at moderate Reynolds number ($Re = \rho UD/\eta > 10$, in which ρ is the fluid density, U is the characteristic flow speed, D is the dimension of microchannel cross section, and η is the dynamic viscosity), the inertial lift force F_i ($F_i \sim a^4$) induces lateral migration of particles toward equilibrium positions between the centerline and walls of a microchannel (Amini et al. 2014; Liu et al. 2015a; Lu and Xuan 2015; Xiang et al. 2014; Zhang et al. 2014, 2016a). The combined effects of F_e and F_i can reduce the multiple focusing positions of particles into a single one along the centerline (elasto-inertial focusing), which have been extensively investigated for cell manipulation in Non-Newtonian microflows (Fig. 1a) (Lim et al. 2014; Liu et al. 2015b; Yang et al. 2011). For manipulation of bio-nanoparticles by non-Newtonian microfluidics, F_e could play a dominate role over F_i by proper tuning of rheological properties of non-Newtonian fluids (Ciftlik et al. 2013; Kim et al. 2012).

2.1 Cells

There are heterogeneous groups of bio-microparticles with diverse sizes, including circulating tumor cells (CTCs, 15–25 μm), white blood cells (WBCs, 7–12 μm), red blood cells (RBCs, 6–8 μm), platelets (2–3 μm), and pathological bacteria (1–2 μm) (Bhagat et al. 2011; Tan et al. 2009; Wang et al. 2015). Non-Newtonian microfluidics featuring precise manipulation of particles over a wide size range provides a promising avenue for label-free separation of diverse bio-microparticles (Li et al. 2018; Nam et al. 2012; Tan et al. 2017; Yang et al. 2012). For example, a viscoelastic microfluidic device has been designed to isolate MCF-7 cells (human breast cancer cell line) from lysed blood (Fig. 1b) (Nam et al. 2015). Using 0.1 wt% of hyaluronic acid (HA) as the additive in the lysed blood, MCF-7 cells and WBCs were pre-aligned into a single stream at the centerline of a circular capillary (inner diameter of 50 μm) by elasto-inertial focusing, followed by size-dependent lateral separation induced by the elasto-inertial effect in bifurcated rectangular microchannels. At a high flow rate of 12 mL h^{-1} (2.4×10^7 cells h^{-1}), the device achieved a high separation efficiency of 94% and a high purity of 97% for MCF-7 cells with a size cutoff of 16 μm. This design was further adapted to isolate malaria parasites (1.5–2 μm) from lysed blood at a flow rate of 24 mL h^{-1} with a high recovery rate of 94% and a high purity of 99% (Nam et al. 2016). An efficient removal of WBCs and a 7-fold enrichment of malaria parasites allowed for sensitive PCR detection of malaria parasites. This elasto-inertial separation relies on a size-dependent

