Protein motors induced enhanced diffusion in intracellular transport

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\textbf{A B S T R A C T}

Diffusion of transported particles in the intracellular medium is described by means of a generalized diffusion equation containing forces due to the cytoskeleton network and to the protein motors. We find that the enhanced diffusion observed in experiments depends on the nature of the force exerted by the protein motors and on parameters characterizing the intracellular medium which is described in terms of a generalized Debye spectrum for the noise density of states.

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1. Introduction

The study of the spatio-temporal organization of vesicles, organelles and other particles inside the cellular medium plays a primary role in the behavior of cells and constitutes a central problem in physical biology [1,2].

In order to carry out this study, it is important to consider the fact that the intracellular medium consists of a wide variety of polymers and particles whose presence is the cause of the observed viscoelastic behavior [3]. As a consequence, during their motion inside the cell the particles may experience elastic, electrochemical and entropic forces that introduce memory effects. These effects must be taken into account in order to correctly describe the dynamics of the particles.

Particles in the intracellular medium undergo different forms of diffusion which depends on the activity of the protein motors and the size of the particles [4–16]. Subdiffusion has been observed in the passive transport of particles in the cellular medium [4,5,9–11] whereas an enhanced diffusion has been reported for particles driven by protein motors [3,4,12].

A complete description of particle transport must take into account the activity of protein motors [3,4,12]. These entities are chemo-mechanical transducers which, in the presence of sufficiently high cation concentration, trap particles and then use the free energy arising from the hydrolysis of ATP molecules to drive them along defined trajectories inside the cell [1,17,18] giving rise to the enhanced diffusion observed in these systems [3,4]. Experiments seem to justify the assumption that the activation as well as the duration of the activity of these protein motors constitutes a random process [3].

In this article, we use mesoscopic nonequilibrium thermodynamics [19–21] to formulate a mesoscopic model that accounts for the enhanced diffusion of particles in the intracellular medium. We propose a generalized diffusion equation, that incorporates the memory effects due to the viscoelasticity of the intracellular medium and the activity of protein motors, to compute the mean square displacement (MSD) and to analyze the density of states of the intracellular medium [5,9,22]. Memory effects can be incorporated through effective mobility and diffusion coefficients that can be memory kernels, [5,22–24] or time-dependent coefficients [6–9,22]. In our approach, the generalized diffusion equation incorporates memory effects through time-dependent coefficients. We choose this way because in the linear force case it is possible to show the equivalence of this description with that given by means of generalized Langevin equations with memory kernels [6,7]. This relation between both descriptions is also used in order to calculate the noise density of states arising in the case of enhanced
diffusion. However, in this case the stochastic forces are of non-thermal nature due to the activity of protein motors. It is convenient to mention here that, in the general case, there is not a clear criterion in order to choose between time-dependent coefficients and memory kernels, see, for example, Ref. [25].

The article is organized as follows. In Section 2, we derive a generalized diffusion equation (GDE) describing the dynamics of the system. In Section 3, we analyze the case of a harmonic force model and compare the results obtained with experiments. Section 4 is devoted to derive the explicit form of the noise density of states (NDS). In Section 5 we summarize and discuss our main results.

2. Mesoscopic thermodynamics approach to anomalous diffusion

We consider a Brownian particle moving in an intracellular medium having viscoelastic nature [3]. In addition, we will assume that under the appropriate conditions the particle can also be driven by protein motors. As we have mentioned previously, these factors introduce memory effects that will be taken into account through the effective time-dependent mobility and diffusion coefficients.

These effects can appropriately be described in terms of a generalized diffusion equation for the single particle distribution function \( f(\vec{r}, t) \), which gives the probability of finding the particle at position \( \vec{r} \) at time \( t \). This distribution function satisfies the normalization condition \( \int f(\vec{r}, t) \, d\vec{r} = 1 \), and its evolution in time is governed by the continuity equation

\[
\frac{\partial}{\partial t} f(\vec{r}, t) = -\nabla \cdot [f(\vec{r}, t) \vec{V}_r(\vec{r}, t)],
\]

which expresses probability conservation and where \( \nabla = \partial / \partial \vec{r} \). The quantity \( f \vec{V}_r \) represents an unknown probability current and the explicit expression of the streaming velocity \( \vec{V}_r \) can be calculated with mesoscopic nonequilibrium thermodynamics (MNET) using the generalized Gibbs entropy postulate [5,19,20]

\[
S(t) = -k_B \int f(\vec{r}, t) \frac{\ln f(\vec{r}, t)}{f_0(\vec{r})} \, d\vec{r} + S_0,
\]

where \( k_B \) is Boltzmann’s constant and \( f_0(\vec{r}) \) and \( S_0 \) are the distribution function and the entropy of the reference local equilibrium state. The local equilibrium distribution function is given by \( f_0(\vec{r}) = e^{(\mu_0 - \phi(\vec{r}))/(k_B T)} \), in which \( m \) is the mass of the particle, \( T \) is the temperature of the system, \( \phi(\vec{r}) \) is an external potential per unit mass and \( \mu_0 \) is the chemical potential per unit mass at local equilibrium.

