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Inertial effects in diffusion-limited reactions

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Abstract

Diffusion-limited reactions are commonly found in biochemical processes such as enzyme catalysis, colloid and protein aggregation and binding between different macromolecules in cells. Usually, such reactions are modeled within the Smoluchowski framework by considering purely diffusive boundary problems. However, inertial effects are not always negligible in real biological or physical media on typical observation time frames. This is all the more so for non-bulk phenomena involving physical boundaries, that introduce additional time and space constraints. In this paper, we present and test a novel numerical scheme, based on event-driven Brownian dynamics, that allows us to explore a wide range of velocity relaxation times, from the purely diffusive case to the underdamped regime. We show that our algorithm perfectly reproduces the solution of the Fokker–Planck problem with absorbing boundary conditions in all the regimes considered and is thus a good tool for studying diffusion-guided reactions in complex biological environments.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Diffusion-limited reactions are commonly found in biochemical processes such as enzyme catalysis, colloid and protein aggregation or binding between different macromolecules, for instance antigens and antibodies in cells [1, 2]. These processes are characterized by their reaction rate, that is the number of reactions per unit time. Within the simplest approximation, a bi-molecular diffusion-controlled reaction is modeled as an irreversible absorption process of the kind $a + b \rightarrow a \rightarrow a'$, where a is the *sink* moiety, b is the *reactant* and a' is the product. The first step is the diffusion-guided *encounter*, the second is the chemical fixation of the encounter complex and the overall reaction rate can be computed from the two corresponding rates. In the limit of infinite dilution, the encounter rate can be evaluated directly from the solution of the diffusion equation (DE). Smoluchowski was the first to derive an analytical solution of the DE in presence of an absorbing boundary [3]. As a matter of fact, his solution is still the starting point for describing chemical and biological reactions in a wide range of cases [4–9].

Despite its success, an important limitation to Smoluchowski's theory is that inertial effects on the particle dynamics are neglected. In other words, the DE approach assumes that the velocities of the particles are always relaxed and consequently distributed according to a Maxwell distribution at any time. This assumption is fully legitimate for phenomena that occur on times much longer than the velocity relaxation time. However, diffusion problems in the presence of absorbing boundaries introduce an additional, intrinsic timescale (the inverse of the encounter rate), such that bulk and near-to-sink regions may be characterized by different relaxation properties. Harris proposed a more comprehensive approach based on an approximate solution of the Fokker–Planck equation (FPE) [10]. The FPE allows one to set boundary conditions that depend on the velocities. In this way, one avoids the inconsistency of imposing a vanishing density at contact, a condition that is strictly fulfilled only in the limit

of instantaneous relaxation. From an experimental point of view, it is essential to evaluate *a priori* whether the traditional overdamped scheme is reasonable or not for describing the system of interest.

In this paper we present a novel algorithm for simulating the classical absorption problem of a spherical sink in a solution of non-interacting particles. The core of the algorithm is based on event-driven Brownian dynamics (EDBD). The generalization of the same problem to the case of hard-core diffusing particles will be reported elsewhere [11]. We performed simulations under several conditions and used both the DE and FPE formalisms to model the results. We show that our dynamics reproduce precisely the FPE predictions, the differences with the DE results being indeed due to inertial effects in close agreement with Harris's predictions. The paper is organized as follows. In section 2 we introduce the necessary theoretical background, more specifically the DE and FPE frameworks. Following the theory, we present the details of our numerical algorithm and simulation scheme in section 3. The results of our simulations are reported and compared with the theoretical predictions in section 4. In the final section, we summarize our findings and present possible applications of our numerical protocol (section 5).