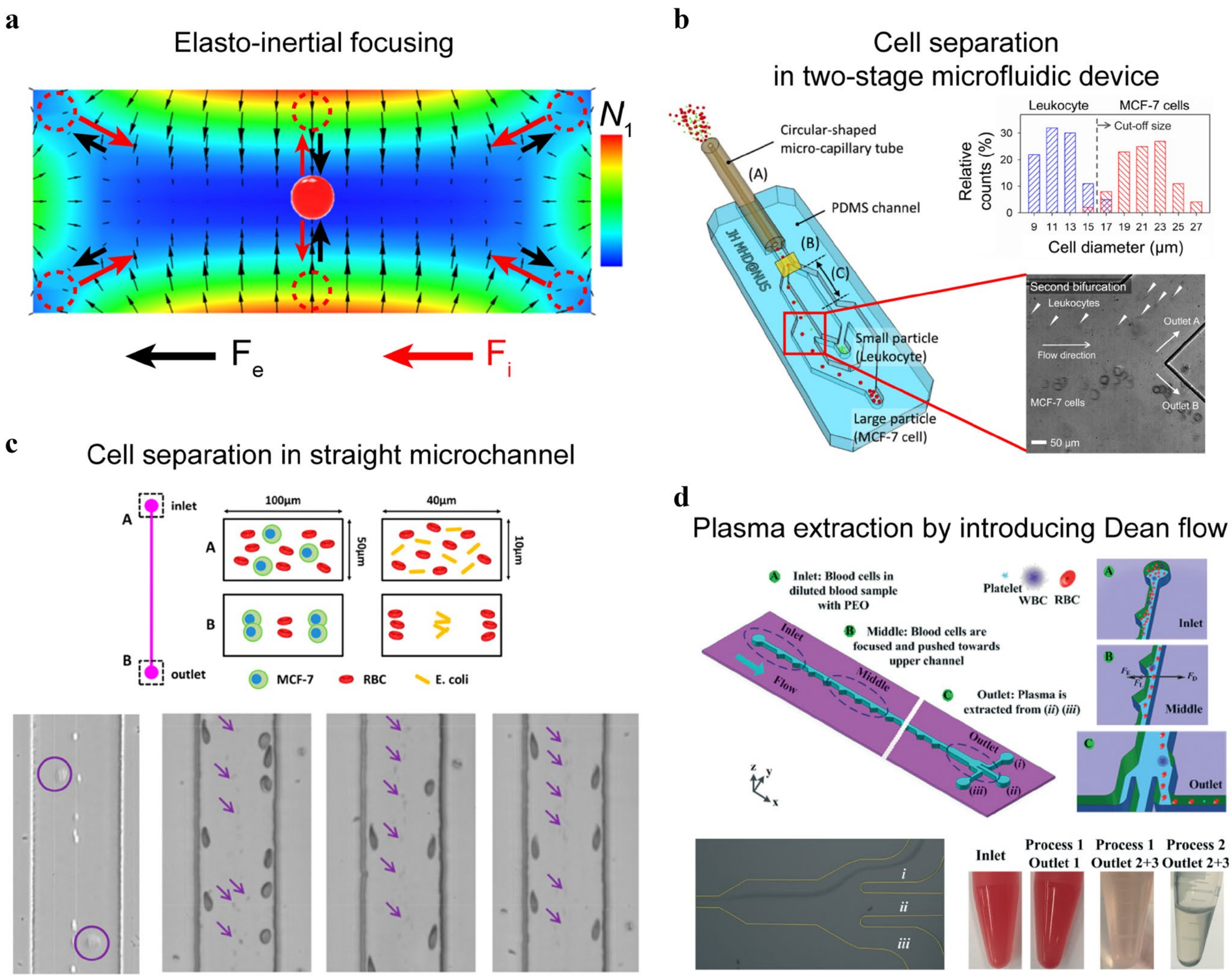

Fig. 1 Bio-microparticle manipulation in viscoelastic fluids. **a** Elasto-inertial focusing of microparticles along the centreline of a microchannel. F_e is the elastic lift force, and F_i is the inertial lift force. Reproduced with permission (Liu et al. 2017). Copyright 2017, American Chemical Society. **b** Elasto-inertial separation of MCF-7 cells from white blood cells with a cutoff size of 16 μm in a two-stage microfluidic device. Reproduced with permission (Nam et al. 2015). Copyright 2015, Elsevier. **c** Separation of MCF-7 cells with a large blockage ratio in straight rectangular microchannels. Reproduced with permission (Liu et al. 2015b). Copyright 2015, American Chemical Society. **d** The elasto-inertial focusing coupled with Dean flow for plasma extraction. Reproduced with permission (Yuan et al. 2016b). Copyright 2016, Royal Society of Chemistry

lateral migration speed of particles in non-Newtonian microflows. Through optimization of the length of microchannel, accurate separation of a variety of bio-microparticles can be achieved.

In contrast to the typical focusing of particles along the centerline of microchannel in non-Newtonian microfluidics, particles with a large blockage ratio (the ratio of particle diameter to channel diameter ≥ 0.25) tend to be focused toward the sidewalls due to the enhanced compressive elastic stress at the near-center part of the particle (Huang et al. 1997; Li et al. 2016; Liu et al. 2015b). This strategy has been used for sheathless separation of MCF-7 cells from RBCs in a straight microchannel with 100 μm wide and 50 μm high (Fig. 1c) (Liu et al. 2015b). When using 0.2 wt % denaturized poly(ethylene oxide) (PEO) solution as the carrier fluid, a separation efficiency of 91.4% and an enrichment ratio of 11.7 were obtained for MCF-7 cells at a throughput of 3×10^8 cells h^{-1} (Liu et al. 2015b). This mechanism was extended to isolate *E. coli* bacteria from RBCs with 99.9% separation efficiency in a small microchannel with 40 μm wide and 10 μm high (Fig. 1c).

Moreover, the elasto-inertial focusing coupled with Dean flow in non-Newtonian microfluidics was exploited for separation of blood cells and plasma in diluted whole blood (Fig. 1d) (Lee et al. 2013; Yuan et al. 2016b). With the assistance of PEO solutions, blood cells including WBCs, RBCs, and platelets were aligned at the middle plane within the microchannel by elasto-inertial focusing. Meanwhile, Dean vortices generated within the contraction–expansion triangular cavities pushed the cells toward the opposite side of the cavities (Yuan et al. 2016b). After passing through the microchannel containing an array of asymmetrical cavities, the focused stream of cells was aligned toward the side outlet, while the plasma was collected at all other outlets. Under the flow rate of 3 mL h^{-1} and PEO concentration of 0.1 wt%, this platform removed 99.99% of blood cells from the whole blood samples after two consecutive runs. The coupling of Dean flow with elasto-inertial focusing was also investigated in spiral microchannels (Liu et al. 2016a; Xiang et al. 2016). Systematic optimization of spiral channel geometry and flow conditions resulted in a three-dimensional single-line focusing of particles in a single-spiral microchannel (Xiang et al. 2016). In a double-spiral microchannel, a size-based separation of the mixture of λ-DNA molecules and blood platelets with efficiencies over 95% was demonstrated in PEO solutions (Liu et al. 2016a).

2.2 Extracellular vesicles

Extracellular vesicles (EVs), including exosomes (30–200 nm in diameter) and microvesicles (200–1000 nm in diameter), are membrane-bound phospholipid nanovesicles actively secreted by mammalian cells into the circulation (Peinado et al. 2012; Shao et al. 2018; Shurtleff et al. 2018). EVs are extensively involved in intercellular communication and pathological processes, serving as promising diagnostic or prognostic biomarkers of diseases (Colombo et al. 2014; Lee et al. 2018; Thery et al. 2002). Isolation of EVs from biofluids such as serum and plasma is a prerequisite for sensitive detection of EVs. However, it is challenging to manipulate EVs by conventional bulk methods owing to the small size of EVs (Contreras-Naranjo et al. 2017; Witwer et al. 2013).

Viscoelastic microfluidics has emerged as an efficient tool for focusing and separating bio-nanoparticles (De Santo et al. 2014). Using the PEO solution with minimized shear-thinning effect (molecular weight of 0.6×10^6 g/mol, and 0.6 wt%) as the carrier fluid in a spiral microchannel, a sheathless focusing of 100 nm particles and λ-DNA molecules with efficiency over 80% was demonstrated at a flow rate of 0.32 μL h^{-1} (Fig. 2a) (Liu et al. 2016a). A sheath flow design of viscoelastic microfluidics enabled separation of exosomes and microvesicles using PEO as the additive (0.1 wt%) in serum samples (Fig. 2b) (Liu et al. 2017). The viscoelastic sheath fluid was injected from the middle inlet to pre-align EVs into a tight stream along the sidewalls. The size-selective lateral migration of EVs driven by the elastic lift resulted in efficient separation of small exosomes and large microvesicles after passing through the microchannel. Under an optimal sample flow rate of 0.2 mL h^{-1}, the isolated exosomes by viscoelastic microfluidics had a high purity of > 90% and a high recovery rate of > 80%, much higher than the recovery rate of 5–25% by conventional gold-standard ultracentrifugation (Lamparski et al. 2002). These investigations suggest an important role of viscoelastic microfluidics in manipulation of bio-nanoparticles.

