Finite-size effects in microrheology

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We propose a model to explain finite-size effects in intracellular microrheology observed in experiments. The constrained dynamics of the particles in the intracellular medium, treated as a viscoelastic medium, is described by means of a diffusion equation in which the interactions of the particles with the cytoskeleton are modelled by a harmonic force. The model reproduces the observed power-law behavior of the mean-square displacement in which the exponent depends on the ratio between particle-to-cytoskeleton-network sizes.

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I. INTRODUCTION

Transport of particles as vesicles, lipid granules or chromosomes through the intracellular environment of eukaryotic cells has been subject of intense theoretical and experimental research in recent years.1,2,3,4,5,6,7,8,9,10,11,12 In these systems, the presence of molecular motors as well as of the cytoskeleton may introduce strong spatial inhomogeneities and elastic forces which are responsible for anomalous transport of the particle.

A manifestation of this anomalous transport, observed through video-based and diffusing wave spectroscopy methods, is the power law behavior of the mean-square displacement (MSD) as a function of time.2,6,7,8,9,10,11,12,13 These microrheology experiments have shown that the power-law exponent depends on the ratio between the size of the particles to the characteristic length of the polymer network constituting the cytoskeleton.2,6,8,9 There are two limiting cases. The first one in which the radius of the particle $a$ is larger than the characteristic length of the polymer network $\xi$, $a/\xi > 1$; and the second one in which the radius of the particle is smaller than $\xi$, $a/\xi < 1$.

The results of video-based microrheology experiments in in vitro F-actin networks shown in Fig. 1 are an example of the MSD behavior in the second situation. It is important to stress that these results are consistent with those obtained from living cells and in vitro microtubule arrays by using also video-based methods, in which the MSD of probe particles also shown subdiffusion with different exponents.6,7

FIG. 1: MSD vrs time as obtained from the proposed model for different particle-to-network-size ratio $a/\xi$. Solid lines correspond to the solution of Eq. (9) with (12) whereas dotted lines represent the power-law given in Eq. (15) and valid at short times. Experimental data (symbols) have been taken from Ref. [8] and correspond to particles with radius $a = 0.25\,\mu m$ and F-actin characteristic network sizes: $0.75\,\mu m$ (triangles), $0.55\,\mu m$ (circles), $0.30\,\mu m$ (squares) and $0.25\,\mu m$ (diamonds).

In this article, we give an explanation of this effect in the case when the particles have a characteristic length smaller than the characteristic length of the polymer network. We propose a diffusion model, taking into account the viscoelastic and bounded natures of the intracellular medium, to analyze the behavior
of the MSD through a non-Markovian Brownian dynamics,\textsuperscript{14,15,16,17,18,19,20,21,22} which considers particle finite-size effects and confinement.

At short times, our results lead to a power law behavior for the shear modulus $G''(\omega)$ as a function of the frequency $\omega$ in which the exponent is a function of the particle-to-network-size ratio $a/\xi$. We also show the relation between the measured mean square displacement with an effective diffusion coefficient $D(t)$ and an effective friction $\beta(t)$. It is necessary to stress that these coefficients, containing memory effects through its dependence on time,\textsuperscript{16,17} are related with the position relaxation function of the Brownian particle and, only in the Markovian approximation, they reduce to the usual diffusion and friction coefficients.

The article is organized as follows. Section II will be devoted to introduce the generalized diffusion equation for a Brownian particle of finite size and the main ingredients of the model. In Sec. III we apply the model to describe results of microrheological experiments in the intracellular media and in vitro systems. In the discussion section we will summarize our main results.

II. THE GENERALIZED DIFFUSION MODEL

For times much larger than the characteristic time $\beta_0^{-1} = m/6\pi a\eta_s$, where $a$ is the radius of the particle, $m$ its mass and $\eta_s$ the viscosity of the solvent, the dynamics of the Brownian particle through a viscoelastic medium can be described in terms of a non-Markovian diffusion equation of the form\textsuperscript{19,20,21,22}

\[
\frac{\partial \rho}{\partial t} = D(t) \nabla^2 \rho - \beta^{-1}(t) \nabla \cdot \left[ \rho \vec{F}(\vec{x}) \right],
\]

in which the effective diffusion coefficient $D(t)$ is related to the effective mobility $\beta^{-1}(t)$ through

\[
D(t) = \frac{k_B T}{m} \beta^{-1}(t),
\]

where $k_B T$ is the thermal energy. In Eq. 1, $\rho(\vec{x}, t)$ is the probability density, and $\vec{F}$ the force accounting for the interactions of the particle with the viscoelastic medium. It contains the elastic forces exerted by the polymer network over the particle and takes into account finite-size effects in the dynamics of the particle.

