RESOURCE LETTER

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This is one of a series of Resource Letters on different topics intended to guide college physicists, astronomers, and other scientists to some of the literature and other teaching aids that may help improve course content in specified fields. [The letter E after an item indicates elementary level or material of general interest to persons becoming informed in the field. The letter I, for intermediate level, indicates material of somewhat more specialized nature; and the letter A indicates rather specialized or advanced material.] No Resource Letter is meant to be exhaustive and complete; in time there may be more than one letter on some of the main subjects of interest. Comments on these materials as well as suggestions for future topics will be welcomed. Please send such communications to Professor Roger H. Stuewer, Editor, AAPT Resource Letters, School of Physics and Astronomy, University of Minnesota, 116 Church Street SE, Minneapolis, MN 55455; e-mail: rstuewer@physics.spa.umn.edu.

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

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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.
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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 nanomechanical 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 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

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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 underrepresented. 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,'' M. P. Sheetz, in **Methods in Cell Biology**, Vol. 55, edited by L. Wilson and P. Matsudaira (Academic, San Diego, 1998). Includes a number of topics in laser tweezers and applications. (I,A,E)
2. ''Optical Tweezers: A New Tool for Biophysics,'' S. M. Block, in **Noninvasive Techniques in Cell Biology**, edited by B. H. Satir (Wiley-Liss, New York, 1990), pp. 375–402. 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. ''Laser Manipulations of Atoms and Particles,'' S. Chu, Science **253**, 861–866 (1991). Discussion of applications to atoms and particles. (E)
4. ''Making light work with optical tweezers,'' S. M. Block, Nature **360** (6403), 493–495 (1992). A short review with basic principles. (E)
5. ''Laser Trapping of Neutral Particles,'' S. Chu, Sci. Am. **268** (2), 71–76 (1992). Good introduction to trapping capabilities. (E)
6. ''Optical tweezers in cell biology,'' S. C. Kuo and M. P. Sheetz, Trends Cell Biol. **2**, 116–118 (1992). A short review. (E)
7. ''Optical Tweezers: Glasperlenspiel—II,'' R. M. Simmons and J. T. Finer, Curr. Biol. **3** (5), 309–311 (1993). A general discussion of optical tweezers is provided. (E)
8. ''Biological applications of optical forces,'' K. Svoboda and S. M. Block, Annu. Rev. Biophys. Biomol. Struct. **23**, 247–285 (1994). 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. ''Optical trapping and manipulation of microscopic particles and biological cells by laser beams,'' S. Sato and H. Inaba, Opt. Quantum Electron. **28**, 1–16 (1996). Review of basic principles and features of single beam optical trapping of cells, latex spheres, crystals, and metal particles. A review. (E)
10. ''Optical trapping and manipulation of neutral particles using lasers,'' A. Ashkin, Proc. Natl. Acad. Sci. USA **94** (10), 4853–4860 (1997). Outlines the history and recent developments of optical trapping. (I)
11. ''Laser scissors and tweezers,'' M. W. Berns, Sci. Am. **278** (4), 62–67 (1998). (E)
12. ''Versatile optical traps with feedback control,'' K. Visscher and S. M. Block, Methods Enzymol. **298**, 460–489 (1998). (I)
13. ''Single-molecule biomechanics with optical methods,'' A. D. Mehta, M. Rief, J. A. Spudich, D. A. Smith, and R. M. Simmons, Science **283** (5408), 1689–1695 (1999). A review that describes a number of single molecule methods using optical tweezers. (E)
14. ''History of optical trapping and manipulation of small-neutral particle, atoms, and molecules,'' A. Ashkin, IEEE J. Sel. Top. Quantum Electron **6** (6), 841–856 (2000). A review. (I)
15. ''Single molecule nanomanipulation of biomolecules,'' Y. Ishii, A. Ishijima, and T. Yanagida, Trends Biotechnol. **19** (6), 211–216 (2001). A good introduction to combined single molecule imaging and manipulation techniques for the study of molecular motors. (E)
16. ''Single molecule nanobioscience,'' A. Ishijima and T. Yanagida, Trends Biochem. Sci. **26** (7), 438–444 (2001). Exciting advances in single molecule fluorescence and manipulation methods including combined SMF with optical tweezers are reviewed. (E)
17. ''Using optics to measure biological forces and mechanics,'' S. C. Kuo, Traffic **2** (11), 757–763 (2001). A review including optical stretching. (I)

IV. OPTICAL TWEEZERS, CURRENT RESEARCH TOPICS

A. Earlier works on radiation pressure

18. ''Optical levitation by radiation pressure,'' A. Ashkin and J. M. Dziedzic, Appl. Phys. Lett. **19**, 283–285 (1971). Glass spheres are levitated with radiation pressure in air and vacuum. (I)
19. ''Acceleration and trapping of particles by radiation pressure,'' A. Ashkin, Phys. Rev. Lett. **24** (4), 156–159 (1970). The first observation of the acceleration of suspended particles using radiation pressure. (I)
20. ''Optical Levitation of Liquid Drops by Radiation Pressure,'' A. Ashkin and J. M. Dziedzic, Science **187** (4181), 1073–1075 (1975). Drops in the size range of 1 to 40 micrometers are levitated and manipulated with the trap. (I)
21. ''Optical Levitation in High-Vacuum,'' A. Ashkin and J. M. Dziedzic, Appl. Phys. Lett. **28** (6), 333–335 (1976). Optical levitation down to a pressure of 10^{-6} Torr was observed under high-vacuum. (I)
22. ''Feedback Stabilization of Optically Levitated Particles,'' A. Ashkin and J. M. Dziedzic, Appl. Phys. Lett. **30** (4), 202–204 (1977). (I)
23. ''Trapping of atoms by resonance radiation pressure,'' A. Ashkin, Phys. Rev. Lett. **40** (12), 729–732 (1978). A method for trapping, cooling, and manipulating sodium atoms is described. (I)
24. ''Applications of Laser Radiation Pressure,'' A. Ashkin, Science **210** (5), 1081–1088 (1980). Radiation pressure is discussed for neutral particles, including applications for microscopic particles and atoms. (I)

25. ''Observation of light scattering from nonspherical particles using optical levitation,'' A. Ashkin and J. M. Dziedzic, Appl. Opt. **19** (5), 660–668 (1980). Objects including spheroids, spherical doublets, triplets, etc. were studied. (I)
26. ''Continuous-wave self-focusing and self-trapping of light in artificial Kerr media,'' A. Ashkin, J. M. Dziedzic, and P. W. Smith, Opt. Lett. **7** (6), 276–278 (1982). 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. ''Observation of a Single-Beam Gradient Force Optical Trap for Dielectric Particles,'' A. Ashkin, J. M. Dziedzic, J. E. Bjorkholm, and S. Chu, Opt. Lett. **11** (5), 288–290 (1986). 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. ''Optical trapping and manipulation of viruses and bacteria,'' A. Ashkin and J. M. Dziedzic, Science **235** (4795), 1517–1520 (1987). Tobacco mosaic virus and single *Escherichia coli* bacteria. One of the first reports of biological applications of optical traps. (E)
29. ''Optical trapping and manipulation of single cells using infrared laser beams,'' A. Ashkin, J. M. Dziedzic, and T. Yamane, Nature **330** (6150), 769–771 (1987). 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 acousto-optic 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,'' S. M. Block, in **Cell Biology: A Laboratory Manual**, edited by D. Spector, R. Goldman, and L. Leinward (Cold Spring Harbor, Cold Spring Harbor, NY, 1998). A good place to start. (E)
31. ''Single beam optical trapping integrated in a confocal microscope for biological applications,'' K. Visscher and G. J. Brakenhoff, Cytometry **12** (6), 486–491 (1991). Includes trapping theory, force calculation, and a description of the principle of trap manipulation by objective lens movement. (I)
32. ''Optical tweezers using a diode laser,'' R. S. Afzal and E. B. Treacy, Rev. Sci. Instrum. **63** (4), 2157–2163 (1992). Straightforward demonstration of using a diode laser to form an optical trap. (E)
33. ''Optical-Trapping Micromanipulation Using 780-Nm Diode-Lasers,'' T. C. B. Schut, E. F. Schipper, B. G. de Grooth, and J. Greve, Opt. Lett. **18** (6), 447–449 (1993). (E)
34. ''Micromanipulation by 'multiple' optical traps created by a single fast scanning trap integrated with the bilateral confocal scanning laser microscope,'' K. Visscher, G. J. Brakenhoff, and J. J. Krol, Cytometry **14** (2), 105–114 (1993). Includes a description of the instrument with fast scanning by acousto-optic modulation and galvanometric scan mirrors. (A)
35. ''Beam Magnification and the Efficiency of Optical Trapping with 790-nm AlGaAs Laser Diodes,'' G. J. Escandon, Y. Liu, G. J. Sonek, and M. W. Berns, IEEE Photonics Technol. Lett. **6** (5), 597–600 (1994). Discussion of trap efficiency with respect to input beam shape. Includes correction of diode output elipticity using anamorphic prisms. (E)
36. ''Constructions and Applications of a Simple Optical Tweezers,'' Y. C. Jong, H. M. Chen, J. H. Hsu, and W. S. Fann, Zool. Stu. **34** (S1), 209–210 (1995). (E)
37. ''Construction of multiple-beam optical traps with nanometer-resolution position sensing,'' K. Visscher, S. P. Gross, and S. M. Block, IEEE J. Sel. Top. Quantum Electron. **2** (4), 1066–1076 (1996). 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. ''Quantitative measurements of force and displacement using an optical trap,'' R. M. Simmons, J. T. Finer, S. Chu, and J. A. Spudich, Biophys. J. **70** (4), 1813–1822 (1996). Includes a schematic of the optical trap and detection system along with circuits with feedback arrangements. (I)
39. ''Interferometric optical tweezers,'' A. E. Chiou, W. Wang, G. J. Sonek, J. Hong, and M. W. Berns, Opt. Commun. **133** (1-6), 7–10 (1997). Two beams generate an interference fringe for trapping and micro-manipulation. (I)
40. ''Design for fully steerable dual-trap optical tweezers,'' E. Fallman and O. Axner, Appl. Opt. **36** (10), 2107–2113 (1997). A detailed recipe for the construction is provided. (E)
41. ''Optical tweezers based on near infrared diode laser,'' S. Grego, E. Arirnondo, and C. Frediani, J. Biomed. Opt. **2** (3), 332–339 (1997). A single-mode 100 mW diode operating at 840 nm was used. (E)
42. ''Self-aligned dual-beam optical laser trap using photorefractive phase conjugation,'' W. Wang, A. E. Chiou, G. J. Sonek, and M. W. Berns, J. Opt. Soc. Am. B **14** (4), 697–704 (1997). 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. ''Optical tweezer arrays and optical substrates created with diffractive optics,'' E. R. Dufresne and D. G. Grier, Rev. Sci. Instrum. **69** (5), 1974–1977 (1998). A diffractive optical element is used to create multiple optical tweezers from a single laser beam. (I)
44. ''Inexpensive optical tweezers for undergraduate laboratories,'' S. P. Smith, S. R. Bhalotra, A. L. Brody, B. L. Brown, E. K. Boyda, and M. Prentiss, Am. J. Phys. **67** (1), 26–35 (1999). General introduction to setting up an instrument. (E)
45. ''Optical tweezers for confocal microscopy,'' A. Hoffmann, G. Meyer zu Horste, G. Pilarczyk, S. Monajembashi, V. Uhl, and K. O. Greulich, Appl. Phys. B **71** (5), 747–753 (2000). A method is presented to keep the trap fixed while doing 3D z-sectioning imaging. (I)
46. ''Multi-functional optical tweezers using computer-generated holograms,'' J. Liesener, M. Reicherter, T. Haist, and H. J. Tiziani, Opt. Commun. **185** (1-3), 77–82 (2000). Seven spheres are trapped independently. (I)
47. ''Design of a scanning laser optical trap for multiparticle manipulation,'' C. Mio, T. Gong, A. Terray, and D. W. M. Marr, Rev. Sci. Instrum. **71** (5), 2196–2200 (2000). 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. ''Construction of an optical tweezers: Calculation and experiments,'' W. Sun, Y. Q. Wang, and C. M. Gao, Chin. Phys. **9** (11), 855–860 (2000). (I)
49. ''An integrated laser trap/flow control video microscope for the study