3 Passive manipulation of bioparticles in non-Newtonian hybrid microflows

In recent years, microfluidic hybrid systems of non-Newtonian and Newtonian fluids have been proposed for label-free and high-resolution manipulation of bioparticles with improved capability for handling complex biofluids (Ha et al. 2016; Tian et al. 2017, 2018; Yuan et al. 2016c, 2017, 2018). The microfluidic co-flow of viscoelastic (PEO solutions) and Newtonian fluids (water or PBS) can generate a stable viscoelastic/Newtonian interface, inducing an interfacial elastic lift force ($F_e \sim a^3$) to compete with the inertial lift force ($F_i \sim a^4$). The competition between the two forces led to lateral migration of bioparticles across the interface in a size-dependent manner (Fig. 3). This non-Newtonian hybrid microfluidics was applied to a variety of bio-microparticles including CTCs, WBCs, RBCs, platelets, and bacteria.

3.1 Cells

Isolation of CTCs from untreated whole blood is a difficult task due to the extreme rarity and high heterogeneity of CTCs. The non-Newtonian hybrid microfluidics offered a new avenue for label-free size-based isolation of rare tumor cells from blood samples (Fig. 4) (Tian et al. 2018). Using a high flow rate ratio between viscoelastic fluid (PEO solutions, 0.05 wt%) and whole blood, two shape flow interfaces were generated near the walls of a straight microchannel. Large tumor cells could pass through the interface due to the dominant F_i, whereas small blood cells were intercepted by the interface due to the dominant F_e. A separation efficiency of 95.1%, a recovery rate of 77.5%, and a cell viability of approximately 100% were achieved after microfluidic isolation of tumor cells (50 cells mL^{-1}) from untreated whole blood (Fig. 4a). A similar strategy based on the combined effect of F_i and F_e was also adapted to transport tumor cells from non-Newtonian fluid to Newtonian buffer with 92.8% efficiency (Ha et al. 2016; Yuan et al. 2016c, 2017).

3.2 Bacteria

Rapid isolation and identification of infectious bacteria from whole blood can significantly improve the outcome of antimicrobial treatment. Due to the similar sizes of bacteria and

