Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Chemical Biology

Towards biological applications of nanophotonic tweezers

Ryan P. Badman[1], Fan Ye[1,2] and Michelle D. Wang[1,2]

Abstract

Optical trapping (synonymous with optical tweezers) has become a core biophysical technique widely used for interrogating fundamental biological processes on size scales ranging from the single-molecule to the cellular level. Recent advances in nanotechnology have led to the development of 'nanophotonic tweezers,' an exciting new class of 'on-chip' optical traps. Here, we describe how nanophotonic tweezers are making optical trap technology more broadly accessible and bringing unique biosensing and manipulation capabilities to biological applications of optical trapping.

Addresses

[1] Department of Physics & LASSP, Cornell University, Ithaca, NY 14853, USA

[2] Howard Hughes Medical Institute, Cornell University, Ithaca, NY 14853, USA

Corresponding author: Wang, Michelle D. (mwang@physics.cornell.edu)

Current Opinion in Chemical Biology 2019, **53**:158–166

This review comes from a themed issue on **Chemical Biophysics**

Edited by **Yan Jie** and **Terence Strick**

For a complete overview see the Issue and the Editorial

https://doi.org/10.1016/j.cbpa.2019.09.008

Keywords

Nanophotonic tweezers, Optical trapping, Mechanical manipulation, Biosensing, Transport, Single molecule biophysics, Lab on a chip.

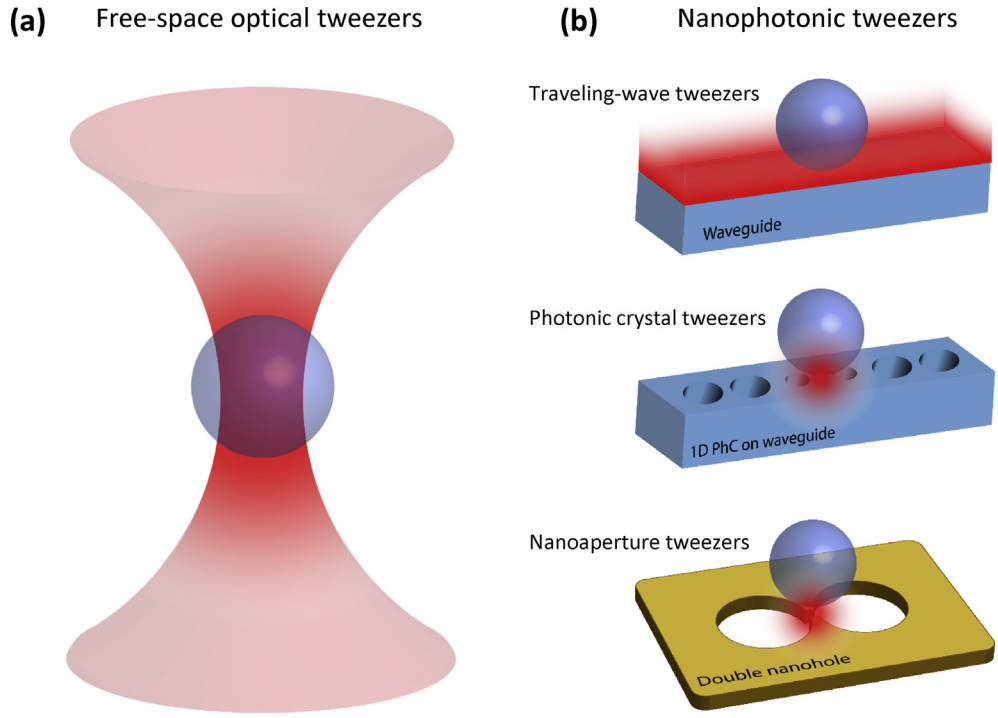
Introduction

Since Johannes Kepler, and then Leonhard Euler, first studied the tails of comets centuries ago [1], we have known that light can exert radiation pressure on matter. The resulting 'scattering force' propels an object in the initial direction of the light as a result of light absorption, reflection, and radiation. However, the magnitude of these forces was thought to be too low to have applications outside of astronomy and celestial mechanics [2]. This perception went through a revolutionary transformation owing to the seminal work by Ashkin [3] and Ashkin et al [4] in the 1970s to 1980s exploring the interactions of laser beams with matter. Ashkin and Dziedzic [5] and Ashkin et al [6] found that a tightly focused laser beam can optically trap a dielectric object, such as a virus or bacterium, near its focal point (Figure 1a). This led to the discovery of the 'gradient force' that directs the object toward the light focus, counteracting the scattering force and resulting in stable 3D trapping [3,4]. As a result of Ashkin's discovery, we now know that radiation pressure can manifest as not only the scattering force but also the gradient force that counteracts the scattering force to allow stable trapping. Ashkin's cumulative work in optical trapping has far-reaching impacts and has paved the way for three Nobel Prizes in physics, one in 1997 for the use of optical traps in laser trapping and cooling of atoms, a second in 2001 for the use of magneto-optical traps in cooling atoms to form Bose–Einstein condensates, and the third in 2018, shared by Ashkin himself, for his contributions to optical trap applications primarily in single-molecule biophysics.

Optical trapping (synonymous with optical tweezers) has now become a core biophysical technique. Its ability to probe piconewton forces occurring at the nanometer (nm) scale allows detailed insight into cellular and molecular interactions [7], including the forces and step sizes of motor proteins [8–11], protein folding [12], probing the biophysical properties of DNA [13,14] and RNA [15], and disruption of proteins bound to DNA [16].

