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Automation and flow control for particle manipulation

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In recent years, several new methods have been developed to precisely manipulate small particles using optical, electric, acoustic, magnetic, or fluidic fields. Automated fluidic trapping has emerged as a particularly powerful method to control colloidal particles, cells, or single polymers using only fluid flow. Here, we discuss recent advances in the automation of particle manipulation, focusing on flow-based and electric field-based methods. Broadly, automated flow control enables the precise manipulation of multiple freely suspended particles using gentle flow, thereby enabling new directions in chemical and biological systems.

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Introduction

Recent advances in automation have enabled the development of several new methods for manipulating small particles in solution. In general, particle trapping methods rely on an external force field (optical, magnetic, electric, acoustic, fluidic) to control particle position or suppress the thermal fluctuations of small Brownian particles [1–4,5••]. Single-beam optical traps (known as laser tweezers) [1] can stably confine particles without active feedback control due to the nature of the gradient restoring force [1,6]. On the other hand, most trapping methods rely on active feedback control to suppress thermal motion and control particle position in solution [5••]. Broadly speaking, particle trapping methods have enabled transformative studies across science and engineering, with a handful of examples including measurement of RNA hairpin folding energy in strongly non-equilibrium regimes [7], direct observation of single molecule polymer dynamics [8], directed assembly of colloidal particles into two-dimensional (2D) crystals [9], conformational dynamics of single proteins such as G protein-coupled receptors [10•], and detailed studies of vesicle dynamics in defined flows [11•,12].

Despite the popularity of optical traps and magnetic tweezers, these methods are generally limited to trapping particles with specific material properties (e.g. index of refraction, magnetic susceptibility). In particular, optical traps may not be suitable for long-time trapping of biological specimens due to local heating or photo-induced damage [13]. In contrast, methods such as electrokinetic traps [14•,15] and hydrodynamic traps [15,5••] confine particles in solution without restrictions on the intrinsic material properties of trapped particles. Moreover, electric field and flow-based traps generally rely on model predictive or model-free controllers [16] to manipulate particles using active feedback control. Electrokinetic traps manipulate particles using a combination of electrophoretic forces and electro-osmotic flows [4,17,18••] and have been used for numerous studies in single-molecule biophysics and nanoscience. However, electric field-based methods generally require the use of strong electric fields and field gradients that can perturb trapped chemical or biological samples.

In recent years, automated flow control has emerged as a simple, potent, and non-perturbative method for trapping particles in free solution [5••,15]. The Stokes trap allows for the simultaneous manipulation of Brownian particles using only fluid flow [5••]. In this article, we provide an overview of recent advances in particle trapping methods relying on automation and feedback control, focusing on flow-based traps and electrokinetic traps. We discuss the strengths, limitations, and practical considerations of these methods while considering applications to several chemical and biological systems, with a major focus on flow-based trapping. Overall, automated flow control holds strong potential to enable new fundamental studies in science and engineering.

Feedback control using fluid flow

Hydrodynamic trapping enables particle confinement using active feedback to control the location of one or more stagnation points (zero-velocity positions) in a two-dimensional flow field [20,21]. Owing to the gentle nature of viscous-dominated flow, hydrodynamic trapping presents a non-perturbative method to confine particles without the need for optical or electric fields. Moreover, flow-based traps manipulate particles using hydrodynamic friction, which avoids restrictions on intrinsic material properties such as surface charge, polarizability, index of refraction, or magnetic susceptibility. Given these advantages, flow-based trapping holds strong promise for a wide range of applications in engineering, materials science, and biotechnology.

Single particle hydrodynamic trap

In 2010, Schroeder and coworkers developed an automated hydrodynamic trap for manipulating a single particle in solution using the sole action of fluid flow [15,22–24]. The first-generation hydrodynamic trap setup consisted of a double-layer PDMS-based microfluidic device mounted on the stage of an inverted microscope and an electronic pressure regulator for actuating an on-chip dynamic valve to control the stagnation point position. The two-layer microfluidic device contains a fluidic layer for delivering sample and buffer streams into the trapping region, in addition to a control layer for manipulating flow rate (and stagnation point position) in the fluidic layer using the on-chip valve. Using this approach, Tanyeri *et al.* [15] demonstrated the fine degree to which small particles can be manipulated using fluid flow by confining a 500 nm diameter particle in water with a positional accuracy of 180 nm during confinement. The trapping stiffness of flow-based manipulation was shown to scale linearly with particle radius and viscosity of the suspending buffer, which provides a facile approach for tuning trap performance. In subsequent work, pneumatic valves were used to drive flow in all channels of a 4-arm device, allowing for full two-dimensional control over particle position by enabling arbitrary assignment of the compressional and extensional axes in a planar extensional flow generated in a cross-slot device [23]. However, the first-generation device was limited to controlling the center-of-mass position of only a single particle, and method was generally not capable of manipulating particle position in the absence of a net imposed flow.