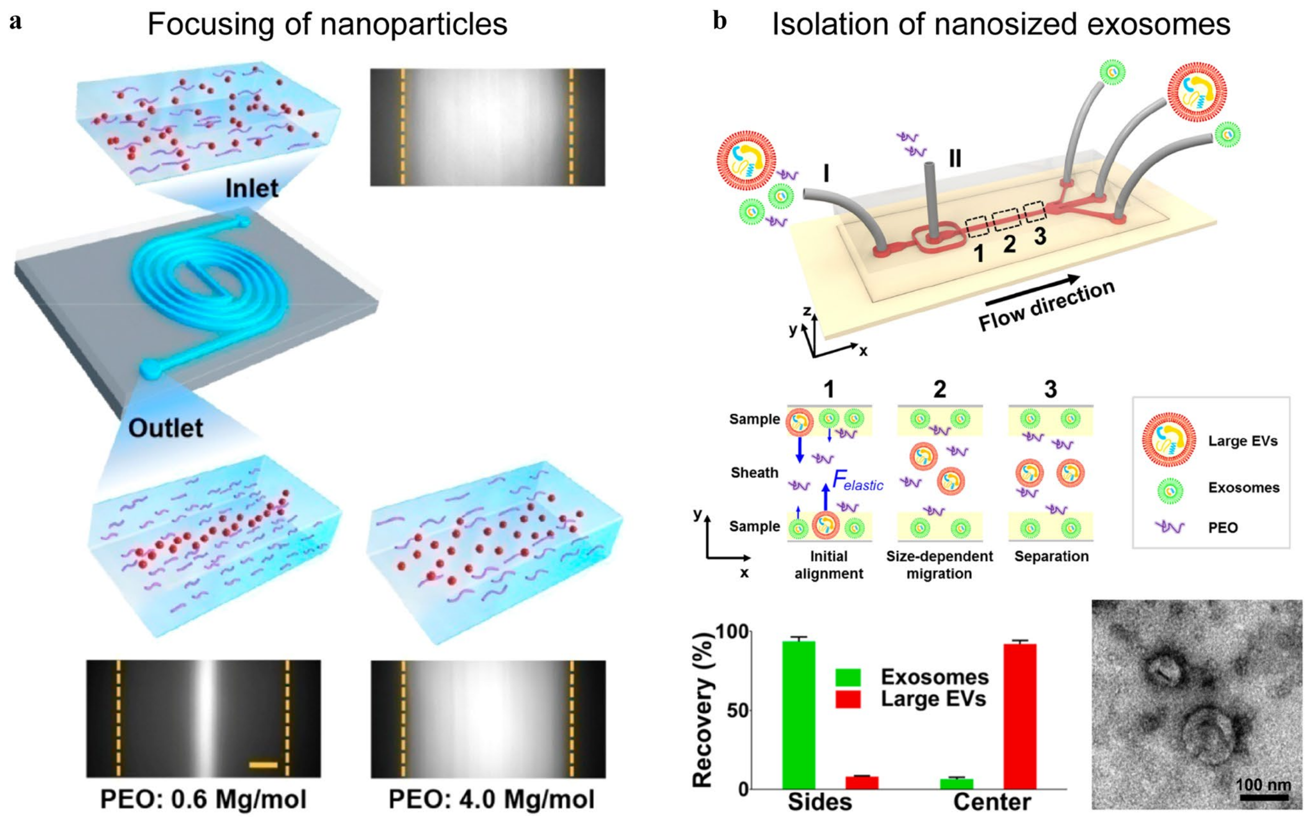

Fig. 2 Manipulation of bio-nanoparticles in viscoelastic fluids. **a** Sheathless focusing of 100 nm particles and λ-DNA molecules using the PEO solution as the carrier fluid in a spiral microfluidic device. Reproduced with permission (Liu et al. 2016a). Copyright 2016, American Chemical Society. **b** Label-free separation of exosomes and microvesicles with a viscoelastic sheath flow. Reproduced with permission (Liu et al. 2017). Copyright 2017, American Chemical Society

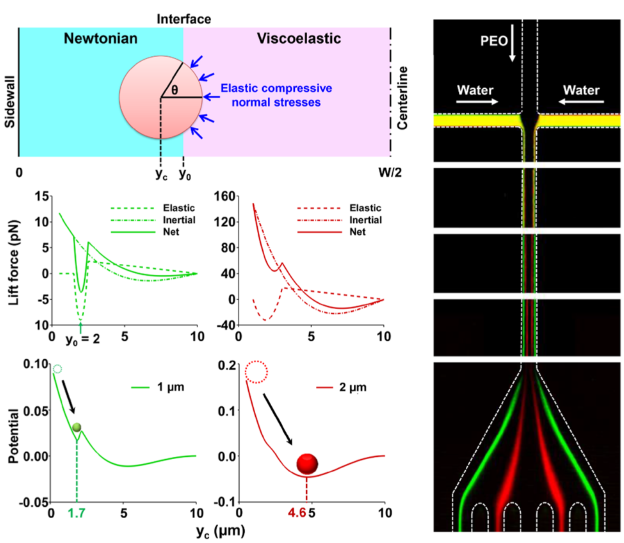

Fig. 3 Particle manipulation in microfluidic hybrid systems of non-Newtonian and Newtonian fluids. The competition between interfacial elastic lift force and inertial lift force led to lateral migration of particles across the interface in a size-dependent manner (Reproduced with permission (Tian et al. 2017). Copyright 2017, Royal Society of Chemistry)

platelets, precise manipulation methods, such as non-Newtonian hybrid microfluidics, are required for label-free separation of bacteria and platelets (Fig. 4b) (Tian et al. 2017). To generate stable flow interfaces in a straight microchannel of 20 µm wide, the sample fluid was the mixture of *Staphylococcus aureus* (1 µm) and platelets (2–3 µm) in PBS, and the sheath fluid was the viscoelastic PEO solution (0.01 wt%). The absence of elastic stresses at the Newtonian fluid (PBS) gave rise to an effective elastic lift force at the interface to compete with the inertial lift force on bioparticles, enabling size-selective separation of *Staphylococcus aureus* and platelets with 97% separation efficiency. The non-Newtonian hybrid microfluidics provided a high-resolution tool for manipulating bioparticles with size range of 1–15 µm in complex biofluids.

4 Active manipulation of bioparticles in non-Newtonian microflows

Active microfluidic methods allow for precise manipulation of bioparticles under an external electric or magnetic field, which are less dependent on channel design and flow

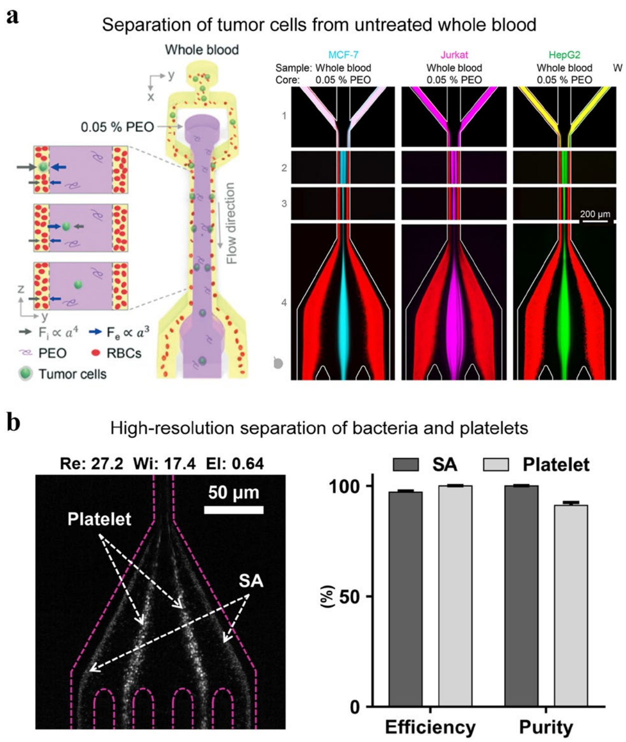

Fig. 4 The non-Newtonian hybrid microfluidics for high-resolution separation of bioparticles. **a** Isolation of rare tumor cells from untreated whole blood. Reproduced with permission (Tian et al. 2018). Copyright 2018, Royal Society of Chemistry. **b** Separation of *Staphylococcus aureus* and platelets. Reproduced with permission (Tian et al. 2017). Copyright 2017, Royal Society of Chemistry

conditions. The coupling of active manipulation with non-Newtonian microfluidics is expected to improve the performance of particle focusing and separation in microchannels (Li and Xuan 2018; Yan et al. 2017; Yuan et al. 2016a).

