Micro- and nanorheology

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Abstract

'Microrheology', the determination of viscoelastic properties of soft media from the observed motion of microscopic-sized tracer particles, has undergone a recent surge of development because it allows access to an unprecedented range of frequency response with unprecedented spatial resolution. Several complementary techniques have been developed, but discrepancies have been found among different experiments especially in complex systems, and the validity of interpretation is under debate. 'Nanorheology' after explicit confinement of samples to variable thickness, 1 nm to 1 μm, is also enjoying rapid development, particularly nanorheology integrated with spectroscopy. Developments, limitations, and opportunities are discussed. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Microrheology; Nanorheology; Viscoelastic; Soft matter spectroscopy

1. Introduction

Consider the following experiment where a micron-sized probe particle is doped inside a rheologically complex fluid (e.g. a polymer network) and its Brownian fluctuations are recorded. What can we conclude about the mechanical properties of the medium from the observed motion of the particle? If the fluid is Newtonian and the probe molecule is spherical, we can determine the viscosity of the medium from the measured diffusion coefficient by using the standard Stokes–Einstein (SE) relation. However, a polymer network is generally viscoelastic, with a complex shear modulus $G^*(\omega)$ having both elastic (solid-like) and viscous (liquid-like) components of similar magnitudes over a large range of frequencies, ω. Is it possible to extend the Stokes–Einstein relation to determine $G^*(\omega)$ for such a medium from this experiment? The answer to this

question is important in a variety of problems. An affirmative answer would allow one to measure the local rheological properties not only in inhomogeneous materials but also at high frequencies that are inaccessible using mechanical rheometers.

Consider a similar experiment where a small ($\sim$ nm linear dimension) fluorescent molecule is used instead. It may be doped within an ultrathin film of liquid and its translational and rotational diffusion measured, either at rest or under the application of external shear forces. This is also a viscoelastic medium because, for molecularly thin films, the relaxation times of shear stress are enormously prolonged. With current instrumentation, it is possible to achieve single-molecule sensitivity. It is natural to ask: how is the rate of molecular probe diffusion, within a confined fluid, related to the stress relaxation time?

In this review we survey some of the current developments in the fields of microrheology and thin film nanorheology. This review will not cover micro/nanorheology based upon atomic force microscopy (AFM) or near-field scanning optical microscopy (NSOM), but some of the recent work based on those

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complementary approaches can be found in refs. [1–3•,4].

2. Development of techniques

2.1. Tracer microrheology

The fundamental assumption is that the Brownian motion of the micron-sized particles dispersed within the fluid is determined by the mechanical properties of the surrounding medium. Typical data consists of mean-square-displacement (MSD) of the probe as a function of various lag times τ, $< \Delta r^2(\tau) > =$ average$[(r(t + \tau) - r(t))^2]$ of the particle's trajectory [5] (here r denotes spatial position and t denotes time). The measured MSD can be analyzed either by relating it directly to the time-dependent shear creep compliance [6] or by extending the SE equation (called generalized Stokes–Einstein relation, GSER) to a frequency-dependent viscosity that accounts for the elasticity [7]. The latter method of data analysis allows a direct comparison of $G^*(\omega)$ between microrheological and mechanical rheometer measurements and therefore is used most often.

Good agreement between these two measurements have been found in some systems, but for unclear reasons. Conventional microrheology infers the complex viscoelastic modulus from the Laplace transform of the tracer's MSD [7]. Even for a relatively simple system (e.g. a polymer solution), the transform correspondence is valid only within the limited frequency window, $(\omega_L < \omega < \omega_U$ [8]. The lower frequency (ω_L) is set by the longitudinal compression mode of the network which is not included in the GSER. The upper frequency (ω_U) cutoff originates from the fluid inertia effect which determines the extent of the perturbation of the medium around the particle.

In addition to this fundamental restriction, there are other subtle effects, which can be difficult to quantify and limit many interesting potential applications of microrheology. For example, the probe particle may locally modify the structure of the medium, or it may bind to a certain extent with the material being probed; either possibility would hinder its long-time, large-length-scale displacements [9].

A recent theoretical result shows that the correlated fluctuations of two beads, separated in space, are a more exact measure of the bulk rheological properties. This 'two-point microrheology' does not depend on details of the tracer's size, shape and boundary conditions with the medium and overcomes many of the limitations of conventional microrheology experiments [10•]. The basic principle of this technique is illustrated in Fig. 1.