Stokes trap: multiplexed particle manipulation

Recently, Schroeder and coworkers multiplexed the fluidic trapping method to enable simultaneous manipulation of multiple small particles in free solution [5••]. In this way, the Stokes trap can be used to precisely control the center-of-mass position, orientation, and trajectories of multiple particles using a model predictive control scheme [25••,19•]. Four-channel and six-channel microfluidic devices are used for controlling one and two particles, respectively, as shown in Figure 1a–d. A six-channel device permits zero, one, or two stagnation points as shown in Figure 1e–g, thereby enabling simultaneous manipulation of two particles to draw the letter 'I' (see Figure 1c). The Stokes trap also enables the directed assembly of two sticky particles in a highly precise and controlled manner using only flow [5••]. Interestingly, Shenoy *et al.* [19•] have recently shown that optimal control of two particles in a six-channel device relies on flow patterns with zero or one stagnation points (Figure 1h–j), as opposed to positioning two particles using two distinct stagnation points. Broadly speaking, these advances highlighted the use of model predictive control which offers several advantages for particle manipulation, including: (1) improved trap performance, yielding a 10× higher trapping stiffness compared to the first-generation hydrodynamic trap under similar experimental conditions, (2) ease of scalability to trap and control multiple particles by simply changing the objective function of the nonlinear optimization problem, and (3) robust control over Brownian particles by canceling thermal motion using flow-based corrections to deviations in system behavior from model predictions.