4.1 Electrophoresis

Electrophoresis refers to the particle motion relative to the ambient fluid induced by an electric field (Einarsson and Mehlig 2017; Ko et al. 2018). The integration of electrophoresis with viscoelastic fluids (PEO solutions) resulted in electrophoretic slip-tuned migration of microparticles in a straight microchannel (Fig. 5a) (Li and Xuan 2018). A leading (positive electrophoretic slip velocity) or lagging (negative electrophoretic slip velocity) particle in a combined pressure- and electric field-driven viscoelastic flow experienced an electrophoresis-induced extra lift force toward the microchannel sidewalls or the centreline. By tuning the direction and magnitude of a direct-current (DC) electric field, particles could be focused at the sidewalls or centreline of a straight microchannel filled with viscoelastic fluids (Li and Xuan 2018). The coupling of electrophoresis and viscoelastic focusing could be exploited for cell manipulation in a surface charge- and size-dependent manner in further studies (Abercrombie and Ambrose 1962; Chen et al. 2016).

4.2 Magnetophoresis

Magnetophoresis is the particle motion induced by a non-uniform magnetic field (Zhao et al. 2016). The hybridization of magnetophoresis and viscoelastic focusing was demonstrated for particle separation with high efficiency. In an H-shaped microchannel, magnetic particles suspended in a viscoelastic, diamagnetic solution (0.5 wt% polyacrylamide) were pre-focused along the centreline of the microchannel, followed by being deflected toward a magnet placed at the side of microchannel by positive magnetophoresis (Del Giudice et al. 2015b). The viscoelastic pre-focusing yielded a high deflection efficiency up to 96% for magnetic particles, which was much higher than that obtained without pre-focusing on a Newtonian fluid. Using a similar separation strategy, negative magnetophoresis in a ferrofluid combined with viscoelastic focusing was applied to separate non-magnetic particles (Zhang et al. 2016b). In a viscoelastic PEO solution (0.2 wt%) spiked with magnetite nanoparticles (0.11 wt%), a binary mixture of 5 μm and 13 μm particles was separated with purities up to 99.3% under an optimal flow rate of 0.9 mL h^{-1} (Fig. 5b). As ferrofluids showed good biocompatibility and remained stable in the presence of polymers, a hybrid platform combining ferrofluid-based negative magnetophoresis and viscoelastic focusing could allow for label-free cell manipulation with high efficiency and versatility.

5 Conclusions and outlook

Passive and active non-Newtonian microfluidics has been exploited for label-free, size-dependent, and continuous manipulation of a variety of bioparticles including CTCs, WBCs, RBCs, platelets, bacteria, and EVs with high efficiencies. Hybrid microfluidic systems containing both non-Newtonian and Newtonian fluids further improved the capability for handling complex biofluids and the size resolution for separation of bioparticles. The coupling of active manipulation in non-Newtonian fluids could provide new avenues for label-free bioparticle manipulation with high efficiency and versatility. However, several challenges need to be tackled to further enable bioparticle manipulation in non-Newtonian microfluidics. The biocompatibility of the additive polymers, both synthetic and biological, to living cells should be investigated rigorously. The physical properties of cells, such as shape and deformability, may affect the manipulation task, but are rarely considered in non-Newtonian microfluidics. To facilitate the cell analysis and disease diagnostics in practical clinical applications, further