Despite the many successful biophysics applications of optical tweezers, the requirement for specialized laboratory space and complex tabletop equipment has historically limited broader accessibility to the technology. A promising solution to these constraints was first suggested by Kawata and Sugiura [17] and Kawata and Tani [18] in the 1990s. They found that dielectric and metallic particles could be trapped and propelled by near-field evanescent waves on the surface of waveguide on-chip structures. This groundbreaking discovery initiated the field of nanophotonic trapping, where waveguide or plasmonic-based nanostructures are used to trap small biomolecules and particles (Figure 1b). These new trapping platforms, also referred to as 'nanophotonic tweezers,' are highly efficient in trapping small particles, more compact than traditional optical tweezers and inherently robust against noise [19,20]. These features open new windows of opportunities to study individual biological molecules, viruses, and cells at high throughput.

Figure 1



Comparison of free-space optical tweezers and nanophotonic tweezers. The gradient force directs a dielectric particle to the region of the strongest light intensity. **(a)** A dielectric particle is trapped near the focal point of a tightly focused Gaussian-profiled laser beam. **(b)** A dielectric particle is trapped at the surface of a nanophotonic waveguide (top), near a defect in a photonic crystal resonator (middle), or in close vicinity to a nanoaperture on a thin metal film (bottom).

Now, after almost three decades of development and innovation, nanophotonic tweezers have begun to solidify their status as a powerful, accessible optical trapping tool with some unique advantages over traditional free-space optical trapping [20,21]. In the past few years, there has been substantial development in the biological applications of nanophotonic tweezers. Here, we provide a brief overview of the physical principles of optical trapping and highlight a few recent nanophotonic devices that have demonstrated potential for biological applications.

Basic principles of optical trapping

Stable optical trapping requires that all forces on a particle, including scattering and gradient, are balanced at the trap center and the particle is directed toward the trap center upon displacement from the center. A general solution of the time-averaged, net optical force experienced by a particle in an electromagnetic (EM) field is given by the surface integral of the Maxwell stress tensor $\overleftrightarrow{T}$ over the boundary of the particle:

$$\boldsymbol{F} = \langle \oint \overleftrightarrow{T} \cdot d\boldsymbol{S} \rangle \tag{1}$$

Although this formulation is commonly used to obtain numerical solutions of the optical force, it does not provide physical intuition of optical forces.

Optical forces may be more readily understood under the Rayleigh limit where the particle is much smaller than the wavelength λ of the EM wave. Considering a spherical particle of radius r, the response of the particle to the EM wave can be approximated by an induced point dipole. Under this limit, the time-averaged scattering force acting on the particle originates from the linear momentum transfer from the photons:

$$\boldsymbol{F}_{\text{scatt}} = \frac{n_s \langle \boldsymbol{S} \rangle}{c} \sigma \tag{2}$$

where n_s is the refractive index of the surrounding medium and c is the speed of light. $\langle \boldsymbol{S} \rangle$ is the time-averaged Poynting vector of the EM wave, and thus, the scattering force is always in the direction of light propagation [22]. The extinction cross section of the particle σ has contributions from both scattering and absorption: $\sigma = \sigma_{\text{scatt}} + \sigma_{\text{abs}}$. When the particle is purely dielectric,

$\sigma = \sigma_{\text{scatt}} = \frac{8}{3}\pi k^4 r^6 \left(\frac{m^2-1}{m^2+2}\right)^2$, where $k \equiv 2\pi/\lambda$ and $m \equiv n_p/n_s$, with n_p being the refractive index of the particle. Furthermore, the time-averaged gradient force acting on the particle comes from the nonzero Lorentz force due to the electric field gradient:

$$\boldsymbol{F}_{\text{grad}} = \frac{\alpha}{2}\nabla\langle \boldsymbol{E}^2 \rangle \tag{3}$$

where $\alpha = 4\pi\varepsilon_0 n_s^2 r^3 \left(\frac{m^2-1}{m^2+2}\right)$, which is the polarizability of the dipole, with ε_0 being the vacuum permittivity. The gradient force always directs the particle toward the point with the highest field intensity.

In conventional tabletop optical tweezers, the diffraction limit of light is a fundamental obstacle for the generation of a large gradient force. Two strategies have been most commonly used to achieve stable trapping. For single-beam optical tweezers, a strong gradient force may be achieved via the use of a high numerical aperture objective that focuses the laser to a tight spot near the specimen plane, such that the gradient force pulling the trapping particle toward the laser beam waist is sufficiently strong to overcome the scattering force that pushes the particle downstream of the laser beam waist. Alternatively, stable trapping may be obtained by the use of counter-propagating laser beams whose scattering forces cancel near the specimen plane [3,13,23]. Although Ashkin [3] and Ashkin et al [4] demonstrated both implementations, single-beam optical tweezers are by far more prevalent and comparably easier to implement and operate.

While the diffraction limit of light significantly restricts the magnitude of the gradient force in conventional optical tweezers [21], nanophotonic tweezers overcome this limitation by taking advantage of the high intensity gradient of the near field in the vicinity of a nanostructure surface. Although trapping force analysis of nanophotonic devices is more complex owing to a broad variation of device configurations, the basic principles behind the scattering force and gradient force remain unaltered.

Molecular sensing

Nanophotonic tweezers offer tremendous promise for the biosensing of ultrasmall particles particularly in the study of protein conformational changes, nucleic acid denaturation, or protein–biomolecule interactions [24–26]. Two types of nanophotonic tweezers, nanoaperture tweezers and photonic crystal resonator tweezers, (Figure 1b), have proven to be especially well suited for studies for molecular sensing. Both types of nanophotonic tweezers create a strong localized resonance of the EM field at predefined positions, generating $\nabla\langle \boldsymbol{E}^2 \rangle$ orders of magnitude higher than the focused laser beam in free space [27]. In fact, in many cases, the mode volume is so small that the trapped particle plays an important role in reshaping the mode distribution, leading to the self-induced back action, a phenomenon that is qualitatively different from that described in Eq. (3) [27,28]. With the ability of nanophotonic tweezers to generate an ultrastrong field gradient in a tightly confined space, they can trap single nm-scale particles and single molecules considerably more readily than conventional optical tweezers [21].

