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Resource Letter: LBOT-1: Laser-based optical tweezers

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Abstract

This Resource Letter provides a guide to the literature on optical tweezers, also known as laser-based, gradient-force optical traps. Journal articles and books are cited for the following main topics: general papers on optical tweezers, trapping instrument design, optical detection methods, optical trapping theory, mechanical measurements, single molecule studies, and sections on biological motors, cellular measurements and additional applications of optical tweezers.

I. INTRODUCTION

The field of optical tweezers has enjoyed a wide range of applications since its inception in the early 1970s. By using light to trap microscopic objects noninvasively, optical tweezers provide a flexible tool for ultrafine positioning, measurement, and control. In practice, forces up to 200 pN or thereabouts may be applied with sub-pN resolution on objects whose characteristic dimensions are similar to the wavelength of light. Particle positioning and detection capabilities are therefore on a spatial scale of micrometers down to angstroms. The emerging applications of laser-based optical traps are quite diverse and extensive, ranging from atomic physics to the medical sciences. As a result, optical tweezers have been a focal point for interdisciplinary science.

Trapping apparatus ranges from simple, lens-based traps to complex instrumentation integrating multiple optical technologies. A variety of novel techniques have been developed for rapid position detection, trap stiffness determination, and applying controlled, calibrated forces. Instrument advances, such as the use of multiple laser beams, computerized automation of laser beams and sample positioning, and optical tweezers used in combination with other methodologies, such as fluorescence spectroscopy, micropipettes, and optical microbeams, have all helped to make optical tweezers an extremely versatile tool.

Owing to their exquisitely controllable force-exerting properties, optical tweezers are useful for a variety of nano-mechanical measurements, particularly those with biological applications. Objects such as biopolymers (e.g., microtubules, DNA molecules), lipid membranes, intact or fractionated cells, and single biological macromolecules have all been studied successfully with optical tweezers. There are many broad areas of current research in biophysics, including the mechanical unfolding and refolding of proteins or nucleic acids, the strength of receptor-ligand bonding interactions, and the nanoscale mechanics of biological motors, which are especially well suited to work with optical tweezers.

Optical tweezers are also useful purely as manipulators and positioning devices. Tweezers can be used to confine or constrain microscopic objects, as well as to organize, assemble, locate, or modify them. In addition to studies of single proteins, biological applications such as

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intracellular particle tracking and positioning, selective cell harvesting, and probing the mechanics of cell membranes have all been pursued with vigor. Laser-based tweezers also have been used to study the interactions of many-particle systems, e.g., colloids and quasi-crystals.

A full theory of optical tweezers, covering the full range of spatial scales and levels of sophistication, has evolved comparatively slowly over the years, and lags somewhat behind experimental work at the present. Variations in the size, shape, and composition of trapped objects, the nonuniformity of the trapping light distribution, the fact that dimensions of trapped objects are often comparable to the wavelength of light, combined with the large numerical apertures employed (which preclude scalar paraxial approximations, necessitating a full vector treatment), have all conspired to make general theories difficult to develop. However, there has been much current progress, and many papers combine limited aspects of trapping theory with experiment.

Our goal for this Resource Letter is to provide a guide to the literature. Our strategy has been to organize selected papers into a few main categories, rather than to provide a comprehensive review of all literature. Thus, numerous articles were omitted, some of which can be found among the citations papers in the papers we list. We apologize to colleagues whose work may thereby have been under-represented. Inevitably, some of the literature can be classified under multiple categories. Therefore, we strongly encourage reader to browse related titles and topics. For example, sections of research reports frequently include design details not necessarily covered in specific instrument papers.

We present a general section on optical tweezers first, including books and reviews on the subject. However, we caution readers that this is a fast-moving area, and much of the material found in books and early reviews is not particularly up-to-date. A focus on the earliest literature follows, including the seminal papers on optical tweezers. Papers relevant to optical instrument construction, calibration, and detection are listed next, followed by papers that deal mainly with optical trapping theory. The remaining sections are geared towards specific biological applications, including uses with cells, molecular motors, and additional applications of optical tweezers.

II. JOURNALS

The following are selected journals carrying articles on optical tweezers:

Applied Optics

Applied Physics Letters

Biophysical Journal

Cytometry

Experimental Cell Research

Fertility and Sterility

Human Reproduction

Journal of Applied Physics

Journal of Modern Optics

Methods in Cell Biology

Nature

Optics Letters

Physical Review Letters

Proceedings of the National Academy of Sciences Science

III. BOOKS, REVIEWS, AND GENERAL PAPERS

1. Laser Tweezers in Cell Biology. In: Wilson, L.; Matsudaira, P., editors. *Methods in Cell Biology*. 55. San Diego: Academic; 1998. Includes a number of topics in laser tweezers and applications. (I,A,E)
2. Block, SM. Optical Tweezers: A New Tool for Biophysics. In: Satir, BH., editor. *Noninvasive Techniques in Cell Biology*. New York: Wiley-Liss; 1990. p. 375-402.pp.The working principle of optical tweezers is described, including details on instrument construction. Examples of trapped cells and inner structures are presented. A good all-around introduction. (E)
3. Chu S. Laser Manipulations of Atoms and Particles. *Science* 1991;253:861–866. [PubMed: 17751820] Discussion of applications to atoms and particles. (E)
4. Block SM. Making light work with optical tweezers. *Nature* 1992;360(6403):493–495. [PubMed: 1448176]A short review with basic principles. (E)
5. Chu S. Laser Trapping of Neutral Particles. *Sci Am* 1992;268(2):71–76.Good introduction to trapping capabilities. (E)
6. Kuo SC, Sheetz MP. Optical tweezers in cell biology. *Trends Cell Biol* 1992;2:116–118. [PubMed: 14732016]A short review. (E)
7. Simmons RM, Finer JT. Optical Tweezers: Glasperlenspiel—II. *Curr Biol* 1993;3(5):309–311. [PubMed: 15335758]A general discussion of optical tweezers is provided. (E)
8. Svoboda K, Block SM. Biological applications of optical forces. *Annu Rev Biophys Biomol Struct* 1994;23:247–285. [PubMed: 7919782]This review provides a good foundation for general understanding of optical tweezers for the serious reader. Includes an introduction to instrument construction, trapping theory, calibration and detection methods, and a table of objective transmittances in the near infrared. (I)
9. Sato S, Inaba H. Optical trapping and manipulation of microscopic particles and biological cells by laser beams. *Opt Quantum Electron* 1996;28:1–16.Review of basic principles and features of single beam optical trapping of cells, latex spheres, crystals, and metal particles. A review. (E)
10. Ashkin A. Optical trapping and manipulation of neutral particles using lasers. *Proc Natl Acad Sci USA* 1997;94(10):4853–4860. [PubMed: 9144154]Outlines the history and recent developments of optical trapping. (I)
11. Berns MW. Laser scissors and tweezers. *Sci Am* 1998;278(4):62–67. [PubMed: 9532771](E)
12. Visscher K, Block SM. Versatile optical traps with feedback control. *Methods Enzymol* 1998;298:460–489. [PubMed: 9751903](I)
13. Mehta AD, Rief M, Spudich JA, Smith DA, Simmons RM. Single-molecule biomechanics with optical methods. *Science* 1999;283(5408):1689–1695. [PubMed: 10073927]A review that describes a number of single molecule methods using optical tweezers. (E)
14. Ashkin A. History of optical trapping and manipulation of small-neutral particle, atoms, and molecules. *IEEE J Sel Top Quantum Electron* 2000;6(6):841–856.A review. (I)
15. Ishii Y, Ishijima A, Yanagida T. Single molecule nanomanipulation of biomolecules. *Trends Biotechnol* 2001;19(6):211–216. [PubMed: 11356282]A good introduction to combined single molecule imaging and manipulation techniques for the study of molecular motors. (E)
16. Ishijima A, Yanagida T. Single molecule nanobioscience. *Trends Biochem Sci* 2001;26(7):438–444. [PubMed: 11440856]Exciting advances in single molecule fluorescence and manipulation methods including combined SMF with optical tweezers are reviewed. (E)
17. Kuo SC. Using optics to measure biological forces and mechanics. *Traffic* 2001;2(11):757–763. [PubMed: 11733041]A review including optical stretching. (I)

IV. OPTICAL TWEEZERS, CURRENT RESEARCH TOPICS

A. Earlier works on radiation pressure

18. Ashkin A, Dziedzic JM. Optical levitation by radiation pressure. *Appl Phys Lett* 1971;19:283–285. Glass spheres are levitated with radiation pressure in air and vacuum. (I)
19. Ashkin A. Acceleration and trapping of particles by radiation pressure. *Phys Rev Lett* 1970;24(4):156–159. The first observation of the acceleration of suspended particles using radiation pressure. (I)
20. Ashkin A, Dziedzic JM. Optical Levitation of Liquid Drops by Radiation Pressure. *Science* 1975;187(4181):1073–1075. [PubMed: 17799687] Drops in the size range of 1 to 40 micrometers are levitated and manipulated with the trap. (I)
21. Ashkin A, Dziedzic JM. Optical Levitation in High-Vacuum. *Appl Phys Lett* 1976;28(6):333–335. Optical levitation down to a pressure of 10^{-6} Torr was observed under high-vacuum. (I)
22. Ashkin A, Dziedzic JM. Feedback Stabilization of Optically Levitated Particles. *Appl Phys Lett* 1977;30(4):202–204. (I)
23. Ashkin A. Trapping of atoms by resonance radiation pressure. *Phys Rev Lett* 1978;40(12):729–732. A method for trapping, cooling, and manipulating sodium atoms is described. (I)
24. Ashkin A. Applications of Laser Radiation Pressure. *Science* 1980;210(5):1081–1088. [PubMed: 17831450] Radiation pressure is discussed for neutral particles, including applications for microscopic particles and atoms. (I)
25. Ashkin A, Dziedzic JM. Observation of light scattering from nonspherical particles using optical levitation. *Appl Opt* 1980;19(5):660–668. Objects including spheroids, spherical doublets, triplets, etc. were studied. (I)
26. Ashkin A, Dziedzic JM, Smith PW. Continuous-wave self-focusing and self-trapping of light in artificial Kerr media. *Opt Lett* 1982;7(6):276–278. Beam trajectory and shapes arising from self-trapping are presented for laser modes exhibiting self-focusing in suspensions of submicroscopic particles. (I)

B. Seminal studies on optical tweezers

27. Ashkin A, Dziedzic JM, Bjorkholm JE, Chu S. Observation of a Single-Beam Gradient Force Optical Trap for Dielectric Particles. *Opt Lett* 1986;11(5):288–290. This is the original paper describing the invention of optical tweezers. Trapping of particles ranging from 10 μm to ~ 25 nm was observed in this single beam trap. (I)
28. Ashkin A, Dziedzic JM. Optical trapping and manipulation of viruses and bacteria. *Science* 1987;235(4795):1517–1520. [PubMed: 3547653] Tobacco mosaic virus and single *Escherichia coli* bacteria. One of the first reports of biological applications of optical traps. (E)
29. Ashkin A, Dziedzic JM, Yamane T. Optical trapping and manipulation of single cells using infrared laser beams. *Nature* 1987;330(6150):769–771. [PubMed: 3320757] One of the first reports of biological applications of optical trapping including the manipulation of particles within the cytoplasm of cells. (E)

C. Instrument design

The most common and straightforward method of building optical tweezers instrumentation is to custom-fit an optical microscope that already incorporates imaging capabilities and a good objective lens used for forming a trap. Attention to stable instrument construction and alignment details will improve the usability of the instrument. When deciding where to place an instrument, minimizing room temperature variations, acoustical noise, and mechanical vibrations should all be considered.