of single biomolecules,'' G. J. L. Wuite, R. J. Davenport, A. Rappaport, and C. Bustamante, Biophys. J. **79** (2), 1155–1167 (2000). 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. ''Computer-generated holographic optical tweezer arrays,'' E. R. Dufresne, G. C. Spalding, M. T. Dearing, S. A. Sheets, and D. G. Grier, Rev. Sci. Instrum. **72** (3), 1810–1816 (2001). An adaptive-additive algorithm method is presented for creating planar arrays of holographic optical tweezers. (A)

51. ''Design and construction of a space-borne optical tweezer apparatus,'' A. Resnick, Rev. Sci. Instrum. **72** (11), 4059–4065 (2001). Optical tweezers in space; a rugged design is detailed. (E)

52. ''An Automated 2D Force Clamp for Single Molecule Studies,'' M. J. Lang, C. L. Asbury, J. W. Shaevitz, and S. M. Block, Biophys. J. **83**, 491–501 (2002). This paper describes a fully-automated trapping instrument used as a two-dimensional force clamp for kinesin motility mesurements. 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 subpixel 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. ''Direct Measurement of Nanometric Displacement under an Optical Microscope,'' S. Kamimura, Appl. Opt. **26** (16), 3425–3427 (1987). (I)

54. ''Optical measurement of picometer displacements of transparent microscopic objects,'' W. Denk and W. W. Webb, Appl. Opt. **29** (16), 2382–2391 (1990). Description of the instrument and interferometer including signal detection and amplification circuitry. (A)

55. ''High-resolution axial and lateral position sensing using two-photon excitation of fluorophores by a continuous-wave Nd:YAG laser,'' E.-L. Florin, J. K. H. Horber, and E. H. K. Stelzer, Appl. Phys. Lett. **69** (4), 446–448 (1996). Changes in fluorescence due to displacement are used as a spatial sensor. Includes a fluorescence intensity versus z-position graph. (I)

56. ''Determination of the force constant of a single-beam gradient trap by measurement of backscattered light,'' M. E. J. Friese, H. Rubinsztein-Dunlop, N. R. Heckenberg, and E. W. Dearden, Appl. Opt. **35** (36), 7112–7116 (1996). Model of the trap as a harmonic oscillator with measurements. (I)

57. ''Improved nm displacement detector for microscopic beads at frequencies below 10 Hz,'' D. Q. Li and B. J. Schnapp, Rev. Sci. Instrum. **68** (5), 2195–2199 (1997). Laser interferometry detection is outlined in this paper. (E)

58. ''Detection of single-molecule interactions using correlated thermal diffusion,'' A. D. Mehta, J. T. Finer, and J. A. Spudich, Proc. Natl. Acad. Sci. U.S.A. **94** (15), 7927–7931 (1997). Methods are described to detect and correlate the motion of optically trapped beads attached to both ends of a single actin filament. (I)

59. ''Three-dimensional potential analysis of radiation pressure exerted on a single microparticle,'' K. Sasaki, M. Tsukima, and H. Masuhara, Appl. Phys. Lett. **71** (1), 37–39 (1997). Total internal reflection microscopy is used in this three-dimensional position sensing method. (I)

60. ''Interference model for back-focal-plane displacement detection in optical tweezers,'' F. Gittes and C. F. Schmidt, Opt. Lett. **23** (1), 7–9 (1998). Description including a model comparison with experiment for the signal of back-focal-plane imaging using a quadrant photodiode. (A)

61. ''Three dimensional single-particle tracking with nanometer resolution,'' I. M. Peters, B. G. de Grooth, J. M. Schins, C. G. Figdor, and J. Greve, Rev. Sci. Instrum. **69** (7), 2762–2766 (1998). 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. ''Three-dimensional imaging with optical tweezers,'' M. E. J. Friese, A. G. Truscott, H. Rubinsztein-Dunlop, and N. R. Heckenberg, Appl. Opt. **38** (31), 6597–6603 (1999). This paper reports that features of approximately 200 nm can be resolved with a sensitivity of 5 nm. (I)

63. ''Nanometer-displacement detection of optically trapped metallic particles based on critical angle method for small force detection,'' E. Higurashi, R. Sawada, and T. Ito, Rev. Sci. Instrum. **70** (7), 3068–3073 (1999). Detection is based on critical-angle prisms where angle changes originating from trapped particle motion provide a sensitive measure of position. (I)

64. ''3D single-particle tracking and optical trap measurements on adhesion proteins,'' I. M. Peters, Y. vanKooyk, S. J. van Vliet, B. G. de Grooth, C. G. Figdor, and J. Greve, Cytometry **36** (3), 189–194 (1999). Cell adhesion studies. (I)

65. ''Three-dimensional high-resolution particle tracking for optical tweezers by forward scattered light,'' A. Pralle, M. Prummer, E. L. Florin, E. H. K. Stelzer, and J. K. H. Horber, Microsc. Res. Tech. **44** (5), 378–386 (1999). 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. ''Optical binding,'' M. M. Burns, J. M. Fournier, and J. A. Golovchenko, Phys. Rev. Lett. **63** (12), 1233–1236 (1989). 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. ''Measurement of small forces using an optical trap,'' L. P. Ghislain, N. A. Switz, and W. W. Webb, Rev. Sci. Instrum. **65**, 2762–2768 (1994). Includes calibration using drag force and signal source considerations. (A)

68. ''Calibration of Light Forces in Optical Tweezers,'' H. Felgner, O. Muller, and M. Schliwa, Appl. Opt. **34** (6), 977–982 (1995). It is shown that trapping in different axial positions is possible. (I)

69. ''Optical Trapping and Fluorescence Detection in Laminar-Flow Streams,'' W. Wang, Y. Liu, G. J. Sonek, M. W. Berns, and R. A. Keller, Appl. Phys. Lett. **67** (8), 1057–1059 (1995). Escape velocities are measured relative to the position within the flow stream. (A)

70. ''Three-dimensional optical trapping and evanescent wave light scattering for direct measurement of long range forces between a colloidal particle and a surface,'' A. R. Clapp, A. G. Ruta, and R. B. Dickinson,