Nanoaperture tweezers consist of a plasmonic nanoscale aperture in a thin gold film for generation of high field gradients [29]. Because of the ability to trap single biomolecules, nanoaperture tweezers offer unique, compelling capabilities for exploring biomolecular dynamics, conformational changes, and biomolecular interactions [30], without the use of labels or tether particles that may distort native protein behavior [31]. Small proteins and biomolecules (e.g. streptavidin proteins and 10-bp DNA) may be trapped at low laser powers ($\sim$5 mW) with minimal requirement on polarizability of the protein of interest [29,32,33]. Protein conformational changes or interactions with biomolecules can thus be directly and reversibly probed via the laser power transmission through the nanoaperture [30,34,35] as solution conditions such as pH or trap power are varied over tens of minutes [29,34]. This transmission sensitivity can be understood by examining the optical transmission T through a subwavelength circular aperture of radius r in a metal film, approximated as follows [34]:

$$T \propto \left(\frac{r}{\lambda_e}\right)^4, \quad \lambda_e = \frac{\lambda}{n_p} \tag{4}$$

where the effective trapping wavelength λ_e is the original trapping wavelength λ reduced by the trapped particle's refractive index. Thus, if the aperture was fully occupied by the particle, the transmission would increase by approximately a factor of n_p^4, such that conformational changes of a protein, for example, which cause minute changes in n_p would still provide large observable signals in the transmission. This discriminatory power of nanoaperture tweezers has recently been used for identifying different native proteins even in heterogeneous 'dirty' solutions, which may be encountered in a clinical setting [36]. Such protein identification would normally require complicated, protein altering, and expensive gel electrophoresis or mass spectroscopy [36].

As a specific interesting example, Kotnala and Gordon [32] showed that nanoaperture tweezers were able to optically trap a tether-free DNA hairpin and to

quantitatively detect protein interactions with the hairpin (Figure 2a). Upon entering the nanoaperture tweezers, the DNA hairpin was found to change its conformation, which the authors referred to as 'unzipping,' based on measurements of a shift in the light transmission through the nanoaperture. This unzipping appears to be a result of a transition that unfolds the hairpin. Although the molecular mechanisms of this transition under a high EM field remain to be elucidated, local heating was ruled out as an unzipping mechanism because the temperature increase was only determined to be 0.1 K [32].

Photonic crystal resonator tweezers are dielectric photonic resonator cavities that can generate high field gradients [37] and can be adapted to trap objects ranging from the size of single-protein molecules up to the cellular scale. Photonic crystal resonators have comparable benefits with nanoaperture tweezers for label-free and high field gradient single-molecule trapping studies because of the ultrahigh gradient force, but are based on dielectric cavity resonators rather than the surface plasmon resonances generated in nanoaperture tweezers. Chen et al. [25] have used photonic crystal resonator tweezers to trap proteins, and Kang et al. [38] used a similar device to trap and detect influenza virus and its binding to antibodies in real time (Figure 2b). Interestingly, a recent photonic crystal resonator trapping study by Liang et al. [31] found that protein–DNA interactions could be significantly altered by the presence of fluorescent labels (Figure 2c).

In summary, these nanophotonic tweezers demonstrate appealing features for biosensing of individual biomolecules. The strong power confinement of these devices allows a single molecule to be trapped at an input power substantially lower than that used in traditional free-space laser trapping [21]. The presence of the biomolecule and its conformational changes may be detected without the need to tag the molecule.

Cellular sensing

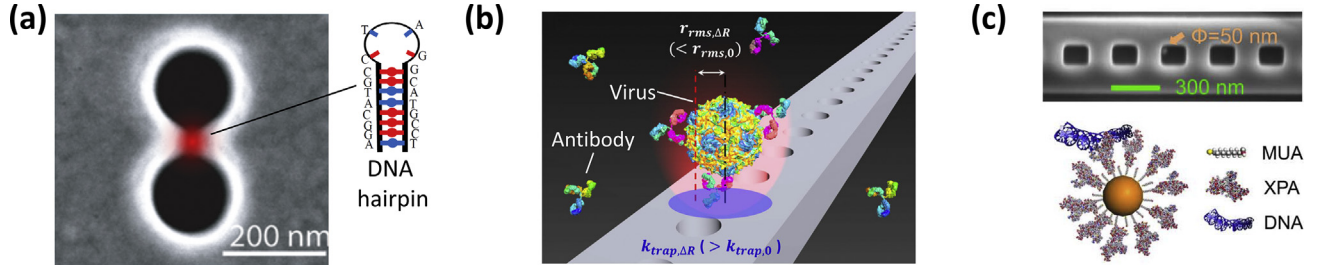
The ability to sense trapped cells label-free has enabled nanophotonic tweezers to be extended to public health, biomedical, and biological applications. Traditional diagnostic methods for identifying bacterial infection or contamination of water or food require large bacterial samples, use time-consuming bacterial culture protocols, and deplete samples during testing [39]. In comparison, nanophotonic tweezer–based assays generally require smaller sample volumes, offer label-free, nondestructive measurements for repeatable sample testing [40], and have the potential to make faster and more accurate diagnoses.