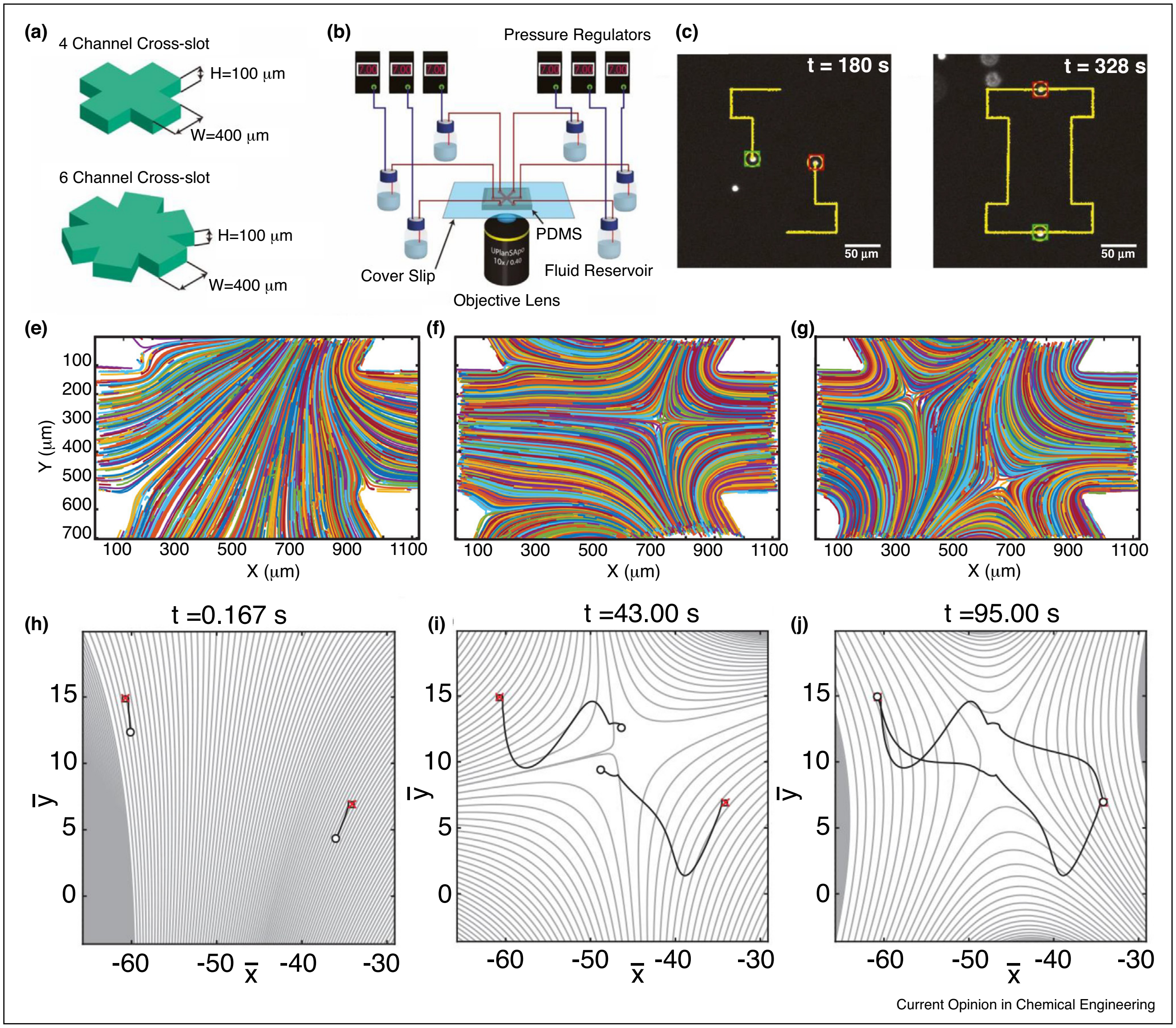
Orientation and trajectory control

Recently, the Stokes trap was used to demonstrate simultaneous flow-based control of the orientation and center-of-mass of an anisotropic Brownian particle [25••], as shown in Figure 2a–c. Further advances in automation using model predictive control have also been used to precisely manipulate the trajectories of small particles (e.g. velocity and position) [25••]. In prior versions of the trap, particle manipulation along a path was achieved by stepping set-points at a constant rate along a reference trajectory. However, this approach is generally slow and prone to large errors between a particle's position and the set-point, which arises due to a lack of control of the path taken by the particle between the current position and the target position. Kumar *et al.* [25••] overcame these challenges by developing a new model predictive control scheme that coordinates the set-point motion with particle movement. In this way, colloidal particles can be moved along parametric curves with speeds 20× faster compared to prior control schemes, as shown in Figure 2d–g.

Stokes trap for studying soft material dynamics

The Stokes trap provides an ideal platform for studying single polymer dynamics in controlled flow fields [8]. In recent work, Zhou *et al.* directly observed the transient and long-time unsteady dynamics of single DNA molecules in large amplitude oscillatory extensional (LAOE) flow [26,27]. In addition, the Stokes trap was used to characterize the non-equilibrium stretching dynamics of single comb polymers in extensional flow [28•]. Aside from single polymer dynamics, the Stokes trap allows for detailed studies