In the absence of molecular motors the dynamics of the particle is subdiffusive. In this case one may assume, within an effective medium approximation, that its motion is coupled to the medium through a harmonic force

\[
\vec{F}(\vec{x}) = -\omega_0^2 \epsilon \vec{x},
\]

where $\omega_0$ is a characteristic frequency of the polymer network.

The parameter $\epsilon$ incorporates the mentioned finite-size effects of the particles. In particular, it reflects the effects of the stresses exerted by the fluid over the surface of the particle during its motion through the fluid. Its general form, $\epsilon \approx \frac{m}{6 k_B T} a^2 \beta \cdot \beta$, has been calculated in Ref. [20] for the case of a particle moving into a fluid under flow conditions by taking into account the Faxén theorem: the drag force over the particle is $\vec{F}_\text{drag} \propto \vec{v} - \vec{v}_0$ with $\vec{v}$ the velocity of the particle, and $\vec{v}_0 \sim \vec{v}_0 + a^2 \nabla^2 \vec{v}_0$ the average of the velocity of the fluid $\vec{v}_0$ over the surface of the particle.\textsuperscript{22} For convenience, we will assume that $\epsilon = \tau_D \beta(t_0)$ with $\tau_D = m a^2 \beta(t_0)/6 k_B T$ the characteristic diffusion time over the distance $a$.\textsuperscript{22} Therefore, the form of the elastic force then assumes that it originates from the fact that particles have finite size and that point particles are not affected by the network in the time interval we are considering.

It is important to mention that the non-Markovian character of equation 1 is incorporated through the time dependence of the effective mobility $\beta^{-1}(t)$. This time dependence can be shown to arise from a description given in terms of a generalized Langevin equations\textsuperscript{14,15,16,17,18,19,20} or from a slow-varying-field approximation of the corresponding equation obtained from the theory of continuous time random walks.\textsuperscript{24} Also important to mention is the fact that, in the general case, the effective mobility $\beta^{-1}(t)$ is not the usual transport coefficient of the Markovian approximation. However, it can be shown that
it recovers its usual form in the corresponding approximation.\textsuperscript{16,20}  

During the motion of the particle through the viscoelastic fluid, hydrodynamic interactions with the polymer network introduce corrections to the mobility of the particle which are similar in form to those arising form the presence of other particles or from the presence of a wall or a liquid-like membrane.\textsuperscript{24,25,26,27} For example, in the presence of a wall, these corrections depend on the ratio $a/h$ in the form: $\beta_{\text{wall}}^{-1} \simeq \beta_0^{-1} (1 - 0.625a/h)$ with $h$ the distance to the wall.\textsuperscript{24} It is then plausible to assume that the distance of the particle to the ”wall” of the ”cage” formed by the polymer network is of the same order as the characteristic length of the polymer network $\xi$, and then write in first approximation  

$$\beta^{-1}(t) = \beta_0^{-1} (1 - B_1 a/\xi) \tilde{\beta}^{-1}(t), \quad (4)$$  

where $\tilde{\beta}^{-1}(t)$ is the dimensionless function of time accounting for the memory effects.\textsuperscript{16,17,18,20} As already mentioned, the coefficient $\left(1 - B_1 a/\xi\right)$ introduces finite-size effects through the ratio $a/\xi$ and the parameter $B_1$ takes its value depending on the nature of the boundary.\textsuperscript{24,25,28}

### III. CONFINED DIFFUSION OF A FINITE SIZED PARTICLE

Once introduced the general aspects of the model, we will analyze the particular case of a particle moving in a viscoelastic medium in which the effects of constraining are also present. Finally, we will compare our results with experiments.