Taking the time derivative of Eq. (2) and using Eq. (1) one obtains the expression \( \partial S(t)/\partial t = -k_B \int \frac{\ln f}{f_0} \nabla \cdot (f \vec{V}_r) \, d\vec{r} \).

Now, integrating by parts assuming that the current vanishes at the boundary, we find the entropy production \( \sigma(t) \)

\[
\sigma(t) = \frac{m}{T} \int f(\vec{r}, t) \vec{V}_r(\vec{r}, t) \cdot \nabla \mu(\vec{r}, t) \, d\vec{r} \geq 0,
\]

where \( \mu(\vec{r}, t) = (k_B T/m) \ln f/f_0 + \mu_0 \) is the nonequilibrium chemical potential per unit mass. According to nonequilibrium thermodynamics, we will assume that the force \( \nabla \mu(\vec{r}, t) \) and the current \( f(\vec{r}, t) \vec{V}_r(\vec{r}, t) \) are coupled linearly: \( f \vec{V}_r \propto \nabla \mu \). Using the expression for \( f_0(\vec{r}) \) one obtains

\[
\vec{F}(\vec{r}) = -\nabla \phi(\vec{r}) = \beta^{-1}(t) f(\vec{r}, t) \left( \vec{F}(\vec{r}) - \frac{k_B T}{m} \nabla \ln f(\vec{r}, t) \right),
\]

where \( \vec{F}(\vec{r}) = \beta^{-1}(t) f(\vec{r}, t) \vec{F}(\vec{r}) \) is the total force applied on the particle. As mentioned previously, the time-dependent Onsager coefficient \( \beta^{-1}(t) \) accounts for the presence of memory effects. In general, this quantity is related with the correlation function of the position vector of the particle. We have chosen this coupling between the current and force because in the linear force case our results are equivalent to those obtained from a GLE in Refs. [7,8]. The case when the coupling is given through a memory kernel has been discussed in Ref. [6]. In the absence of memory effects, \( \beta^{-1}(t) \) reduces to the Stokes mobility \( \beta_0^{-1} = (6 \pi a \eta_s/\mu_0 m)^{-1} \) with \( a \) and \( m \) the radius and mass of the particle and \( \eta_s \) the viscosity of the medium [6,26]. Substituting Eq. (4) into (1), we finally obtain the generalized diffusion equation

\[
\frac{\partial}{\partial t} f(\vec{r}, t) = \frac{k_B T}{m} \beta^{-1}(t) \nabla^2 f(\vec{r}, t) \beta^{-1}(t) \nabla \cdot \left[ f(\vec{r}, t) \vec{F}(\vec{r}) \right].
\]

A similar equation has been proposed to describe finite-size and confinement effects on the dynamics of passively diffusing particles moving through the intracellular medium [5,9].

3. Enhanced diffusion in the intracellular medium

A physical model describing the dynamics of a particle driven by protein motors must take into account two forces. The first one is a trapping force of elastic nature which in first approximation can be modelled by the linear force: \( \vec{F}_t(\vec{r}) = -\omega_0^2 \vec{r} \), with \( \omega_0 \) a characteristic frequency. The second one is the driving force exerted by molecular motors on the particles that can also be modelled by \( \vec{F}_m(\vec{r}) = \omega_1^2 \vec{r} \), with a characteristic frequency \( \omega_1 \).
Substitution of the total force \( F(\vec{r}) = \vec{F}_{el}(\vec{r}) + \vec{F}_{pm}(\vec{r}) \) into Eq. (5) yields

\[
\frac{\partial}{\partial t} f(\vec{r}, t) = \beta^{-1}(t) \left[ (\omega_0^2 - \omega_1^2) \nabla \cdot [\vec{f}(\vec{r}, t)] + \frac{k_B T}{m} \nabla^2 f(\vec{r}, t) \right],
\]