of the linear and non-linear rheology of complex fluids. As one example, the Stokes trap was used in a tour de force non-linear microrheology experiment to determine the extensional viscosity of a polymeric solution [29•]. Recently, the Stokes trap was used to study the dynamics of soft deformable particles, with a particular

Figure 1



Overview of the Stokes trap for multiplexed particle manipulation using flow control. **(a)** Schematics of the four-channel and six-channel microfluidic devices for manipulating one and two particles. Reproduced with permission from [5••]. **(b)** Schematic of the experimental setup with six pressure regulators connected to fluid reservoirs, which are further connected to the microfluidic device on the stage of an inverted microscope. Reproduced with permission from [5••]. **(c,d)** Manipulation of two particles using Stokes trap along the letter 'I' with yellow lines showing the past history of both particles. Reproduced with permission from [5••]. **(e,f,g)** Flow topologies during manipulation of two particles using the Stokes trap determined by particle imaging velocimetry. Three primary flow topologies are determined in a 6-channel cross-slot device exhibiting zero, one, and two stagnation points. Reproduced with permission from [19•]. **(h,i,j)** Streamlines from numerical simulations for the case of interchanging the positions of two particles in a Stokes trap, which is accomplished using flows with only zero or one stagnation point. Reproduced with permission from [19•].

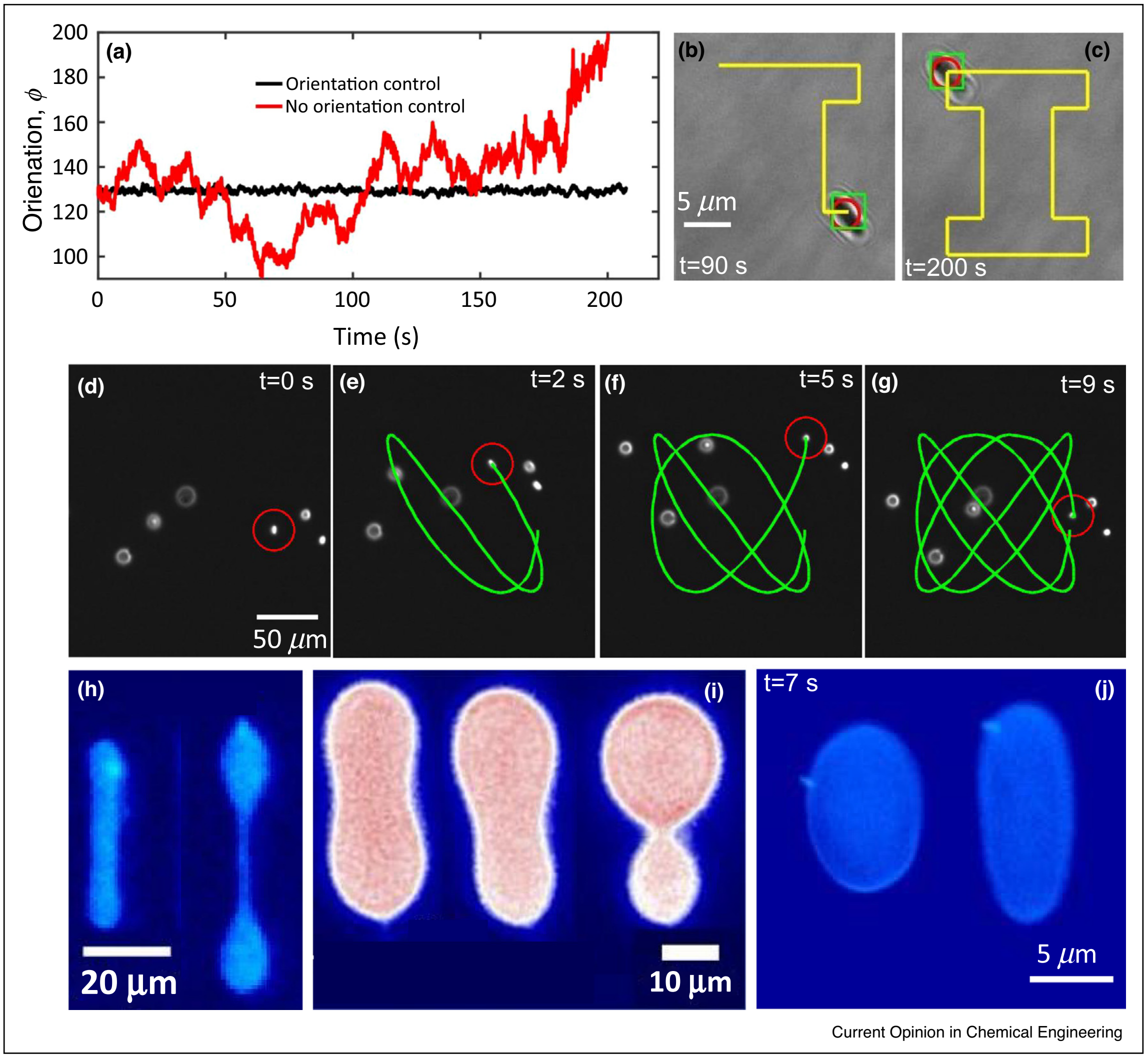
focus on the phase behavior and non-equilibrium conformational dynamics of giant lipid vesicles in extensional flow (see Figure 2h–j).