Rev. Sci. Instrum. **70** (6), 2627–2636 (1999). Total internal reflection of a laser beam creates an evanescent wave that is used to determine particle position. (I)
71. ''Three-dimensional force calibration of optical tweezers,'' W. Singer, S. Bernet, N. Hecker, and M. RitschMarte, J. Mod. Opt. **47** (14–15), 2921–2931 (2000). (I)
72. ''Optical tweezers as sub-pico-newton force transducers,'' C. C. Huang, C. F. Wang, D. S. Mehta, and A. Chiou, Opt. Commun. **195** (1–4), 41–48 (2001). 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. ''Demonstration of a fiberoptic light-force trap,'' A. Constable, J. Kim, J. Mervis, F. Zarinetchi, and M. Prentiss, Opt. Lett. **18** (21), 1867–1869 (1993). Single-mode fibers. Includes sample cell construction information. (I)
74. ''Confinement and bistability in a tapered hemispherically lensed optical fiber trap,'' E. R. Lyons and G. J. Sonek, Appl. Phys. Lett. **66** (13), 1584–1586 (1995). Axial and transverse trap efficiencies are predicted and confirmed. (I)
75. ''Trapping forces in a multiple-beam fiber-optic trap,'' E. Sidick, S. D. Collins, and A. Knoesen, Appl. Opt. **36** (25), 6423–6433 (1997). Forces are calculated for microspheres located both on and off axis relative to the beam axis. (A)
76. ''Microinstrument gradient-force optical trap,'' S. D. Collins, R. J. Baskin, and D. G. Howitt, Appl. Opt. **38** (28), 6068–6074 (1999). Consists of four single-mode fibers. (I)
77. ''Laser guidance and trapping of mesoscale particles in hollow-core optical fibers,'' M. J. Renn, R. Pastel, and H. J. Lewandowski, Phys. Rev. Lett. **82** (7), 1574–1577 (1999). Laser light coupled into a hollow-core fiber can be used to trap and guide mesoscale particles over relatively long distances. (I)
78. ''The optical stretcher: a novel laser tool to micromanipulate cells,'' J. Guck, R. Ananthakrishnan, H. Mahmood, T. J. Moon, C. C. Cunningham, and J. Kas, Biophys. J. **81** (2), 767–784 (2001). 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. ''Internal and near-surface electromagnetic fields for a spherical particle irradiated by a focused light beam,'' J. P. Barton, J. Appl. Phys. **64** (4), 1632–1639 (1988). (I)
80. ''Fifth-order corrected electromagnetic field components for a fundamental Gaussian beam,'' J. P. Barton and D. R. Alexander, J. Appl. Phys. **66** (7), 2800–2802 (1989). (I)
81. ''Theoretical determination of net radiation force and torque for a spherical particle illuminated by a focused laser beam,'' J. P. Barton, D. R. Alexander, and S. A. Schaub, J. Appl. Phys. **66** (10), 4594–4602 (1989). Calculations for a 5 μm diameter water droplet levitated in air. (A)
82. ''Forces of a Single-Beam Gradient Laser Trap on a Dielectric Sphere in the Ray Optics Regime,'' A. Ashkin, Biophys. J. **61** (2), 569–582 (1992). Includes the effect of index of refraction on the performance of a trap. (A)
83. ''Calculation of the Trapping Force in a Strongly Focused Laser-Beam,'' R. Gussgard, T. Lindmo, and I. Brevik, J. Opt. Soc. Am. B **9** (10), 1922–1930 (1992). (I)
84. ''Theoretical study of optically induced forces on spherical particles in a single beam trap I: Rayleigh scatterers,'' K. Visscher and G. J. Brakenhoff, Optik **89** (2), 174–180 (1992). Uses electromagnetic diffraction theory. (I)
85. ''Theoretical study of optically induced forces on spherical particles in a single beam trap II: Mie scatterers,'' K. Visscher and G. J. Brakenhoff, Optik **90** (2), 57–60 (1992). Vector diffraction theory of Mie scatterers. (A)
86. ''Radiation trapping forces on microspheres with optical tweezers,'' W. H. Wright, G. J. Sonek, and M. W. Berns, Appl. Phys. Lett. **63** (6), 715–717 (1993). Forces are predicted and compared, for spheres of various size and composition, with experimental measurements. (I)
87. ''Radiation Pressure Forces Exerted on a Particle Arbitrarily Located in a Gaussian-Beam by Using the Generalized Lorenz-Mie Theory, and Associated Resonance Effects,'' K. F. Ren, G. Greha, and G. Gouesbet, Opt. Commun. **108** (4–6), 343–354 (1994). (A)
88. ''Parametric study of the forces on microspheres held by optical tweezers,'' W. H. Wright, G. J. Sonek, and M. W. Berns, Appl. Opt. **33** (9), 1735–1748 (1994). 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. ''Radiation Forces on a Micrometer-Sized Sphere in an Evanescent Field,'' E. Almaas and I. Brevik, J. Opt. Soc. Am. B **12** (12), 2429–2438 (1995). Theoretical investigation used to predict the radiation forces in an evanescent wave of given polarization. (A)
90. ''Radiation forces on a dielectric sphere in the Rayleigh scattering regime,'' Y. Harada and T. Asakura, Opt. Commun. **124** (5–6), 529–541 (1996). (I)
91. ''Theoretical determination of the influence of the polarization on forces exerted by optical tweezers,'' T. Wohland, A. Rosin, and E. H. K. Stelzer, Optik **102** (4), 181–190 (1996). Significant differences in lateral forces can occur depending on the polarization orientation. (A)
92. ''Thermal noise limitations on micromechanical experiments,'' F. Gittes and C. F. Schmidt, Eur. Biophys. J. with Biophys. Lett **27** (1), 75–81 (1998). Strategies for maximizing signal-to-noise ratios are investigated theoretically. Includes experimental examples. (I)
93. ''Dynamics and dynamic light scattering properties of Brownian particles under laser radiation pressure,'' Y. Harada and T. Asakura, Pure Appl. Opt. **7** (5), 1001–1012 (1998). (A)
94. ''Localized dynamic light scattering: A new approach to dynamic measurements in optical microscopy,'' A. Meller, R. Bar-Ziv, T. Tlusty, E. Moses, J. Stavans, and S. A. Safran, Biophys. J. **74** (3), 1541–1548 (1998). The force constants for a single bead and pair of beads are calculated. (A)
95. ''Heating by absorption in the focus of an objective lens,'' A. Schonle and S. W. Hell, Opt. Lett. **23** (5), 325–327 (1998). Numerical results for local heating under typical optical trapping conditions are presented. (I)
96. ''Optical gradient forces of strongly localized fields,'' T. Tlusty, A. Meller, and R. Bar-Ziv, Phys. Rev. Lett. **81** (8), 1738–1741 (1998). Predictions for force-dependent curves, maximal trapping forces, and force constants are derived. (I)
97. ''Optical forces on microparticles in an evanescent laser field,'' M. Lester and M. Nieto-Vesperinas, Opt. Lett. **24** (14), 936–938 (1999). Theory of forces in an evanescent laser field. (A)
98. ''Optical traps as force transducers: The effects of focusing the trapping beam through a dielectric interface,'' A. C. Dogariu and R. Rajagopalan, Langmuir **16** (6), 2770–2778 (2000). Trap forces are calculated using wave optics calculations. Includes the identification of secondary traps. (A)
99. ''Analysis of the scattered light distribution of a tightly focused laser beam by a particle near a substrate,'' W. Inami and Y. Kawata, J. Appl. Phys. **89** (11), 5876–5880 (2001). Scattering fields near a substrate are calculated. (I)
100. ''Calculation and optical measurement of laser trapping forces on non-spherical particles,'' T. A. Nieminen, H. Rubinsztein-Dunlop, and N. R. Heckenberg, J. Quant. Spectrosc. Radiat. Transf. **70** (4–6),