Photonic crystal resonators can be used to trap micrometer (μm)-scale cells with properly designed resonator defects [41]. The presence of a trapped cell introduces a small change in the refractive index near the trap center and causes a change in the frequency of the optical mode in the photonic crystal resonator. Based on the analysis previously laid out [42,43], here, we define the following figure of merit to characterize a resonator device's biosensing sensitivity:

$$\mathrm{FOM} \equiv \frac{\Delta\omega_r}{\Delta n}\frac{1}{2\omega_r}Q \tag{5}$$

where ω_r is the cavity resonance frequency and $\Delta\omega_r$ is the shift of the resonance frequency in response to a change in refractive index Δn in the trapping region due to the analyte. $\Delta\omega_r/\Delta n$ is proportional to the fractional mode volume of the perturbed region. Q is the quality factor of the resonator. A larger Q value corresponds to a higher figure of merit. Typical Q values of photonic

Figure 2



Single-molecule detection by nanophotonic tweezers. **(a)** Scanning electron microscopy (SEM) image of nanoaperture tweezers formed by a double nanohole on a gold substrate. Single biomolecules (such as a DNA hairpin) can be trapped at the center, which has a high field gradient. Adapted with permission from Pang and Gordon [29] and Kotnala and Gordon [32]. **(b)** Detection of binding of an antibody to an influenza virus using nanophotonic tweezers formed by a 1D nanophotonic crystal resonator along a waveguide. Adapted with permission from Kang et al [38]. **(c)** (Top) SEM image of a 1D nanophotonic crystal resonator cavity formed by a single 50-nm-diameter gold particle (orange arrow) located in the central grating of a nanocavity and (bottom) cartoon illustration of a biofunctionalized gold nanoparticle. XPA proteins, which are immobilized to a self-assembled monolayer of 11-mercaptoundecanoic acid (11-MUA) on gold, can interact with DNA. Adapted with permission from Liang et al [31].

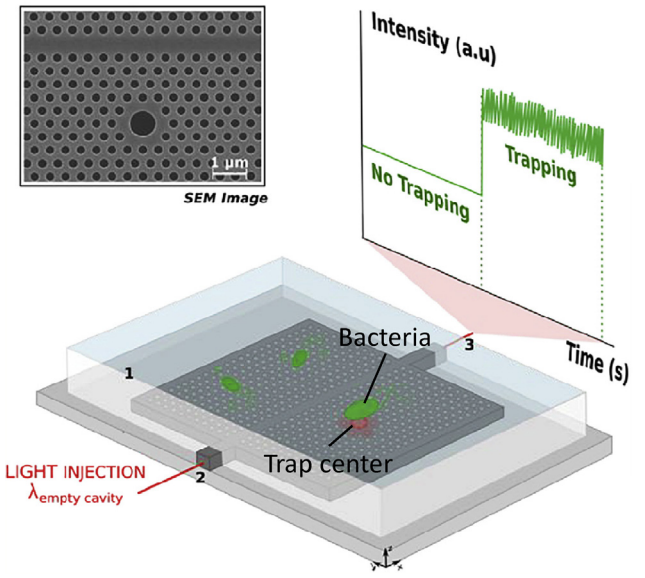
crystal resonators for biological, dual trapping–sensing applications are in the range of 1000–10,000 [37,44].

After the first demonstration of bacterial trapping in a photonic crystal resonator tweezer by van Leest and Caro [45], Tardif et al. [44] used a combination of Brownian motion and optical transmission observations to differentiate between bacterial species trapped on a photonic crystal. Therisod et al. [41] further streamlined this concept by using 2D photonic crystal resonator cavity tweezers to rapidly, accurately, and nondestructively identify whether a trapped bacterium was a gram-positive or gram-negative one (Figure 3) by simply quantifying the relative change in the power transmission of the device. Accurately determining the gram type of a bacterial population is essential for the selection of appropriate antibiotics; however, traditional gram-type identification methods require toxic and carcinogenic chemicals and a large volume of bacteria [46]. Yao et al. [47] trapped an individual bacterium in one of the cavities of an array of plasmonic structures and then used surface-enhanced Raman scattering to detect bacterial spore biomarkers, demonstrating the potential for detection sensitivity at the ultralow zeptomole–attamole range. Lotan et al. [48] further explored highly sensitive, fluorescently labeled single-cell bacterial detection using nanophotonic tweezer technology. Specifically, the authors demonstrated the potential for microscope-free, low volume detection of bacteria using plasmonic V-groove waveguides that could transmit the fluorescent emission light of trapped bacteria to an output detector [48]. Nanophotonic tweezers are not limited to trapping bacteria as researchers have shown red blood cells may be trapped on a waveguide and transported along it [49–51]. Ahluwalia et al. [50] and Ahmad et al [51] have used this capability to study how compression forces generated by the waveguide evanescent field affect blood cell deformation and cellular structural changes. These initial cellular applications of nanophotonic tweezers suggest significant promise for using this technology in both biomedical research and the clinical setting.

Precision molecular manipulation

While nanophotonic tweezers have demonstrated promise for biosensing, the ability to manipulate biomolecules with precision [20] in a controlled manner is a critical need for nanophotonic tweezers. An ideal device should encompass the full capabilities of traditional optical tweezers for precision manipulation and measurement experiments, including nm-precision manipulation resolution, comparable trap stiffness to traditional optical tweezers, μm-scale long-range manipulation, low heating, and biocompatibility [52,53]. Enabling these capacities in nanophotonic tweezers would make optical tweezers more accessible to a larger scientific community.