The references below describe a range of instruments from simple, single-beam traps to sophisticated multi-component systems. The incorporation of technologies in optical tweezers designs, frequently requiring ingenuity, has led to powerful new experimental methods. A broad range of components including trapping lasers, lenses, detection systems, calibration methods, and beam steering solutions has been incorporated into tweezers designs.

Technologies for beam steering and multiple trap generation, including acoustooptic deflectors and galvanometer scanning mirrors, are outlined in some of the following papers. Computer control, automation, and data acquisition are critical components of optical tweezers experiments. The experimental requirements (speed of a motor, required position sensitivity, force regime desired) should provide a guide for optimizing the design of an instrument. Multiple feedback methods for force and position clamping have been implemented. Note that many research papers, found in other sections of this Resource Letter, contain instrument design details outlined in materials and methods sections.

30. Constructing optical tweezers. In: Spector, D.; Goldman, R.; Leinward, L., editors. *Cell Biology: A Laboratory Manual*. NY: Cold Spring Harbor, Cold Spring Harbor; 1998. A good place to start. (E)
31. Visscher K, Brakenhoff GJ. Single beam optical trapping integrated in a confocal microscope for biological applications. *Cytometry* 1991;12(6):486–491. [PubMed: 1764973]Includes trapping theory, force calculation, and a description of the principle of trap manipulation by objective lens movement. (I)
32. Afzal RS, Treacy EB. Optical tweezers using a diode laser. *Rev Sci Instrum* 1992;63(4):2157–2163. Straightforward demonstration of using a diode laser to form an optical trap. (E)
33. Schut TCB, Schipper EF, de Grooth BG, Greve J. Optical-Trapping Micromanipulation Using 780-Nm Diode-Lasers. *Opt Lett* 1993 E;18(6):447–449.
34. Visscher K, Brakenhoff GJ, Krol JJ. Micromanipulation by ‘multiple’ optical traps created by a single fast scanning trap integrated with the bilateral confocal scanning laser microscope. *Cytometry* 1993;14(2):105–114. [PubMed: 8440145]Includes a description of the instrument with fast scanning by acoustooptic modulation and galvanometric scan mirrors. (A)
35. Escandon GJ, Liu Y, Sonek GJ, Berns MW. Beam Magnification and the Efficiency of Optical Trapping with 790-nm AlGaAs Laser Diodes. *IEEE Photonics Technol Lett* 1994;6(5):597–600. Discussion of trap efficiency with respect to input beam shape. Includes correction of diode output ellipticity using anamorphic prisms. (E)
36. Jong YC, Chen HM, Hsu JH, Fann WS. Constructions and Applications of a Simple Optical Tweezers. *Zool Stu* 1995;34(S1):209–210. (E)
37. Visscher K, Gross SP, Block SM. Construction of multiple-beam optical traps with nanometer-resolution position sensing. *IEEE J Sel Top Quantum Electron* 1996;2(4):1066–1076. This paper discusses two types of optical tweezers instruments. Includes calibration methods, time-shared traps, instrument construction details, and a discussion of general desired features. (I)
38. Simmons RM, Finer JT, Chu S, Spudich JA. Quantitative measurements of force and displacement using an optical trap. *Biophys J* 1996;70(4):1813–1822. [PubMed: 8785341]Includes a schematic of the optical trap and detection system along with circuits with feedback arrangements. (I)
39. Chiou AE, Wang W, Sonek GJ, Hong J, Berns MW. Interferometric optical tweezers. *Opt Commun* 1997;133(1–6):7–10. Two beams generate an interference fringe for trapping and micromanipulation. (I)
40. Fallman E, Axner O. Design for fully steerable dual-trap optical tweezers. *Appl Opt* 1997;36(10):2107–2113. A detailed recipe for the construction is provided. (E)
41. Grego S, Arimondo E, Frediani C. Optical tweezers based on near infrared diode laser. *J Biomed Opt* 1997;2(3):332–339. A single-mode 100 mW diode operating at 840 nm was used. (E)
42. Wang W, Chiou AE, Sonek GJ, Berns MW. Self-aligned dual-beam optical laser trap using photorefractive phase conjugation. *J Opt Soc Am B* 1997;14(4):697–704. Phase conjugation in a crystal is used to form a dual trap in a counterpropagating arrangement. Includes a description of the instrument, theoretical analysis, and a performance comparison against a single beam trap. (A)
43. Dufresne ER, Grier DG. Optical tweezer arrays and optical substrates created with diffractive optics. *Rev Sci Instrum* 1998;69(5):1974–1977. A diffractive optical element is used to create multiple optical tweezers from a single laser beam. (I)
44. Smith SP, Bhalotra SR, Brody AL, Brown BL, Boyda EK, Prentiss M. Inexpensive optical tweezers for undergraduate laboratories. *Am J Phys* 1999;67(1):26–35. General introduction to setting up an instrument. (E)

45. Hoffmann A, Meyerzu Horste G, Pilarczyk G, Monajembashi S, Uhl V, Greulich KO. Optical tweezers for confocal microscopy. *Appl Phys B* 2000;71(5):747–753. A method is presented to keep the trap fixed while doing 3D z-sectioning imaging. (I)
46. Liesener J, Reicherter M, Haist T, Tiziani HJ. Multi-functional optical tweezers using computer-generated holograms. *Opt Commun* 2000;185(1–3):77–82. Seven spheres are trapped independently. (I)
47. Mio C, Gong T, Terray A, Marr DWM. Design of a scanning laser optical trap for multiparticle manipulation. *Rev Sci Instrum* 2000;71(5):2196–2200. Scanning is achieved using a piezo-actuated mirror. Details of the experimental arrangement and demonstration of trapping of multiple particles simultaneously is provided. (I)
48. Sun W, Wang YQ, Gao CM. Construction of an optical tweezers: Calculation and experiments. *Chin Phys* 2000;9(11):855–860. (I)
49. Wuite GJL, Davenport RJ, Rappaport A, Bustamante C. An integrated laser trap/flow control video microscope for the study of single biomolecules. *Biophys J* 2000;79(2):1155–1167. [PubMed: 10920045] Detailed description of an instrument that combines optical tweezers and micropipettes to perform experiments deep within a flow chamber. Video microscopy and deflection are used for detection. Forces are applied with optical tweezers and a computer-controlled flow system. Used to study the transcription of RNA polymerase. (A)
50. Dufresne ER, Spalding GC, Dearing MT, Sheets SA, Grier DG. Computer-generated holographic optical tweezer arrays. *Rev Sci Instrum* 2001;72(3):1810–1816. An adaptive-additive algorithm method is presented for creating planar arrays of holographic optical tweezers. (A)
51. Resnick A. Design and construction of a space-borne optical tweezer apparatus. *Rev Sci Instrum* 2001;72(11):4059–4065. Optical tweezers in space; a rugged design is detailed. (E)
52. Lang MJ, Asbury CL, Shaevitz JW, Block SM. An Automated 2D Force Clamp for Single Molecule Studies. *Biophys J* 2002;83:491–501. [PubMed: 12080136] This paper describes a fully-automated trapping instrument used as a two-dimensional force clamp for kinesin motility measurements. The instrument is capable of simultaneous optical tweezers and single molecule fluorescence. (I)

1. Detection method: video, quadrant photodiode, interferometry, and others

Position detection may be achieved in many ways including video, quadrant photodiode, and interferometric methods. Time response and position sensitivity should be considered when deciding on a detection method. Video microscopy is straightforward and can be used to track a particle with sub-pixel resolution. Video detection has limited time response and is not as convenient for systems requiring fast positional feedback. Quadrant photodiodes, placed in either an image or back focal plane, can be used for two- or three-dimensional position sensing. Quadrant-photodiode detection, which in some instances utilizes a separate detector beam for convenience, has both a faster time response and greater position sensitivity. Interferometry is another sensitive position-sensing method that is used to detect displacement along one axis.

53. Kamimura S. Direct Measurement of Nanometric Displacement under an Optical Microscope. *Appl Opt* 1987;26(16):3425–3427. (I)
54. Denk W, Webb WW. Optical measurement of picometer displacements of transparent microscopic objects. *Appl Opt* 1990;29(16):2382–2391. Description of the instrument and interferometer including signal detection and amplification circuitry. (A)
55. Florin EL, Horber JKH, Stelzer EHK. High-resolution axial and lateral position sensing using two-photon excitation of fluorophores by a continuous-wave Nd:YAG laser. *Appl Phys Lett* 1996;69(4):446–448. Changes in fluorescence due to displacement are used as a spatial sensor. Includes a fluorescence intensity versus z-position graph. (I)
56. Friesen MEJ, Rubinsztein-Dunlop H, Heckenberg NR, Dearden EW. Determination of the force constant of a single-beam gradient trap by measurement of backscattered light. *Appl Opt* 1996;35(36):7112–7116. Model of the trap as a harmonic oscillator with measurements. (I)
57. Li DQ, Schnapp BJ. Improved nm displacement detector for microscopic beads at frequencies below 10 Hz. *Rev Sci Instrum* 1997;68(5):2195–2199. Laser interferometry detection is outlined in this paper. (E)

58. Mehta AD, Finer JT, Spudich JA. Detection of single-molecule interactions using correlated thermal diffusion. *Proc Natl Acad Sci USA* 1997;94(15):7927–7931. [PubMed: 9223289]Methods are described to detect and correlate the motion of optically trapped beads attached to both ends of a single actin filament. (I)
59. Sasaki K, Tsukima M, Masuhara H. Three-dimensional potential analysis of radiation pressure exerted on a single microparticle. *Appl Phys Lett* 1997;71(1):37–39.Total internal reflection microscopy is used in this three-dimensional position sensing method. (I)
60. Gittes F, Schmidt CF. Interference model for back-focal-plane displacement detection in optical tweezers. *Opt Lett* 1998;23(1):7–9. [PubMed: 18084394]Description including a model comparison with experiment for the signal of back-focal-plane imaging using a quadrant photodiode. (A)
61. Peters IM, de Grooth BG, Schins JM, Figdor CG, Greve J. Three dimensional single-particle tracking with nanometer resolution. *Rev Sci Instrum* 1998;69(7):2762–2766.Axial position sensitivity is achieved by positioning a photodiode so that it captures on the order of half of the transmitted light intensity. A feedback system controls the position of the collection objective using a piezo tube. (I)
62. Friesen MEJ, Truscott AG, Rubinsztein-Dunlop H, Heckenberg NR. Three-dimensional imaging with optical tweezers. *Appl Opt* 1999;38(31):6597–6603.This paper reports that features of approximately 200 nm can be resolved with a sensitivity of 5 nm. (I)
63. Higurashi E, Sawada R, Ito T. Nanometer-displacement detection of optically trapped metallic particles based on critical angle method for small force detection. *Rev Sci Instrum* 1999;70(7):3068–3073.Detection is based on critical-angle prisms where angle changes originating from trapped particle motion provide a sensitive measure of position. (I)
64. Peters IM, vanKooyk Y, van Vliet SJ, de Grooth BG, Figdor CG, Greve J. 3D single-particle tracking and optical trap measurements on adhesion proteins. *Cytometry* 1999;36(3):189–194. [PubMed: 10404967]Cell adhesion studies. (I)
65. Pralle A, Prummer M, Florin EL, Stelzer EHK, Horber JKH. Three-dimensional high-resolution particle tracking for optical tweezers by forward scattered light. *Microsc Res Tech* 1999;44(5):378–386. [PubMed: 10090214]The ratio of the intensity of scattered light to the total amount of light is used for axial position determination. A model for the position signal is presented. (A)

