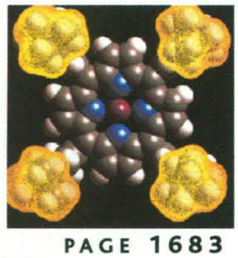
INTRODUCTION

Single Molecules

Recent years have seen significant advances in the characterization and manipulation of individual molecules. Scanning probe techniques allow study of single molecules on surfaces, and optical techniques enable their characterization in complex condensed environments. With such techniques, heterogeneities in a population of molecules can be identified and related to their molecular environment. Time-dependent reactions or the action of a molecular motor can be studied without the need for synchronizing a population of molecules. Single-molecule techniques can thus provide information on the structure and function of molecules that is difficult or impossible to obtain using conventional techniques, which generally average over many molecules. Furthermore, manipulation of molecules with scanning probe techniques may lead to the construction of artificial molecular machines. This section of *Science* highlights advances in this rapidly expanding field and looks at future opportunities.



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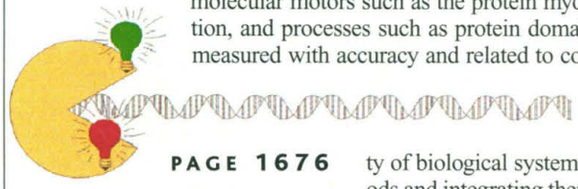
The principles of optical probing of single molecules in condensed environments are reviewed by Moerner and Orrit. Detection of the signal from a single molecule is complicated by interference from the surrounding material, whether crystal or solvent. Increased signal-to-noise ratios are achieved with ultrasensitive fluorescence techniques, careful choice of fluorescent probes, and experimental designs that limit the excited volume. Studies at cryogenic temperatures have probed the nanoenvironment of a single molecule and allowed fundamental quantum-mechanical effects to be observed. At room temperature, single-molecule techniques can be applied to biomolecules in physiologically relevant environments. Weiss describes how single fluorescent dye molecules attached covalently to macromolecules at specific sites offer insight into molecular interactions, enzymatic activity, reaction kinetics, and other properties of the molecule and its environment. Future improvements in site-specific labeling, dye chemistry, and instrumentation, and the combination of single-molecule fluorescence with single-molecule manipulation, will permit several observable parameters to be monitored simultaneously. In a related report, Smith *et al.* (p. 1724) study single DNA polymer chains in shear flow by fluorescence microscopy.

As reviewed by Mehta *et al.*, optical tweezers have been used to study molecular motors such as the protein myosin, which drives muscle contraction, and processes such as protein domain unfolding. Small forces can be measured with accuracy and related to conformational changes and molecular motion as a function of time. Future challenges include increasing the range and complexity of biological systems studied by optical tweezer methods and integrating them with other biochemical and single-molecule techniques. Scanning probe techniques are another set of tools for manipulating molecules (Gimzewski and Joachim). Atomic force microscopy has, for example, been used to measure the forces required for breaking antigen-antibody interactions and for inducing conformational changes in sugar molecules; in a related report, Grandbois *et al.* (p. 1727) demonstrate measurements of the force required for breaking covalent bonds. Scanning tunneling microscopy can provide detailed information on the conformational and mechanical properties of individual molecules adsorbed on a surface. It can also be used to manipulate molecules and construct supramolecular assemblies, such as a nanoscale molecular rotor in a supramolecular bearing, pointing the way toward future technologies.



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In a News story (p. 1668), *Science* correspondent Robert Service looks at recent single-molecule studies of the cell's database, DNA. Building on work in the late 1980s and early 1990s which probed the mechanics of DNA molecules by twisting, turning, and stretching them, researchers are now focusing on the molecular machinery of the cell: how proteins work to cut, copy, and splice DNA. Service also takes a look at efforts to bypass electrophoresis and to sequence strands of DNA directly with molecular probes.

–JULIA UPPENBRINK AND DANIEL CLERY

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See also related reports on pp. 1724 and 1727.

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