Figure 3

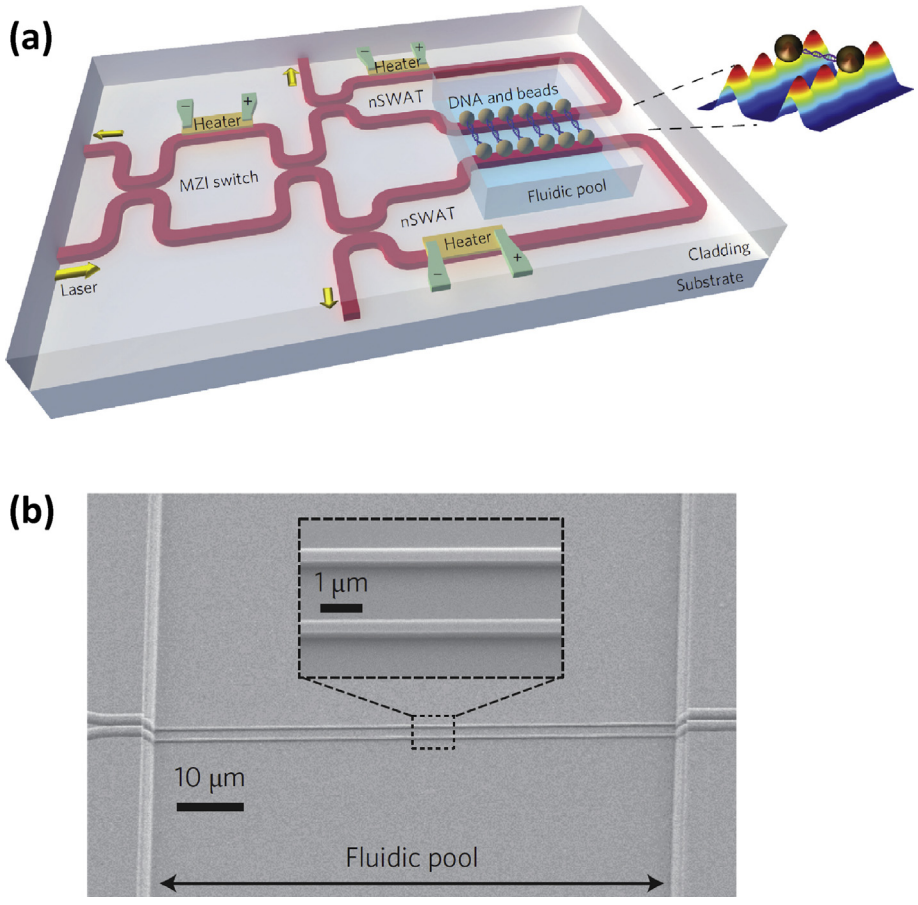


Detection of a single bacterium by nanophotonic tweezers. An SEM image of a 2D hollow photonic crystal resonator cavity and illustration of the experimental setup. The presence of a bacterium (green) when trapped near a cavity (red) is determined by an intensity change of the transmitted light. Adapted with permission from Therisod et al [41]. SEM, scanning electron microscopy.

These requirements are not readily attainable via the most commonly used nanophotonic structures. Traveling-wave waveguides represent the simplest nanostructure for trapping, where a particle of interest is captured at the surface of the waveguide and then transported unidirectionally along the waveguide [54], but precision control of the particle position is not possible. Photonic crystal resonators and nanoaperture tweezers, discussed previously, are excellent in trapping a particle at a fixed location for interrogation [29,37]; however, this trapping location also cannot be relocated in a controllable fashion. Other tunable nanophotonic structures, such as loss-based devices [55,56] and near-field mode-beating optical lattices [57], can achieve trap control, but only at μm precision.

To overcome these challenges, a standing-wave waveguide–based trapping platform has been developed by Soltani et al. [19], Ye et al. [58,59], and Badman et al. [60] (Figure 4a). The nanophotonic standing-wave array trap (nSWAT) has two coherent lasers that counter-propagate along a single-mode waveguide, forming an array of trapping centers at the antinode positions of a standing wave [19]. To stretch an array of

Figure 4



Single-molecule manipulation by nanophotonic tweezers. **(a)** Schematic of the design of an nSWAT device. Laser input to the waveguide is partitioned into two nSWATs using a Mach–Zehnder interferometer (MZI). Each nSWAT has a 50/50 waveguide beam splitter with output arms connected to generate counter-propagating waves. Three microheaters are located above the waveguides, one above the MZI to control partitioning of the laser into the two nSWATs and two above the two nSWATs to independently control the trap position of each nSWAT. Adapted with permission from Soltani et al [19]. **(b)** Tilted-angle SEM image of the fluid pool region of an nSWAT device. Adapted with permission from Soltani et al [19]. nSWAT, nanophotonic standing-wave array trap.

DNA molecules, two copies of an nSWAT were incorporated into a single device, each controlled independently by its own microheater (Figure 4b). DNA dumbbells — single molecules of DNA with a bead attached at each end — were trapped between the two nSWATs via beads at the DNA ends and smoothly stretched via control of the microheaters [19]. This experiment is analogous to DNA stretching in conventional optical tweezers [61–63], except that manipulation was performed on multiple DNA molecules simultaneously, thus highlighting the potential for nSWAT-based high-throughput on-chip precision manipulation.

Besides being high-throughput, an nSWAT device has several notable advantages in comparison with conventional tabletop tweezers. The counter-prorogating lasers cancel out the scattering force, allowing stable trapping by the gradient force. This resulting standing wave naturally creates an array of traps by recycling the laser power without the need to proportionally increase trapping laser power with an increase in the trap number [20]. The elimination of the scattering force allows high-refractive-index particles to be stably trapped [60], which would be challenging for single-beam conventional optical tweezers, and because of the short optical paths creating the trap array on chip, the nSWAT device is inherently robust against drift [19].