2. Calibration

The force exerted on an object by an optical trap depends both on the trap (shape and intensity) and the object (size and composition). Detailed knowledge of the force exerted on a particle is a critical quantity in biochemical, kinetic, and mechanical trapping experiments. Force calibration is achieved by a number of methods, each with different advantages. The drag or escape force method is performed by moving an object or stage while monitoring an “escape” velocity, and is particularly useful to check the linearity of trapping potential in regions far from the trap center. The equipartition method, which is straightforward and fast, measures thermal fluctuations in position of a trapped particle. The power spectral method provides stiffness information in addition to a diagnostic for noise sources at various frequencies. In addition to the methods having different advantages, multiple methods provide a good consistency check of the overall trap stiffness.

66. Burns MM, Fournier JM, Golovchenko JA. Optical binding. *Phys Rev Lett* 1989;63(12):1233–1236. [PubMed: 10040510]Long-range bound states of plastic spheres, detection using fringe spacing, in the presence of an optical field are presented. Fringe spacing is used for detection. (I)
67. Ghislain LP, Switz NA, Webb WW. Measurement of small forces using an optical trap. *Rev Sci Instrum* 1994;65:2762–2768.Includes calibration using drag force and signal source considerations. (A)
68. Felgner H, Muller O, Schliwa M. Calibration of Light Forces in Optical Tweezers. *Appl Opt* 1995;34(6):977–982.It is shown that trapping in different axial positions is possible. (I)
69. Wang W, Liu Y, Sonek GJ, Berns MW, Keller RA. Optical Trapping and Fluorescence Detection in Laminar-Flow Streams. *Appl Phys Lett* 1995;67(8):1057–1059.Escape velocities are measured relative to the position within the flow stream. (A)

70. Clapp AR, Ruta AG, Dickinson RB. Three-dimensional optical trapping and evanescent wave light scattering for direct measurement of long range forces between a colloidal particle and a surface. *Rev Sci Instrum* 1999;70(6):2627–2636. Total internal reflection of a laser beam creates an evanescent wave that is used to determine particle position. (I)
71. Singer W, Bernet S, Hecker N, RitschMarte M. Three-dimensional force calibration of optical tweezers. *J Mod Opt* 2000;47(14–15):2921–2931.(I)
72. Huang CC, Wang CF, Mehta DS, Chiou A. Optical tweezers as sub-pico-newton force transducers. *Opt Commun* 2001;195(1–4):41–48. A drag method was used to determine the trapping force, including a weak probing beam. (I)

3. Fiber-based traps

Light exiting from a fiber, because of its steep spatial gradient, can be used to trap objects, provided that the repulsive scattering force is more than balanced. The most common fiber-based trap involves two counter-propagating beams, to neutralize the scattering force in the central region. Because there are no local lenses, fiber-based traps have the advantage of being able to penetrate deep into solution. Fiber-based traps have also been used for cell stretching studies.

73. Constable A, Kim J, Mervis J, Zarinetchi F, Prentiss M. Demonstration of a fiberoptic light-force trap. *Opt Lett* 1993;18(21):1867–1869. Single-mode fibers. Includes sample cell construction information. (I)
74. Lyons ER, Sonek GJ. Confinement and bistability in a tapered hemispherically lensed optical fiber trap. *Appl Phys Lett* 1995;66(13):1584 –1586. Axial and transverse trap efficiencies are predicted and confirmed. (I)
75. Sidick E, Collins SD, Knoesen A. Trapping forces in a multiple-beam fiber-optic trap. *Appl Opt* 1997;36(25):6423–6433. Forces are calculated for microspheres located both on and off axis relative to the beam axis. (A)
76. Collins SD, Baskin RJ, Howitt DG. Microinstrument gradient-force optical trap. *Appl Opt* 1999;38(28):6068–6074. [PubMed: 11543218] Consists of four single-mode fibers. (I)
77. Renn MJ, Pastel R, Lewandowski HJ. Laser guidance and trapping of mesoscale particles in hollow-core optical fibers. *Phys Rev Lett* 1999;82(7):1574 –1577. Laser light coupled into a hollow-core fiber can be used to trap and guide mesoscale particles over relatively long distances. (I)
78. Guck J, Ananthakrishnan R, Mahmood H, Moon TJ, Cunningham CC, Kas J. The optical stretcher: a novel laser tool to micromanipulate cells. *Biophys J* 2001;81(2):767–784. [PubMed: 11463624] Objects trapped between two fibers are stretched in a nonfocused geometry. (I)

D. Theory of optical tweezers

A wide range of models and degrees of sophistication have been applied to the theory of optical tweezers. The size, shape, and composition of an object are important quantities when determining an appropriate theory. Laser focusing properties such as the mode, input beam diameter, and numerical aperture of the lens are also critical. Theories have been developed for describing the expected signal detection shapes. Many of the references below include both theory and experiments.

79. Barton JP. Internal and near-surface electromagnetic fields for a spherical particle irradiated by a focused light beam. *J Appl Phys* 1988;64(4):1632–1639.(I)
80. Barton JP, Alexander DR. Fifth-order corrected electromagnetic field components for a fundamental Gaussian beam. *J Appl Phys* 1989;66(7):2800–2802.(I)
81. Barton JP, Alexander DR, Schaub SA. Theoretical determination of net radiation force and torque for a spherical particle illuminated by a focused laser beam. *J Appl Phys* 1989;66(10):4594 –4602. Calculations for a 5 μm diameter water droplet levitated in air. (A)
82. Ashkin A. Forces of a Single-Beam Gradient Laser Trap on a Dielectric Sphere in the Ray Optics Regime. *Biophys J* 1992;61(2):569–582. Includes the effect of index of refraction on the performance of a trap. (A)

83. Gussgard R, Lindmo T, Brevik I. Calculation of the Trapping Force in a Strongly Focused Laser-Beam. *J Opt Soc Am B* 1992;9(10):1922–1930.(I)
84. Visscher K, Brakenhoff GJ. Theoretical study of optically induced forces on spherical particles in a single beam trap I: Rayleigh scatterers. *Optik* 1992;89(2):174–180.Uses electromagnetic diffraction theory. (I)
85. Visscher K, Brakenhoff GJ. Theoretical study of optically induced forces on spherical particles in a single beam trap II: Mie scatterers. *Optik* 1992;90(2):57–60.Vector diffraction theory of Mie scatterers. (A)
86. Wright WH, Sonek GJ, Berns MW. Radiation trapping forces on microspheres with optical tweezers. *Appl Phys Lett* 1993;63(6):715–717.Forces are predicted and compared, for spheres of various size and composition, with experimental measurements. (I)
87. Ren KF, Greha G, Gouesbet G. Radiation Pressure Forces Exerted on a Particle Arbitrarily Located in a Gaussian-Beam by Using the Generalized Lorenz-Mie Theory, and Associated Resonance Effects. *Opt Commun* 1994;108(4–6):343–354.(A)
88. Wright WH, Sonek GJ, Berns MW. Parametric study of the forces on microspheres held by optical tweezers. *Appl Opt* 1994;33(9):1735–1748.Includes theory and tables of trapping parameters through various microscope objectives and trapping efficiencies for different sizes and types of spheres and input polarizations. (A)
89. Almaas E, Brevik I. Radiation Forces on a Micrometer-Sized Sphere in an Evanescent Field. *J Opt Soc Am B* 1995;12(12):2429–2438.Theoretical investigation used to predict the radiation forces in an evanescent wave of given polarization. (A)
90. Harada Y, Asakura T. Radiation forces on a dielectric sphere in the Rayleigh scattering regime. *Opt Commun* 1996;124(5–6):529–541.(I)
91. Wohland T, Rosin A, Stelzer EHK. Theoretical determination of the influence of the polarization on forces exerted by optical tweezers. *Optik* 1996;102(4):181–190.Significant differences in lateral forces can occur depending on the polarization orientation. (A)
92. Gittes F, Schmidt CF. Thermal noise limitations on micromechanical experiments. *Eur Biophys J with Biophys Lett* 1998;27(1):75–81.Strategies for maximizing signal-to-noise ratios are investigated theoretically. Includes experimental examples. (I)
93. Harada Y, Asakura T. Dynamics and dynamic light scattering properties of Brownian particles under laser radiation pressure. *Pure Appl Opt* 1998;7(5):1001–1012.(A)
94. Meller A, Bar-Ziv R, Tlustý T, Moses E, Stavans J, Safran SA. Localized dynamic light scattering: A new approach to dynamic measurements in optical microscopy. *Biophys J* 1998;74(3):1541–1548. [PubMed: 9512050]The force constants for a single bead and pair of beads are calculated. (A)
95. Schonle A, Hell SW. Heating by absorption in the focus of an objective lens. *Opt Lett* 1998;23(5):325–327. [PubMed: 18084500]Numerical results for local heating under typical optical trapping conditions are presented. (I)
96. Tlustý T, Meller A, Bar-Ziv R. Optical gradient forces of strongly localized fields. *Phys Rev Lett* 1998;81(8):1738–1741.Predictions for force-dependent curves, maximal trapping forces, and force constants are derived. (I)
97. Lester M, Nieto-Vesperinas M. Optical forces on microparticles in an evanescent laser field. *Opt Lett* 1999;24(14):936–938. [PubMed: 18073901]Theory of forces in an evanescent laser field. (A)
98. Dogariu AC, Rajagopalan R. Optical traps as force transducers: The effects of focusing the trapping beam through a dielectric interface. *Langmuir* 2000;16(6):2770–2778.Trap forces are calculated using wave optics calculations. Includes the identification of secondary traps. (A)
99. Inami W, Kawata Y. Analysis of the scattered light distribution of a tightly focused laser beam by a particle near a substrate. *J Appl Phys* 2001;89(11):5876–5880.Scattering fields near a substrate are calculated. (I)
100. Nieminen TA, Rubinsztein-Dunlop H, Heckenberg NR. Calculation and optical measurement of laser trapping forces on non-spherical particles. *J Quant Spectrosc Radiat Transf* 2001;70(4–6):627–637.Includes calculations of force and torque. (I)
101. Rohrbach A, Stelzer EHK. Optical trapping of dielectric particles in arbitrary fields. *J Opt Soc Am A* 2001;18(4):839–853.In-depth study of calculating trapping potentials. (A)

102. Agayan R, Gittes F, Kopelman R, Schmidt CF, SPIE. Optical trapping near-resonance absorption. (Int Soc Opt Eng) Proc 2001;4431:341–351. Theory and analysis for enhanced trapping forces of near-resonant frequencies are presented. (A)

E. Experiments using optical tweezers

1. Mechanical and single molecule measurements

Mechanical properties such as elasticity, stiffness, rigidity, and torque can be measured using optical tweezers. Light is easily manipulated and relatively noninvasive, making laser-based mechanical measurements straightforward for studying biological systems. Cells, intracellular structures, filaments, and single molecules have all been probed. Multiple traps can be used to construct additional geometries for mechanical measurements. Combinations of optical tweezers and other methods, such as micropipettes, fluorescence microscopy, and microsurgery, provide very powerful tools for studying biological systems.