Feedback control using electric fields

Manipulation of individual particles

In recent years, electrokinetic traps have been used to confine and manipulate single nanoparticles [4,30,14•], fluorescently labeled protein molecules [17], and single fluorophores in solution [18••]. In one approach, the anti-Brownian electrokinetic (ABEL) trap uses 4 electrodes placed at the corners of a diamond shape inside a microfluidic device (Figure 3a,b) that is mounted on the stage of an inverted fluorescence microscope [4]. The electrodes generate electrokinetic forces that push aparticle to a desired target position in 2D, thus cancelling out thermal

Figure 2

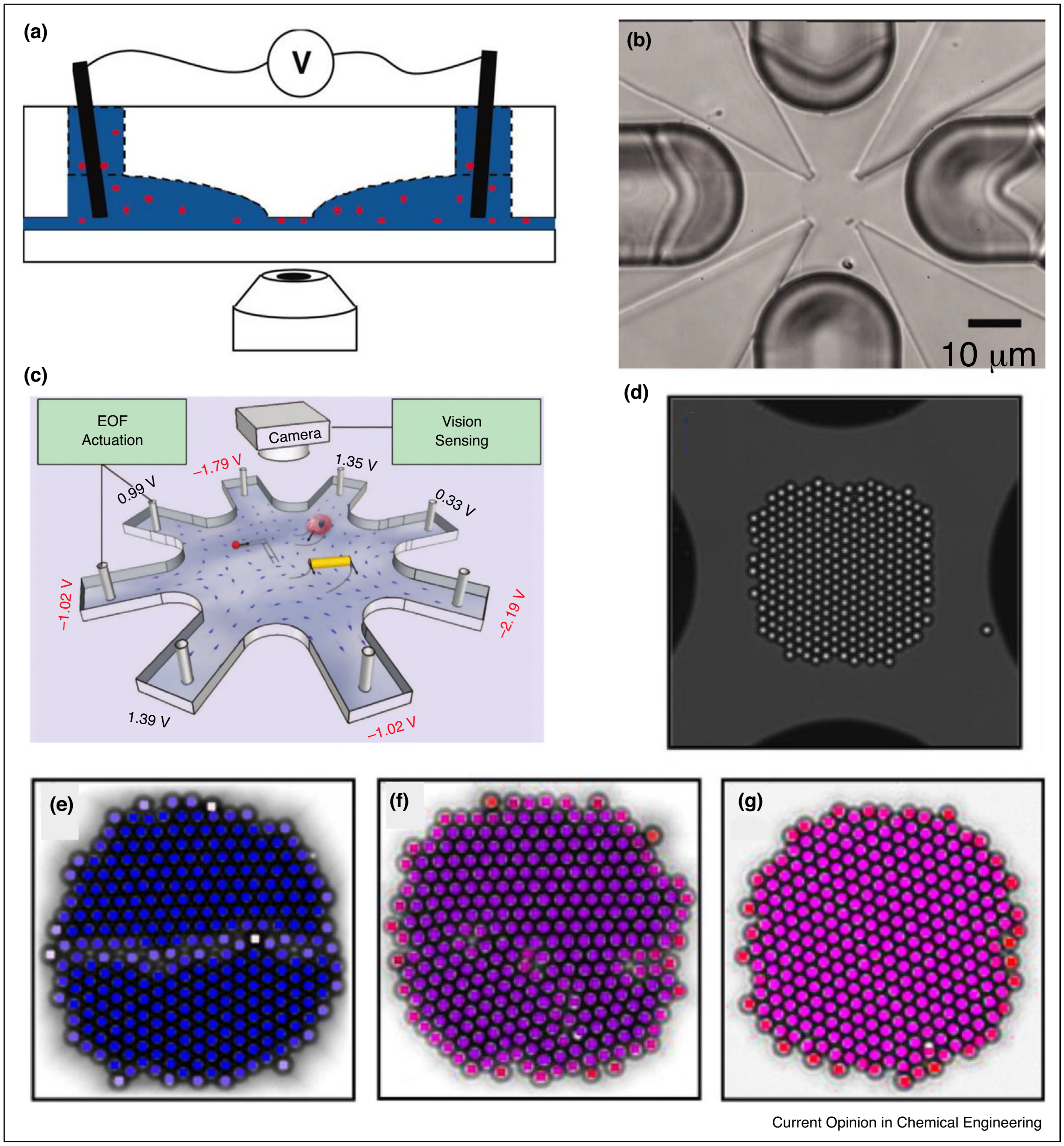


Stokes trap allows for orientation and trajectory control of microscopic particles. **(a)** Comparison between active control and no control over rod orientation angle as a function of time during manipulation of rod along the 'I' trajectory. Reproduced with permission from [25••]. **(b,c)** Snapshots showing simultaneous 2D center-of-mass and orientation control of a rod-like particle using a Stokes trap. The position of a rod-like particle was controlled to trace the letter 'I' while maintaining a constant orientation angle throughout the path. Reproduced with permission from [25••]. **(d,e,f, g)** Trajectory control for manipulating a Brownian particle (2.2 µm diameter bead) over a complex parametric curve. The positional history of the particle is shown with the green line. The particle closely follows a complex parametric path and traverses a distance of several hundred microns in only ≈9 s. Reproduced with permission from [25••]. (h) Snapshots of a tubular lipid vesicle undergoing a shape transition to a symmetric dumbbell in an extensional flow using a Stokes trap. Reproduced from [11•]. (i) Snapshots of a spheroidal lipid vesicle undergoing a shape transition to an asymmetric dumbbell in an extensional flow using a Stokes trap. Reproduced from [11•]. (j) Snapshots of a quasi-spherical vesicle with a stable ellipsoid shape in a planar extensional flow using a Stokes trap. Reproduced from [11•].

motion. Hydrodynamic and electrokinetic forces are particularly suited for trapping nanoscale particles because they scale with particle size, rather than with particle volume for dielectrophoretic, magnetic, or optical trapping methods.

In some cases, the ABEL trap is used together with a charge-coupled device (CCD) camera to image fluorescently labeled particles. A simple, centroid-based image processing scheme determined particle position for tracking movements. However, the camera-based method was limited by a feedback bandwidth of ≈4 ms due to electronics and was only used to trap particles larger than 20 nm in size. The distance between a particle and the target position is affected by both the finite restoring force of the electrokinetic trap and the response

Figure 3



Schematics of electric field-based traps using feedback control. **(a)** Side view of the anti-Brownian electrokinetic (ABEL) trap setup showing only two of the four electrodes with the microfluidic cell that sits above the objective lens in an inverted fluorescence microscope. Reproduced with permission from [30]. Copyright (2007) National Academy of Sciences, U.S.A. **(b)** Top view of the microfluidic cell in an ABEL trap setup showing the trapping region. Reproduced with permission from [30]. Copyright (2007) National Academy of Sciences, U.S.A. **(c)** Schematic of an 8-electrode microfluidic cell showing the electroosmotic flow actuation, particle vision acquisiton, and camera for simultaneous trapping a quantum dot (small red dot), a cell (pink sphere), and a wire (yellow rod). Adapted from [3]. **(d)** Optical microscopy image of colloidal particle assembly in a quadrupolar microfluidic device. The diameter of each colloidal particle is 2.8 μm which provides an internal scale bar. Reproduced with permission from [36••]. **(e)** Representative microstructure of a crystal assembly with large grain boundary. The size of 2.8 μm for each colloidal provides an internal scale bar. Reproduced with permission from [36••]. **(f)** Representative microstructure of a crystal assembly with small grain boundary. Reproduced with permission from [36••]. **(g)** Representative microstructure of a crystal assembly with no grain boundaries, that is, a perfect crystal. Reproduced with permission from [36••].

time of the feedback loop, which is in turn limited by image acquisition, data transfer, determining centroid position, calculating an updated voltage for the electrodes, and implementation for actuation. Trap stiffness was improved by switching to an all-hardware method [18••,31] that reduced the feedback time by estimating particle position for each photon detection event. The hardware version of the ABEL trap uses a 2D laser scan pattern with a single photon detector, such that particle position can be estimated by the location of the laser at the instant of photon arrival. Using this method, Moerner and coworkers have performed multiple single molecule biophysical studies on ABEL-trapped photosynthetic antenna and light harvesting proteins [32,33].