2. Diffusion and Fokker–Planck equations

Brownian motion in the presence of an absorbing spherical sink is described at the macroscopic level by the diffusion equation (DE)

$$\frac{\partial \rho(r,t)}{\partial t} = D\nabla^2 \rho(r,t) \tag{1}$$

with the boundary conditions

$$\rho(r = R_0, t) = 0 \qquad \lim_{r\to\infty} \rho(r,t) = \rho_\infty \tag{2}$$

where R_0 is the contact distance at the sink. The solution to this problem was first derived by Smoluchowski in the pioneering work on diffusion-limited reactions [3, 12, 13]. Within Smoluchowski theory, an encounter between two spherical particles is assumed and a macroscopic constitutive relation is used relating the current to the gradient of the density, namely Fick's law

$$j(r,t) = -D\frac{\partial \rho(r,t)}{\partial r} \tag{3}$$

where D is the diffusion coefficient. This relation is used to calculate the absorption rate κ_s as the stationary flux across a spherical surface outside the sink

$$\kappa_s = 4\pi R_0^2 D \left.\frac{\partial \rho(r,t)}{\partial r}\right|_{r=R_0}. \tag{4}$$

The steady-state solution of the boundary problem, equations (1) and (2), reads

$$\rho(r) = \rho_\infty \left(1 - \frac{R_0}{r}\right) \tag{5}$$

where $R_0 = R_P + R_R$, R_P and R_R being the radii of the substrate particles and of the reactive sink, respectively. By inserting the above expression into equation (4), the known Smoluchowski rate is obtained:

$$\kappa_s = 4\pi D R_0 \rho_\infty. \tag{6}$$

The diffusion equation provides a good macroscopic description of an overdamped stochastic dynamics. However, when inertial effects are important, the appropriate macroscopic paradigm is that of the Fokker–Planck equation (FPE), describing the evolution of a probability measure in the phase space. In particular, when inertial effects are to be considered in the presence of an absorbing boundary, the condition of vanishing density (2) is no longer adequate for times shorter than the relaxation time of the velocity autocorrelation function. In this case, more general boundary conditions should be imposed, including velocities, in the picture. An approximate solution to this generalized boundary problem was derived by Harris in the early 1980s [10]. Within the FPE framework, one considers the full phase-space distribution function $f(\mathbf{r}, \mathbf{v}, t)$, thus retaining the ability to discriminate between incoming and outgoing particles at the absorbing boundary. Thus, the correct boundary conditions can be imposed by picking out only particles *leaving* the sink, so only the density of the latter is strictly set to zero.

Following Harris [10], the stationary solution of the FPE in the presence of an absorbing spherical sink reads

$$\rho(r) = \rho_0 \left\{1 - \frac{\alpha(r) R_0}{r} + \mathcal{O}\left[\left(\frac{R_0}{r}\right)^2\right]\right\} \tag{7}$$

where

$$\alpha(r) = \frac{4\lambda R_0}{3\pi C(R_0)}\left[1 + 1.85\lambda R_0 + 1.05 e^{-\lambda(r-R_0)}\frac{A(r)}{A(R_0)}\right] \tag{8}$$

with $A(r) = [1 + 8\lambda r/(3\pi)]^{(8\pi/18)-1}$ and $C(r) = 0.79(\lambda r)^2 + 2.35\lambda r + 2.27$. The crucial parameter is the inverse boundary-layer length

$$\lambda = \frac{3}{2}\sqrt{\frac{\pi}{2D\tau}} \tag{9}$$

incorporating inertial effects through the velocity relaxation time

$$\tau = \frac{mD}{k_B T}. \tag{10}$$

The dimensionless parameter λR_0 gauges the weight of inertial effects and thus quantifies the deviation from the purely diffusive regime. It expresses the ratio between the length traveled at the thermal velocity before relaxation, λ^{-1}, and the typical length associated with the symmetry breaking implied by the sink, i.e. the contact distance R_0. In the limit $\lambda R_0 \gg 1$, the system is overdamped and inertial effects become negligible. In contrast, when $\lambda R_0 \sim 1$, the system behavior deviates substantially from the results of the DE and the FPE formalism must be used instead.