Single molecule mechanical measurements using optical tweezers, including biological motor motility, protein-protein unbinding, and protein unfolding, have experienced a tremendous growth in recent years. Throughout these papers, assay development remains a critical component, including details of slide/flow cell construction, methods for attaching samples to microspheres, and general assay conditions.

103. Kurachi M, Hoshi M, Tashiro H. Buckling of a Single Microtubule by Optical Trapping Forces: Direct Measurement of Microtubule Rigidity. *Cell Motil Cytoskeleton* 1995;30(3):221–228. [PubMed: 7758138]The microtubule rigidity was found to be dependent on length. (I)
104. Chiu DT, Zare RN. Biased diffusion; optical trapping; and manipulation of single molecules in solution. *J Am Chem Soc* 1996;118(27):6512–6513. (I)
105. Felgner H, Frank R, Schliwa M. Flexural rigidity of microtubules measured with the use of optical tweezers. *J Cell Sci* 1996;109(2):509–516. [PubMed: 8838674]Microtubules are actively moved with optical tweezers while the microtubule shape is observed. (I)
106. Miyata H, Yasuda R, Kinoshita K Jr. Strength and lifetime of the bond between actin and skeletal muscle alpha-actinin studied with an optical trapping technique. *Biochim Biophys Acta* 1996;1290(1):83–88. [PubMed: 8645711]Suggestion of two classes of actin-actinin bonds, based on unbinding time measurements. (I)
107. Optical tweezers for single molecule mechanics. In: Coombs, RRH.; Robinson, DW., editors. *Nanotechnology in Medicine and the Biosciences, Developments in Nanotechnology*. The Netherlands: Gordon & Breach; 1996. A short book chapter that includes a design for studying actin myosin muscle proteins. (E)
108. Tsuda Y, Yasutake H, Ishijima A, Yanagida T. Torsional rigidity of single actin filaments and actin-actin bond breaking force under torsion measured directly by *in vitro* micromanipulation. *Proc Natl Acad Sci USA* 1996;93(23):12937–12942. [PubMed: 8917522]This study includes the use of optical tweezers and fluorescent beads to measure rotational Brownian motion. (I)
109. Chiu DT, Hsiao A, Gaggar A, GarzaLopez RA, Orwar O, Zare RN. Injection of ultrasmall samples and single molecules into tapered capillaries. *Anal Chem* 1997;69(10):1801–1807. [PubMed: 9164157]Optical tweezers place objects at or near the inlet of tapered capillaries. (I)
110. Dupuis DE, Guilford WH, Wu J, Warshaw DM. Actin filament mechanics in the laser trap. *J Muscle Res Cell Motil* 1997;18(1):17–30. [PubMed: 9147990]Independent laser traps were used in this study to determine the compliance of actin filaments. (I)
111. Funatsu T, Harada Y, Higuchi H, Tokunaga M, Saito K, Ishii Y, Vale RD, Yanagida T. Imaging and nano-manipulation of single biomolecules. *Biophys Chem* 1997;68(1–3):63–72. [PubMed: 9468610]Early experiments with combined single molecule fluorescence and optical tweezers. (I)
112. Kellermayer MSZ, Smith SB, Granzier HL, Bustamante C. Folding-Unfolding Transitions in Single Titin Molecules Characterized with Laser Tweezers. *Science* 1997;276:1112–1116. [PubMed: 9148805]Includes unfolding and refolding curves. A combined micropipette and optical trap geometry is employed. (I)

113. Luo ZP, Bolander ME, An KN. A method for determination of stiffness of collagen molecules. *Biochem Biophys Res Commun* 1997;232(1):251–254. [PubMed: 9125142](I)
114. Tskhovrebova L, Trinick J, Sleep JA, Simmons RM. Elasticity and unfolding of single molecules of the giant muscle protein titin. *Nature* 1997;387(6630):308–312. [PubMed: 9153398]Single molecule mechanical experiment of titin with optical tweezers. (I)
115. Kellermayer MSZ, Smith SB, Bustamante C, Granzier HL. Complete unfolding of the titin molecule under external force. *J Struct Biol* 1998;122(1–2):197–205. [PubMed: 9724621]Titin molecules are stretched with forces above 400 pN. (I)
116. Wang MD. Manipulation of single molecules in biology. *Curr Opin Biotechnol* 1999;10(1):81–86. [PubMed: 10047511]Highlights optical tweezers single molecule motor assays. (E)
117. Bustamante C, Macosko JC, Wuite GJL. Grabbing the cat by the tail: Manipulating molecules one by one. *Nat Rev Mol Cell Biol* 2000;1(2):130–136. [PubMed: 11253365]A review. (E)
118. Gerbal F, Laurent V, Ott A, Carlier MF, Chaikin P, Prost J. Measurement of the elasticity of the actin tail of *Listeria monocytogenes*. *Eur Biophys J with Biophys Lett* 2000;29(2):134–140.(I)
119. Thoumine O, Kocian P, Kottelat A, Meister JJ. Short-term binding of fibroblasts to fibronectin: optical tweezers experiments and probabilistic analysis. *Eur Biophys J with Biophys Lett* 2000;29(6):398–408.Adhesion tests of fibroblasts on fibronectin-coated glass. (I)
120. Merkel R. Force spectroscopy on single passive biomolecules and single bio-molecular bonds. *Phys Rep Phys Lett* 2001;346(5):344–385.A review. (I)
121. Nieminen TA, Heckenberg NR, Rubinsztein-Dunlop H. Optical measurement of microscopic torques. *J Mod Opt* 2001;48(3):405–413.(I)
122. Kellermayer MSZ, Smith SB, Bustamante C, Granzier HL. Mechanical fatigue in repetitively stretched single molecules of titin. *Biophys J* 2001;80(2):852–863. [PubMed: 11159452]Optical tweezers were used to repetitively stretch and release titin to study mechanical fatigue. (I)
123. Stout AL. Detection and characterization of individual intermolecular bonds using optical tweezers. *Biophys J* 2001;80(6):2976–2986. [PubMed: 11371470]Details of the instrument, technique and geometry for rupture force measurements are shown. (I)
124. Sun YL, Luo ZP, An KN. Stretching short biopolymers using optical tweezers. *Biochem Biophys Res Commun* 2001;286(4):826–830. [PubMed: 11520072]The stiffness of procollagen molecules was studied. (I)
125. Wang K, Forbes JG, Jin AJ. Single molecule measurements of titin elasticity. *Prog Biophys Mol Biol* 2001;77(1):1–44. [PubMed: 11473785]A review. (I)
126. Takasone T, Juodkazis S, Kawagishi Y, Yamaguchi A, Matsuo S, Sakakibara H, Nakayama H, Misawa H. Flexural rigidity of a single microtubule. *Jpn J Appl Phys* 2002;41(5):3015–3019.Shear compression and bending stress on a microtubule was studied using optical tweezers. (I)

2. Biological motors

Biological motors are excellent model systems for observing protein motions and conformational changes, and are a subject of intense research. Motor properties such as speed, force, processivity, working stroke distance, and substrate should be considered when designing an experiment. Many technological developments, including force clamping, the three-bead assay, and computer automation of trap and sample positioning have been used in biological motor research. We encourage the reader to explore experimental innovations implemented in multiple motor systems.

a. General motors

127. Cooke R. *Molecular Motors: Structure, Mechanics and Energy Transduction* edited by . *Biophys J* 1995;68(4):1s–382s. [PubMed: 7787050]This supplemental issue is a Biophysical Discussions conference proceedings dedicated to molecular motors, and contains several papers related to optical trapping studies. (E)
128. Gittes F, Schmidt CF. Microscopic approaches to dynamics and structure of biological motors. *Curr Opin Solid State Mater Sci* 1996;1(3):412–424.A review. (I)
129. Simmons R. Molecular motors: single-molecule mechanics. *Curr Biol* 1996;6(4):392–394.(E)

130. Block SM. Real engines of creation. *Nature* 1997;386(6622):217–219. [PubMed: 9069274]An introduction to the study of molecular motors with new biophysical techniques. (E)
131. Khan S, Sheetz MP. Force effects on biochemical kinetics. *Annu Rev Biochem* 1997;66:785–805. [PubMed: 9242924]Applications of force measurements to enzyme activity and motor proteins are presented including a comparison with other force measurement methods. (I)
132. Allersma MW, Gittes F, deCastro MJ, Stewart RJ, Schmidt CF. Two-dimensional tracking of ncd motility by back focal plane interferometry. *Biophys J* 1998;74(2):1074–1085. [PubMed: 9533719] Includes 2D detection with a quadrant photodiode and theory. (A)
133. Mehta AD, Finer JT, Spudich JA. Use of optical traps in single-molecule study of nonprocessive biological motors. *Methods Enzymol* 1998;298:436–459. [PubMed: 9751902]A review. (I)
134. Shingyoji C, Higuchi H, Yoshimura M, Katayama E, Yanagida T. Dynein arms are oscillating force generators. *Nature* 1998;393(6686):711–714. [PubMed: 9641685](I)
135. Welte MA, Gross SP, Postner M, Block SM, Wieschaus EF. Developmental regulation of vesicle transport in *Drosophila* embryos: Forces and kinetics. *Cell* 1998;92(4):547–557. [PubMed: 9491895](I)
136. Mehta AD, Rief M, Spudich JA. Biomechanics, one molecule at a time. *J Biol Chem* 1999;274(21):14517–14520. [PubMed: 10329637]Focus on some single molecule optical tweezers measurements. (E)
137. deCastro MJ, Fondecave RM, Clarke LA, Schmidt CF, Stewart RJ. Working strokes by single molecules of the kinesin-related microtubule motor ncd. *Nat Cell Biol* 2000;2(10):724–729. [PubMed: 11025663]Uses a three-bead geometry to measure the working stroke of ncd. (I)
138. Hirakawa E, Higuchi H, Toyoshima YY. Processive movement of single 22S dynein molecules occurs only at low ATP concentrations. *Proc Natl Acad Sci USA* 2000;97(6):2533–2537. [PubMed: 10706634]Stepwise movement of dynein is shown. (I)

b. Kinesin

Kinesin, which hydrolyzes ATP to move along microtubules, is a processive motor that takes about 100 steps before detaching. Kinesin's processivity makes it ideal for optical tweezers studies. Optical tweezers measurements have identified that kinesin steps in discrete, 8 nm increments and hydrolyzes one ATP per step. Instrumental innovations specifically geared towards measuring kinesin motility have led to a number of advances in optical tweezers.