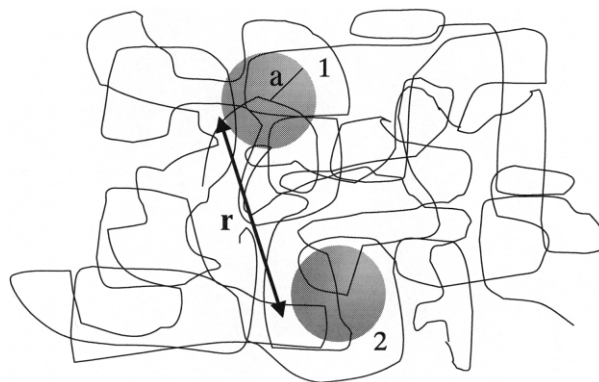The mean-squared displacement of the tracer can

Fig. 1. Schematic description of two-point microrheology. The displacement of the bead 1 produces a strain field that decays as $1/r$ for $r \gg a$ (r is spatial separation, a is bead diameter). Bead 2 follows the displacement field produced by bead 1 and by cross-correlating the motion of two beads the shear modulus of the intervening medium can be inferred. Unlike single-particle microrheology this technique is not sensitive to the immediate particle environment.

be measured in two ways: (i) indirectly from the autocorrelation function of the light multiply scattered by an ensemble of probe particles by using diffusing wave spectroscopy (DWS); or (ii) by direct time-averaging the motion of a single isolated sphere using the laser deflection particle tracking (LDPT) technique. If the material under study is ergodic, these two averages will give identical results.

In diffusing wave spectroscopy, the intensity fluctuations of scattered light reveal the dynamics of the medium through the decay of the temporal autocorrelation function. Unlike traditional dynamic light scattering experiments, DWS can probe motions of several thousands of particles simultaneously with subnanometer spatial resolution and microsecond temporal resolution [7]. However, much information is lost because DWS measurements are intrinsically ensemble-averaged, and hence, cannot measure the MSD distribution. Laser deflection particle tracking (LDPT) microrheology tracks the trajectory of a single thermally-excited colloidal probe sphere by detecting the laser light scattered by a tightly focused beam [11]. If the sphere moves even slightly away from the beam's axis, the scattered light will contain an off-axis intensity asymmetry reflecting the sphere's position. Similar to LDPT are the laser interferometric methods that measure the power spectrum of the position fluctuations of dielectric particles using phase-sensitive detection. They have similar spatial and temporal resolution as LDPT, and make direct use of the Kramers–Kronig dispersion integral to obtain the storage and loss moduli. This method of data analysis avoids the truncation errors introduced by numerical Laplace transform in the former two methods and is less sensitive to noise and systematic errors [12,13].

Video particle tracking (VPT) can also track a large number of particles concurrently, but is limited by the crude temporal and spatial resolution of present-day video analysis. This technique is not suitable for studying extremely elastic complex fluids, but future improvement will be possible with faster video hardware and by using fluorescent beads as tracers. Particle tracking methods have the advantage of addressing heterogeneity, but require explicit averaging over many particles–a feature that is performed automatically by DWS.

The single-particle tracking technique can also be used by combining the optical tweezer approach with high, but variable, laser intensity [14]. Optical tweezers function as harmonic potential wells and thus can approximate a variety of possible local forces. An acousto-optic modulator can displace the optical trap in the focal plane of the objective to create multiple tweezers. In addition, microrheology based on magnetic beads, pioneered 40 years ago by Crick and Hughes [15], has made a resurgence in recent years because it has became possible to generate a constant magnetic field onto which large magnetic field gradients are easily superposed [16]. Sackmann and co-workers have developed a method for the gold plating and biofunctionalization of ferromagnetic cobalt and iron particles for application as magnetic tweezers that generate large magnetic forces with relatively small beads [17]. However, the broad size distribution of the beads produced to date remains a problem.

2.2. Thin-film rheology integrated with spectroscopy

The surface forces apparatus (SFA) modified to measure interfacial rheology has been used widely in last few years to study the viscoelasticity of molecularly-thin films [18]. A recent application of this technique is illustrated in Fig. 2 [19]. However, direct measurements of the field-induced structural changes or the relaxation dynamics of individual molecules confined within molecularly thin films have not emerged because of technical difficulties to combine any form of spectroscopy with the SFA [20]. The semi-reflective silver layer at the backside of mica sheets, which is used to measure their separation distance by interferometry, does not allow sufficient excitation source intensity to illuminate the buried interfaces.