627–637 (2001). Includes calculations of force and torque. (I)
101. ''Optical trapping of dielectric particles in arbitrary fields,'' A. Rohrbach and E. H. K. Stelzer, J. Opt. Soc. Am. A **18** (4), 839–853 (2001). In-depth study of calculating trapping potentials. (A)
102. ''Optical trapping near-resonance absorption,'' R. Agayan, F. Gittes, R. Kopelman, and C. F. Schmidt, S. P. I. E. (Int. Soc. Opt. Eng.) Proc. **4431**, 341–351 (2001). 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. ''Buckling of a Single Microtubule by Optical Trapping Forces: Direct Measurement of Microtubule Rigidity,'' M. Kurachi, M. Hoshi, and H. Tashiro, Cell Motil. Cytoskeleton **30** (3), 221–228 (1995). The microtubule rigidity was found to be dependent on length. (I)
104. ''Biased diffusion; optical trapping; and manipulation of single molecules in solution,'' D. T. Chiu and R. N. Zare, J. Am. Chem. Soc. **118** (27), 6512–6513 (1996). (I)
105. ''Flexural rigidity of microtubules measured with the use of optical tweezers,'' H. Felgner, R. Frank, and M. Schliwa, J. Cell Sci. **109** (2), 509–516 (1996). Microtubules are actively moved with optical tweezers while the microtubule shape is observed. (I)
106. ''Strength and lifetime of the bond between actin and skeletal muscle alpha-actinin studied with an optical trapping technique,'' H. Miyata, R. Yasuda, and K. Kinosita, Jr., Biochim. Biophys. Acta **1290** (1), 83–88 (1996). Suggestion of two classes of actin-actinin bonds, based on unbinding time measurements. (I)
107. ''Optical tweezers for single molecule mechanics,'' R. M. Simmons, J. A. Sleep, A. Trombetta, and P. Marya, in **Nanotechnology in Medicine and the Biosciences, Developments in Nanotechnology**, edited by R. R. H. Coombs and D. W. Robinson (Gordon & Breach, The Netherlands, 1996). A short book chapter that includes a design for studying actin myosin muscle proteins. (E)
108. ''Torsional rigidity of single actin filaments and actin-actin bond breaking force under torsion measured directly by *in vitro* micromanipulation,'' Y. Tsuda, H. Yasutake, A. Ishijima, and T. Yanagida, Proc. Natl. Acad. Sci. U.S.A. **93** (23), 12937–12942 (1996). This study includes the use of optical tweezers and fluorescent beads to measure rotational Brownian motion. (I)
109. ''Injection of ultrasmall samples and single molecules into tapered capillaries,'' D. T. Chiu, A. Hsiao, A. Gaggar, R. A. GarzaLopez, O. Orwar, and R. N. Zare, Anal. Chem. **69** (10), 1801–1807 (1997). Optical tweezers place objects at or near the inlet of tapered capillaries. (I)
110. ''Actin filament mechanics in the laser trap,'' D. E. Dupuis, W. H. Guilford, J. Wu, and D. M. Warshaw, J. Muscle Res. Cell Motil. **18** (1), 17–30 (1997). Independent laser traps were used in this study to determine the compliance of actin filaments. (I)
111. ''Imaging and nano-manipulation of single biomolecules,'' T. Funatsu, Y. Harada, H. Higuchi, M. Tokunaga, K. Saito, Y. Ishii, R. D. Vale, and T. Yanagida, Biophys. Chem. **68** (1–3), 63–72 (1997). Early experiments with combined single molecule fluorescence and optical tweezers. (I)
112. ''Folding-Unfolding Transitions in Single Titin Molecules Characterized with Laser Tweezers,'' M. S. Z. Kellermayer, S. B. Smith, H. L. Granzier, and C. Bustamante, Science **276**, 1112–1116 (1997). Includes unfolding and refolding curves. A combined micropipette and optical trap geometry is employed. (I)
113. ''A method for determination of stiffness of collagen molecules,'' Z. P. Luo, M. E. Bolander, and K. N. An, Biochem. Biophys. Res. Commun. **232** (1), 251–254 (1997). (I)
114. ''Elasticity and unfolding of single molecules of the giant muscle protein titin,'' L. Tskhovrebova, J. Trinick, J. A. Sleep, and R. M. Simmons, Nature **387** (6630), 308–312 (1997). Single molecule mechanical experiment of titin with optical tweezers. (I)
115. ''Complete unfolding of the titin molecule under external force,'' M. S. Z. Kellermayer, S. B. Smith, C. Bustamante, and H. L. Granzier, J. Struct. Biol. **122** (1–2), 197–205 (1998). Titin molecules are stretched with forces above 400 pN. (I)
116. ''Manipulation of single molecules in biology,'' M. D. Wang, Curr. Opin. Biotechnol. **10** (1), 81–86 (1999). Highlights optical tweezers single molecule motor assays. (E)
117. ''Grabbing the cat by the tail: Manipulating molecules one by one,'' C. Bustamante, J. C. Macosko, and G. J. L. Wuite, Nat. Rev. Mol. Cell Biol. **1** (2), 130–136 (2000). A review. (E)
118. ''Measurement of the elasticity of the actin tail of Listeria monocytogenes,'' F. Gerbal, V. Laurent, A. Ott, M. F. Carlier, P. Chaikin, and J. Prost, Eur. Biophys. J. with Biophys. Lett. **29** (2), 134–140 (2000). (I)
119. ''Short-term binding of fibroblasts to fibronectin: optical tweezers experiments and probabilistic analysis,'' O. Thoumine, P. Kocian, A. Kottelat, and J. J. Meister, Eur. Biophys. J. with Biophys. Lett. **29** (6), 398–408 (2000). Adhesion tests of fibroblasts on fibronectin-coated glass. (I)
120. ''Force spectroscopy on single passive biomolecules and single biomolecular bonds,'' R. Merkel, Phys. Rep. Phys. Lett. **346** (5), 344–385 (2001). A review. (I)
121. ''Optical measurement of microscopic torques,'' T. A. Nieminen, N. R. Heckenberg, and H. Rubinsztein-Dunlop, J. Mod. Opt. **48** (3), 405–413 (2001). (I)
122. ''Mechanical fatigue in repetitively stretched single molecules of titin,'' M. S. Z. Kellermayer, S. B. Smith, C. Bustamante, and H. L. Granzier, Biophys. J. **80** (2), 852–863 (2001). Optical tweezers were used to repetitively stretch and release titin to study mechanical fatigue. (I)
123. ''Detection and characterization of individual intermolecular bonds using optical tweezers,'' A. L. Stout, Biophys. J. **80** (6), 2976–2986 (2001). Details of the instrument, technique and geometry for rupture force measurements are shown. (I)
124. ''Stretching short biopolymers using optical tweezers,'' Y. L. Sun, Z. P. Luo and K. N. An, Biochem. Biophys. Res. Commun. **286** (4), 826–830 (2001). The stiffness of procollagen molecules was studied. (I)
125. ''Single molecule measurements of titin elasticity,'' K. Wang, J. G. Forbes, and A. J. Jin, Prog. Biophys. Mol. Biol. **77** (1), 1–44 (2001). A review. (I)
126. ''Flexural rigidity of a single microtubule,'' T. Takasone, S. Juodkazis, Y. Kawagishi, A. Yamaguchi, S. Matsuo, H. Sakakibara, H. Nakayama, and H. Misawa, Jpn. J. Appl. Phys. **41** (5), 3015–3019 (2002). 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 re-

search. We encourage the reader to explore experimental innovations implemented in multiple motor systems.

a. General motors

127. ''Molecular Motors: Structure, Mechanics and Energy Transduction,'' edited by R. Cooke, Biophys. J. **68** (4), 1s–382s (1995). This supplemental issue is a Biophysical Discussions conference proceedings dedicated to molecular motors, and contains several papers related to optical trapping studies. (E)

128. ''Microscopic approaches to dynamics and structure of biological motors,'' F. Gittes and C. F. Schmidt, Curr. Opin. Solid State Mater. Sci. **1** (3), 412–424 (1996). A review. (I)

129. ''Molecular motors: single-molecule mechanics,'' R. Simmons, Curr. Biol. **6** (4), 392–394 (1996). (E)

130. ''Real engines of creation,'' S. M. Block, Nature **386** (6622), 217–219 (1997). An introduction to the study of molecular motors with new biophysical techniques. (E)

131. ''Force effects on biochemical kinetics,'' S. Khan and M. P. Sheetz, Annu. Rev. Biochem. **66**, 785–805 (1997). Applications of force measurements to enzyme activity and motor proteins are presented including a comparison with other force measurement methods. (I)

132. ''Two-dimensional tracking of ncd motility by back focal plane interferometry,'' M. W. Allersma, F. Gittes, M. J. deCastro, R. J. Stewart, and C. F. Schmidt, Biophys. J. **74** (2), 1074–1085 (1998). Includes 2D detection with a quadrant photodiode and theory. (A)

133. ''Use of optical traps in single-molecule study of nonprocessive biological motors,'' A. D. Mehta, J. T. Finer, and J. A. Spudich, Methods Enzymol. **298**, 436–459 (1998). A review. (I)

134. ''Dynein arms are oscillating force generators,'' C. Shingyoji, H. Higuchi, M. Yoshimura, E. Katayama, and T. Yanagida, Nature **393** (6686), 711–714 (1998). (I)

135. ''Developmental regulation of vesicle transport in Drosophila embryos: Forces and kinetics,'' M. A. Welte, S. P. Gross, M. Postner, S. M. Block, and E. F. Wieschaus, Cell **92** (4), 547–557 (1998). (I)

136. ''Biomechanics, one molecule at a time,'' A. D. Mehta, M. Rief, and J. A. Spudich, J. Biol. Chem. **274** (21), 14517–14520 (1999). Focus on some single molecule optical tweezers measurements. (E)

137. ''Working strokes by single molecules of the kinesin-related microtubule motor ncd,'' M. J. deCastro, R. M. Fondecave, L. A. Clarke, C. F. Schmidt, and R. J. Stewart, Nat. Cell Biol. **2** (10), 724–729 (2000). Uses a three-bead geometry to measure the working stroke of ncd. (I)

138. ''Processive movement of single 22S dynein molecules occurs only at low ATP concentrations,'' E. Hirakawa, H. Higuchi, and Y. Y. Toyoshima, Proc. Natl. Acad. Sci. U.S.A **97** (6), 2533–2537 (2000). 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. ''Bead movement by single kinesin molecules studied with optical tweezers,'' S. M. Block, L. S. Goldstein, and B. J. Schnapp, Nature **348** (6299), 348–352 (1990). (E)

140. ''Nucleotide-dependent single-to double-headed binding of kinesin,'' K. Kawaguchi and S. Ishiwata, Science **291** (5504), 667–669 (2001). Optical tweezers were used to measure the unbinding force of kinesin attached to microtubules under various nuclotide conditions. (I)

141. ''Direct observation of kinesin stepping by optical trapping interferometry,'' K. Svoboda, C. F. Schmidt, B. J. Schnapp, and S. M. Block, Nature **365** (6448), 721–727 (1993). Kinesin moves with 8 nm steps. (I)

142. ''Force and velocity measured for single kinesin molecules,'' K. Svoboda and S. M. Block, Cell **77** (5), 773–784 (1994). Optical trapping combined with interferometry. (I)

143. ''Fluctuation Analysis of Motor Protein Movement and Single Enzyme-Kinetics,'' K. Svoboda, P. P. Mitra, and S. M. Block, Proc. Natl. Acad. Sci. U.S.A. **91** (25), 11782–11786 (1994). (I)