Future outlook

Nanophotonic tweezers offer an exciting alternative to conventional optical tweezers, presenting unique advantages that include on-chip, label-free, ultrasensitive single-molecule biosensing and high-throughput precision manipulation. As nanophotonic tweezer devices are used for broader biological applications, a greater variety

of more complex experiments may be realized. Indeed, increasingly impactful biological and biomedical experimentation, beyond just a proof of principle, is already being performed using nanophotonic trapping technology.

This expansion also requires development of nanophotonic tweezers with further enhanced capabilities. While label-free and tether-free sensing methods (nanoaperture tweezers and photonic crystal resonator tweezers) minimally alter the native state of the molecule of interest, the molecule cannot be interrogated via controlled application of forces to gain additional insight via mechanical perturbation. Conversely, the precision manipulation allowed by the nSWAT critically relies on the use of trapping particles as handles to manipulate the molecule of interest and thus does not afford some of the advantages of the label-free techniques. New platforms that integrate label-free and precision manipulation would significantly broaden the applicability of nanophotonic tweezers.

In addition, the advent of nanophotonic tweezers requires increased comprehensive understanding of the interactions between a trapping laser and biological systems. For example, nanoaperture tweezers present unique opportunities to not only trap biomolecules but also induce their molecular conformational changes [29,32,34]. Elucidating the mechanism inducing these changes will allow better assessment of how to best use the technology. For another example, a trapping laser is also known to potentially induce photodamage to the molecule of interest as a result of photon absorption [64] and singlet oxygen formation [65,66]. This is of particular importance, given the high local field intensity of nanophotonic tweezers [40]. The exact mechanism inducing the photodamage requires better understanding and characterization to develop methods and devices that minimize this impact.

Although nanophotonic tweezers have begun to move beyond proof of concept, this technology still has significant potential that is just beginning to be unlocked. The full realization of their capabilities will allow increased accessibility and expansion of application to a wide range of biological and biomedical research topics and encourage broad adoption of these dynamic platforms.

Conflicts of interest statement

Nothing declared.

Acknowledgements

The authors thank S.L. Moore, J.T. Inman, and R.M. Fulbright for helpful comments. This work was supported by the Howard Hughes Medical Institute (HHMI).

References

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

- • of special interest
- •• of outstanding interest

1. Beyer RT: **Radiation pressure – history of a mislabeled tensor**. *J Acoust Soc Am* 1978, **63**:1025–1030.

2. Parkinson RW, Jones HM, Shapiro II : **Effects of solar radiation pressure on earth satellite orbits**. *Science* 1960, **131**:920–921.

3. Ashkin A: **Acceleration and trapping of particles by radiation pressure**. *Phys Rev Lett* 1970, **24**:156–&.

4. Ashkin A, Dziedzic JM, Bjorkholm JE, Chu S: **Observation of a single-beam gradient force optical trap for dielectric particles**. *Opt Lett* 1986, **11**:288–290.

5. Ashkin A, Dziedzic JM: **Optical trapping and manipulation of viruses and bacteria**. *Science* 1987, **235**:1517–1520.

6. Ashkin A, Dziedzic JM, Yamane T: **Optical trapping and manipulation of single cells using infrared-laser beams**. *Nature* 1987, **330**:769–771.

7. Killian JL, Ye F, Wang MD: **Optical tweezers: a force to be reckoned with**. *Cell* 2018, **175**:1445–1448.

8. Svoboda K, Schmidt CF, Schnapp BJ, Block SM: **Direct observation of kinesin stepping by optical trapping interferometry**. *Nature* 1993, **365**:721–727.

9. Finer JT, Simmons RM, Spudich JA: **Single myosin molecule mechanics – piconewton forces and nanometer steps**. *Nature* 1994, **368**:113–119.

10. Yin H, Wang MD, Svoboda K, Landick R, Block SM, Gelles J: **Transcription against an applied force**. *Science* 1995, **270**: 1653–1657.

11. Wang MD, Schnitzer MJ, Yin H, Landick R, Gelles J, Block SM: **Force and velocity measured for single molecules of RNA polymerase**. *Science* 1998, **282**:902–907.

12. Cecconi C, Shank EA, Bustamante C, Marqusee S: **Direct observation of the three-state folding of a single protein molecule**. *Science* 2005, **309**:2057–2060.

13. Smith SB, Cui YJ, Bustamante C: **Overstretching B-DNA: the elastic response of individual double-stranded and single-stranded DNA molecules**. *Science* 1996, **271**:795–799.

14. Wang MD, Yin H, Landick R, Gelles J, Block SM: **Stretching DNA with optical tweezers**. *Biophys J* 1997, **72**:1335–1346.

15. Liphardt J, Onoa B, Smith SB, Tinoco I, Bustamante C: **Reversible unfolding of single RNA molecules by mechanical force**. *Science* 2001, **292**:733–737.

16. Brower-Toland BD, Smith CL, Yeh RC, Lis JT, Peterson CL, Wang MD: **Mechanical disruption of individual nucleosomes reveals a reversible multistage release of DNA**. *Proc Natl Acad Sci USA* 2002, **99**:1960–1965.

17. Kawata S, Sugiura T: **Movement of micrometer-sized particles in the evanescent field of a laser-beam**. *Opt Lett* 1992, **17**: 772–774.

18. Kawata S, Tani T: **Optically driven Mie particles in an evanescent field along a channeled waveguide**. *Opt Lett* 1996, **21**:1768–1770.

19. •• Soltani M, Lin J, Forties RA, Inman JT, Saraf SN, Fulbright RM, Lipson M, Wang MD: **Nanophotonic trapping for precise manipulation of biomolecular arrays**. *Nat Nanotechnol* 2014, **9**: 448–452.