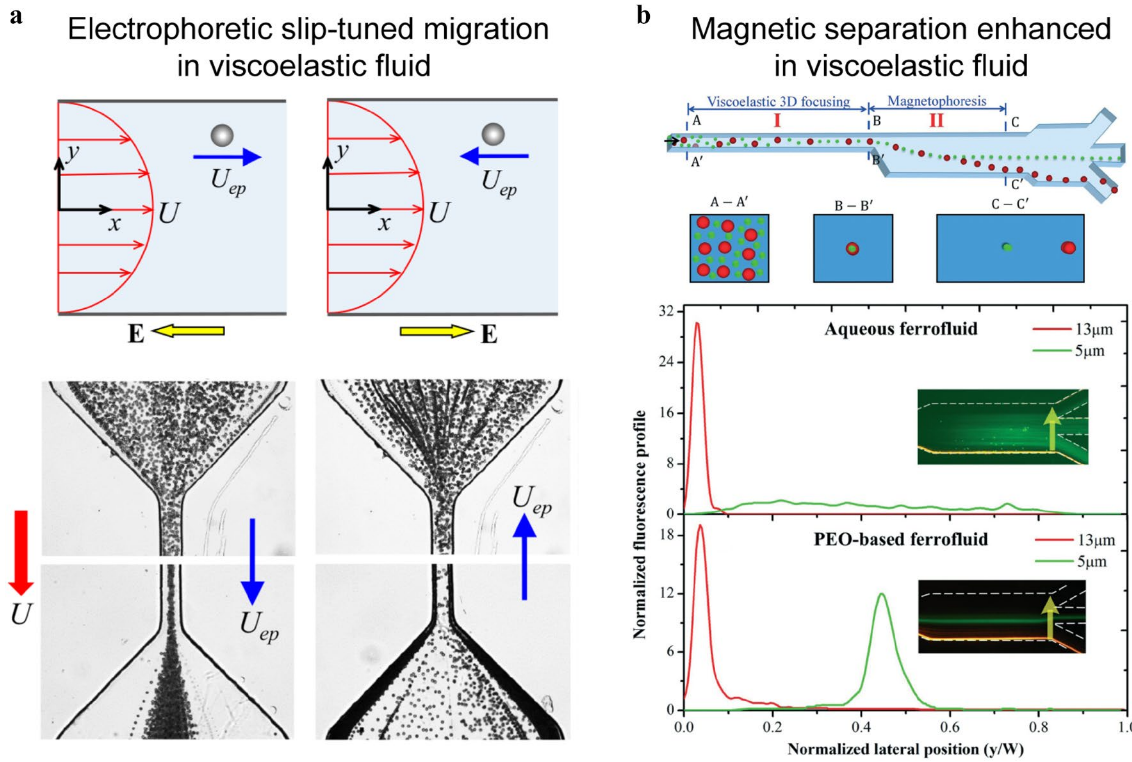

Fig. 5 Active manipulation of microparticles in non-Newtonian fluids. **a** Particle migration tuned by electrophoretic slip in a viscoelastic fluid. Reproduced with permission (Li and Xuan 2018). Copyright 2018, American Physical Society. **b** A hybrid platform combining ferrofluid-based negative magnetophoresis and viscoelastic focusing for sheathless particle separation. Reproduced with permission (Zhang et al. 2016b). Copyright 2016, Royal Society of Chemistry

technical improvements would be required to improve the throughput and to integrate bioparticle purification and downstream analysis into a single microfluidic device. We believe that non-Newtonian microfluidics may become a promising tool for manipulation of bio-micro/nanoparticles in diverse biochemical fields.

Acknowledgements This work was supported financially by NSFC (21622503), Youth Innovation Promotion Association CAS (2016035), and the open research fund of Jiangsu Key Laboratory for Design and Manufacture of Micro-Nano Biomedical Instruments, Southeast University (KF201804).

References

Abercrombie M, Ambrose EJ (1962) Surface properties of cancer cells—a review. Cancer Res 22:525–548

Ahmed MG et al (2017) Isolation, detection, and antigen-based profiling of circulating tumor cells using a size-dictated immunocapture chip. Angew Chem Int Ed 56:10681–10685

Amini H, Lee W, Di Carlo D (2014) Inertial microfluidic physics. Lab Chip 14:2739–2761

Bhagat AAS, Hou HW, Li LD, Lim CT, Han J (2011) Pinched flow coupled shear-modulated inertial microfluidics for high-throughput rare blood cell separation. Lab Chip 11:1870–1878

Campo-Deaño L, Dullens RPA, Aarts DGAL, Pinho FT, Oliveira MSN (2013) Viscoelasticity of blood and viscoelastic blood analogues for use in polydymethylsiloxane in vitro models of the circulatory system. Biomicrofluidics 7:034102

Chen B et al (2016) Targeting negative surface charges of cancer cells by multifunctional nanoprobes. Theranostics 6:1887–1898

Ciftlik AT, Ettori M, Gijs MAM (2013) High throughput-per-footprint inertial focusing. Small 9:2764–2773

Colombo M, Raposo G, Théry C (2014) Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu Rev Cell Dev Biol 30:255–289

Contreras-Naranjo JC, Wu H-J, Ugaz VM (2017) Microfluidics for exosome isolation and analysis: enabling liquid biopsy for personalized medicine. Lab Chip 17:3558–3577

D'Avino G, Romeo G, Villone MM, Greco F, Netti PA, Maffettone PL (2012) Single line particle focusing induced by viscoelasticity of the suspending liquid: theory, experiments and simulations to design a micropipe flow-focuser. Lab Chip 12:1638–1645

D'Avino G, Greco F, Maffettone PL (2017) Particle migration due to viscoelasticity of the suspending liquid and its relevance in microfluidic devices. Annu Rev Fluid Mech 49:341–360

De Santo I, D'Avino G, Romeo G, Greco F, Netti PA, Maffettone PL (2014) Microfluidic lagrangian trap for brownian particles: three-dimensional focusing down to the nanoscale. Phys Rev Applied 2:064001

Del Giudice F, D'Avino G, Greco F, De Santo I, Netti PA, Maffettone PL (2015a) Rheometry-on-a-chip: measuring the relaxation time of a viscoelastic liquid through particle migration in microchannel flows. Lab Chip 15:783–792

Del Giudice F et al (2015b) Magnetophoresis 'meets' viscoelasticity: deterministic separation of magnetic particles in a modular microfluidic device. Lab Chip 15:1912–1922

Einarsson J, Mehlig B (2017) Spherical particle sedimenting in weakly viscoelastic shear flow. Phys Rev Fluids 2:063301

Gay LJ, Felding-Habermann B (2011) Contribution of platelets to tumour metastasis. Nat Rev Cancer 11:123

Ha B, Park J, Destgeer G, Jung JH, Sung HJ (2016) Transfer of microparticles across laminar streams from non-Newtonian to Newtonian fluid. Anal Chem 88:4205–4210

Hejazian M, Li W, Nguyen N-T (2015) Lab on a chip for continuous-flow magnetic cell separation. Lab Chip 15:959–970

Ho BP, Leal LG (1976) Migration of rigid spheres in a 2-dimensional unidirectional shear-flow of a 2nd-order fluid. J Fluid Mech 76:783–799

Huang PY, Feng J, Hu HH, Joseph DD (1997) Direct simulation of the motion of solid particles in Couette and Poiseuille flows of viscoelastic fluids. J Fluid Mech 343:73–94

Kale A, Song L, Lu X, Yu L, Hu G, Xuan X (2018) Electrothermal enrichment of submicron particles in an insulator-based dielectrophoretic microdevice. Electrophoresis 39:887–896

Kang K, Lee SS, Hyun K, Lee SJ, Kim JM (2013) DNA-based highly tunable particle focuser. Nat Commun 4:2567

Karlsen JT, Qiu W, Augustsson P, Bruus H (2018) Acoustic streaming and its suppression in inhomogeneous fluids. Phys Rev Lett 120:054501

Kim JY, Ahn SW, Lee SS, Kim JM (2012) Lateral migration and focusing of colloidal particles and DNA molecules under viscoelastic Flow. Lab Chip 12:2807–2814