Shapiro and coworkers have demonstrated 2D position control [14•], orientation control [34], and nanoassembly [35] of particles using electrokinetic forces. Here, particles are moved using a combination of electrokinetic and electrophoretic flow generated by the application of voltages to electrodes. A simple model based on Navier–Stokes and Maxwell's equations relates the velocity of particles in the microfluidic cell to the applied voltages (Figure 3c). Correction voltages are calculated using feedback linearization to handle errors between a particle's actual position and the desired position. Mathai *et al.* demonstrated control of angular orientation of a single nanowire with a precision of 5.4° [34]. This method can be scaled to precisely steer multiple particles simultaneously by adding more channels in the microfluidic cell, as shown in Figure 3c. However, it is generally not possible to bring two particles within close proximity or intimate contact using this method, as it requires application of extremely large voltages. From this view, using electrokinetic traps for the directed assembly of small building blocks into larger objects of complex or defined shapes is difficult due to challenges associated with electrode voltages for particles upon close approach.

Shapiro and coworkers have also used electrokinetic traps for 3D tweezing and manipulation of particles in three dimensions [37••]. Here, microfluidic device consists of a 5-layer microfluidic device consisting of a channel for each pair of electrodes in the 8 electrode device [38]. A defocusing mask was required to determine the z-offset of particle with respect to the focal plane of the microscope, and then appropriate voltages are applied to precisely control the z-coordinate of the particle using a proportional control algorithm. Overall, this approach is well suited for precisely manipulating the coordinates of a few individual particles, but controlling the positions of large number of particles is challenging.

Directed self-assembly using dielectrophoresis

Bevan, Grover, and coworkers have recently demonstrated the assembly of a large number of micron-sized particles ($\sim$200 μm) into 2D colloidal crystals using negative dielectrophoresis [39,40,9,36••]. The experimental setup consists of a quadrupolar electrode (Figure 3d) with opposing electrodes actuated by the same signal. Under a large amplitude alternating current (AC) electric field, colloidal particles become polarized and move towards the potential energy minima located near the center of the quadrupole. Interestingly, by using feedback control, it is possible to guide the colloidal assembly process by modulating the amplitude of voltages to achieve defect-free crystals. The dimensionality of system is high (>300 particles), so the ensemble state of the system is can be described in terms of order parameters such as the average number of hexagonally close packed neighboring particles, the average radius of gyration, and global bond orientation order [36••]. Markov state models are used to relate the applied voltages to the order parameters, and a control strategy is designed to push the system towards crystal formation [36••]. Moreover, an objective function can be defined that associates a 'reward' with each step of the process and is chosen to ensure a high degree of global crystallinity. Finally, using the Markov Decision Process (MDP) framework with dynamic programming, the policy (sequence of input voltages) maximizing the reward function is calculated, which yields an optimal policy lookup table that specifies the input voltage to be applied for a given position in the order-parameter space. Overall, this approach has been successfully used for controlling a large number of colloids [40] and building defect-free crystals (Figure 3e–g), by appropriately disassembling and reassembling crystals with grain boundaries [41], at rates faster than a slow ramp in the voltage. Dielectrophoresis has also been used for controlling density and assembling defect-free lines of colloidal particles [42].

Future outlook and conclusion

In recent years, automation has ushered in new and powerful methods for control over microscale to nanoscale particles. Scientists and engineers have leveraged tools from nonlinear control theory to design feedback controllers for manipulating the center-of-mass position, orientation, and trajectories of particles in a systematic fashion using electric fields and hydrodynamic flow. This article focuses specifically on recent progress in flow control and electrokinetic trapping, both of which provide a convenient and effective methods for confining particles in free solution.

Fluidic trapping is a remarkably versatile method for manipulating single and multiple particles in free solution, enabling direct observation of the conformational dynamics of soft materials and biomolecules in solution. Recently, hydrodynamic trapping has facilitated numerous studies in the field of single polymer dynamics, including both linear and ring DNA in dilute and semi-dilute solutions [8]. Broadly, these advances have revealed unexpected behavior in dynamic heterogeneity, molecular individualism, and conformational fluctuations in governing polymer dynamics at the molecular scale [8]. The Stokes trap is further enabling new studies in soft and deformable materials, including the recent observation of non-equilibrium conformational dynamics of lipid vesicles in extensional flow [11•,12].

Despite recent applications of fluidic trapping, the majority of prior work has focused on trapping micron-sized colloidal particles, sub-micron sized DNA molecules, or giant lipid vesicles (1–30+ μm). In future work, the Stokes trap method can be extended to trap nanoscale particles (2-100 nm) and single protein molecules by increasing the rate of flow control and image acquisition. Indeed, such advances will lead to fundamental studies of small biomolecules in their native environments, such as fluorescence resonance energy transfer (FRET) experiments on proteins in free solution without the need for surface tethering, which can perturb the conformational dynamics of single biomolecules. Non-perturbative trapping of nanoscale particles and single molecules is an active research topic in the field and holds strong promise to deliver ground-breaking results in the future. Moreover, fluidic trapping can also be extended to three dimensions. The current version of the Stokes trap achieves particle confinement only in a 2D plane, however, full 3D particle trapping may be implemented either by confining the flow in shallow channels or by using a 3D uniaxial extensional flow. Additional areas of interest include the manipulation of particles suspended in non-Newtonian fluids using reinforcement learning, which would greatly improve our fundamental understanding of the dynamics and rheology of vesicles, cells, polymers, and colloidal particles with bespoke shapes immersed in complex fluids.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Ashkin A, Dziedzic JM, Yamane T: **Optical trapping and manipulation of single cells using infrared laser beams**. *Nature* 1987, **330**:769.