144. ''Nanometers and Piconewtons: The Macromolecular Mechanics of Kinesin,'' S. M. Block, Trends Cell Biol. **5** (4), 169–175 (1995). Perspective on single motor assay measurements on kinesin. (E)

145. ''Detection of sub-8-nm movements of kinesin by high-resolution optical-trap microscopy,'' C. M. Coppin, J. T. Finer, J. A. Spudich, and R. D. Vale, Proc. Natl. Acad. Sci. U.S.A. **93** (5), 1913–1917 (1996). Kinesin steps of both 8 and ~5 nm are presented in this sensitive measurement. (I)

146. ''The load dependence of kinesin's mechanical cycle,'' C. M. Coppin, D. W. Pierce, L. Hsu, and R. D. Vale, Proc. Natl. Acad. Sci. U.S.A. **94** (16), 8539–8544 (1997). Forward loads of kinesin motility are presented in this paper. (I)

147. ''Kinetics of force generation by single kinesin molecules activated by laser photolysis of caged ATP,'' H. Higuchi, E. Muto, Y. Inoue, and T. Yanagida, Proc. Natl. Acad. Sci. U.S.A. **94** (9), 4395–4400 (1997). Combination of optical tweezers and UV photolysis of caged compounds. (I)

148. ''Movements of truncated kinesin fragments with a short or an artificial flexible neck,'' Y. Inoue, Y. Y. Toyoshima, A. H. Iwane, S. Morimoto, H. Higuchi, and T. Yanagida, Proc. Natl. Acad. Sci. U.S.A. **94** (14), 7275–7280 (1997). Stepwise movement of kinesin observed with optical tweezers. (I)

149. ''Mechanics of single kinesin molecules measured by optical trapping nanometry,'' H. Kojima, E. Muto, H. Higuchi, and T. Yanagida, Biophys. J. **73** (4), 2012–2022 (1997). Includes compliance correction to determine the displacement. The measurement was performed on axonemes. (I)

150. ''Coupled chemical and mechanical reaction steps in a processive Neurospora kinesin,'' I. Crevel, N. Carter, M. Schliwa, and R. Cross, EMBO J. **18** (21), 5863–5872 (1999). Shows kinesin stepping. (I)

151. ''Mechanical and chemical properties of cysteine-modified kinesin molecules,'' S. Iwatani, A. H. Iwane, H. Higuchi, Y. Ishii, and T. Yanagida, Biochemistry **38** (32), 10318–10323 (1999). Mechanical properties of kinesin mutants were measured. (I)

152. ''Single kinesin molecules studied with a molecular force clamp,'' K. Visscher, M. J. Schnitzer, and S. M. Block, Nature **400** (6740), 184–189 (1999). Force clamping was implemented to generate force-velocity relationships for kinesin motility. Details of implementing the force clamp are presented. (I)

153. ''A mutant of the motor protein kinesin that moves in both directions on microtubules,'' S. A. Endow and H. Higuchi, Nature **406** (6798), 913–916 (2000). Optical tweezers were used to observe the directional bias of ncd and mutant motors. (I)

154. ''Temperature dependence of force, velocity, and processivity of single kinesin molecules,'' K. Kawaguchi and S. Ishiwata, Biochem. Biophys. Res. Commun. **272** (3), 895–899 (2000). The temperature dependence for various aspects of kinesin motility is measured. (I)

155. ''Force production by single kinesin motors,'' M. J. Schnitzer, K. Visscher, and S. M. Block, Nat. Cell Biol. **2** (10), 718–723 (2000). Kinesin mechanochemistry, obtained from a force clamp, is modeled. (I)

156. ''Substeps within the 8-nm step of the ATPase cycle of single kinesin molecules,'' M. Nishiyama, E. Muto, Y. Inoue, T. Yanagida, and H. Higuchi, Nat. Cell Biol. **3** (4), 425–428 (2001). 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. ''Actin cores of hair-cell stereocilia support myosin motility,'' G. M. Shepherd, D. P. Corey, and S. M. Block, Proc. Natl. Acad. Sci. U.S.A. **87** (21), 8627–8631 (1990). Optical tweezers were used to deposit myosin-coated beads on actin cores of hair-cell stereocilia in an *in vitro* assay. (I)

158. ''Force on single actin filaments in a motility assay measured with an optical trap,'' R. M. Simmons, J. T. Finer, H. M. Warrick, B. Kralik, S. Chu, and J. A. Spudich, Adv. Exp. Med. Biol. **332**, 331–336 (1993). Use of optical tweezers to measure actin filament movement on HMM (heavy meromyosin). Includes quadrant-photodiode detection, acousto-optic 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,'' H. M. Warrick, R. M. Simmons, J. T. Finer, T. Q. P. Uyeda, S. Chu, and J. A. Spudich, in **Methods in Cell Biology 39**, edited by J. M. Scholey (Academic, New York, 1993), pp. 1–21. Includes feedback control using acousto-optic deflectors. (I)

160. ''Single myosin molecule mechanics: piconewton forces and nanometre steps,'' J. T. Finer, R. M. Simmons, and J. A. Spudich, Nature **368** (6467), 113–119 (1994). Contains a description of their feedback-enhanced laser trap system which includes two beams and uses acousto-optic modulation and quadrant photodiode detection. (A)

161. ''Microscopic measurement of sliding and binding force between muscle proteins with optical tweezers,'' T. Nishizaka, H. Miyata, H. Yoshikawa, S. Ishiwata, and K. J. Kinosita, in **Optical Methods in Biomedical and Environmental Sciences**, edited by H. Ohzu and S. Komatsu (Elsevier Science, Amsterdam, 1994), pp. 195–198. 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. ''Movement of single myosin filaments and myosin step size on an actin filament suspended in solution by a laser trap,'' K. Saito, T. Aoki, and T. Yanagida, Biophys. J. **66** (3), 769–777 (1994). The instrument used in this experiment includes dual laser traps that are positioned using galvanometer scanners. (I)

163. ''Movement and force produced by a single myosin head,'' J. E. Molloy, J. E. Burns, J. Kendrick-Jones, R. T. Tregear, and D. C. White, Nature **378** (6553), 209–212 (1995). (I)

164. ''Unbinding force of a single motor molecule of muscle measured using optical tweezers,'' T. Nishizaka, H. Miyata, H. Yoshikawa, S. Ishiwata, and K. Kinosita, Jr., Nature **377** (6546), 251–254 (1995). The unbinding force was measured repeatedly and found to be ~9 pN and angle independent. (I)

165. ''*In vitro* motility of immunoadsorbed brain myosin-V using a Limulus acrosomal process and optical tweezer-based assay,'' J. S. Wolenski, R. E. Cheney, M. S. Mooseker, and P. Forscher, J. Cell Sci. **108** (Pt 4), 1489–1496 (1995). (I)

166. ''Direct measurement of the torsional rigidity of single actin filaments,'' R. Yasuda, H. Miyata, and K. Kinosita, Jr., J. Mol. Biol. **263** (2), 227–236 (1996). 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. ''Smooth muscle and skeletal muscle myosins produce similar unitary forces and displacements in the laser trap,'' W. H. Guilford, D. E. Dupuis, G. Kennedy, J. R. Wu, J. B. Patlak, and D. M. Warshaw, Biophys. J. **72** (3), 1006–1021 (1997). Mean-variance analysis is used to analyze the data in this study. (I)

168. ''Smooth and skeletal muscle single-molecule mechanical experiments,'' J. E. Molloy and D. C. White, Biophys. J. **72** (3), 984–986 (1997). An introduction. (E)

169. ''Simultaneous observation of individual ATPase and mechanical events by a single myosin molecule during interaction with actin,'' A. Ishijima, H. Kojima, T. Funatsu, M. Tokunaga, H. Higuchi, H. Tanaka, and T. Yanagida, Cell **92** (2), 161–171 (1998). 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. ''Orientation dependence of displacements by a single one-headed myosin relative to the actin filament,'' H. Tanaka, A. Ishijima, M. Honda, K. Saito, and T. Yanagida, Biophys. J. **75** (4), 1886–1894 (1998). Use of dual optical traps for angle-resolved measurements; includes epifluorescence. (I)

171. ''The stiffness of rabbit skeletal actomyosin cross-bridges determined with an optical tweezers transducer,'' C. Veigel, M. L. Bartoo, D. C. White, J. C. Sparrow, and J. E. Molloy, Biophys. J. **75** (3), 1424–1438 (1998). An advanced instrument is described including position detection for two traps, acousto-optic deflectors, a piezoelectric substage, and fluorescence visualization of actin filaments. (A)

172. ''Imaging of thermal activation of actomyosin motors,'' H. Kato, T. Nishizaka, T. Iga, K. Kinosita, and S. Ishiwata, Proc. Natl. Acad. Sci. U.S.A. **96** (17), 9602–9606 (1999). 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. ''Myosin-V is a processive actin-based motor,'' A. D. Mehta, R. S. Rock, M. Rief, J. A. Spudich, M. S. Mooseker, and R. E. Cheney, Nature **400** (6744), 590–593 (1999). A dual trap geometry, where the position was determined by oscillating one of the beads. (I)

174. ''The motor protein myosin-I produces its working stroke in two steps,'' C. Veigel, L. M. Coluccio, J. D. Jontes, J. C. Sparrow, R. A. Milligan, and J. E. Molloy, Nature **398** (6727), 530–533 (1999). The temporal aspects of myosin steps are explored. (I)