139. Block SM, Goldstein LS, Schnapp BJ. Bead movement by single kinesin molecules studied with optical tweezers. *Nature* 1990;348(6299):348–352. [PubMed: 2174512](E)
140. Kawaguchi K, Ishiwata S. Nucleotide-dependent single-to double-headed binding of kinesin. *Science* 2001;291(5504):667–669. [PubMed: 11158681]Optical tweezers were used to measure the unbinding force of kinesin attached to microtubules under various nucleotide conditions. (I)
141. Svoboda K, Schmidt CF, Schnapp BJ, Block SM. Direct observation of kinesin stepping by optical trapping interferometry. *Nature* 1993;365(6448):721–727. [PubMed: 8413650]Kinesin moves with 8 nm steps. (I)
142. Svoboda K, Block SM. Force and velocity measured for single kinesin molecules. *Cell* 1994;77(5):773–784. [PubMed: 8205624]Optical trapping combined with interferometry. (I)
143. Svoboda K, Mitra PP, Block SM. Fluctuation Analysis of Motor Protein Movement and Single Enzyme-Kinetics. *Proc Natl Acad Sci USA* 1994;91(25):11782–11786. [PubMed: 7991536](I)
144. Block SM. Nanometers and Piconewtons: The Macromolecular Mechanics of Kinesin. *Trends Cell Biol* 1995;5(4):169–175. [PubMed: 14732153]Perspective on single motor assay measurements on kinesin. (E)
145. Coppin CM, Finer JT, Spudich JA, Vale RD. Detection of sub-8-nm movements of kinesin by high-resolution optical-trap microscopy. *Proc Natl Acad Sci USA* 1996;93(5):1913–1917. [PubMed: 8700858]Kinesin steps of both 8 and ~5 nm are presented in this sensitive measurement. (I)
146. Coppin CM, Pierce DW, Hsu L, Vale RD. The load dependence of kinesin's mechanical cycle. *Proc Natl Acad Sci USA* 1997;94(16):8539–8544. [PubMed: 9238012]Forward loads of kinesin motility are presented in this paper. (I)

147. Higuchi H, Muto E, Inoue Y, Yanagida T. Kinetics of force generation by single kinesin molecules activated by laser photolysis of caged ATP. *Proc Natl Acad Sci USA* 1997;94(9):4395–4400. [PubMed: 9114000]Combination of optical tweezers and UV photolysis of caged compounds. (I)
148. Inoue Y, Toyoshima YY, Iwane AH, Morimoto S, Higuchi H, Yanagida T. Movements of truncated kinesin fragments with a short or an artificial flexible neck. *Proc Natl Acad Sci USA* 1997;94(14):7275–7280. [PubMed: 9207081]Stepwise movement of kinesin observed with optical tweezers. (I)
149. Kojima H, Muto E, Higuchi H, Yanagida T. Mechanics of single kinesin molecules measured by optical trapping nanometry. *Biophys J* 1997;73(4):2012–2022. [PubMed: 9336196]Includes compliance correction to determine the displacement. The measurement was performed on axonemes. (I)
150. Crevel I, Carter N, Schliwa M, Cross R. Coupled chemical and mechanical reaction steps in a processive *Neurospora* kinesin. *EMBO J* 1999;18(21):5863–5872. [PubMed: 10545098]Shows kinesin stepping. (I)
151. Iwatani S, Iwane AH, Higuchi H, Ishii Y, Yanagida T. Mechanical and chemical properties of cysteine-modified kinesin molecules. *Biochemistry* 1999;38(32):10318–10323. [PubMed: 10441125]Mechanical properties of kinesin mutants were measured. (I)
152. Visscher K, Schnitzer MJ, Block SM. Single kinesin molecules studied with a molecular force clamp. *Nature* 1999;400(6740):184–189. [PubMed: 10408448]Force clamping was implemented to generate force-velocity relationships for kinesin motility. Details of implementing the force clamp are presented. (I)
153. Endow SA, Higuchi H. A mutant of the motor protein kinesin that moves in both directions on microtubules. *Nature* 2000;406(6798):913–916. [PubMed: 10972296]Optical tweezers were used to observe the directional bias of *ncd* and mutant motors. (I)
154. Kawaguchi K, Ishiwata S. Temperature dependence of force, velocity, and processivity of single kinesin molecules. *Biochem Biophys Res Commun* 2000;272(3):895–899. [PubMed: 10860848]The temperature dependence for various aspects of kinesin motility is measured. (I)
155. Schnitzer MJ, Visscher K, Block SM. Force production by single kinesin motors. *Nat Cell Biol* 2000;2(10):718–723. [PubMed: 11025662]Kinesin mechanochemistry, obtained from a force clamp, is modeled. (I)
156. Nishiyama M, Muto E, Inoue Y, Yanagida T, Higuchi H. Substeps within the 8-nm step of the ATPase cycle of single kinesin molecules. *Nat Cell Biol* 2001;3(4):425–428. [PubMed: 11283618]This measurement was optimized to observe fast kinesin transients. (I)

c. Myosin

Myosin, which moves on an actin substrate, is the subject of intense research. A three-bead assay has been developed to measure the properties of skeletal muscle myosin, a nonprocessive motor. In this geometry, two trapped beads suspend an actin filament above a third motor-coated bead. Motor interaction and power stroke movement of the filament can be detected by monitoring fluctuations and movement of the double bead system. Many innovations have been implemented to both simultaneously generate multiple traps and detect position in this geometry. More recently, *processive* myosins have been discovered (myosin V being an example) with properties somewhat similar to kinesin, and therefore amenable to many of the same techniques.

157. Shepherd GM, Corey DP, Block SM. Actin cores of hair-cell stereocilia support myosin motility. *Proc Natl Acad Sci USA* 1990;87(21):8627–8631. [PubMed: 2236074]Optical tweezers were used to deposit myosin-coated beads on actin cores of hair-cell stereocilia in an in vitro assay. (I)
158. Simmons RM, Finer JT, Warrick HM, Kralik B, Chu S, Spudich JA. Force on single actin filaments in a motility assay measured with an optical trap. *Adv Exp Med Biol* 1993;332:331–336. [PubMed: 8109348]Use of optical tweezers to measure actin filament movement on HMM. heavy meromyosin Includes quadrant-photodiode detection, acoustooptic modulation, feedback control, and a question and answer discussion. (I)

159. In Vitro Methods for Measuring Force and Velocity of the Actin-Myosin Interaction Using Purified Proteins. In: Scholey, JM., editor. *Methods in Cell Biology*. 39. New York: Academic; 1993. p. 1-21.pp.Includes feedback control using acoustooptic deflectors. (I)
160. Finer JT, Simmons RM, Spudich JA. Single myosin molecule mechanics: piconewton forces and nanometre steps. *Nature* 1994;368(6467):113–119. [PubMed: 8139653]Contains a description of their feedback-enhanced laser trap system which includes two beams and uses acoustooptic modulation and quadrant photodiode detection. (A)
161. Microscopic measurement of sliding and binding force between muscle proteins with optical tweezers. In: Ohzu, H.; Komatsu, S., editors. *Optical Methods in Biomedical and Environmental Sciences*. Amsterdam: Elsevier Science; 1994. p. 195-198.pp.A short report where the sliding and binding force between an actin filament, attached to the bead, and heavy-meromyosin molecules, on the surface, were measured using a dual (fluorescence and phase-contrast) imaging microscope. (E)
162. Saito K, Aoki T, Yanagida T. Movement of single myosin filaments and myosin step size on an actin filament suspended in solution by a laser trap. *Biophys J* 1994;66(3):769–777. [PubMed: 8011909]The instrument used in this experiment includes dual laser traps that are positioned using galvanometer scanners. (I)
163. Molloy JE, Burns JE, Kendrick-Jones J, Tregear RT, White DC. Movement and force produced by a single myosin head. *Nature* 1995;378(6553):209–212. [PubMed: 7477328](I)
164. Nishizaka T, Miyata H, Yoshikawa H, Ishiwata S, Kinoshita K Jr. Unbinding force of a single motor molecule of muscle measured using optical tweezers. *Nature* 1995;377(6546):251–254. [PubMed: 7675112]The unbinding force was measured repeatedly and found to be ~9 pN and angle independent. (I)
165. Wolenski JS, Cheney RE, Mooseker MS, Forscher P. *In vitro* motility of immunoadsorbed brain myosin-V using a Limulus acrosomal process and optical tweezer-based assay. *J Cell Sci* 1995;108 (Pt 4):1489–1496. [PubMed: 7615669](I)
166. Yasuda R, Miyata H, Kinoshita K Jr. Direct measurement of the torsional rigidity of single actin filaments. *J Mol Biol* 1996;263(2):227–236. [PubMed: 8913303]Video detection can underestimate the range of Brownian motion; this paper discusses a method to relate the experimental variance to true variance, enabling position detection calibration using an ordinary video camera. (I)
167. Guilford WH, Dupuis DE, Kennedy G, Wu JR, Patlak JB, Warshaw DM. Smooth muscle and skeletal muscle myosins produce similar unitary forces and displacements in the laser trap. *Biophys J* 1997;72(3):1006–1021. [PubMed: 9138552]Mean-variance analysis is used to analyze the data in this study. (I)
168. Molloy JE, White DC. Smooth and skeletal muscle single-molecule mechanical experiments. *Biophys J* 1997;72(3):984–986. [PubMed: 9138594]An introduction. (E)
169. Ishijima A, Kojima H, Funatsu T, Tokunaga M, Higuchi H, Tanaka H, Yanagida T. Simultaneous observation of individual ATPase and mechanical events by a single myosin molecule during interaction with actin. *Cell* 1998;92(2):161–171. [PubMed: 9458041]Exciting work that combines optical tweezers in a dual-beam geometry with total internal reflection fluorescence for observing single molecule events. A diagram and description of the instrument are provided in the experimental procedures section including quadrant photodiode imaging of the bead. (I)
170. Tanaka H, Ishijima A, Honda M, Saito K, Yanagida T. Orientation dependence of displacements by a single one-headed myosin relative to the actin filament. *Biophys J* 1998;75(4):1886–1894. [PubMed: 9746529]Use of dual optical traps for angle-resolved measurements; includes epifluorescence. (I)
171. Veigel C, Bartoo ML, White DC, Sparrow JC, Molloy JE. The stiffness of rabbit skeletal actomyosin cross-bridges determined with an optical tweezers transducer. *Biophys J* 1998;75(3):1424–1438. [PubMed: 9726944]An advanced instrument is described including position detection for two traps, acousto-optic deflectors, a piezoelectric sub-stage, and fluorescence visualization of actin filaments. (A)
172. Kato H, Nishizaka T, Iga T, Kinoshita K, Ishiwata S. Imaging of thermal activation of actomyosin motors. *Proc Natl Acad Sci USA* 1999;96(17):9602–9606. [PubMed: 10449739]For temperature-dependent motility measurements, an IR laser beam is used as a local heat source that sets up a temperature gradient that is monitored using fluorescence. (I)