2. Gosse C, Croquette V: **Magnetic tweezers: micromanipulation and force measurement at the molecular level**. *Biophys J* 2002, **82**:3314-3329.

3. Probst R, Cummins Z, Ropp C, Waks E, Shapiro B: **Flow control of small objects on chip: manipulating live cells, quantum dots, and nanowires**. *IEEE Control Syst Mag* 2012, **32**:26-53.

4. Cohen AE, Moerner W: **Method for trapping and manipulating nanoscale objects in solution**. *Appl Phys Lett* 2005, **86**:93109.

5. •• Shenoy A, Rao CV, Schroeder CM: **Stokes trap for multiplexed particle manipulation and assembly using fluidics**. *Proc Natl Acad Sci U S A* 2016, **113**:3976-3981

This paper reports a new method for confining, manipulating, and assembling multiple particles in free solution using only fluid flow.

6. Neuman KC, Block SM: **Optical trapping**. *Rev Sci Instrum* 2004, **75**:2787-2809.

7. Collin D, Ritort F, Jarzynski C, Smith SB, Tinoco I, Bustamante C: **Verification of the crooks fluctuation theorem and recovery of RNA folding free energies**. *Nature* 2005, **437**:231-234.

8. Schroeder CM: **Single polymer dynamics for molecular rheology**. *J Rheol* 2018, **62**:371-403.

9. Bevan MA, Ford DM, Grover MA, Shapiro B, Maroudas D, Yang Y, Thyagarajan R, Tang X, Sehgal RM: **Controlling assembly of colloidal particles into structured objects: basic strategy and a case study**. *J Process Control* 2015, **27**:64-75.

10. • Bockenhauer S, Furstenberg A, Yao XJ, Kobilka BK, Moerner W: **Conformational dynamics of single g protein-coupled receptors in solution**. *J Phys Chem B* 2011, **115**:13328-13338

Using the Anti-Brownian Electrokinetic trap, this paper traps and directly observes the conformational dynamics of a single fluorescently labeled beta(2)AR for several seconds.

11. • Kumar D, Richter CM, Schroeder CM: **Conformational dynamics and phase behavior of lipid vesicles in a precisely controlled extensional flow**. *Soft Matter* 2020, **16**:337-347

This paper demonstrates shape transitions and phase behavior of lipid vesicles in a planar elongational flow.

12. Kumar D, Richter CM, Schroeder CM: **Double-mode relaxation of highly deformed vesicles.** *arXiv preprint arXiv:2003.02063* 2020.

13. Neuman KC, Chadd EH, Liou GF, Bergman K, Block SM: **Characterization of photodamage to *Escherichia coli* in optical traps**. *Biophys J* 1999, **77**:2856-2863.

14. • Armani M, Chaudhary S, Probst R, Shapiro B: **Using Feedback Control of Microflows to Independently Steer Multiple ParticlesJ. Microelectromech. Syst.154feedback control of microflows to independently steer multiple particles**. *J Microelectromech Syst* 2006, **15**:945-956

This paper combined electroosmotic flow and feedback control theory in a microfluidic device to demonstrate independent control over multiple particles with micrometer accuracy in two dimensions.

15. Tanyeri M, Johnson-Chavarria EM, Schroeder CM: **Hydrodynamic trap for single particles and cells**. *Appl Phys Lett* 2010, **96**:224101.

16. Curtis MD, Sheard GJ, Fouras A: **Feedback control system simulator for the control of biological cells in microfluidic cross slots and integrated microfluidic systems**. *Lab Chip* 2011, **11**:2343-2351.

17. Cohen AE, Moerner W: **Controlling Brownian motion of single protein molecules and single fluorophores in aqueous buffer**. *Opt Express* 2008, **16**:6941-6956.

18. •• Fields AP, Cohen AE: **Electrokinetic trapping at the one nanometer limit**. *Proc Natl Acad Sci U S A* 2011, **108**:8937-8942

This paper demonstrates effective trapping of 1 nm single fluorophores in aqueous solution using the Anti-Brownian electrokinetic trap.

19. • Shenoy A, Kumar D, Hilgenfeldt S, Schroeder CM: **Flow topology during multiplexed particle manipulation using a stokes trap**. *Phys Rev Appl* 2019, **12**:054010

This paper demonstrates the underlying flow topologies involved in a microfluidic device during multiplexed particle manipulation using the Stokes trap.

20. Leal LG: *Advanced Transport Phenomena: Fluid Mechanics and Convective Transport Processes, vol 7*. Cambridge University Press; 2007.