During this initial development of the nanophotonic standing-wave array trap (nSWAT) platform using silicon waveguides and 1550 nm trapping wavelength, an array of single DNA molecules was suspended between two waveguides and then stretched.

20. Baker JE, Badman RP, Wang MD: **Nanophotonic trapping: precise manipulation and measurement of biomolecular**

arrays. *Wiley Interdiscipl Rev Nanomed Nanobiotechnol* 2018, **10**.

21. Erickson D, Serey X, Chen YF, Mandal S: **Nanomanipulation using near field photonics**. *Lab Chip* 2011, **11**:995–1009.

22. Harada Y, Asakura T: **Radiation forces on a dielectric sphere in the Rayleigh scattering regime**. *Opt Commun* 1996, **124**: 529–541.

23. Smith SB, Cui YJ, Bustamante C: **Optical-trap force transducer that operates by direct measurement of light momentum**. *Biophotonics, Pt B* 2003, **361**:134–162.

24. Yang AHJ, Moore SD, Schmidt BS, Klug M, Lipson M, Erickson D: **Optical manipulation of nanoparticles and biomolecules in sub-wavelength slot waveguides**. *Nature* 2009, **457**:71–75.

25. Chen YF, Serey X, Sarkar R, Chen P, Erickson D: **Controlled photonic manipulation of proteins and other nanomaterials**. *Nano Lett* 2012, **12**:1633–1637.

26. Shoji T, Saitoh J, Kitamura N, Nagasawa F, Murakoshi K, Yamauchi H, Ito S, Miyasaka H, Ishihara H, Tsuboi Y: **Permanent fixing or reversible trapping and release of DNA micropatterns on a gold nanostructure using continuous-wave or femtosecond-pulsed near-infrared laser light**. *J Am Chem Soc* 2013, **135**:6643–6648.

27. Neumeier L, Quidant R, Chang DE: **Self-induced back-action optical trapping in nanophotonic systems**. *New J Phys* 2015, **17**.

28. Juan ML, Gordon R, Pang YJ, Eftekhari F, Quidant R: **Self-induced back-action optical trapping of dielectric nanoparticles**. *Nat Phys* 2009, **5**:915–919.

29. Pang YJ, Gordon R: **Optical trapping of a single protein**. *Nano Lett* 2012, **12**:402–406.

30. Gordon R: **Biosensing with nanoaperture optical tweezers**. *Opt Laser Technol* 2019, **109**:328–335.

31. •• Liang F, Guo YZ, Hou SC, Quan QM: **Photonic-plasmonic hybrid single-molecule nanosensor measures the effect of fluorescent labels on DNA-protein dynamics**. *Sci Adv* 2017, **3**.
Using a hybrid photonic-plasmonic antenna in a nanocavity, protein-DNA dynamics of single molecules were detected with and without using fluorescent labels.

32. • Kotnala A, Gordon R: **Double nanohole optical tweezers visualize protein p53 suppressing unzipping of single DNA-hairpins**. *Biomed Opt Express* 2014, **5**:1886–1894.
Double-nanohole optical tweezers were utilized for the optical unzipping of individual, label-free 10 basepair DNA hairpins to study their interactions with tumor suppressor protein p53.

33. Yoo D, Gurunatha KL, Choi HK, Mohr DA, Ertsgaard CT, Gordon R, Oh SH: **Low-power optical trapping of nanoparticles and proteins with resonant coaxial nanoaperture using 10 nm gap**. *Nano Lett* 2018, **18**:3637–3642.

34. Al Balushi AA, Kotnala A, Wheaton S, Gelfand RM, Rajashekara Y, Gordon R: **Label-free free-solution nanoaperture optical tweezers for single molecule protein studies**. *Analyst* 2015, **140**:4760–4778.

35. • Wheaton S, Gordon R: **Molecular weight characterization of single globular proteins using optical nanotweezers**. *Analyst* 2015, **140**:4799–4803.
Double-nanohole optical tweezers were employed to monitor the change in trapped ovalbumin's molecular weight due to tryptic cleavage using only shifts in transmitted power.

36. Hacohen N, Ip CJX, Laxminarayana GK, DeWolf TS, Gordon R: **Nanohole optical tweezers in heterogeneous mixture analysis**. *Opt Trapp Opt Micromanipulat Xiv* 2017:10347.

37. Mandal S, Serey X, Erickson D: **Nanomanipulation using silicon photonic crystal resonators**. *Nano Lett* 2010, **10**:99–104.

38. • Kang P, Schein P, Serey X, O'Dell D, Erickson D: **Nanophotonic detection of freely interacting molecules on a single influenza virus**. *Sci Rep* 2015, **5**.
A label-free method for analyzing interactions between a single influenza virus and specific antibodies at the single particle level was demonstrated using 1D photonic crystal traps.

39. Manual of clinical microbiology, 9th ed. Manual of Clinical Microbiology, 9th ed. 2007:1-2256.

40. • Jing PF, Wu JD, Liu GW, Keeler EG, Pun SH, Lin LY: **Photonic crystal optical tweezers with high efficiency for live biological samples and viability characterization**. *Sci Rep* 2016, **6**.
Using photonic crystal resonator tweezers, photo-damage of prokaryotic and eukaryotic cells in response to increasing trapping laser power intensity was characterized.

41. •• Therisod R, Tardif M, Marcoux PR, Picard E, Jager JB, Hadji E, Peyrade D, Houdre R: **Gram-type differentiation of bacteria with 2D hollow photonic crystal cavities**. *Appl Phys Lett* 2018, **113**.
Usinig a 2D silicon hollow photonic crystal cavity, the Gram-type of each trapped live bacterium was identified.