173. Mehta AD, Rock RS, Rief M, Spudich JA, Mooseker MS, Cheney RE. Myosin-V is a processive actin-based motor. *Nature* 1999;400(6744):590–593. [PubMed: 10448864]A dual trap geometry, where the position was determined by oscillating one of the beads. (I)
174. Veigel C, Coluccio LM, Jontes JD, Sparrow JC, Milligan RA, Molloy JE. The motor protein myosin-I produces its working stroke in two steps. *Nature* 1999;398(6727):530–533. [PubMed: 10206648]The temporal aspects of myosin steps are explored. (I)
175. Nishizaka T, Seo R, Tadakuma H, Kinoshita K Jr, Ishiwata S. Characterization of single actomyosin rigor bonds: load dependence of lifetime and mechanical properties. *Biophys J* 2000;79(2):962–974. [PubMed: 10920026]A description of the dual-view instrument including the use of fluorescence imaging to visualize the actin filament is provided. The load dependence of the lifetime of the actin filament myosin bond was studied by pulling on an actin filament. (I)
176. Yanagida T, Kitamura K, Tanaka H, Hikikoshi Iwane A, Esaki S. Single molecule analysis of the actomyosin motor. *Curr Opin Cell Biol* 2000;12(1):20–25. [PubMed: 10679365]Optical tweezers of an actin filament, stretched between two beads in a “dumbbell” geometry, combined with single molecule fluorescence produced using total internal reflection fluorescence excitation. (A)
177. Knight AE, Veigel C, Chambers C, Molloy JE. Analysis of single-molecule mechanical recordings: application to acto-myosin interactions. *Prog Biophys Mol Biol* 2001;77(1):45–72. [PubMed: 11473786]Page’s test is compared with other variance methods for analysing mechanical events. (I)
178. Swank DM, Bartoo ML, Knowles AF, Iliffe C, Bernstein SI, Molloy JE, Sparrow JC. Alternative exon-encoded regions of *Drosophila* myosin heavy chain modulate ATPase rates and actin sliding velocity. *J Biol Chem* 2001;276(18):15117–15124. [PubMed: 11134017]Optical tweezers were used to monitor myosin step sizes in a three-bead suspended filament geometry. (I)

d. Nucleic acid-based enzymes

RNA- and DNA-based enzymes with motor-like properties also have been studied with optical tweezers. Multiple geometries for motility assays have been implemented. The stretching properties of DNA have been used as a centering tool and as a ruler to monitor the progress of nucleotide motors. These motor studies have benefited enormously from powerful biochemical, as well as biophysical, methods available for manipulating nucleic acids.

179. O’Brien C. RNA Polymerase gets very pushy. *Science* 1995;70:1568. An introduction to a polymerase, optical tweezers measurement. (E)
180. Yin H, Wang MD, Svoboda K, Landick R, Block SM, Gelles J. Transcription against an Applied Force. *Science* 1995;270(5242):1653–1657. [PubMed: 7502073]Velocity and stall forces are measured for *Escherichia coli* RNA polymerase using interferometry. (I)
181. Harada Y, Funatsu T, Murakami K, Nonoyama Y, Ishihama A, Yanagida T. Single-molecule imaging of RNA polymerase-DNA interactions in real time. *Biophys J* 1999;76(2):709–715. [PubMed: 9929475]DNA was suspended with two beads above a pedestal. Single dye labeled molecules of RNA polymerase were visualized using single molecule fluorescence excited in a total internal reflection geometry. (A,I)
182. Harada Y, Ohara O, Takatsuki A, Itoh H, Shimamoto N, Kinoshita K. Direct observation of DNA rotation during transcription by *Escherichia coli* RNA polymerase. *Nature* 2001;409(6816):113–115. [PubMed: 11343125](I)
183. Smith DE, Tans SJ, Smith SB, Grimes S, Anderson DL, Bustamante C. The bacteriophage phi 29 portal motor can package DNA against a large internal force. *Nature* 2001;413(6857):748–752. [PubMed: 11607035]Optical tweezers are used to pull on DNA as it is packaged by a portal complex. (I)

e. Flagellar motors

184. Block SM, Blair DF, Berg HC. Compliance of bacterial flagella measured with optical tweezers. *Nature* 1989;338(6215):514–518. [PubMed: 2648159]Flagellar torsional compliance measured with a Stokes-calibrated trap for tethered *Escherichia coli* and a motile strain of *Streptococcus*. (I)

185. Charon NW, Goldstein SF, Block SM, Curci K, Ruby JD, Kreiling JA, Limberger RJ. Morphology and dynamics of protruding spirochete periplasmic flagella. *J Bacteriol* 1992;174(3):832–840. [PubMed: 1732217] Cells were held with optical tweezers to observe the motion of protrusions by video-enhanced DIC microscopy. (I)
186. Berry RM, Berg HC. Absence of a barrier to backwards rotation of the bacterial flagellar motor demonstrated with optical tweezers. *Proc Natl Acad Sci USA* 1997;94(26):14433–14437. [PubMed: 9405630] Optical tweezers were used to stall a tethered cell and measure its torque. A piezoelectric stage was used to rotate the cell about this tethered point. (I)
187. Fung DC, Berg HC. Powering the Flagellar Motor of *Escherichia-Coli* with an External Voltage-Source. *Nature* 1995;375(6534):809–812. [PubMed: 7541114](I)
188. Ryu WS, Berry RM, Berg HC. Torque-generating units of the flagellar motor of *Escherichia coli* have a high duty ratio. *Nature* 2000;403(6768):444–447. [PubMed: 10667798](I)

3. Measurements involving DNA

DNA stretching studies have been the subject of much experimental and theoretical development. Measurements ranging from base pair interactions to chromosome mobility have been studied.

189. Perkins TT, Quake SR, Smith DE, Chu S. Relaxation of a single DNA molecule observed by optical microscopy. *Science* 1994;264(5160):822–826. [PubMed: 8171336](I)
190. Perkins TT, Smith DE, Chu S. Direct observation of tube-like motion of a single polymer chain. *Science* 1994;264(5160):819–822. [PubMed: 8171335](I)
191. Perkins TT, Smith DE, Larson RG, Chu S. Stretching of a single tethered polymer in a uniform flow. *Science* 1995;268(5207):83–87. [PubMed: 7701345] Flow-extended, tethered DNA molecules attached to a latex sphere were trapped and visualized with fluorescence microscopy. (I)
192. Smith SB, Cui YJ, Bustamante C. Overstretching B-DNA: The elastic response of individual double-stranded and single-stranded DNA molecules. *Science* 1996;271(5250):795–799. [PubMed: 8628994](I)
193. Shivashankar GV, Libchaber A. Single DNA molecule grafting and manipulation using a combined atomic force microscope and an optical tweezer. *Appl Phys Lett* 1997;71(25):3727–3729. Combined AFM with optical tweezers. (I)
194. Wang MD, Yin H, Landick R, Gelles J, Block SM. Stretching DNA with optical tweezers. *Biophys J* 1997;72(3):1335–1346. [PubMed: 9138579] Force-extension relationships were measured for single DNA molecules using a position clamp. (I)
195. Dapprich J, Nicklaus N. DNA attachment to optically trapped beads in microstructures monitored by bead displacement. *Bio-imaging* 1998;6(1):25–32. Changes in the viscous drag force are used to detect DNA attachment. (I)
196. Binnink ML, Scharer OD, Kanaar R, Sakata-Sogawa K, Schins JM, Kanger JS, de Grooth BG, Greve J. Single-molecule manipulation of double-stranded DNA using optical tweezers: Interaction studies of DNA with RecA and YOYO-1. *Cytometry* 1999;36(3):200–208. [PubMed: 10404969] Uses a combined tweezers, micropipette instrument. (I)
197. Nishimura Y, Misumi O, Matsunaga S, Higashiyama T, Yokota A, Kuroiwa T. The active digestion of uniparental chloroplast DNA in a single zygote of *Chlamydomonas reinhardtii* is revealed by using the optical tweezer. *Proc Natl Acad Sci USA* 1999;96(22):12577–12582. [PubMed: 10535964] Optical tweezers were used to trap cells of interest in a harvesting procedure. (I)
198. Shivashankar GV, Feingold M, Krichevsky O, Libchaber A. RecA polymerization on double-stranded DNA by using single-molecule manipulation: The role of ATP hydrolysis. *Proc Natl Acad Sci USA* 1999;96(14):7916–7921. [PubMed: 10393922] Force extension is used to study the polymerization of RecA on DNA. A model for nucleation and growth is presented. (I)
199. Baumann CG, Bloomfield VA, Smith SB, Bustamante C, Wang MD, Block SM. Stretching of single collapsed DNA molecules. *Biophys J* 2000;78(4):1965–1978. [PubMed: 10733975] Use of optical trap and micropipette to measure the elastic response of DNA. (I)
200. Bustamante C, Smith SB, Liphardt J, Smith D. Single-molecule studies of DNA mechanics. *Curr Opin Struct Biol* 2000;10(3):279–285. [PubMed: 10851197](E)

201. Bennink ML, Leuba SH, Leno GH, Zlatanova J, de Grooth BG, Greve J. Unfolding individual nucleosomes by stretching single chromatin fibers with optical tweezers. *Nat Struct Biol* 2001;8(7):606–610. [PubMed: 11427891]The assembly and stretching of chromatin fibers was studied with optical tweezers. (I)
202. Rusu C, van't Oever R, de Boer MJ, Jansen HV, Berenschot JW, Bennink ML, Kanger JS, de Grooth BG, Elwenspoek M, Greve J, Brugger J, van den Berg A. Direct integration of micromachined pipettes in a flow channel for single DNA molecule study by optical tweezers. *J Micromech Sys* 2001;10(2):238–246. Various shaped micropipettes are presented. (I)
203. Salman H, Zbaida D, Rabin Y, Chatenay D, Elbaum M. Kinetics and mechanism of DNA uptake into the cell nucleus. *Proc Natl Acad Sci USA* 2001;98(13):7247–7252. [PubMed: 11390964]The extension of DNA between a bead and the nucleus was measured. (I)
204. Williams MC, Rouzina I, Wenner JR, Gorelick RJ, Musier-Forsyth K, Bloomfield VA. Mechanism for nucleic acid chaperone activity of HIV-1 nucleocapsid protein revealed by single molecule stretching. *Proc Natl Acad Sci USA* 2001;98(11):6121–6126. [PubMed: 11344257]DNA is stretched with a combined dual-beam optical trap, micropipette instrument. (I)
205. Williams MC, Wenner JR, Rouzina L, Bloomfield VA. Effect of pH on the overstretching transition of double-stranded DNA: Evidence of force-induced DNA melting. *Biophys J* 2001;80(2):874 – 881. [PubMed: 11159454]Solution pH from 6.0 to 10.6 was studied. (I)
206. Williams MC, Wenner JR, Rouzina I, Bloomfield VA. Entropy and heat capacity of DNA melting from temperature dependence of single molecule stretching. *Biophys J* 2001;80(4):1932–1939. [PubMed: 11259306]Temperature ranging from 11 °C to 52 °C was used in this study. (I)

F. Cells and optical tweezers

Optical tweezers have numerous cell biology applications. Intracellular materials including organelles and chromosomes have been probed using optical tweezers. Cell function, in particular mitosis and motility, have been studied by methods such as laser inactivation and tweezers-assisted chromosome movement. Localized studies of membrane rigidity and fluidity have increased our understanding of cell morphology. Many cellular measurements involve combinations of optical tweezers with other methodologies, such as microsurgery and fluorescence characterization, to form powerful tools for cell research.