175. ''Characterization of single actomyosin rigor bonds: load dependence of lifetime and mechanical properties,'' T. Nishizaka, R. Seo, H. Tadakuma, K. Kinosita, Jr., and S. Ishiwata, Biophys. J. **79** (2), 962–974 (2000). 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. ''Single molecule analysis of the actomyosin motor,'' T. Yanagida, K. Kitamura, H. Tanaka, A. Hikikoshi Iwane, and S. Esaki, Curr. Opin. Cell Biol. **12** (1), 20–25 (2000). 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. ''Analysis of single-molecule mechanical recordings: application to acto-myosin interactions,'' A. E. Knight, C. Veigel, C. Chambers, and J. E. Molloy, Prog. Biophys. Mol. Biol. **77** (1), 45–72 (2001). Page's test is compared with other variance methods for analysing mechanical events. (I)

178. ''Alternative exon-encoded regions of Drosophila myosin heavy chain modulate ATPase rates and actin sliding velocity,'' D. M. Swank, M. L. Bartoo, A. F. Knowles, C. Iliffe, S. I. Bernstein, J. E. Molloy, and J. C. Sparrow, J. Biol. Chem. **276** (18), 15117–15124 (2001). 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. ''RNA Polymerase gets very pushy,'' C. O'Brien, Science **70**, 1568 (1995). An introduction to a polymerase, optical tweezers measurement. (E)

180. ''Transcription against an Applied Force,'' H. Yin, M. D. Wang, K. Svoboda, R. Landick, S. M. Block, and J. Gelles, Science **270** (5242), 1653–1657 (1995). Velocity and stall forces are measured for *Escherichia coli* RNA polymerase using interferometry. (I)

181. ''Single-molecule imaging of RNA polymerase-DNA interactions in real time,'' Y. Harada, T. Funatsu, K. Murakami, Y. Nonoyama, A. Ishihama, and T. Yanagida, Biophys. J. **76** (2), 709–715 (1999). 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. ''Direct observation of DNA rotation during transcription by Escherichia coli RNA polymerase,'' Y. Harada, O. Ohara, A. Takatsuki, H. Itoh, N. Shimamoto, and K. Kinosita, Nature **409** (6816), 113–115 (2001). (I)

183. ''The bacteriophage phi 29 portal motor can package DNA against a large internal force,'' D. E. Smith, S. J. Tans, S. B. Smith, S. Grimes, D. L. Anderson, and C. Bustamante, Nature **413** (6857), 748–752 (2001). Optical tweezers are used to pull on DNA as it is packaged by a portal complex. (I)

e. Flagellar motors

184. ''Compliance of bacterial flagella measured with optical tweezers,'' S. M. Block, D. F. Blair, and H. C. Berg, Nature **338** (6215), 514–518 (1989). Flagellar torsional compliance measured with a Stokes-calibrated trap for tethered *Escherichia coli* and a motile strain of *Streptococcus*. (I)

185. ''Morphology and dynamics of protruding spirochete periplasmic flagella,'' N. W. Charon, S. F. Goldstein, S. M. Block, K. Curci, J. D. Ruby, J. A. Kreiling, and R. J. Limberger, J. Bacteriol. **174** (3), 832–840 (1992). Cells were held with optical tweezers to observe the motion of protrusions by video-enhanced DIC microscopy. (I)

186. ''Absence of a barrier to backwards rotation of the bacterial flagellar motor demonstrated with optical tweezers,'' R. M. Berry and H. C. Berg, Proc. Natl. Acad. Sci. U.S.A. **94** (26), 14433–14437 (1997). 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. ''Powering the Flagellar Motor of Escherichia-Coli with an External Voltage-Source,'' D. C. Fung and H. C. Berg, Nature **375** (6534), 809–812 (1995). (I)

188. ''Torque-generating units of the flagellar motor of Escherichia coli have a high duty ratio,'' W. S. Ryu, R. M. Berry, and H. C. Berg, Nature **403** (6768), 444–447 (2000). (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. ''Relaxation of a single DNA molecule observed by optical microscopy,'' T. T. Perkins, S. R. Quake, D. E. Smith, and S. Chu, Science **264** (5160), 822–826 (1994). (I)

190. ''Direct observation of tube-like motion of a single polymer chain,'' T. T. Perkins, D. E. Smith, and S. Chu, Science **264** (5160), 819–822 (1994). (I)

191. ''Stretching of a single tethered polymer in a uniform flow,'' T. T. Perkins, D. E. Smith, R. G. Larson, and S. Chu, Science **268** (5207), 83–87 (1995). Flow-extended, tethered DNA molecules attached to a latex sphere were trapped and visualized with fluorescence microscopy. (I)

192. ''Overstretching B-DNA: The elastic response of individual double-stranded and single-stranded DNA molecules,'' S. B. Smith, Y. J. Cui, and C. Bustamante, Science **271** (5250), 795–799 (1996). (I)

193. ''Single DNA molecule grafting and manipulation using a combined atomic force microscope and an optical tweezer,'' G. V. Shivashankar and A. Libchaber, Appl. Phys. Lett. **71** (25), 3727–3729 (1997). Combined AFM with optical tweezers. (I)

194. ''Stretching DNA with optical tweezers,'' M. D. Wang, H. Yin, R. Landick, J. Gelles, and S. M. Block, Biophys. J. **72** (3), 1335–1346 (1997). Force-extension relationships were measured for single DNA molecules using a position clamp. (I)

195. ''DNA attachment to optically trapped beads in microstructures monitored by bead displacement,'' J. Dapprich and N. Nicklaus, Bioimaging **6** (1), 25–32 (1998). Changes in the viscous drag force are used to detect DNA attachment. (I)

196. ''Single-molecule manipulation of double-stranded DNA using optical tweezers: Interaction studies of DNA with RecA and YOYO-1,'' M. L. Bennink, O. D. Scharer, R. Kanaar, K. Sakata-Sogawa, J. M. Schins, J. S. Kanger, B. G. de Grooth, and J. Greve, Cytometry **36** (3), 200–208 (1999). Uses a combined tweezers, micropipette instrument. (I)

197. ''The active digestion of uniparental chloroplast DNA in a single zygote of *Chlamydomonas reinhardtii* is revealed by using the optical tweezer,'' Y. Nishimura, O. Misumi, S. Matsunaga, T. Higashiyama, A. Yokota, and T. Kuroiwa, Proc. Natl. Acad. Sci. U.S.A. **96** (22), 12577–12582 (1999). Optical tweezers were used to trap cells of interest in a harvesting procedure. (I)

198. ''RecA polymerization on double-stranded DNA by using single-molecule manipulation: The role of ATP hydrolysis,'' G. V. Shivashankar, M. Feingold, O. Krichevsky, and A. Libchaber, Proc. Natl. Acad. Sci. U.S.A. **96** (14), 7916–7921 (1999). Force extension is used to study the polymerization of RecA on DNA. A model for nucleation and growth is presented. (I)

199. ''Stretching of single collapsed DNA molecules,'' C. G. Baumann, V. A. Bloomfield, S. B. Smith, C. Bustamante, M. D. Wang, and S. M. Block, Biophys. J. **78** (4), 1965–1978 (2000). Use of optical trap and micropipette to measure the elastic response of DNA. (I)

200. ''Single-molecule studies of DNA mechanics,'' C. Bustamante, S. B. Smith, J. Liphardt, and D. Smith, Curr. Opin. Struct. Biol. **10** (3), 279–285 (2000). (E)

201. ''Unfolding individual nucleosomes by stretching single chromatin fibers with optical tweezers,'' M. L. Bennink, S. H. Leuba, G. H. Leno, J. Zlatanova, B. G. de Grooth, and J. Greve, Nat. Struct. Biol. **8** (7), 606–610 (2001). The assembly and stretching of chromatin fibers was studied with optical tweezers. (I)

202. ''Direct integration of micromachined pipettes in a flow channel for single DNA molecule study by optical tweezers,'' C. Rusu, R. van't Oever, M. J. de Boer, H. V. Jansen, J. W. Berenschot, M. L. Bennink, J. S. Kanger, B. G. de Grooth, M. Elwenspoek, J. Greve, J. Brugger, and A. van den Berg, J. Micromech. Sys. **10** (2), 238–246 (2001). Various shaped micropipettes are presented. (I)

203. ''Kinetics and mechanism of DNA uptake into the cell nucleus,'' H. Salman, D. Zbaida, Y. Rabin, D. Chatenay, and M. Elbaum, Proc. Natl. Acad. Sci. U.S.A. **98** (13), 7247–7252 (2001). The extension of DNA between a bead and the nucleus was measured. (I)

204. ''Mechanism for nucleic acid chaperone activity of HIV-1 nucleocapsid protein revealed by single molecule stretching,'' M. C. Williams, I. Rouzina, J. R. Wenner, R. J. Gorelick, K. Musier-Forsyth, and V. A. Bloomfield, Proc. Natl. Acad. Sci. U.S.A. **98** (11), 6121–6126 (2001). DNA is stretched with a combined dual-beam optical trap, micropipette instrument. (I)

205. ''Effect of *p*H on the overstretching transition of double-stranded DNA: Evidence of force-induced DNA melting,'' M. C. Williams, J. R. Wenner, L. Rouzina, and V. A. Bloomfield, Biophys. J. **80** (2), 874–881 (2001). Solution *p*H from 6.0 to 10.6 was studied. (I)

206. ''Entropy and heat capacity of DNA melting from temperature dependence of single molecule stretching,'' M. C. Williams, J. R. Wenner, I. Rouzina, and V. A. Bloomfield, Biophys. J. **80** (4), 1932–1939 (2001). 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. ''Optical Trapping and Manipulation of Single Living Cells Using