Ko C-H, Li D, Malekanfard A, Wang Y-N, Fu L-M, Xuan X (2018) Electroosmotic flow of non-Newtonian fluids in a constriction microchannel. Electrophoresis. https://doi.org/10.1002/elps.201800315

Lamparski HG, Metha-Damani A, Yao J-Y, Patel S, Hsu D-H, Ruegg C, Le Pecq J-B (2002) Production and characterization of clinical grade exosomes derived from dendritic cells. J Immunol Methods 270:211–226

Laurell T, Petersson F, Nilsson A (2007) Chip integrated strategies for acoustic separation and manipulation of cells and particles. Chem Soc Rev 36:492–506

Lee DJ, Brenner H, Youn JR, Song YS (2013) Multiplex particle focusing via hydrodynamic force in viscoelastic fluids. Sci Rep 3:3258

Lee K et al (2018) Multiplexed profiling of single extracellular vesicles. ACS Nano 12:494–503

Leshansky AM, Bransky A, Korin N, Dinnar U (2007) Tunable nonlinear viscoelastic "focusing" in a microfluidic device. Phys Rev Lett 98:234501

Li D, Xuan X (2018) Electrophoretic slip-tuned particle migration in microchannel viscoelastic fluid flows. Phys Rev Fluids 3:074202

Li M, Li WH, Zhang J, Alici G, Wen W (2014) A review of microfabrication techniques and dielectrophoretic microdevices for particle manipulation and separation. J Phys D Appl Phys 47:063001

Li D, Lu X, Xuan X (2016) Viscoelastic separation of particles by size in straight rectangular microchannels: a parametric study for a refined understanding. Anal Chem 88:12303–12309

Li D, Zielinski J, Kozubowski L, Xuan X (2018) Continuous sheath-free separation of drug-treated human fungal pathogen *Cryptococcus neoformans* by morphology in biocompatible polymer solutions. Electrophoresis 39:2362–2369

Lim EJ et al (2014) Inertio-elastic focusing of bioparticles in microchannels at high throughput. Nat Commun 5:4120

Liu C, Hu G, Jiang X, Sun J (2015a) Inertial focusing of spherical particles in rectangular microchannels over a wide range of Reynolds numbers. Lab Chip 15:1168–1177

Liu C, Xue C, Chen X, Shan L, Tian Y, Hu G (2015b) Size-based separation of particles and cells utilizing viscoelastic effects in straight microchannels. Anal Chem 87:6041–6048

Liu C, Ding B, Xue C, Tian Y, Hu G, Sun J (2016a) Sheathless focusing and separation of diverse nanoparticles in viscoelastic solutions with minimized shear thinning. Anal Chem 88:12547–12553

Liu C, Xue C, Sun J, Hu G (2016b) A generalized formula for inertial lift on a sphere in microchannels. Lab Chip 16:884–892

Liu C et al (2017) Field-free isolation of exosomes from extracellular vesicles by microfluidic viscoelastic flows. ACS Nano 11:6968–6976

Liu C, Feng Q, Sun J (2019a) Lipid nanovesicles by microfluidics: manipulation, synthesis, and drug delivery. Adv Mater. https://doi.org/10.1002/adma.201804788

Liu C et al (2019b) Low-cost thermophoretic profiling of extracellular vesicle surface proteins for the early detection and classification of cancers. Nat Biomed Eng 3:183–193

Lu X, Xuan X (2015) Inertia-enhanced pinched flow fractionation. Anal Chem 87:4560–4565

Lu X, Zhu L, R-m Hua, Xuan X (2015) Continuous sheath-free separation of particles by shape in viscoelastic fluids. Appl Phys Lett 107:264102

Lu X, Liu C, Hu G, Xuan X (2017) Particle manipulations in non-Newtonian microfluidics: a review. J Colloid Interface Sci 500:182–201

Nam J, Lim H, Kim D, Jung H, Shin S (2012) Continuous separation of microparticles in a microfluidic channel via the elasto-inertial effect of non-Newtonian fluid. Lab Chip 12:1347–1354

Nam J, Namgung B, Lim CT, Bae J-E, Leo HL, Cho KS, Kim S (2015) Microfluidic device for sheathless particle focusing and separation using a viscoelastic fluid. J Chromatogr A 1406:244–250

Nam J, Shin Y, Tan JKS, Lim YB, Lim CT, Kim S (2016) High-throughput malaria parasite separation using a viscoelastic fluid for ultrasensitive PCR detection. Lab Chip 16:2086–2092

Peinado H et al (2012) Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nat Med 18:883–891

Plaks V, Koopman CD, Werb Z (2013) Circulating tumor cells. Science 341:1186–1188

Poudineh M, Sargent EH, Pantel K, Kelley SO (2018) Profiling circulating tumour cells and other biomarkers of invasive cancers. Nat Biomed Eng 2:72–84

Shao H, Im H, Castro CM, Breakefield X, Weissleder R, Lee H (2018) New technologies for analysis of extracellular vesicles. Chem Rev 118:1917–1950

Shurtleff MJ, Temoche-Diaz MM, Schekman R (2018) Extracellular vesicles and cancer: caveat lector. Annu Rev Cancer Biol 2:395–411

Stickel JJ, Powell RL (2005) Fluid mechanics and rheology of dense suspensions. Annu Rev Fluid Mech 37:129–149

Sun J et al (2018) Control over the emerging chirality in supramolecular gels and solutions by chiral micro vortices in milliseconds. Nat Commun 9:2599

Tan SJ, Yobas L, Lee GYH, Ong CN, Lim CT (2009) Microdevice for the isolation and enumeration of cancer cells from blood. Biomed Microdevices 11:883–892