1. General cells

Cell types including mammalian cells, *Escherichia coli*, red blood cells, nerve cells and gametes have been studied.

207. Ashkin A, Dziedzic JM. Optical Trapping and Manipulation of Single Living Cells Using Infrared-Laser Beams. *Ber Bunsenges Phys Chem* 1989;93(3):254 –260. Plant cell cytoplasmic viscoelasticity is measured. (I)
208. Ashkin A, Dziedzic JM. Internal cell manipulation using infrared laser traps. *Proc Natl Acad Sci USA* 1989;86(20):7914 –7918. [PubMed: 2813368]The cytoplasmic viscoelasticity in plant cells was measured. (I)
209. Berns MW, Wright WH, Tromberg BJ, Profeta GA, Andrews JJ, Walter RJ. Use of a laser-induced optical force trap to study chromosome movement on the mitotic spindle. *Proc Natl Acad Sci USA* 1989;86(12):4539–4543. [PubMed: 2734304]Chromosome motility against the trapping force was demonstrated. (I)
210. Ashkin A, Schutze K, Dziedzic JM, Euteneuer U, Schliwa M. Force generation of organelle transport measured *in vivo* by an infrared laser trap. *Nature* 1990;348(6299):346–348. [PubMed: 2250707] Study in the giant amoeba *Reticulomyxa* of organelle transport. (E)
211. Wright WH, Sonek GJ, Tadir Y, Berns MW. Laser Trapping in Cell Biology. *IEEE J Quantum Electron* 1990;26(12):2148–2157. The movement of chromosomes and motile sperm cells was altered with the optical trap. Calculations modeling the forces exerted on dielectric spheres are presented. (I)

212. Ashkin A. The study of cells by optical trapping and manipulation of living cells using infrared laser beams. *ASGMB Bull* 1991;4(2):133–146. [PubMed: 11537176]A review of the use of optical traps in manipulating cells. (I)
213. Block SM, Blair DF, Berg HC. Compliance of bacterial polyhooks measured with optical tweezers. *Cytometry* 1991;12(6):492–496. [PubMed: 1764974]Cells are tethered to the glass by single flagellum in these measurements. (I)
214. Kucik DF, Kuo SC, Elson EL, Sheetz MP. Preferential attachment of membrane glycoproteins to the cytoskeleton at the leading edge of lamella. *J Cell Biol* 1991;114(5):1029–1036. [PubMed: 1874785]Particles were tracked for different placement points on cells and tracked to localize attachment and transport properties. (I)
215. Aufderheide KJ, Du Q, Fry ES. Directed positioning of nuclei in living *Paramecium tetraurelia*: use of the laser optical force trap for developmental biology. *Dev Genet* 1992;13:235–240.Used to reposition small structures inside a living cell. Includes a discussion on damage and a straightforward discussion on incorporating the trap into a microscope. (E)
216. Greulich KO. Chromosome microtechnology: microdissection and microcloning. *Trends Biotechnol* 1992;10(1–2):48–51. [PubMed: 1367933]Introduction to the technique. (E)
217. The isolated human red blood skeleton: an example of a flexible tethered membrane. In: Lipowsky, R.; Richter, D.; Kremer, K., editors. *The Structure and Conformation of Amphiphilic Membranes*. Berlin: Springer-Verlag; 1992. p. 128–132.pp.(I)
218. Svoboda K, Schmidt CF, Branton D, Block SM. Conformation and elasticity of the isolated red blood cell membrane skeleton. *Biophys J* 1992;63(3):784 –793. [PubMed: 1420914](I)
219. Grimbergen JA, Visscher K, Gomes de Mesquita DS, Brakenhoff GJ. Isolation of single yeast cells by optical trapping. *Yeast* 1993;9(7):723–732. [PubMed: 8368006]Selected cells are transferred to a plastic capillary using optical tweezers. (I)
220. Liang H, Wright WH, Cheng S, He W, Berns MW. Micromanipulation of chromosomes in PTK-2 cells using laser microsurgery (optical scalpel) in combination with laser-induced optical force (optical tweezers). *Exp Cell Res* 1993;204(1):110–120. [PubMed: 8416789]Microsurgery was used to laser-dissect chromosomes and optical tweezers were used to inhibit movement. The fate of the fragments is discussed and pictures of the process are presented. (I)
221. Liang H, Wright WH, Rieder CL, Salmon ED, Profeta G, Andrews J, Liu Y, Sonek GJ, Berns MW. Directed movement of chromosome arms and fragments in mitotic newt lung cells using optical scissors and optical tweezers. *Exp Cell Res* 1994;213(1):308–312. [PubMed: 8020604] Demonstrates a high degree of facility in manipulating chromosomes. (I)
222. Vorobjev IA, Liang H, Wright WH, Berns MW. Optical trapping for chromosome manipulation: a wavelength dependence of induced chromosome bridges. *Biophys J* 1993;64(2):533–538. [PubMed: 8457677]A Ti:sapphire laser is used in a wavelength comparison from 700 to 840 nm of biological response. Wavelength sensitivities are presented. (I)
223. Dai J, Sheetz MP. Mechanical properties of neuronal growth cone membranes studied by tether formation with laser optical tweezers. *Biophys J* 1995;68(3):988–996. [PubMed: 7756561]IgG-coated beads were used to measure membrane mechanical properties through the extension of filopodia-like tethers. Membrane viscosity in the presence of various reagents is presented. (I)
224. Huber R, Burggraf S, Mayer T, Barns SM, Rossnagel P, Stetter KO. Isolation of a hyperthermophilic archaeum predicted by in situ RNA analysis. *Nature* 1995;376(6535):57–58. [PubMed: 7541115] (I)
225. Leitz G, Schnepf E, Greulich KO. Micromanipulation of statoliths in gravity-sensing *Chara* rhizoids by optical tweezers. *Planta* 1995;197(2):278–288. [PubMed: 11540723](I)
226. Kusumi A, Sako Y. Cell surface organization by the membrane skeleton. *Curr Opin Cell Biol* 1996;8(4):566–574. [PubMed: 8791449](I)
227. Mammen M, Helmerson K, Kishore R, Choi SK, Phillips WD, Whitesides GM. Optically controlled collisions of biological objects to evaluate potent polyvalent inhibitors of virus-cell adhesion. *Chem Biol* 1996;3(9):757–763. [PubMed: 8939692]Two particles are caused to collide using independently controlled optical tweezers. (I)

228. Liang H, Vu KT, Trang TC, Shin D, Lee YE, Nguyen DC, Tromberg B, Berns MW. Giant cell formation in cells exposed to 740 nm and 760 nm optical traps. *Lasers Surg Med* 1997;21(2):159–165. [PubMed: 9261793](I)
229. Townes-Anderson E, St Jules RS, Sherry DM, Lichtenberger J, Hassanain M. Micromanipulation of retinal neurons by optical tweezers. *Mol Vis* 1998;4:12. [PubMed: 9701608]Optical tweezers are used to position and group neuron cells. The outgrowth of manipulated cells is compared to unmanipulated cells. (I)
230. Galbraith CG, Sheetz MP. Keratocytes pull with similar forces on their dorsal and ventral surfaces. *J Cell Biol* 1999;147(6):1313–1323. [PubMed: 10601343]A laser trap was used to place and hold a fibronectin-coated bead on the lamella of a keratocyte to monitor cellular force and displacement. (I)
231. Sleep J, Wilson D, Simmons R, Gratzner W. Elasticity of the red cell membrane and its relation to hemolytic disorders: an optical tweezers study. *Biophys J* 1999;77(6):3085–3095. [PubMed: 10585930]Two beads were used to measure the force-extension relation of red cell membranes. (I)
232. Winckler B, Forscher P, Mellman I. A diffusion barrier maintains distribution of membrane proteins in polarized neurons. *Nature* 1999;397(6721):698–701. [PubMed: 10067893]In this study, optical tweezers are used to measure the lateral mobility of membrane proteins. (I)
233. Buer CS, Weathers PJ, Swartzlander GA. Changes in Hechtian strands in cold-hardened cells measured by optical microsurgery. *Plant Physiol* 2000;122(4):1365–1377. [PubMed: 10759533]In this study concanavalin-coated spheres were inserted through an ablated hole in the cell wall and attached to a hechtian strand. (I)
234. Liang MN, Smith SP, Metallo SJ, Choi IS, Prentiss M, Whitesides GM. Measuring the forces involved in polyvalent adhesion of uropathogenic *Escherichia coli* to mannose-presenting surfaces. *Proc Natl Acad Sci USA* 2000;97(24):13092–13096. [PubMed: 11078520]Optical tweezers are used to orient the bacteria relative to a surface of functionalized self assembled monolayers. (I)
235. Guck J, Ananthakrishnan R, Moon TJ, Cunningham CC, Kas J. Optical deformability of soft biological dielectrics. *Phys Rev Lett* 2000;84(23):5451–5454. [PubMed: 10990966]Includes some information on damage. (I)
236. Raucher D, Sheetz MP. Cell spreading and lamellipodial extension rate is regulated by membrane tension. *J Cell Biol* 2000;148(1):127–136. [PubMed: 10629223]Optical tweezers were used to determine membrane tension in a tether-force measurement. (I)
237. Mendelson NH, Sarlls JE, Wolgemuth CW, Goldstein RE. Chiral self-propulsion of growing bacterial macrofibers on a solid surface. *Phys Rev Lett* 2000;84(7):1627–1630. [PubMed: 11017584]Optical tweezers were used to measure the Young's modulus of the bacterial cell wall. (I)
238. Bayouth S, Mehta M, Rubinsztein-Dunlop H, Heckenberg NR, Critchley C. Micromanipulation of chloroplasts using optical tweezers. *J Microsc* 2001;203(Pt 2):214–222. [PubMed: 11489079]Dual optical tweezers were used to probe chloroplast arrangement. (I)
239. Lenormand G, Henon S, Richert A, Simeon J, Gallet F. Direct measurement of the area expansion and shear moduli of the human red blood cell membrane skeleton. *Biophys J* 2001;81(1):43–56. [PubMed: 11423393]Galvanometric mirrors form the traps in this three-bead measurement. (I)
240. Velegol D, Lanni F. Cell traction forces on soft biomaterials. I. Microrheology of Type I collagen gels. *Biophys J* 2001;81(3):1786–1792. [PubMed: 11509388]A refraction plate on a galvanometric scanner was used to translate the trapped particle. (I)
241. Guck J, Ananthakrishnan R, Casey Cunningham C, Kas J. Stretching biological cells with light. *J Phys: Condens Matter* 2002 A description of the experimental setup is provided Cell viability is also discussed I;14:4843–4856.