Infrared-Laser Beams,'' A. Ashkin and J. M. Dziedzic, Ber. Bunsenges. Phys. Chem. **93** (3), 254–260 (1989). Plant cell cytoplasmic viscoelasticity is measured. (I)

208. ''Internal cell manipulation using infrared laser traps,'' A. Ashkin and J. M. Dziedzic, Proc. Natl. Acad. Sci. U.S.A. **86** (20), 7914–7918 (1989). The cytoplasmic viscoelasticity in plant cells was measured. (I)

209. ''Use of a laser-induced optical force trap to study chromosome movement on the mitotic spindle,'' M. W. Berns, W. H. Wright, B. J. Tromberg, G. A. Profeta, J. J. Andrews, and R. J. Walter, Proc. Natl. Acad. Sci. U.S.A. **86** (12), 4539–4543 (1989). Chromosome motility against the trapping force was demonstrated. (I)

210. ''Force generation of organelle transport measured *in vivo* by an infrared laser trap,'' A. Ashkin, K. Schutze, J. M. Dziedzic, U. Euteneuer, and M. Schliwa, Nature **348** (6299), 346–348 (1990). Study in the giant amoeba *Reticulomyxa* of organelle transport. (E)

211. ''Laser Trapping in Cell Biology,'' W. H. Wright, G. J. Sonek, Y. Tadir, and M. W. Berns, IEEE J. Quantum Electron. **26** (12), 2148–2157 (1990). 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. ''The study of cells by optical trapping and manipulation of living cells using infrared laser beams,'' A. Ashkin, ASGSB Bull. **4** (2), 133–146 (1991). A review of the use of optical traps in manipulating cells. (I)

213. ''Compliance of bacterial polyhooks measured with optical tweezers,'' S. M. Block, D. F. Blair, and H. C. Berg, Cytometry **12** (6), 492–496 (1991). Cells are tethered to the glass by single flagellum in these measurements. (I)

214. ''Preferential attachment of membrane glycoproteins to the cytoskeleton at the leading edge of lamella,'' D. F. Kucik, S. C. Kuo, E. L. Elson, and M. P. Sheetz, J. Cell Biol. **114** (5), 1029–1036 (1991). Particles were tracked for different placement points on cells and tracked to localize attachment and transport properties. (I)

215. ''Directed positioning of nuclei in living *Paramecium tetraurelia:* use of the laser optical force trap for developmental biology,'' K. J. Aufderheide, Q. Du, and E. S. Fry, Dev. Genet. **13**, 235–240 (1992). 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. ''Chromosome microtechnology: microdissection and microcloning,'' K. O. Greulich, Trends Biotechnol. **10** (1–2), 48–51 (1992). Introduction to the technique. (E)

217. ''The isolated human red blood skeleton: an example of a flexible tethered membrane,'' C. F. Schmidt, K. Svoboda, N. Lei, C. F. Safinya, S. M. Block, and D. Branton, in **The Structure and Conformation of Amphilic Membranes**, edited by R. Lipowsky, D. Richter, and K. Kremer (Springer-Verlag, Berlin, 1992), pp. 128–132. (I)

218. ''Conformation and elasticity of the isolated red blood cell membrane skeleton,'' K. Svoboda, C. F. Schmidt, D. Branton, and S. M. Block, Biophys. J. **63** (3), 784–793 (1992). (I)

219. ''Isolation of single yeast cells by optical trapping,'' J. A. Grimbergen, K. Visscher, D. S. Gomes de Mesquita, and G. J. Brakenhoff, Yeast **9** (7), 723–732 (1993). Selected cells are transferred to a plastic capillary using optical tweezers. (I)

220. ''Micromanipulation of chromosomes in PTK-2 cells using laser microsurgery (optical scalpel) in combination with laser-induced optical force (optical tweezers),'' H. Liang, W. H. Wright, S. Cheng, W. He, and M. W. Berns, Exp. Cell Res. **204** (1), 110–120 (1993). 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. ''Directed movement of chromosome arms and fragments in mitotic newt lung cells using optical scissors and optical tweezers,'' H. Liang, W. H. Wright, C. L. Rieder, E. D. Salmon, G. Profeta, J. Andrews, Y. Liu, G. J. Sonek, and M. W. Berns, Exp. Cell Res. **213** (1), 308–312 (1994). Demonstrates a high degree of facility in manipulating chromosomes. (I)

222. ''Optical trapping for chromosome manipulation: a wavelength dependence of induced chromosome bridges,'' I. A. Vorobjev, H. Liang, W. H. Wright, and M. W. Berns, Biophys. J. **64** (2), 533–538 (1993). A Ti:sapphire laser is used in a wavelength comparison from 700 to 840 nm of biological response. Wavelength sensitivities are presented. (I)

223. ''Mechanical properties of neuronal growth cone membranes studied by tether formation with laser optical tweezers,'' J. Dai and M. P. Sheetz, Biophys. J. **68** (3), 988–996 (1995). 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. ''Isolation of a hyperthermophilic archaeum predicted by in situ RNA analysis,'' R. Huber, S. Burggraf, T. Mayer, S. M. Barns, P. Rossnagel, and K. O. Stetter, Nature **376** (6535), 57–58 (1995). (I)

225. ''Micromanipulation of statoliths in gravity-sensing Chara rhizoids by optical tweezers,'' G. Leitz, E. Schnepf, and K. O. Greulich, Planta **197** (2), 278–288 (1995). (I)

226. ''Cell surface organization by the membrane skeleton,'' A. Kusumi and Y. Sako, Curr. Opin. Cell Biol. **8** (4), 566–574 (1996). (I)

227. ''Optically controlled collisions of biological objects to evaluate potent polyvalent inhibitors of virus-cell adhesion,'' M. Mammen, K. Helmerson, R. Kishore, S. K. Choi, W. D. Phillips, and G. M. Whitesides, Chem. Biol. **3** (9), 757–763 (1996). Two particles are caused to collide using independently controlled optical tweezers. (I)

228. ''Giant cell formation in cells exposed to 740 nm and 760 nm optical traps,'' H. Liang, K. T. Vu, T. C. Trang, D. Shin, Y. E. Lee, D. C. Nguyen, B. Tromberg, and M. W. Berns, Lasers Surg. Med. **21** (2), 159–165 (1997). (I)

229. ''Micromanipulation of retinal neurons by optical tweezers,'' E. Townes-Anderson, R. S. St Jules, D. M. Sherry, J. Lichtenberger, and M. Hassanain, Mol. Vis. **4**, 12 (1998). Optical tweezers are used to position and group neuron cells. The outgrowth of manipulated cells is compared to unmanipulated cells. (I)

230. ''Keratocytes pull with similar forces on their dorsal and ventral surfaces,'' C. G. Galbraith and M. P. Sheetz, J. Cell Biol. **147** (6), 1313–1323 (1999). 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. ''Elasticity of the red cell membrane and its relation to hemolytic disorders: an optical tweezers study,'' J. Sleep, D. Wilson, R. Simmons, and W. Gratzer, Biophys. J. **77** (6), 3085–3095 (1999). Two beads were used to measure the force-extension relation of red cell membranes. (I)

232. ''A diffusion barrier maintains distribution of membrane proteins in polarized neurons,'' B. Winckler, P. Forscher, and I. Mellman, Nature **397** (6721), 698–701 (1999). In this study, optical tweezers are used to measure the lateral mobility of membrane proteins. (I)

233. ''Changes in Hechtian strands in cold-hardened cells measured by optical microsurgery,'' C. S. Buer, P. J. Weathers, and G. A. Swartzlander, Plant Physiol. **122** (4), 1365–1377 (2000). In this study concanavalin-coated spheres were inserted through an ablated hole in the cell wall and attached to a hechtian strand. (I)

234. ''Measuring the forces involved in polyvalent adhesion of uropathogenic Escherichia coli to mannose-presenting surfaces,'' M. N. Liang, S. P. Smith, S. J. Metallo, I. S. Choi, M. Prentiss, and G. M. Whitesides, Proc. Natl. Acad. Sci. U.S.A. **97** (24), 13092–13096 (2000). Optical tweezers are used to orient the bacteria relative to a surface of functionalized self assembled monolayers. (I)

235. ''Optical deformability of soft biological dielectrics,'' J. Guck, R. Ananthakrishnan, T. J. Moon, C. C. Cunningham, and J. Kas, Phys. Rev. Lett. **84** (23), 5451–5454 (2000). Includes some information on damage. (I)

236. ''Cell spreading and lamellipodial extension rate is regulated by membrane tension,'' D. Raucher and M. P. Sheetz, J. Cell Biol. **148** (1), 127–136 (2000). Optical tweezers were used to determine membrane tension in a tether-force measurement. (I)

237. ''Chiral self-propulsion of growing bacterial macrofibers on a solid surface,'' N. H. Mendelson, J. E. Sarlls, C. W. Wolgemuth, and R. E. Goldstein, Phys. Rev. Lett. **84** (7), 1627–1630 (2000). Optical tweezers were used to measure the Young's modulus of the bacterial cell wall. (I)

238. ''Micromanipulation of chloroplasts using optical tweezers,'' S. Bayoudh, M. Mehta, H. Rubinsztein-Dunlop, N. R. Heckenberg, and C. Critchley, J. Microsc. **203** (Pt 2), 214–222 (2001). Dual optical tweezers were used to probe chloroplast arrangement. (I)

239. ''Direct measurement of the area expansion and shear moduli of the human red blood cell membrane skeleton,'' G. Lenormand, S. Henon,