In order to determine how inertial effects shape diffusion around the sink, Harris worked out a space-dependent expression for the diffusion coefficient, showing that diffusion close to the boundary is inhibited, while at large distance Fick's law is recovered with the diffusion coefficient given by

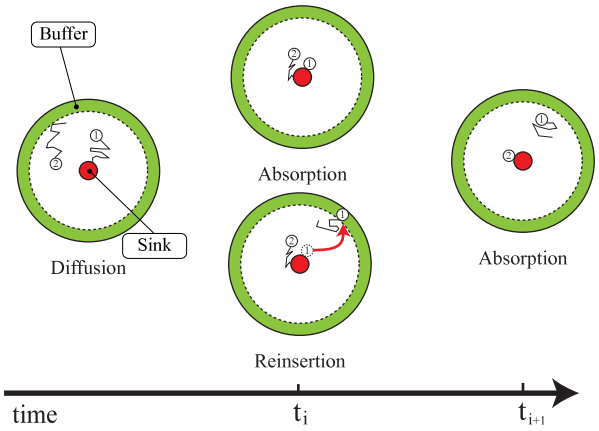

Figure 1. Cartoon illustrating the simulation scheme. Particles diffuse across the spherical bounding box. When a particle comes in contact with the sink (here at time t_i) an absorption event occurs and the particle is instantaneously reinserted in the buffer. The internal wall of the buffer is semi-permeable, allowing particles from the buffer to enter the box but blocking the opposite flux.

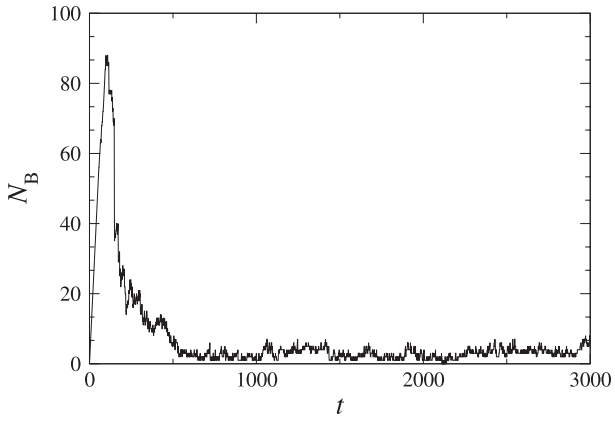

Figure 2. Evolution of the number of particles contained in the buffer, following an initial random distribution of the particles within the bounding box. The equilibration can be estimated from this monitoring. After the equilibration steps the constant number of particles in the buffer ensures the condition of constant flux at the outer boundary.

Einstein's relation $D = k_B T/m\tau$. In line with this effect, the absorbing rate is also depressed:

$$\frac{\kappa}{\kappa_s} = \frac{4\lambda R_0}{3\pi C(R_0)}(1 + 1.85\lambda R_0). \tag{11}$$

The amplitude of the rate reduction depends on the dimensionless parameter λR_0, the Smoluchowski expression κ_s being recovered in the limit $\lambda R_0 \to \infty$. The lowest-order correction to the Smoluchowski rate can be obtained by expanding expression (11) in the vicinity of $(\lambda R_0)^{-1} = 0$, which gives

$$\frac{\kappa}{\kappa_s} = 1 - \frac{2.42}{\lambda R_0} + \mathcal{O}[(\lambda R_0)^{-2}]. \tag{12}$$

3. Event-driven Brownian dynamics

Event-driven Brownian Dynamics has been introduced recently for hard-sphere systems [14]. The algorithm employs a combination of event-driven and Brownian velocity randomization steps to simulate efficiently the stochastic dynamics of a many-body hard-sphere system, when the singular nature of the potential prevents the use of standard Brownian dynamics techniques. The algorithm consists of the following steps:

(i) the particles move according to standard event-driven molecular dynamics (EDMD) [15];
(ii) at regular intervals Δt, velocities are randomized by drawing from a Maxwell distribution corresponding to a given temperature T.