where we have assumed that the effective friction coefficient is given by \( \beta(t) = \beta_0 \tilde{\beta}(t) \). \( \tilde{\beta}(t) \) is a dimensionless function accounting for memory effects. Eq. (6) clearly manifests the competition between trapping and driving forces that will regulate the behavior of the MSD of the particle. By introducing the dimensionless variables \( \tilde{x} = a^{-1} \vec{r} \) and \( \tilde{t} = \tau_D^{-1} t \), with \( \tau_D \) a characteristic time, and scaling time with \( z(t) = \int_0^t \tilde{\beta}^{-1}(t') dt' \), we obtain

\[
\langle \chi^2(\tilde{t}) \rangle = 3 \frac{\omega_1^2}{(\omega_0^2 - \omega_1^2)} \left[ 1 - e^{-2(\omega_0^2 - \omega_1^2) \int_0^{\tilde{t}} z(\tilde{t})} \right],
\]

where we have introduced the constant \( \alpha_0^2 = k_B T/ma^2 \) and \( \langle \chi^2(\tilde{t}) \rangle = \int \chi^2 f d\tilde{x} \). Eq. (7) gives the behavior of the MSD in the case when \( \omega_0^2 - \omega_1^2 > 0 \), that is, when the friction is larger than the force exerted by the protein motors. The case when \( \omega_0^2 - \omega_1^2 < 0 \) will be described later.

The time dependence of \( z(t) \) is related to the behavior of the time correlation function \( \chi(\tilde{t}) = \langle \tilde{x} \cdot \tilde{x}_0(\tilde{t}) \rangle \) in the absence of molecular motors, in the subdiffusion regime \( \omega_1 = 0 \). The evolution equation for \( \chi(\tilde{t}) \) is given by [6,7,9]

\[
\frac{d}{d\tilde{t}} \chi(\tilde{t}) = -\omega_0^2 \frac{\tau_D}{\beta_0} \tilde{\beta}^{-1}(t) \chi(\tilde{t}),
\]

which can also be calculated by using the dimensionless form of Eq. (6). Now by taking into account the expression of \( z(t) \) in terms of \( \tilde{\beta}^{-1} \), after solving (8) one arrives at the relation

\[
z_{sub}(\tilde{t}) = -\frac{\beta_0}{\tau_D \omega_0^2} \ln R(\tilde{t}),
\]

where we have defined the normalized correlation \( R(\tilde{t}) = \chi(\tilde{t})/\chi(0) \). From this relation it follows that the scaling of time depends on the relaxation dynamics of the system.

At short times, one may obtain the behavior of \( z(\tilde{t}) \) by expanding the logarithm in its argument around one:

\[
\ln |R^{-\beta_0/\tau_D \omega_0^2}| \simeq R^{-\beta_0/\tau_D \omega_0^2} - 1 + O(R^2).
\]

Then taking into account that \( R(\tilde{t}) \) must be an even function of time [15], a first order expansion leads to:

\[
R^{-1}(\tilde{t}) \simeq 1 + B_2 \tilde{t}^2 + O(\tilde{t}^4).
\]

Thus, at short times we obtain the expression

\[
z_{sub}(\tilde{t}) \sim B_2 \tilde{t}^2 \beta_0/\tau_D \omega_0^2,
\]

where \( B_2 \propto B_0^2 \) is a parameter characterizing the type of relaxation [9]. Now, by expanding the exponential in Eq. (7) up to first order in its argument and substituting (10) into the result, we find

\[
\langle \chi^2(\tilde{t}) \rangle_{sub} \simeq 6B_2 \tau_D \omega_0^2 \beta_0 \tilde{t}^{-1} \frac{\omega_0^2}{\beta_0} \tilde{t}^2 \beta_0/\tau_D \omega_0^2.
\]

The exponent characterizing the subdiffusion process of the particle is a function of parameters of the bath and the forces acting on the particle [11,9]. The coefficient \( B_2 \) depends in general on the concentration of polymers in the medium and the size of the particles, thus characterizing the magnitude of the MSD, [9]. For \( t = \tau_D \), Eq. (11) yields \( B_2 = (\beta_0/\tau_D \omega_0^2) \langle \chi^2(1) \rangle_{sub} \).

Using the definition of the running diffusion coefficient \( D_{sub}(\tilde{t}) = d(\langle \chi^2(\tilde{t}) \rangle/d\tilde{t}) \), [22], Eq. (11) leads to the relation

\[
\tilde{\beta}^{-1}(\tilde{t}) \simeq \tilde{t}^{-1+2\beta_0/\tau_D \omega_0^2}.
\]

This expression can be used to obtain the shear modulus characterizing the viscoelastic properties of the material [5,9].