A. Richert, J. Simeon, and F. Gallet, Biophys. J. **81** (1), 43–56 (2001). Galvanometric mirrors form the traps in this three-bead measurement. (I)

240. ''Cell traction forces on soft biomaterials. I. Microrheology of Type I collagen gels,'' D. Velegol and F. Lanni, Biophys. J. **81** (3), 1786–1792 (2001). A refraction plate on a galvanometric scanner was used to translate the trapped particle. (I)

241. ''Stretching biological cells with light,'' J. Guck, R. Ananthakrishnan, C. Casey Cunningham, and J. Kas, J. Phys.: Condens. Matter **14**, 4843–4856 (2002). A description of the experimental setup is provided. Cell viability is also discussed. (I)

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. ''Micromanipulation of sperm by a laser generated optical trap,'' Y. Tadir, W. H. Wright, O. Vafa, T. Ord, R. H. Asch, and M. W. Berns, Fertil. Steril. **52**, 870–873 (1989). (E)

243. ''Force generated by human sperm correlated to velocity and determined using a laser generated optical trap,'' Y. Tadir, W. H. Wright, O. Vafa, T. Ord, R. H. Asch, and M. W. Berns, Fertil. Steril. **53** (5), 944–947 (1990). (I)

244. ''Micromanipulation of gametes using laser microbeams,'' Y. Tadir, W. H. Wright, O. Vafa, L. H. Liaw, R. Asch, and M. W. Berns, Hum. Reprod. **6** (7), 1011–1016 (1991). A review. (E)

245. ''Controlled micromanipulation of human sperm in three dimensions with an infrared laser optical trap: effect on sperm velocity,'' J. M. Colon, P. Sarosi, P. G. McGovern, A. Askin, J. M. Dziedzic, J. Skurnick, G. Weiss, and E. M. Bonder, Fertil. Steril. **57** (3), 695–698 (1992). (I)

246. ''Lasers for gamete micromanipulation: basic concepts,'' Y. Tadir, J. Neev, P. Ho, and M. W. Berns, J. Assist. Reprod. Genet. **10** (2), 121–125 (1993). A review. (E)

247. ''Exposure of human spermatozoa to the cumulus oophorus results in increased relative force as measured by a 760 nm laser optical trap,'' L. M. Westphal, I. el Dansasouri, S. Shimizu, Y. Tadir, and M. W. Berns, Hum. Reprod. **8** (7), 1083–1086 (1993). (I)

248. ''Relative force of human epididymal sperm,'' E. Araujo, Jr., Y. Tadir, P. Patrizio, T. Ord, S. Silber, M. W. Berns, and R. H. Asch, Fertil. Steril. **62** (3), 585–590 (1994). (I)

249. ''Optical manipulations of human gametes,'' J. Conia and S. Voelkel, Biotechniques **17** (6), 1162–1165 (1994). Male gamete selection and laser-assisted fertilization is described using a commercially available system. (E)

250. ''Zona drilling and sperm insertion with combined laser microbeam and optical tweezers,'' K. Schutze, A. Clement-Sengewald, and A. Ashkin, Fertil. Steril. **61** (4), 783–786 (1994). Demonstration of combined micromachine optical tweezers used to transport a sperm through a UV laser-drilled hole. (I)

251. ''Effect of freezing on the relative escape force of sperm as measured by a laser optical trap,'' Z. N. Dantas, E. Araujo, Jr., Y. Tadir, M. W. Berns, M. J. Schell, and S. C. Stone, Fertil. Steril. **63** (1), 185–188 (1995). Clinical trial. (I)

252. ''Spatiotemporal relationships among early events of fertilization in sea urchin eggs revealed by multiview microscopy,'' K. Suzuki, Y. Tanaka, Y. Nakajima, K. Hirano, H. Itoh, H. Miyata, T. Hayakawa, and K. Kinosita, Jr., Biophys. J. **68** (3), 739–748 (1995). A multiview microscopy system for both polarization and fluorescence wavelength imaging was implemented. (I)

253. ''Zona thinning with the use of laser: a new approach to assisted hatching in humans,'' S. Antinori, C. Panci, H. A. Selman, B. Caffa, G. Dani, and C. Versaci, Hum. Reprod. **11** (3), 590–594 (1996). Clinical trial. (I)

254. ''Animal experimentation. Fertilization of bovine oocytes induced solely with combined laser microbeam and optical tweezers,'' A. Clement-Segenwald and K. Schutze, J. Assist. Reprod. Gen. **13**, 259–265 (1996). (I)

255. ''Determination of motility forces of human spermatozoa using an 800 nm optical trap,'' K. Konig, L. Svaasand, Y. G. Liu, G. Sonek, P. Patrizio, Y. Tadir, M. W. Berns, and B. J. Tromberg, Cell. Mol. Biol. **42** (4), 501–509 (1996). (I)

256. ''Palm Robot-MicroBeam for laser-assisted fertilization, embryo hatching and single-cell prenatal diagnosis,'' A. Clement-Segenwald, K. Schütze, S. Sandow, C. Nevinny, and H. Pösl, in **Photomedicine in Gynecology and Reproduction**, edited by P. Wyss, Y. Dadir, B. J. Tromberg, and U. Haller (Karger, Basel, 2000), pp. 340–351. (I)

257. ''Effect of pentoxifylline on the intrinsic swimming forces of human sperm assessed by optical tweezers,'' P. Patrizio, Y. Liu, G. J. Sonek, M. W. Berns, and Y. Tadir, J. Androl. **21** (5), 753–756 (2000). (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. ''Evidence for localized cell heating induced by infrared optical tweezers,'' Y. Liu, D. K. Cheng, G. J. Sonek, M. W. Berns, C. F. Chapman, and B. J. Tromberg, Biophys. J. **68** (5), 2137–2144 (1995). Environmental and temperature-sensitive dye was used with spatially-resolved fluorescence in this study. A heat conduction model is also presented. (I)

259. ''*In-situ* microparticle analysis of marine phytoplankton cells using infrared laser-based optical tweezers,'' G. J. Sonek, Y. Liu, and R. H. Iturriga, Appl. Opt. **34**, 7731–7741 (1995). Spectroscopic observation of cellular physiology related to chlorophyll in the presence of the optical trap. (A)

260. ''Cell damage in near-infrared multimode optical traps as a result of multiphoton absorption,'' K. Konig, H. Liang, M. W. Berns, and B. J. Tromberg, Opt. Lett. **21** (14), 1090–1092 (1996). Cell damage is shown to be greater in lasers that have unstable temporal power outputs. (I)

261. ''Effects of ultraviolet exposure and near infrared laser tweezers on human spermatozoa,'' K. Konig, Y. Tadir, P. Patrizio, M. W. Berns, and B. J. Tromberg, Hum. Reprod. **11** (10), 2162–2164 (1996). (I)

262. ''Wavelength dependence of cell cloning efficiency after optical trapping,'' H. Liang, K. T. Vu, P. Krishnan, T. C. Trang, D. Shin, S. Kimel, and M. W. Berns, Biophys. J. **70** (3), 1529–1533 (1996). 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. ''Physiological monitoring of optically trapped cells: assessing the effects of confinement by 1064-nm laser tweezers using microfluorometry,'' Y. Liu, G. J. Sonek, M. W. Berns, and B. J. Tromberg, Biophys. J. **71** (4), 2158–2167 (1996). Two-photon excited fluorescence is collected to monitor the physiology of optically trapped cells. (A)

264. ''Characterization of photodamage to *Escherichia coli* in optical traps,'' K. C. Neuman, E. H. Chadd, G. F. Liou, K. Bergman, and S. M. Block, Biophys. J. **77** (5), 2856–2863 (1999). 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. ''Cell viability and DNA denaturation measurements by two-photon fluorescence excitation in CWAl:GaAs diode laser optical traps,'' Z. X. Zhang, G. J. Sonek, X. B. Wei, C. Sun, M. W. Berns, and B. J. Tromberg, J. Biomed. Opt. **4** (2), 256–259 (1999). (I)

266. ''Cell viability in optical tweezers: high power red laser diode versus Nd:YAG laser,'' H. Schneckenburger, A. Hendinger, R. Sailer, M. H. Gschwend, W. S. L. Strauss, M. Bauer, and K. Schutze, J. Biomed. Opt. **5** (1), 40–44 (2000). (I)

4. Tools for cells

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268. ''Optical Trapping, Cell Manipulation, and Robotics,'' T. N. Buican, D. L. Neagley, W. C. Morrison, and B. D. Upham, New Technol. Cytom. **1063**, 190–197 (1989). 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. ''Laser microbeam as a tool in cell biology,'' M. W. Berns, W. H. Wright, and R. Wiegand Steubing, Int. Rev. Cytol. **129**, 1–44 (1991). Gives a general introduction to optical tweezers, construction tips, and applications to cell biology, including combinations with microbeam methods. (E)

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274. ''Manipulation of cells, organelles, and genomes by laser microbeam and optical trap,'' G. Weber and K. O. Greulich, Int. Rev. Cytol. **133**, 1–41 (1992). 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)

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G. Trapping various objects

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287. ''Spatial Pattern-Formation, Size Selection, and Directional Flow of Polymer Latex-Particles by Laser Trapping Technique,'' H. Misawa, M. Koshioka, K. Sasaki, N. Kitamura, and H. Masuhara, Chem. Lett. (3), 469–472 (1991). Ring and line image patterns are shown. (I)

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2. Vesicles and membranes

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H. Nonstandard traps and trapped objects

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I. Optical tweezers and other technologies

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