It can be shown that the above dynamics is Brownian with a short-time diffusivity given by

$$D_s = \frac{\Delta t}{2}\frac{k_B T}{m} \tag{13}$$

where m is the mass of the particles and $(2m/\Delta t)$ plays the role of an effective friction coefficient [16]. Hence, the characteristic velocity randomization time Δt, which is chosen *a priori*, is directly proportional to the single-particle diffusion and should be consistent with the physical properties of the system that one wants to simulate. In particular, a short Δt will result in an overdamped dynamics, while a large Δt will yield an underdamped regime. Clearly, in the limit $\Delta t \to \infty$ the system follows standard EDMD. So far, EDBD has been used for bulk conditions, where the fluid is placed in a box with periodic boundary conditions. For instance, it has been successfully applied to study gelation of colloidal particles [14, 17]. In principle, EDBD can also be employed to simulate systems with given boundary conditions and thus describe, e.g., diffusion-driven absorbing processes.

In the present study, we adapted the EDBD to the particular configuration of an absorbing sink of radius R_R located at the center of a spherical bounding box with particles of mass $m = 1$ that diffuse around it and, eventually, get absorbed. The temperature is fixed at $T = 1$. The simulation scheme is depicted in figure 1. Particles diffuse inside the box and, as they come in contact with the sink, they are instantaneously absorbed. Following one such event, a particle is reinserted in a buffer layer outside the bounding box. The internal spherical surface marking the boundary between the buffer and the box is semi-permeable: particles within the buffer can cross it freely while particles inside the box get reflected back. The total number of particles $N = N_B + N_S$ is fixed, N_B and N_S being the number of particles inside the buffer and within the box, respectively. At the beginning of the simulations, the particles are uniformly distributed within the bounding box. To describe how a typical simulation proceeds, N_B is plotted as a function of time in figure 2. Initially, a large number of particles close to the sink are absorbed, which marks a rapid increase of N_B. After such transients, fluctuations flatten rapidly and a steady state is reached. In this situation, a constant flux of particles from the buffer to the

sink is established, corresponding to a well-defined value of the absorption rate.

Different methods have been introduced to describe chemical associations [18–20]. Here, we present a simulation scheme that is very efficient and has several advantages. The computation of the encounter rate is usually based on first-passage-time techniques, where a bunch of trajectories are followed while individual runs are stopped as soon as a particle either reaches the sink or escapes beyond a certain distance from it [21]. However, even if such schemes allow the use of variable-step integration algorithms, they do not allow a straight evaluation of the density profiles $\rho(r)$. With the present method, we can easily monitor such static quantities, that can carry precious information on the dynamics. This is the case, for example, if one wishes to relax the infinite-dilution approximation and consider the diffusion of interacting particles [11]. Another advantage is that the condition of absorption is imposed on the velocity field, i.e. when a particle and the sink collide. In this way, the boundary conditions are imposed similarly to the FPE, i.e. on the velocities. One slight disadvantage is that the reflective boundary conditions will induce a structuring close to the outer shell when non-ideal (e.g. hard-core) particles are considered, akin to the density oscillations that emerge in a liquid close to a wall [22]. However, such modulation is rapidly damped in the bulk, and this problem can be simply overcome by considering a box large enough that the sink and boundary regions are decoupled up to the desired accuracy. More precisely, R_S should be chosen such that the boundary conditions of the diffusion equation are well approximated, that is

$$\rho(R^*) \simeq \rho(r \to \infty) = \rho_\infty \tag{14}$$

meaning that there exists a distance $R^* < R_S$ where the density fluctuations in the steady state do not exceed a chosen tolerance. In this study, we determine R^* by requiring that $|\Delta\rho|/\rho < 5 \times 10^{-3}$ and approximate the bulk density of the system as $\rho_\infty = \rho(R^*)$.