Substituting the harmonic force $\text{Eq. (8)}$, the relation for the effective diffusion coefficient $\text{Eq. (2)}$ and the effective mobility $\text{Eq. (4)}$, the generalized diffusion equation $\text{Eq. (1)}$ takes the form  

$$\frac{\partial \rho}{\partial t} = \beta^{-1}(t) \left[ \frac{k_B T}{m} \nabla^2 \rho + \epsilon \omega_0^2 \nabla \cdot (\bar{x} \rho) \right]. \quad (5)$$  

A non-stationary solution of Eq. (5) can be obtained by first introducing the dimensionless coordinates $\tilde{x} = a^{-1} \bar{x}$ and the dimensionless time $\tilde{t} = t_0^{-1} t$, with $t_0 = \beta_0^{-1}$, and scaling time with  

$$\tau = \int_0^t \tilde{\beta}^{-1}(\tilde{t}) \, d\tilde{t}. \quad (6)$$  

Assuming a probability distribution of the form:  

$$\rho(\bar{x}, \tau) = f(\tau) \exp \left[ -\frac{\bar{x}^2}{A(\tau)} \right],$$  

one arrives at the solution  

$$\rho = \frac{\rho_0}{\left(1 - e^{-2\omega_0^2 \tau / \alpha \omega_T^2}\right)^2} \exp \left[ -\frac{\omega_0^2 \beta_0^2 \bar{x}^2}{\omega_T^2 2\alpha^2} \left(1 - e^{-\frac{2\alpha^2}{\omega_0^2 \tau}}\right)^{-1} \right],$$  

in which $\rho_0$ is a normalization constant and we have defined the frequency $\omega_T^2 = k_B T / ma^2$ and, according to Eq. (4), $\alpha$ is given by  

$$\alpha = \left(1 - B_1 a/\xi\right). \quad (8)$$  

Eq. (7) gives the probability distribution for a single particle in the case of constrained diffusional motion.\textsuperscript{12} It leads to the following expression for the mean square displacement of the particle  

$$\langle \tilde{x}^2 \rangle(\tau) = \frac{3\omega_T^4}{\beta_0^2 \omega_0^2 \alpha^2} \left[1 + \coth \left(\frac{2\alpha^2}{\omega_0^2 \tau}\right)\right]^{-1}, \quad (9)$$  

which can be obtained by using the definition $\langle \tilde{x}^2 \rangle = \int \tilde{x}^2 \rho(\tilde{x}) \, d\tilde{x}$. In Fig. 2, we show a fit (with Eq. (9)) of the experimental data of constrained diffusion of chromatin inside the nucleus of living cells, see caption of the figure for details.

Experiments measuring the mean square displacement of Brownian particles in \textit{in vitro} F-actin networks shown a power law behavior characteristic of subdiffusion in which the exponent is a function of the particle-to-network-size ratio $a/\xi$ (see Fig. 1).\textsuperscript{8} To explain the origin of this short-time power law behavior of the MSD, we will first obtain the explicit dependence of $\tau(\tilde{t})$ at short times. To achieve this objective, it is convenient to analyze the evolution equation for the relaxation function $\chi(\tilde{t}) = \int \tilde{x} \cdot f_0 \rho d\tilde{x}$\textsuperscript{20,29}  

$$\frac{d}{d\tilde{t}} \chi(\tilde{t}) = -\frac{\omega_0^2}{\alpha \omega_T^2} \tilde{\beta}^{-1}(\tilde{t}) \chi(\tilde{t}). \quad (10)$$
and (10) one may obtain the relation

\[ \langle x^2 \rangle = \alpha t_0 \gamma_0^2 / \omega_0^2 \]

which is a stretched exponential characteristic of the relaxation of systems with strong spatial inhomogeneities.

The MSD can now be calculated by using the short time approximation of Eq. (7), which can be obtained by expanding the exponential

\[ e^{-\frac{\alpha^2}{\omega_0^2} \tau} \] up to first order in \( \tau \), from where one obtains

\[ \rho(\tilde{x}, \tau) \cong \frac{\rho_0}{(2 \omega_0^2 \omega_T^2 \alpha^{-1} \tau)} e^{\left[ -\frac{\beta_1^2}{\omega_0} \right]} \] (14)

Then, from Eqs. (14) and (12) one obtains in the original variables

\[ \langle \tilde{x}^2 \rangle(t) \cong 6D_0 \beta_0^{-2} \alpha B_2 \left[ \frac{t}{t_0} \right]^{\alpha \omega_0^2 / \omega_0^2} \] (15)

where \( D_0 = k_B T / m \beta_0 \) is the usual expression for the diffusion coefficient in terms of the Stokes friction coefficient \( \beta_0 \). The result clearly shows that the finite size of the particles affect the expression of the MSD through the factor \( a / \xi \).