In Fig. 1, we compare our results with experiments (symbols) reported in Ref. [4], where the motion of a microsphere through a living eukaryotic cell was observed with video-based methods. The value of \( \omega_0 \) can be determined by considering the case when the particle performs subdiffusion or is attached to the cytoskeleton (\( \omega_1 = 0 \)). From the experimental results represented by open circles in Fig. 1 it follows that the short time behavior of the MSD satisfies a power law with exponent \( \sim 3/4 \), [4,10,27]. Using the parameters \( B_2 \) and \( \tau_D \) to fit the curve (dot-dashed line) with Eqs. (7) and (10), one obtains \( \omega_0^2 \sim (8/3) \beta_0 \tau_D^{-1} \), implying that \( \omega_0 \) is proportional to the geometric mean of the fast \( \sim \beta_0 \) and slow \( \sim \tau_D^{-1} \) modes (see the caption of Fig. 1). Since \( \omega_0 \) describes subdiffusion, it must satisfy the condition \( \omega_0 \geq \sqrt{2 \beta_0/\tau_D} \). It is worth noting that the exponent depends on the friction coefficient \( \beta_0 \), the characteristic frequency \( \omega_0 \) of the elastic force exerted by the medium on the particle and a scaling time \( \tau_D \) which is related with the time at which the MSD saturates. In a previous study this power law behavior was obtained by simply inferring the exponent from direct comparison with the experimental results [4]. Here, we show that it is connected with the interactions between the particles and the medium.

The observed enhancement of diffusion can be described by taking into account the activity of the motors (\( \omega_1^2 \neq 0 \)) in Eq. (6). Defining \( \omega_0^2 = \omega_1^2 - \omega_0^2 > 0 \), we use Eq. (6) in order to obtain a linear evolution equation for \( \tilde{x}(\tilde{t}) = \int \tilde{x} f(\tilde{x}, t) d\tilde{x} \) whose solution is \( \tilde{x}(\tilde{t}) = \exp \left[ \omega_0^2 \tau_D \beta_0^{-1} \int \tilde{z}_{sub}^{-1}(\tilde{t'}) d\tilde{t}' \right] \). Assuming that \( \omega_0^2 \tau_D \beta_0^{-1} < 1 \), an expansion of the exponential up
to first order yields
\[
\langle \vec{x}(t) \rangle \simeq 1 + \bar{\omega}^2 \tau_D \beta_0^{-1} \langle x^2(t) \rangle_{\text{sub}},
\]
where we have used the relation \( z_{\text{sub}}(t) = \int \bar{P} \omega^2(\vec{I}) \omega \rangle dt \). Considering that, in general, protein motors are randomly distributed in the cell, we will assume that during the motion of the particle the parameter \( \bar{\omega}^2 \) is a fluctuating quantity with zero mean and \( \langle \bar{\omega}^2(\vec{I}) \bar{\omega}^2(\vec{I}') \rangle = \bar{\omega}^2 \exp[-(\vec{I} - \vec{I}')/\tau_c] \), with \( \tau_c \) the correlation time of the noise and \( \bar{\omega}^2 = \omega_0^2 - \omega_0^2 \) its magnitude. Now, by evaluating \( \langle \vec{x}(t) \rangle \langle \vec{x}(t') \rangle \) and taking the average over the realizations of the random force, represented by \( \langle \vec{x}(t) \rangle^2 \), one finally obtains
\[
\langle \vec{x}(t)^2 \rangle^2 \simeq 1 + \bar{\omega}^2 \tau_D \beta_0^{-1} \langle x^2(t) \rangle_{\text{sub}}.
\]

Fig. 1 shows a comparison between experiments (filled symbols) and theory (solid and dashed lines) of enhanced diffusion due to the presence of protein motors. For \( 2\beta_0/\langle \omega_0^2 \rangle \tau_D = 3/4 \), from Eq. (14) it follows that the exponent characterizing the enhanced diffusion is \( \alpha_{\text{ed}} \sim 3/2 \). The results (11) and (14) constitute an alternative way to calculate the Hurst exponent of the MSD typically arising in systems in which self-avoiding random walks (SAWR) appear frequently, such as crystallization or cluster–cluster aggregation in a viscoelastic medium [5,28–30]. This fact allows one to interpret the present results within the scope of SAWR formalism [28] in which the exponent obtained is \( 3/2 = 2/d \) with \( d \) the dimension of the space. The value of \( d \) corresponding to our problem in the enhanced diffusion case is therefore \( d = 4/3 \). Thus, the molecular motors act as elastic scatters inducing a SARW in a space with slightly reduced (motion-oriented) degrees of freedom.

4. The noise density of states of the intracellular medium

A global characterization of the intracellular medium can be performed through the noise density if states (NDS). This quantity contains in average form the statistical properties of the intracellular medium, assimilated to an effective medium in which both thermal and non-thermal (motor-induced) fluctuations control the dynamics of the transported particles.