In the authors' laboratory, a special multilayer dielectric coating has been developed to replace this traditional silver coating and has been used to enable fluorescence spectroscopy experiments in combination with the SFA geometry (Fig. 3a). In fluorescence experiments, a dye molecule is doped into the sample, acting as a probe of its environment (Fig. 3b). Monitoring motions of the probe over time and in the
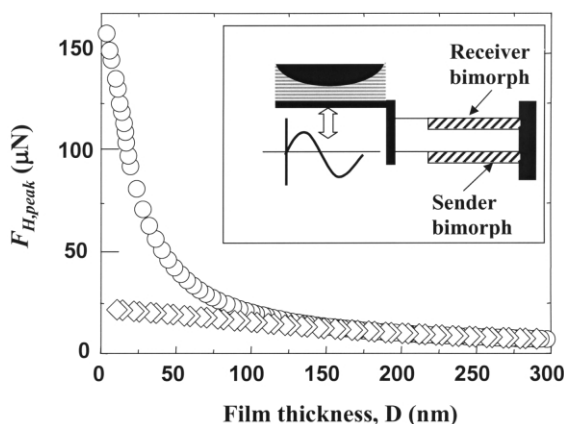

Fig. 2. Hydrodynamic force between cross cylinders, $F_{H,peak}$ is plotted against surface separation D for tetradecane placed between molecularly smooth surfaces of mica within SFA. The surface was wetting (mica; circles) or a self-assembled monolayer of partially-wetting surface (condensed octadecyltriethoxysiloxane; diamonds). For the wetting surface the force was inversely proportional to D at all surface separations in accordance with classical continuum prediction and the noslip boundary condition. For the partially-wetted surface, the force was systematically less, indicating lesser resistance to flow and breakdown of the noslip boundary condition. The inset shows schematic of the SFA modified to apply small-amplitude oscillatory displacements in the normal direction.

presence of external fields can offer insights about changes in this local environment within which the dye molecule is embedded.

For example, fluorescence correlation spectroscopy with two-photon excitation can achieve single-molecule sensitivity and probe the 'global' viscosity of the surrounding medium by monitoring the translational diffusion of the probe molecule from nanosecond to second time-scales. Measurements of rotational anisotropy with time-correlated-single photon counting can probe the 'local' viscosity by measuring the rotational diffusion on time scales as fast as a picosecond and as slow as hundreds of nanoseconds. These two techniques, when combined with the SFA, have the potential to provide new molecular details about the dynamics of ultrathin films.

The length scales of many complex fluids, e.g. long polymer chains, colloidal particles and biological cells, fall in an intermediate or 'meso' scale domain (0.1–10 μm). This regime of intermediate length scales is still poorly explored but it is important physically, especially when self-organized structures of larger scale come into play. In the microrheometer developed by Dhinojwala et al. the fluid is confined between parallel optically-flat windows whose separation can be controlled from a few tens of nanometers to tens of micrometers [21]. It has the advantage of larger surface area ($\sim$ cm^2) than the SFA ($\sim$ μm^2) and it is relatively easy to combine spectroscopy (FTIR, Fourier transform infrared spectroscopy; and dielec-
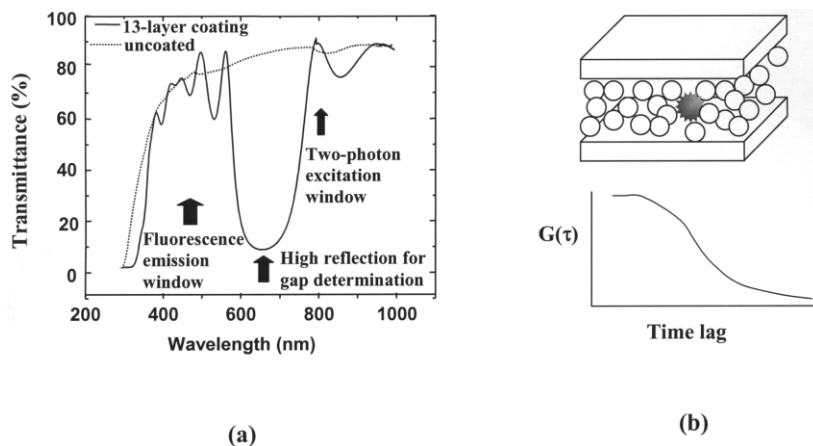
(a)

(b)

Fig. 3. Schematic illustration of the utility of fluorescence spectroscopy in a confined geometry. (a) Optical transmittance of mica coated with a multilayer dielectric, showing the feasibility of performing optical spectroscopies in the region 400−600 nm while also measuring surface-surface separation by multiple beam interferometry in the region 650−750 nm. (b) Top: A fluorescent molecule is doped within an ultrathin film of fluids (e.g. simple alkanes, polymers, colloidal particles) confined between two solid surfaces whose separation can be controlled from 0.1 nm to 1 μm. The translational and rotational diffusion of this molecule can be analyzed to determine the 'global' and 'local' viscosity of the medium and their relation with the nanorheological properties of the liquid. Bottom: From the temporal decay of the fluctuation autocorrelation function, $G(\tau)$, the diffusion coefficient of the probe molecule can be determined.