2. Gamete cells

Optical tweezers can be used to manipulate and determine the force generation and swimming properties of sperm. Implantation and fertilization developments use combinations of zonal drilling with short-wavelength (blue-to-UV) lasers and manipulation with optical tweezers. Laser-assisted hatching has also been investigated to possibly improve implantation efficiency.

242. Tadir Y, Wright WH, Vafa O, Ord T, Asch RH, Berns MW. Micromanipulation of sperm by a laser generated optical trap. *Fertil Steril* 1989;52:870–873. [PubMed: 2680630](E)
243. Tadir Y, Wright WH, Vafa O, Ord T, Asch RH, Berns MW. Force generated by human sperm correlated to velocity and determined using a laser generated optical trap. *Fertil Steril* 1990;53(5):944–947. [PubMed: 2332067](I)
244. Tadir Y, Wright WH, Vafa O, Liaw LH, Asch R, Berns MW. Micromanipulation of gametes using laser microbeams. *Hum Reprod* 1991;6(7):1011–1016. [PubMed: 1761652]A review. (E)
245. Colon JM, Sarosi P, McGovern PG, Askin A, Dziedzic JM, Skurnick J, Weiss G, Bonder EM. Controlled micromanipulation of human sperm in three dimensions with an infrared laser optical trap: effect on sperm velocity. *Fertil Steril* 1992;57(3):695–698. [PubMed: 1740221](I)
246. Tadir Y, Neev J, Ho P, Berns MW. Lasers for gamete micromanipulation: basic concepts. *J Assist Reprod Genet* 1993;10(2):121–125. [PubMed: 8339014]A review. (E)
247. Westphal LN, el Dansasouri I, Shimizu S, Tadir Y, Berns MW. Exposure of human spermatozoa to the cumulus oophorus results in increased relative force as measured by a 760 nm laser optical trap. *Hum Reprod* 1993;8(7):1083–1086. [PubMed: 8408492](I)
248. Araujo E Jr, Tadir Y, Patrizio P, Ord T, Silber S, Berns MW, Asch RH. Relative force of human epididymal sperm. *Fertil Steril* 1994;62(3):585–590. [PubMed: 8062955](I)
249. Conia J, Voelkel S. Optical manipulations of human gametes. *Biotechniques* 1994;17(6):1162–1165. [PubMed: 7873187]Male gamete selection and laser-assisted fertilization is described using a commercially available system. (E)
250. Schutze K, Clement-Sengewald A, Ashkin A. Zona drilling and sperm insertion with combined laser microbeam and optical tweezers. *Fertil Steril* 1994;61(4):783–786. [PubMed: 8150126] Demonstration of combined micromachine optical tweezers used to transport a sperm through a UV laser-drilled hole. (I)
251. Dantas ZN, Araujo E Jr, Tadir Y, Berns MW, Schell MJ, Stone SC. Effect of freezing on the relative escape force of sperm as measured by a laser optical trap. *Fertil Steril* 1995;63(1):185–188. [PubMed: 7805910]Clinical trial. (I)
252. Suzuki K, Tanaka Y, Nakajima Y, Hirano K, Itoh H, Miyata H, Hayakawa T, Kinoshita K Jr. Spatiotemporal relationships among early events of fertilization in sea urchin eggs revealed by multiview microscopy. *Biophys J* 1995;68(3):739–748. [PubMed: 7756541]A multiview microscopy system for both polarization and fluorescence wavelength imaging was implemented. (I)
253. Antinori S, Panci C, Selman HA, Caffa B, Dani G, Versaci C. Zona thinning with the use of laser: a new approach to assisted hatching in humans. *Hum Reprod* 1996;11(3):590–594. [PubMed: 8671273]Clinical trial. (I)
254. Clement-Sengewald A, Schutze K. Animal experimentation. Fertilization of bovine oocytes induced solely with combined laser microbeam and optical tweezers. *J Assist Reprod Gen* 1996;13:259–265.(I)
255. Konig K, Svaasand L, Liu YG, Sonek G, Patrizio P, Tadir Y, Berns MW, Tromberg BJ. Determination of motility forces of human spermatozoa using an 800 nm optical trap. *Cell Mol Biol* 1996;42(4):501–509. [PubMed: 8828905](I)
256. Palm Robot-MicroBeam for laser-assisted fertilization, embryo hatching and single-cell prenatal diagnosis. In: Wyss, P.; Dadir, Y.; Tromberg, BJ.; Haller, U., editors. *Photomedicine in Gynecology and Reproduction*. Basel: Karger; 2000. p. 340-351.pp.(I)
257. Patrizio P, Liu Y, Sonek GJ, Berns MW, Tadir Y. Effect of pentoxifylline on the intrinsic swimming forces of human sperm assessed by optical tweezers. *J Androl* 2000;21(5):753–756. [PubMed: 10975423](I)

3. Cell damage

In general, optical tweezers are much more “cell friendly” than many alternative methods because of the noninvasive character of light. Cell photodamage remains an issue, however, one that has been investigated for various systems using a range of trapping wavelengths. The papers below discuss a number of relevant issues, and possible solutions to tweezers-induced cell damage.

258. Liu Y, Cheng DK, Sonek GJ, Berns MW, Chapman CF, Tromberg BJ. Evidence for localized cell heating induced by infrared optical tweezers. *Biophys J* 1995;68(5):2137–2144. [PubMed: 7612858]Environmental and temperature-sensitive dye was used with spatially-resolved fluorescence in this study. A heat conduction model is also presented. (I)
259. Sonek GJ, Liu Y, Iturriga RH. *In-situ* microparticle analysis of marine phytoplankton cells using infrared laser-based optical tweezers. *Appl Opt* 1995;34:7731–7741. Spectroscopic observation of cellular physiology related to chlorophyll in the presence of the optical trap. (A)
260. König 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(14):1090–1092. Cell damage is shown to be greater in lasers that have unstable temporal power outputs. (I)
261. König K, Tadir Y, Patrizio P, Berns MW, Tromberg BJ. Effects of ultraviolet exposure and near infrared laser tweezers on human spermatozoa. *Hum Reprod* 1996;11(10):2162–2164. [PubMed: 8943522](I)
262. Liang H, Vu KT, Krishnan P, Trang TC, Shin D, Kimel S, Berns MW. Wavelength dependence of cell cloning efficiency after optical trapping. *Biophys J* 1996;70(3):1529–1533. [PubMed: 8785310] Wavelengths from 700 to 900 nm and 1064 nm were investigated. Includes growth by exposure time and wavelength for various durations. Lasers include a Nd:YAG and Ti:sapphire. (I)
263. Liu Y, Sonek GJ, Berns MW, Tromberg BJ. Physiological monitoring of optically trapped cells: assessing the effects of confinement by 1064-nm laser tweezers using microfluorometry. *Biophys J* 1996;71(4):2158–2167. [PubMed: 8889192]Two-photon excited fluorescence is collected to monitor the physiology of optically trapped cells. (A)
264. Neuman KC, Chadd EH, Liou GF, Bergman K, Block SM. Characterization of photodamage to *Escherichia coli* in optical traps. *Biophys J* 1999;77(5):2856–2863. [PubMed: 10545383]A study of cell damage through the wavelength range of (790–1064 nm) using a tunable Ti:sapphire laser by measuring the rotation rates of *Escherichia coli* cells tethered to glass. Includes a table and curves for microscope objective transmission. (A)
265. Zhang ZX, Sonek GJ, Wei XB, Sun C, Berns MW, Tromberg BJ. Cell viability and DNA denaturation measurements by two-photon fluorescence excitation in CWAl:GaAs diode laser optical traps. *J Biomed Opt* 1999;4(2):256–259.(I)
266. Schneckenburger H, Hendinger A, Sailer R, Gschwend MH, Strauss WSL, Bauer M, Schutze K. Cell viability in optical tweezers: high power red laser diode versus Nd:YAG laser. *J Biomed Opt* 2000;5(1):40–44. [PubMed: 10938764](I)

4. Tools for cells

267. Buican TN, Smyth MJ, Crissman HA, Salzman GC, Stewart C, Martin JC. Automated single-cell manipulation and sorting by light trapping. *Appl Opt* 1987;26(24):5311–5316. Optical tweezers are used to sort and transport cells automatically without mechanical contact or significant fluid flow. (I)
268. Buican TN, Neagley DL, Morrison WC, Upham BD. Optical Trapping, Cell Manipulation, and Robotics. *New Technol Cytom* 1989;1063:190–197. A tool for cytometry; image analysis is used to locate particles inside an enclosed manipulation chamber. Automated positioning and biological microrobotic applications are presented. (I)
269. With lasers, you can operate on cells R. Lewis Photon. Spectra July, 74–78 (1990). An introduction to the technology of moving and cutting cells with light. (E)
270. Berns MW, Wright WH, Wiegand Steubing R. Laser microbeam as a tool in cell biology. *Int Rev Cytol* 1991;129:1–44. [PubMed: 1917379] Gives a general introduction to optical tweezers, construction tips, and applications to cell biology, including combinations with micro-beam methods. (E)
271. Seeger S, Monajembashi S, Hutter KJ, Futterman G, Wolfrum J, Greulich KO. Application of laser optical tweezers in immunology and molecular genetics. *Cytometry* 1991;12(6):497–504. [PubMed: 1684929] Microsorting and trap-induced cell contact is presented. (I)
272. Wiegand-Steubing R, Cheng S, Wright WH, Numajiri Y, Berns MW. Laser induced cell fusion in combination with optical tweezers: the laser cell fusion trap. *Cytometry* 1991;12(6):505–510.

- [PubMed: 1764975]The optical trap is used to bring the cells together while a UV beam initiates the cell fusion. (I)
273. Greulich KO, Weber G. The light microscope on its way from an analytical to a preparative tool. *J Microsc* 1992;167(2):127–151. Description and applications of a combined microbeam and optical trap instrument. (I)
 274. Weber G, Greulich KO. Manipulation of cells, organelles, and genomes by laser microbeam and optical trap. *Int Rev Cytol* 1992;133:1–41. [PubMed: 1577585]The working principle of the optical trap is presented along with biological applications including cell fusion and cell wall perforation. Microdissection of chromosomes is also presented as a tool. Organelle movement is also presented. Includes many references. (I)
 275. Poniel N, Scheef J, Harim A, Leitz G, Greulich KO. Laser micromanipulators for biotechnology and genome research. *J Biotechnol* 1994;35(2–3):109–120. [PubMed: 7765052]A review. (E)
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