The main quantity that we wish to determine is the steady-state encounter rate κ. The usual way is to estimate κ by fitting the long-time tail of the survival probability $S(t)$ of the substrate particles around the reactive sink [23]. Within our simulation scheme, the time marking each absorption event t_i, $i = 1, 2, \ldots, n$ is recorded during a simulation run and the reaction rate is calculated from the distribution of time intervals between consecutive events

$$\kappa = \left[\frac{1}{n}\sum_{i=1}^{n-1}(t_{i+1} - t_i)\right]^{-1}. \tag{15}$$

Our algorithm provides a natural way to weight inertial effects, namely tuning the time interval Δt between two consecutive randomization events. By doing this, we can adjust the relative weights of the event-driven and BD steps, and consequently modulate the dynamics from underdamped to overdamped regimes. Thus, our simulations enable us to compare the numerical results for the rate κ and the stationary profiles $\rho(r)$ against the analytical predictions for both the diffusion and Fokker–Planck boundary problems in the case of non-interacting particles. More generally, we stress that our numerical scheme allows us to introduce an interaction between particles in a natural way. We can, for example, consider hard-core repulsion and examine the interplay of inertial and excluded-volume effects as a function of the packing fraction [11].

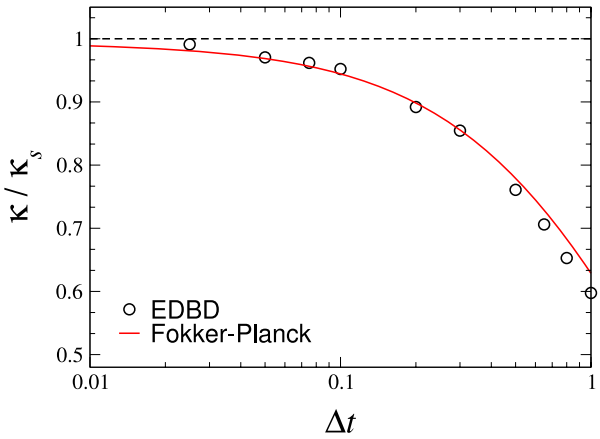

Figure 3. Normalized rate as a function of the velocity relaxation time Δt. The Fokker–Planck solution (solid line) and the simulation results (circles) are shown together with the solution of the diffusion equation (dashed line). $N = 20\,000$.

Our reference unit length is the sink diameter. In the cases discussed here, we chose a ratio of 1.5 between the radii of the diffusing particles ($R_P = 0.75$) and the radius of the sink ($R_R = 0.5$). By using almost similar radii, one can determine the rate of absorption with good statistical accuracy through relatively short simulation runs. Indeed, the $1 - (R_R + R_P)/r$ functional form of the density profiles away from the sink implies that the latter converge to the bulk density less rapidly for smaller R_P, so a larger bounding box should be used to achieve the desired accuracy at the box edge. This, in turn, would require a larger number of particles N, since the rate is directly proportional to the density. With the chosen size ratio, we attained the required precision with N up to 20 000. Moreover, such size ratio proves useful for the generalization of our simulations to the case of interacting particles, as tracer- and sink-induced spatial signatures in the density profiles can still be recognized [11].

4. Results

The Harris solution predicts that the discrepancy between the rate of absorption computed through the FPE and that of the diffusion boundary problem increases linearly with Δt for moderate strength of the inertial effects, as attested to by the lowest-order correction to the Smoluchowski rate (12). Figure 3 shows the ratio between the numerically measured rate of absorption κ and the one expressed by equation (4) as a function of Δt. It is manifest that our numerical scheme reproduces perfectly the FPE rate (11) for a range of Δt between 0.01 and 0.3. For larger values of Δt, the agreement is slightly worse. However, it must be stressed that under such conditions we are not able to discern whether this is due

to numerical artifacts associated with our numerical scheme or simply to the fact that the approximations made in the derivation of equation (7) are no longer valid.

What is important to remark here, however, is the discrepancy with respect to the Smoluchowski rate. Indeed, figure 3 confirms that the use of the DE is legitimate only in the overdamped limit. In this case $\Delta t \to 0$ and the velocities of the Brownian particles are almost instantaneously randomized. As soon as Δt increases, the rate starts decreasing due to the emergence of inertial effects. This fact has implications that reach far beyond the test of our numerical algorithm, since deviations from the purely diffusive behavior have been demonstrated in many contexts, such as for solvate ions in water or aerosol particle coagulation [10]. This can have important consequences when the Smoluchowski framework is used in the interpretation of experiments performed in a regime where inertial effects are non-negligible.