tric spectroscopy) or scattering (X-ray and neutron) techniques with the proper choice of window materials. The window separation can be measured accurately using either capacitance sensors or optical interferometers with submicrometer accuracy. Piezoelectric bimorphs can be used to apply periodic shear displacements in the frequency range of 0.1 to 500 Hz and in the amplitude range of 0.1 nm to 10 μm.

The practical challenge in using this microrheometer is to keep the plates parallel within a negligible fraction of the gap. In addition, the application of large-amplitude shear is difficult with this device, as then the shear force is no longer in the plane of the plates. A recent modification of this technique utilizes an electromagnetic coil and a magnet instead of piezoelectric bimorph [22]. An inductive sensor is used to track the lateral displacement of the surface. This arrangement increases the sensitivity of the apparatus so that lower-viscosity materials can also be studied.

3. Recent experimental results

3.1. Tracer microrheology

The semi-flexible polymer, F-actin, has been a favorite model system in microrheology experiments [23]. For a flexible polymer network and ignoring hydrodynamic interactions, the Rouse theory predicts $\langle \Delta r^2(\tau) \rangle \sim \tau^{0.5}$ which has been confirmed by experiments with poly(acrylamide) gels [11]. However, currently there are only a few molecular models of viscoelasticity for semiflexible polymers and even they differ greatly in their predictions [24].

Fluorescence microscopy has been used to probe the degree of spatial heterogeneity of F-actin gels and networks by monitoring the displacement of embedded polystyrene (PS) microspheres [25]. Schmidt et al. found significant disagreement between the low-frequency moduli values measured using magnetic tweezer microrheometry and rotating disk macrorheometry [26]. The discrepancy disappeared if the probe size exceeded the mean filament length.

DWS has been used to study the high-frequency rheological responses of F-actin network using surface-modified polystyrene latex particles as probes [27−29]. At small times, MSD increased subdiffusively as $\tau^{3/4}$, but crossed to a plateau at longer times such that MSD was only weakly-dependent on time. However, the magnitude of the plateau modulus and the crossover frequency varied widely from sample to sample. This variation was believed due to the presence of a small number of crosslinks, which when nearby would dramatically obstruct longitudinal fluctuations, and thus significantly raise the modulus [27].

A recent experiment using two-point microrheology by multiparticle video tracking of rhodamine-labeled PS beads in F-actin solution found $\langle \Delta r^2(\tau) \rangle \sim \tau^{0.5}$ without any crossover, instead of $\tau^{3/4}$ scaling as found in one-point microrheology experiments [30•]. The scaling behavior $\tau^{0.5}$ agrees well with conventional rheometer measurements at low frequencies. It has been suggested that the actin filaments form a 'cage' around the particle and that in one-point microrheology what is being probed is the tracer's microenvironment and not the fluctuation spectrum of the actin solution. This disagreement between conventional microrheology and two-point microrheology experiment

demonstrates that a clearer understanding of the interaction between probe molecule and the medium is necessary for proper interpretation of the experimental results in microrheology experiments.

Within a living cell, many of the semiflexible polymers (F-actin, microtubules etc.) associate with motor proteins to generate directed forces resulting in an enhanced diffusion scaling in proportion to $\tau^{1.5}$ at short times (compared to $\tau^{3/4}$ scaling in a passive network of F-actin) [31]. The viscoelastic behavior of self-assembled complexes of lipid membrane and actin filaments have been investigated recently using optical tweezers and single-particle tracking [32,33]. A micrometer-sized bead was bound using the tweezer to the composite membrane and the power spectrum of its Brownian motions was recorded. When the same bead was attached to a vesicle instead, the power spectrum was modified by the forces exerted on the bead by the membrane. The presence of the actin network decreased significantly the amplitude of the power spectrum for the out-of-plane motion of the bead, suggesting an increase of the bending rigidity in the presence of actin. Surprisingly it was found that the in-plane motion of two beads attached to the vesicle was coupled, indicating that the composite membrane possessed a shear modulus.