42. Sherry LJ, Chang SH, Schatz GC, Van Duyne RP, Wiley BJ, Xia YN: **Localized surface plasmon resonance spectroscopy of single silver nanocubes**. *Nano Lett* 2005, **5**:2034–2038.

43. Joannopoulos JD, Johnson SG, Winn JN, Meade RD: *Photonic crystals: molding the flow of light*. 2nd ed. 2008:1–286.

44. Tardif M, Jager JB, Marcoux PR, Uchiyamada K, Picard E, Hadji E, Peyrade D: **Single-cell bacterium identification with a SOI optical microcavity**. *Appl Phys Lett* 2016, **109**.

45. van Leest T, Caro J: **Cavity-enhanced optical trapping of bacteria using a silicon photonic crystal**. *Lab Chip* 2013, **13**: 4358–4365.

46. Mani S, Bharagava RN: **Exposure to crystal violet, its toxic, genotoxic and carcinogenic effects on environment and its degradation and detoxification for environmental safety**. *Rev Environ Contam Toxicol* 2016, **237**:71–104.

47. • Yao YY, Ji J, Zhang HD, Zhang K, Liu BH, Yang PY: **Three-dimensional plasmonic trap array for ultrasensitive surface-enhanced Raman scattering analysis of single cells**. *Anal Chem* 2018, **90**:10394–10399.
A plasmonic trap array was implemented for simultaneously compartmentalizing and sensitively detecting single-cell metabolites.

48. Lotan O, Bar-David J, Smith CLC, Yagur-Kroll S, Belkin S, Kristensen A, Levy U: **Nanoscale plasmonic V-groove waveguides for the interrogation of single fluorescent bacterial cells**. *Nano Lett* 2017, **17**:5481–5488.

49. Gaugiran S, Getin S, Fedeli JM, Colas G, Fuchs A, Chatelain F, Derouard J: **Optical manipulation of microparticles and cells on silicon nitride waveguides**. *Opt Express* 2005, **13**: 6956–6963.

50. Ahluwalia BS, McCourt P, Oteiza A, Wilkinson JS, Huser TR, Helleso OG: **Squeezing red blood cells on an optical waveguide to monitor cell deformability during blood storage**. *Analyst* 2015, **140**:223–229.

51. Ahmad A, Dubey V, Singh VR, Tinguely JC, Oie CI, Wolfson DL, Mehta DS, So PTC, Ahluwalia BS: **Quantitative phase microscopy of red blood cells during planar trapping and propulsion**. *Lab Chip* 2018, **18**:3025–3036.

52. Inman JT, Smith BY, Hall MA, Forties RA, Jin J, Sethna JP, Wang MD: **DNA Y structure: a versatile, multidimensional single molecule assay**. *Nano Lett* 2014, **14**:6475–6480.

53. Killian JL, Inman JT, Wang MD: **High-performance image-based measurements of biological forces and interactions in a dual optical trap**. *ACS Nano* 2018, **12**:11963–11974.

54. Ng LN, Luff BJ, Zervas MN, Wilkinson JS: **Propulsion of gold nanoparticles on optical waveguides**. *Opt Commun* 2002, **208**: 117–124.

55. Kuhn S, Measor P, Lunt EJ, Phillips BS, Deamer DW, Hawkins AR, Schmidt H: **Loss-based optical trap for on-chip particle analysis**. *Lab Chip* 2009, **9**:2212–2216.

56. Rahman M, Stott MA, Li YC, Hawkins AR, Schmidt H: **Single-particle analysis with 2D electro-optical trapping on an integrated optofluidic device**. *Optica* 2018, **5**:1311–1314.

57. Pin C, Jager JB, Tardif M, Picard E, Hadji E, de Fornel F, Cluzel B: **Optical tweezing using tunable optical lattices along a few-mode silicon waveguide**. *Lab Chip* 2018, **18**:1750–1757.

58. • Ye F, Badman RP, Inman JT, Soltani M, Killian JL, Wang MD: **Biocompatible and high stiffness nanophotonic trap array for precise and versatile manipulation**. *Nano Lett* 2016, **16**: 6661–6667.
A second generation of the nSWAT platform was introduced, using silicon nitride waveguides and a 1064 nm trapping laser for greater trapping power intensity and increased biocompatibility.

59. Ye F, Soltani M, Inman JT, Wang MD: **Tunable nanophotonic array traps with enhanced force and stability**. *Opt Express* 2017, **25**:7907–7918.

60. Badman RP, Ye F, Caravan W, Wang MD: **High trap stiffness microcylinders for nanophotonic trapping**. *ACS Appl Mater Interfaces* 2019, **11**:25074–25080.

61. Sun B, Johnson DS, Patel G, Smith BY, Pandey M, Patel SS, Wang MD: **ATP-induced helicase slippage reveals highly coordinated subunits**. *Nature* 2011, **478**:132–U148.

62. Sun B, Pandey M, Inman JT, Yang Y, Kashlev M, Patel SS, Wang MD: **T7 replisome directly overcomes DNA damage**. *Nat Commun* 2015, **6**.

63. Sun B, Singh A, Sultana S, Inman JT, Patel SS, Wang MD: **Helicase promotes replication re-initiation from an RNA transcript**. *Nat Commun* 2018, **9**.

64. Konig K, Liang H, Berns MW, Tromberg BJ: **Cell damage in near-infrared multimode optical traps as a result of multiphoton absorption**. *Opt Lett* 1996, **21**:1090–1092.

65. 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.

66. Landry MP, McCall PM, Qi Z, Chemla YR: **Characterization of photoactivated singlet oxygen damage in single-molecule optical trap experiments**. *Biophys J* 2009, **97**:2128–2136.