In Fig. 1, we compare our results for the MSD with the experimental data reported in Ref. [8]. The slopes of the dotted lines were obtained by using Eq. (15) and the relation \( \alpha = 1 - B_1 a / \xi \), with \( B_1 = 2 / 3 \) (a value similar to that obtained from hydrodynamics). \( D_0 \sim 10^{12} \text{cm}^2 \text{s}^{-1} \), \( \beta_0 \sim 10^6 \text{s}^{-1} \), \( \omega_T \sim 2.25 \cdot 10^3 \text{s}^{-1} \) and \( \omega_0 \sim 2 \cdot 10^3 \text{s}^{-1} \) for the different values of \( a / \xi \) indicated in the caption. With these values of the constants, the experimental magnitude of the MSD were well fitted by assuming that \( a \sim (1 - (2 / 3)(a / \xi)) \exp[-5(a / \xi)] \). Finally, in figure 1 solid lines represent the fit of the data using Eq. (3) and thus indicating the effects of confinement due to the material surrounding the particle.

At short times, the viscoelastic properties of the intracellular medium become manifest through the effective diffusion coefficient \( D(t) \) given in Eq. (2), and which can explicitly be obtained by taking the time derivative of Eq. (15). After using the definition of \( \langle \tilde{x}^2 \rangle \) and Eqs. (11), (15) and (8), we have identified \( B_2 = \alpha^{-1} \omega_0^2 / \omega_T^2 \) and the explicit expression for the dimensionless function \( \beta^{-1}(t) \) which incorporates memory and finite-size effects

\[ \beta^{-1}(t) = \left[ \frac{t}{t_0} \right]^{\alpha \omega_0^2 / \omega_0^2} \] (16)

The relation between the effective mobility per unit mass (9) with the effective viscosity of...
the intracellular medium can be established by realizing that $\beta(t)$ represents a temporal average of the form

$$\beta(t) = \int_{\tau_D}^{t} \zeta(z)dz,$$

(17)

where $\zeta(t)$ is a memory function related with the frequency-dependent effective viscosity through the inverse Laplace transform of $\zeta(\omega) \sim \eta(\omega)$.\cite{11.22,31} and we have introduced $\tau_D$ as a cut-off time. After calculating $\zeta(\omega)$ from Eqs. $16$ and $17$, the Laplace transform of the result leads to the scaling law for the effective viscosity

$$\eta(\omega) \sim \omega^{3/2}/\omega^3 - 1.$$

(18)

From this expression, one may calculate the dependence of the shear modulus $G''(\omega) = \omega \eta(\omega)$, as

$$G'' \sim \omega^{3/2}/\omega^3.$$

(19)

As in the experiments\cite{8,9} this expression shows that the shear modulus $G''(\omega)$ inferred through the generalized Stokes-Einstein relation $D(\omega) = k_B T / 6 \pi \alpha \eta(\omega)$ depends in general on the ratio $a/\xi$.

The results here obtained can also be used to explain the subdiffusive behavior, $\langle x^2 \rangle_{exp} \sim t^{3/4}$, found in experiments with passively diffusing particles in living cells.\cite{8} The form of the MSD with $\omega a^2 T/\xi^3 = 3/4$, and Eqs. $15$, $16$ and $17$ then imply the behaviors $\beta(t) \sim t^{-1/4}$, $\eta(\omega) \sim \omega^{-1/4}$ and $G'' \sim \omega^{3/4}$, in good agreement with the results of Refs. [11]. The experiments were performed with particles having diameters in the range $a \simeq 2 - 3 \mu m$. Thus, our relation $a/\xi \sim 2/5$ implies that the characteristic length of the cytoskeleton network is $\xi \simeq 5 - 7.5 \mu m$ which lies within the same range of values as the actin persistence length $\xi_{actin} \simeq 5 - 20 \mu m$.

**IV. DISCUSSION**

We have shown that the observed finite-size effects in the anomalous transport of particles in the intracellular environment can be explained on the grounds of a diffusion model which incorporates the viscoelastic nature of the intracellular medium, and the characteristic lengths associated to the size of the particles and of the polymer network constituting the cytoskeleton.

The proposed diffusion equation incorporates memory effects through time dependent coefficients which enables one to calculate the mean-square displacement from which the role played by the mentioned finite-effects effects can be analyzed. These effects correspond to the size of the particles and the characteristic length of the polymer network and of the size of the system, i.e., our description may include the effects of confinement. As a consequence, by assuming that the constants take values typical of experiments, we have found good agreement between our theoretical results and the experimental data taken from microrheological experiments with viscoelastic fluids similar to the intracellular medium. Good agreement has also been found in describing confined diffusion of chromatin within the nucleus of live cells.

In summary, the scheme presented can be applied to explain the observed subdiffusive behavior of particles passively diffusing in the cell.

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