As we discussed above, one of the advantages of the present method is the possibility of computing the density profiles that set in when the absorption process reaches an equilibrium. This is particularly important in the case of interacting particles. In fact, we have shown that modulations in the density distributions can alter the rate of absorption in a highly non-trivial fashion [11]. We are in a position to investigate how the velocity relaxation time Δt affects the stationary profiles. Since we are interested in highlighting the deviation from the DE solutions, we focus on the ratio $\rho(r)/\rho_{\mathrm{DE}}(r)$ for several values of Δt. The outcome of our numerical experiments is summarized in figure 4. There is a clear deviation from the purely diffusive regime. In all cases we observe an important increase of the density with respect to the DE solution (5) close to the sink. Such deviation depends strongly on the value of Δt: while it is around 10% for $\Delta t = 5 \times 10^{-2}$, the true density in the vicinity of the sink becomes more than five times greater than the Smoluchowski solution for $\Delta t = 1$.

Inertial effects in the bulk can in general be ignored, since they extend on timescales that are much shorter than the typical time frame of interest (around picoseconds for a simple liquid). In diffusion-controlled reactions, however, the nature of the boundary conditions causes inertial effects to have a substantial impact on the density profile and, as a consequence, on the rate. Note that, by virtue of the integral relation connecting the two quantities, a significant deviation in the profile still affects the rate to an appreciable extent even if such variation is mostly confined to a restricted region around the sink. Overall, however, due to the long-range nature of the density distributions, a deviation can be measured also at large distances from the sink. To better quantify this effect, we computed the absolute value of the density deviations with respect to diffusion as a function of Δt at a given distance d from the sink

$$\delta\rho(d) = \left| \frac{\rho(d)}{\rho_{\mathrm{DE}}(d)} - 1 \right|. \tag{16}$$

In figure 5 the numerical results are compared to the FPE theory. As expected, the difference between the FPE and DE solutions decreases with the distance from the sink. Far away from the absorbing boundary ($d = 20$) the deviation is less than 5% for all Δt. At intermediate distances ($d = 4$), however, the discrepancy can be up to 20%. This proves that, at distances of a few particle diameters from the absorber, the density profile strongly depends on the friction acting on the particles.

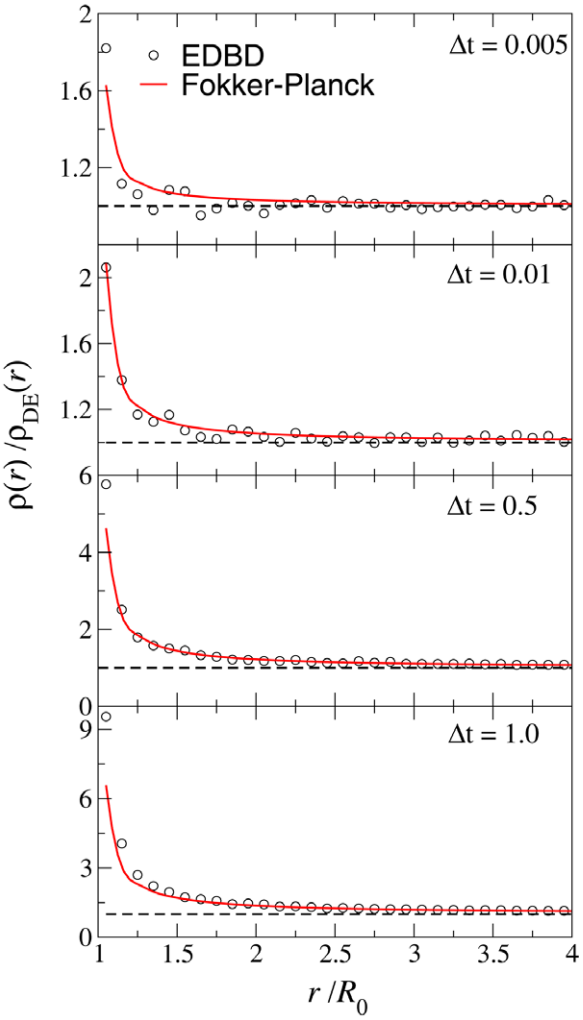

Figure 4. Normalized density distribution for different velocity relaxation times Δt. The Fokker–Planck solution (solid lines) and the simulation results (circles) are shown together with the solution of the diffusion equation (dashed lines). $N = 20\,000$.