Tan JKS, Park S, Leo HL, Kim S (2017) Continuous separation of white blood cells from whole blood using viscoelastic effects. IEEE Trans Biomed Circuits Syst 11:1431–1437

Tang W, Tang D, Ni Z, Xiang N, Yi H (2017) Microfluidic impedance cytometer with inertial focusing and liquid electrodes for high-throughput cell counting and discrimination. Anal Chem 89:3154–3161

Thery C, Zitvogel L, Amigorena S (2002) Exosomes: composition, biogenesis and function. Nat Rev Immunol 2:569–579

Tian F et al (2017) Microfluidic co-flow of Newtonian and viscoelastic fluids for high-resolution separation of microparticles. Lab Chip 17:3078–3085
Tian F, Cai L, Chang J, Li S, Liu C, Li T, Sun J (2018) Label-free isolation of rare tumor cells from untreated whole blood by interfacial viscoelastic microfluidics. Lab Chip 18:3436–3445
van Niel G, D'Angelo G, Raposo G (2018) Shedding light on the cell biology of extracellular vesicles. Nat Rev Mol Cell Biol 19:213–228
Wang J et al (2015) Label-free isolation and mrna detection of circulating tumor cells from patients with metastatic lung cancer for disease diagnosis and monitoring therapeutic efficacy. Anal Chem 87:11893–11900
Witwer KW et al (2013) Standardization of sample collection, isolation and analysis methods in extracellular vesicle research. J Extracell Vesicles 2:20360
Wu M et al (2017) Isolation of exosomes from whole blood by integrating acoustics and microfluidics. Proc Natl Acad Sci USA 114:10584–10589
Wunsch BH et al (2016) Nanoscale lateral displacement arrays for the separation of exosomes and colloids down to 20 nm. Nat Nanotechnol 11:936–940
Xiang N, Chen K, Dai Q, Jiang D, Sun D, Ni Z (2014) Inertia-induced focusing dynamics of microparticles throughout a curved microfluidic channel. Microfluid Nanofluid 18:29–39
Xiang N, Zhang X, Dai Q, Cheng J, Chen K, Ni Z (2016) Fundamentals of elasto-inertial particle focusing in curved microfluidic channels. Lab Chip 16:2626–2635
Xiang N, Ni Z, Yi H (2018) Concentration-controlled particle focusing in spiral elasto-inertial microfluidic devices. Electrophoresis 39:417–424
Xue P, Wu Y, Guo J, Kang Y (2015) Highly efficient capture and harvest of circulating tumor cells on a microfluidic chip integrated with herringbone and micropost arrays. Biomed Microdevices 17:39
Yan S et al (2015) A hybrid dielectrophoretic and hydrophoretic microchip for particle sorting using integrated prefocusing and sorting steps. Electrophoresis 36:284–291
Yan S, Zhang J, Yuan D, Li W (2017) Hybrid microfluidics combined with active and passive approaches for continuous cell separation. Electrophoresis 38:238–249
Yang S, Kim JY, Lee SJ, Lee SS, Kim JM (2011) Sheathless elasto-inertial particle focusing and continuous separation in a straight rectangular microchannel. Lab Chip 11:266–273
Yang S et al (2012) Deformability-selective particle entrainment and separation in a rectangular microchannel using medium viscoelasticity. Soft Matter 8:5011–5019
Yuan D, Pan C, Zhang J, Yan S, Zhao Q, Alici G, Li W (2016a) Tunable particle focusing in a straight channel with symmetric semicircle obstacle arrays using electrophoresis-modified inertial effects. Micromachines 7:195
Yuan D, Zhang J, Sluyter R, Zhao Q, Yan S, Alici G, Li W (2016b) Continuous plasma extraction under viscoelastic fluid in a straight channel with asymmetrical expansion-contraction cavity arrays. Lab Chip 16:3919–3928
Yuan D et al (2016c) Investigation of particle lateral migration in sample-sheath flow of viscoelastic fluid and Newtonian fluid. Electrophoresis 37:2147–2155
Yuan D et al (2017) On-chip microparticle and cell washing using co-flow of viscoelastic fluid and Newtonian fluid. Anal Chem 89:9574–9582
Yuan D, Zhao Q, Yan S, Tang S-Y, Alici G, Zhang J, Li W (2018) Recent progress of particle migration in viscoelastic fluids. Lab Chip 18:551–567
Zhang J, Yan S, Sluyter R, Li W, Alici G, Nguyen N-T (2014) Inertial particle separation by differential equilibrium positions in a symmetrical serpentine micro-channel. Sci Rep 4:4527
Zhang J, Yan S, Yuan D, Alici G, Nguyen N-T, Ebrahimi Warkiani M, Li W (2016a) Fundamentals and applications of inertial microfluidics: a review. Lab Chip 16:10–34
Zhang J, Yan S, Yuan D, Zhao Q, Tan SH, Nguyen N-T, Li W (2016b) A novel viscoelastic-based ferrofluid for continuous sheathless microfluidic separation of nonmagnetic microparticles. Lab Chip 16:3947–3956
Zhang J et al (2018a) Tunable particle separation in a hybrid dielectrophoresis (DEP)-inertial microfluidic device. Sens Actuators B Chem 267:14–25
Zhang L, Xu Z, Kang Y, Xue P (2018b) Three-dimensional microfluidic chip with twin-layer herringbone structure for high efficient tumor cell capture and release via antibody-conjugated magnetic microbeads. Electrophoresis 39:1452–1459
Zhao W, Cheng R, Miller JR, Mao L (2016) Label-free microfluidic manipulation of particles and cells in magnetic liquids. Adv Funct Mater 26:3916–3932
Zhu Z, Yang CJ (2017) hydrogel droplet microfluidics for high-throughput single molecule/cell analysis. Accounts Chem Res 50:22–31