Magnetic bead microrheometer has also been used to measure the viscoelastic properties of the cell surface [16] and cytoplasm [34] by particle-tracking the bead motion after the application of step-force pulses. In this approach, the viscoelastic response of cells typically consisted of an elastic response regime, a relaxation regime and viscous flow. The response curve can be analyzed in terms of equivalent-circuits to determine the local variations of the viscoelastic properties on the cell surface or cytoplasm. However, to relate the viscoelastic parameters of the equivalent-circuit to the viscoelastic moduli requires a model to determine the geometric prefactor. Wirtz et al. have measured the force-extension curve of a single-strand DNA molecule by attaching a microsphere and observing its motion after the application of applied magnetic forces. From this the contour length and the persistence length of the molecule can be determined [35]. Although more difficult to use, the magnetic tweezers approach can also be used for systems that are sensitive to heating or strongly diffusive, where the use of optical traps or light scattering techniques is very difficult.

3.2. Interfacial and thin-film microrheology

The rheology of ultrathin films (e.g. short chain alkanes such as tetradecane or branched alkanes such as squalane) and tethered polymer brushes has been studied by SFA [18]. When a liquid is confined to a thickness comparable to the size of the molecules, the viscosity and the effective shear modulus increase by several orders of magnitude and the terminal relaxation times are enormously prolonged [36,37]. Such ultrathin films behave solid-like in the sense that the confining surfaces cannot slide past one another unless a critical yield is exceeded. Though force measurement using the SFA is a powerful technique, it yields ensemble-averaged values only. Many questions remain that cannot be answered by force measurements alone. Does the observed retardation of mobility stem from a first-order phase transition to a solid film, or is it more closely related to the bulk glass transition [37,38]? What is the rate of molecular diffusion within a confined fluid? Is there significant collective molecular motion or dynamical heterogeneity? These questions can be answered clearly in a laboratory only by finding the distribution of molecular properties, and this requires single-molecule spectroscopy. Among the few attempts to study the orientation and structure of confined molecules within the SFA, Safinya et al. investigated the structure of a thin smectic liquid crystal film under confinement using synchrotron x-ray scattering SFA [39] and Sinha et al. measured the density profile of simple alkane fluids in the direction normal to solid surfaces [40]. The microrheometer developed by Dhinojwala et al. has been used to measure the viscoelastic properties of the nematic liquid crystal, 5-cyanobiphenyl (5CB) and its shear-induced molecular orientation during sinusoidal shear cycle [21]. 5CB molecules were found to follow the shear motion at low frequencies but almost no change was observed at frequencies higher than 400 Hz. The speculative interpretation was that that the kinetics of molecular re-orientation was slower than the applied frequency and thus molecules could not keep up with the shear perturbation. Currently there are few established experimental techniques capable of performing quantitative rheometric measurements on this mesoscale. By combining it with sensitive video imaging and by using fluorescent molecules as tracers, we expect that in the future this technique will be used to study fluid motion at the interface and to measure the anisotropic diffusion coefficient in thin films and in materials having oriented microstructures.

4. Concluding remarks

The theoretical and experimental study of microrheology and nanorheology has made significant progress during the last several years. In many cases, results have altered the picture that had developed from prior macro-scale studies. For example, the modern theory of semiflexible polymers predicts

$G^*(\omega) \sim \omega^{3/4}$ at high frequencies−a previously-unexpected conclusion that originates from considering the undulation modes of wavelength less than the persistence length [24]. There are competitive models; e.g. if the stress relaxation occurs via longitudinal relaxation of a single filament, it is predicted that $G^*(\omega) \sim \omega^{7/8}$ [41]. The frequencies at which this behavior could be tested lie beyond the range of mechanical rheometers. Microrheological measurements of a model semiflexible polymer solution (F-actin) have confirmed that $G^*(\omega) \sim \omega^{3/4}$.

Microrheological measurements are also beginning to add a new level of mechanical information to cell biology and biophysics. It is expected that this technique will be used more and more to probe the spatial and temporal changes within living cells and to monitor fast physiological responses.

There exist presently several discrepancies between the available micro- and macrorheological measurements. Microrheological results depend strongly upon the interaction between the probe molecule and the network. The synthesis of new application-specific probe particles and the monitoring of cross-correlated thermal motion of two probe particles (two-point microrheology) comprise the solutions to this problem at this time.

Fluorescence-based experiments with single molecule sensitivity have the potential to open new doors for studying interfacial and thin film microrheology. These techniques will allow one to look beyond the ensemble-average quantities obtained by traditional rheological measurements and to observe the molecular details. For molecularly-thin films, to understand connections between a tracer molecule's self-diffusion and rotational diffusion, and its ensemble-averaged rheological properties where the generalized Stokes−Einstein relation does not hold, comprises a challenge for future theories.

Acknowledgements

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- of special interest
- of outstanding interest

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