5. Conclusions

In this paper we presented a new numerical scheme, employing event-driven Brownian dynamics simulations in order to study diffusion-limited encounter reactions. Within our method, which is not based on a first-passage-time approach, a stationary current of particles is established across the simulation box to the absorbing sink. As a consequence, the stationary density profiles can be measured directly after a first transient. The bounding box is spherical with reflective boundary conditions from the inside. In this way, the natural symmetry of the system is enforced in the simulations. In this work, we used non-interacting particles to test the algorithm against theoretical predictions, but the same approach can be used to describe systems of interacting particles.

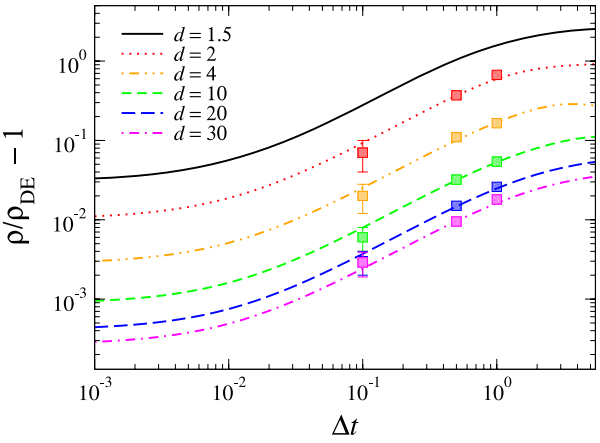

Figure 5. Deviation of the density profiles from the Smoluchowski solution as a function of the velocity relaxation time Δt at different distances d from the sink. The dotted lines are obtained from the theoretical FPE predictions and the squares are the simulation results.

We considered the analytical solutions of two different theoretical models. The first is the traditional Smoluchowski theory, where the microscopic dynamics of the particles is described at the macroscopic level by the diffusion equation with absorbing boundary conditions coupled to Fick's law. The second approach, developed by Harris [10], is based on an approximate solution of the Fokker–Planck equation. Such a method corrects for the intrinsic inconsistency of the boundary conditions at the sink by considering also the velocities. Harris's formulation is more general, since it does not assume that the velocity correlation functions relax instantaneously. In many real systems, inertial effects are relevant and should be taken into account.

We have shown that our numerical results for the absorption rate and for the radial density profiles match to a very good extent the FPE predictions for all the values of the velocity relaxation time Δt considered. In contrast, the purely diffusive model yields accurate estimates of the numerics only at large distances from the sink or in the overdamped regime, that is for small Δt. This confirms that the use of Smoluchowski theory for diffusion-guided reactions requires some care, as already pointed out by several authors [10].

Our method is conceived so as to be naturally applicable to systems of interacting particles. Indeed, we have used it to show that, when excluded-volume effects are non-negligible, the rate does not depend trivially on the density and may display non-monotonic behavior as the packing fraction increases [11]. In the future we plan to apply the present algorithm to describe more complicated reactions of biological relevance and to granular materials. It will be interesting, for example, to investigate the interplay of inertial and excluded-volume effects in systems with multiple reaction centers. In this way we will be able to quantify negative and positive cooperativity effects associated with the presence of multiple sinks as well as the influence of the geometrical arrangement of the latter. For example, such framework is a relevant one in ligand–receptor binding phenomena on cell surfaces, where the timescale associated with receptor clustering on the membrane and the consequent geometrical constraints are likely to play a major role in determining the overall binding efficiency.

In summary, our results confirm that great care needs to be taken when using a simple diffusive model to discuss experimental results, since in many cases the consequences of an underdamped dynamics may be observable beyond the typical particle timescales and length scales, such as for many biological reactions occurring *in vivo* or in colloidal suspensions.

Acknowledgments

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