21. Bentley B, Leal L: **A computer-controlled four-roll mill for investigations of particle and drop dynamics in two-dimensional linear shear flows**. *J Fluid Mech* 1986, **167**:219-240.

22. Tanyeri M, Ranka M, Sittipolkul N, Schroeder CM: **A microfluidic-based hydrodynamic trap: design and implementation**. *Lab Chip* 2011, **11**:1786-1794.

23. Tanyeri M, Schroeder CM: **Manipulation and confinement of single particles using fluid flow**. *Nano Lett* 2013, **13**:2357-2364.

24. Shenoy A, Tanyeri M, Schroeder CM: **Characterizing the performance of the hydrodynamic trap using a control-based approach**. *Microfluid Nanofluid* 2015, **18**:1055-1066.

25. •• Kumar D, Shenoy A, Li S, Schroeder CM: **Orientation control and nonlinear trajectory tracking of colloidal particles using microfluidics**. *Phys Rev Fluids* 2019, **4**:114203

This paper demonstrates facile control over the center-of-mass position, orientation and trajectories of Brownian anisotropic particles using Stokes trap method.

26. Zhou Y, Schroeder CM: **Single polymer dynamics under large amplitude oscillatory extension**. *Phys Rev Fluids* 2016, **1**:53301.

27. Zhou Y, Schroeder CM: **Transient and average unsteady dynamics of single polymers in large-amplitude oscillatory extension**. *Macromolecules* 2016, **49**:8018-8030.

28. • Mai DJ, Saadat A, Khomami B, Schroeder CM: **Stretching dynamics of single comb polymers in extensional flow**. *Macromolecules* 2018, **51**:1507-1517

This paper demonstrates the transient stretching and relaxation dynamics of architecturally complex comb polymers which are freely suspended in a planar elongational flow using single molecule fluorescence microscopy and the Stokes trap.

29. • Hsiao K-W, Dinic J, Ren Y, Sharma V, Schroeder CM: **Passive non-linear microrheology for determining extensional viscosity**. *Phys Fluids* 2017, **29**:121603

This paper uses the Stokes trap to obtain the migration trajectories of spherical particles suspended in a viscoelastic solution and estimate the extensional viscosity of fluid using microrheology.

30. Moerner WE: **New directions in single-molecule imaging and analysis**. *Proc Natl Acad Sci U S A* 2007, **104**:12596-12602.

31. Wang Q, Moerner W: **Optimal strategy for trapping single fluorescent molecules in solution using the Abel trap**. *Appl Phys B* 2010, **99**:23-30.

32. Squires AH, Moerner W: **Direct single-molecule measurements of phycocyanobilin photophysics in monomeric c-phycocyanin**. *Proc Natl Acad Sci U S A* 2017, **114**:9779-9784.

33. Squires AH, Dahlberg PD, Liu H, Magdaong NCM, Blankenship RE, Moerner W: **Single-molecule trapping and spectroscopy reveals photophysical heterogeneity of phycobilisomes quenched by orange carotenoid protein**. *Nat Commun* 2019, **10**:1172.

34. Mathai PP, Carmichael PT, Shapiro BA, Liddle JA: **Simultaneous positioning and orientation of single nano-wires using flow control**. *RSC Adv* 2013, **3**:2677.

35. Ropp C, Cummins Z, Nah S, Qin S, Seog JH, Lee SB, Fourkas JT, Shapiro B, Waks E: **Fabrication of nanoassemblies using flow control**. *Nano Lett* 2013, **13**:3936-3941.

36. •• Tang X, Rupp B, Yang Y, Edwards TD, Grover MA, Bevan MA: **Optimal Feedback Controlled Assembly of Perfect Crystals**. *ACS Nano* 2016, **10**:6791-6798

This paper used feedback control using electric fields to control the assembly of a large number of colloidal particles into perfectly ordered structures.

37. •• Probst R, Shapiro B: **Three-dimensional electrokinetic tweezing: device design, modeling, and control algorithms**. *J Micromech Microeng* 2011, **21**:027004

This paper demonstrates full three dimensional trapping, confinement and manipulation of a single colloidal particle using electrokinetic forces.

38. Cummins Z, Probst R, Shapiro B: **Electrokinetic tweezing: three-dimensional manipulation of microparticles by real-time imaging and flow control**. *Lab Chip* 2013, **13**:4040.

39. Juárez JJ, Bevan MA: **feedback controlled colloidal self-assembly**. *Adv Funct Mater* 2012, **22**:3833-3839.

40. Juárez JJ, Mathai PP, Liddle JA, Bevan MA: **Multiple electrokinetic actuators for feedback control of colloidal crystal size**. *Lab Chip* 2012, **12**:4063.

41. Grover MA, Griffin DJ, Tang X: **control of self-assembly with dynamic programming**. *IFAC-PapersOnLine* 2019, **52**:1-9.

42. Gao Y, Lakerveld R: **Feedback control for defect-free alignment of colloidal particles**. *Lab Chip* 2018, **18**:2099-2110.