The NDS can be analyzed by means of a generalized Langevin equation [14,15] which is equivalent to the following generalized diffusion equation [6,8]
\[
\frac{\partial}{\partial t} f(\vec{r}, t) = D_{\text{eff}}(t) \nabla^2 f(\vec{r}, t),
\]
where \( D_{\text{eff}}(t) = \bar{\omega}^2(\vec{I})/dt \) is an effective diffusion coefficient incorporating the effects of the motors in average form. Eq. (15) is equivalent to the generalized Langevin equation for the velocity \( v(\vec{I}) \) of the particle in the overdamped case [6,8]
\[
\int_0^t \Pi(\vec{I} - \vec{I}') v(\vec{I}') d\vec{I}' = F^R(\vec{I}),
\]
where we have considered the one-dimensional case for simplicity and \( F^R \) is a stochastic force satisfying the conditions \( \langle F^R(\vec{I}) \rangle = 0 \), \( \langle F^R x(0) \rangle = 0 \) and
\[
\langle F^R(\vec{I}) F^R(\vec{I}') \rangle = \langle v^2 \rangle_{\text{eq}} \Pi(\vec{I} - \vec{I}').
\]
with $\langle v^2 \rangle_{eq} = \lim_{t \to \infty} \langle v^2 \rangle(t)$. By Laplace transforming equation (16) and using the results of Ref. [6] in the inertialess free diffusion case we can obtain the relation between the diffusion coefficient and the memory function in the following form

$$D_{eff}(t) = \frac{k_B T}{m} \mathcal{L}^{-1} \left[ \frac{1}{s \hat{\Pi}(s)} \right].$$

(18)

where $\hat{\Pi}(s)$ is the Laplace transform of $\Pi(t)$ and $\mathcal{L}^{-1}[\hat{\Pi}(s)]$ the inverse transform. Using now the definition of $D_{eff}(t)$ in terms of Eq. (14) one obtains

$$\Pi(t) \sim t^{4 \beta_0/\omega_0^2 \tau_D}.$$  

(19)

This equation can be used to calculate the NDS of states $\rho(\omega)$ of the intracellular medium by decomposing the stochastic force $F_R(t)$ of the bath in a set of harmonic oscillators [14, 15]. The relation between the memory function and the NDS is found through the fluctuation dissipation theorem. One obtains

$$\Pi(t) = \int \rho(\omega) \cos(\omega t) d\omega,$$

(20)

where $\omega$ is now a dimensionless frequency.

Taking the Fourier cosine transform of Eq. (20) with (19), the resulting expression for the NDS of the intracellular medium is

$$\rho(\omega) \sim \frac{2}{\pi} \Gamma \left[ 1 + \frac{4 \beta_0}{\omega_0^2 \tau_D} \right] \sin \left[ \frac{2 \pi \beta_0}{\omega_0^2 \tau_D} |\omega|^{-1} \right] t^{1/2}.$$  

(21)

From this equation it follows that the exponent controlling the behavior of the NDS depends on the frequency characterizing the elastic forces ($\omega_0$) in the intracellular medium. It is important to stress that the power law dependence on the frequency of the NDS given by (21) and valid up to the corresponding Debye cutoff frequency, is of the form of the generalized Debye spectrum proposed in Ref. [15].

The results we have obtained enable us to conclude that the activity of protein motors in the intracellular medium modifies the dependence on frequency of the NDS. For example, in accordance with experiments [3, 4] the MSD of the particles grows by following the power law $\langle \vec{x}(t) \rangle^2 \sim t^{3/2}$ implying that the exponent of the generalized Debye spectrum is $1/2$, which contrast with the spectrum for subdiffusion which is $-1/4$.

5. Conclusion

In this paper, we have introduced a general formalism offering a multiscale description of transport processes in an intracellular medium. By taking into account the forces exerted by the cytoskeleton and the protein motors in a generalized diffusion equation, our model explains both enhanced diffusion and subdiffusion observed in experiments in living cells. The exponents associated to these behaviors are given in terms of the parameters characterizing the system. These results could be interpreted within a more general context in which the particle is transported through the elastic medium undergoing a random path through elastic scatters that induce a self-avoiding random walk [28]. This more general scenario permits to relate the diffusion in the intracellular medium studied with other processes in which self-avoiding random walks are an important ingredient.

Finally, we have proposed the density of states as a useful quantity to describe the state of the cell. In the presence of protein motors, this quantity behaves as the Debye spectrum with an exponent larger than one. The model proposed may describe and quantify the observed different forms of diffusion of particles in an intracellular medium.

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