Diffusion-Limited Reactions in Crowded Environments

N. Dorsaz,1 C. De Michele,2 F. Piazza,3,* P. De Los Rios,3 and G. Foffi4
1University of Fribourg, Adolphe Merkle Institute, CH-1723 Marly 1, Switzerland
2Università di Roma La Sapienza, Dipartimento di Fisica, P.le Aldo Moro 2, 00185 Roma, Italy
3Ecole Polytéchnique Fédérale de Lausanne (EPFL), Institute of Theoretical Physics, Laboratory of Statistical Biophysics, 1015 Lausanne, Switzerland
4Ecole Polytéchnique Fédérale de Lausanne (EPFL), Institute of Theoretical Physics, 1015 Lausanne, Switzerland

Diffusion-limited reactions are usually described within the Smoluchowski theory, which neglects interparticle interactions. We propose a simple way to incorporate excluded-volume effects building on simulations of hard sphere in the presence of a sink. For large values of the sink-to-particle size ratio $R_s$, the measured encounter rate is in good agreement with a simple generalization of the Smoluchowski equation at high densities. Reducing $R_s$, the encounter rate is substantially depressed and becomes even nonmonotonic for $R_s \ll 1$. Concurrently with the saturation of the rate, stationary density waves set in close to the sink. A mean-field analysis helps to shed light on the subtle link between such ordering and the slowing down of the encounter dynamics. Finally, we show how an infinitesimal amount of nonreacting impurities can equally slow down dramatically the reaction.

Processes such as gelation, coagulation, crystallization, or self-assembly in colloidal or polymer systems, thin-film growth in materials science and chemical reactions in biology involve, as a first step, the random movement of particles suspended in a fluid [1]. The components diffuse and when they come into contact, a reaction may be triggered, such as aggregation or assembling. As an example, the usual paradigm for biochemical reactions assumes the formation of an encounter complex, which may subsequently undergo chemical transformation, yielding the product. In most cases, the fixation step proceeds much faster than the encounter, in which case the reaction is said to be diffusion limited. Such reactions are commonly found in biochemical processes such as enzyme catalysis, protein aggregation, and complexation in cells [2].

The simplest model of diffusion-limited encounter in three dimensions has been formulated almost one century ago by Smoluchowski under the hypothesis of noninteracting, spherical, and chemically isotropic reactants, a diffusing particle ($\rho$) and a sink ($s$) [3], leading to the Smoluchowski absorption rate

$$\kappa = 4\pi DR\rho_\infty,$$

where $\rho_\infty$ is the (relative) bulk density of the reactants, $D = D_s + D_p$ is the coefficient of relative diffusion and $R = R_s + R_p$ the encounter distance.

The Smoluchowski theory is still nowadays the main theoretical framework within which the aforementioned processes are analyzed. However, this approach is strictly valid only for ideal, infinitely diluted solutions, while most systems become interesting at concentrations far from the ideal gas limit. Cells, for instance, contain a large number of proteins, nucleic acids, and other smaller molecules that occupy up to 30%–40% of the available volume [4] and that cannot overlap with each other. As a matter of fact, crowding effects are expected to impact profoundly on the thermodynamics and kinetics of biological processes in vivo [4–6], such as protein folding and stability [7] and aggregation [8]. Yet, the effects of crowding on diffusion-limited processes have been examined only in the case of low density of diffusing particles [9] or for tracers diffusing in a medium of inert particles [10–13]. In colloidal science, instead, the properties of crowded environments have been investigated widely. Experiments on concentrated suspensions of nearly hard-core particles revealed unexpected phenomena both in their thermodynamics and in the dynamics, spotlighting a subtle entwining between packing, structuration and dynamics [14].

In this Letter, we generalize the classic Smoluchowski problem to arbitrary crowding conditions by means of a novel computational scheme that allows us to efficiently explore the effects of increasing packing on the encounter dynamics. Typical numerical simulations of diffusion-limited reactions employ different declensions of the Brownian dynamics (BD) algorithm [15,16]. Here, we consider a liquid composed of hard spheres of radius $R_p$ described through event driven Brownian dynamics (EDBD) [17–19]. This technique allows us to efficiently simulate the stochastic dynamics of many-body hard-core systems. In order to simulate encounter reactions at finite densities, we adapted the EDBD to the configuration of an absorbing sink of radius $R_s$ located at the center of a spherical bounding box with constant-flux boundary conditions (Fig. 1) [20].

In this way, by tuning the density in the box, we can measure the encounter rate $\kappa$ and the stationary density profile $\rho(r)$, from the infinite-dilution Smoluchowski limit,...
The latter can be well approximated through the Carnahan-Starling (CS) equation of state $Z(\phi) = (1 + \phi + \phi^2 - \phi^3)/(1 - \phi^3)$ [22]. At moderate densities, the virial expansion $\beta \Pi(\rho) = \rho [1 + B_2 \rho + O(\rho^3)]$ yields the Smoluchowski rate at zeroth order and the first-order correction $\kappa/\kappa_S = 1 + B_2 \rho_\infty$, derived in Ref. [9].

For large values of the sink size, the rate increases monotonically with the density in good agreement with Eq. (4), which provides an accurate prediction in the limit $R_s \to \infty$. This is clearly illustrated by inspecting how the rate varies with $R_s$ at fixed packing fraction (inset in Fig. 2).

The density gradient between the sink and the bulk regions induces a net force towards the sink, the latter behaving as a depression in a high pressure environment. The rate is thus directly related to the difference in pressure between the diluted region near the sink and the denser bulk. Remarkably, however, when $R_s$ is decreased the rate gets substantially depressed at intermediate crowding and becomes even nonmonotonic for $R_s \ll 1$, featuring a maximum and a drop at high crowding.

The stationary density distributions of the diffusing particles around the absorbing boundary surface offer a key to understanding the drop in the rate observed at intermediate packing when reducing $R_s$. As illustrated in Fig. 3, we found that (i) oscillations set in progressively while increasing $\phi$ and (ii) the structuration is strongly enhanced, reaching even an eightfold magnification at $\phi = 0.4$ with respect to the infinitely diluted limit.

In order to account for the strongly nonlinear increase of the rate at intermediate crowding, one can consider the Smoluchowski equation and take interparticle interactions into account in the expression of the net flux $\vec{J}$ through a generalized Stokes-Einstein relation for the collective diffusion coefficient [21]. At first order, crowding effects can be accounted for through the density dependence of the pressure in the bulk liquid $\Pi(\rho)$ (vanishing at zero density), yielding a generalized diffusivity $D(\rho) = D_0 d[\beta \Pi(\rho)]/d\rho$, where $\beta^{-1} = k_B T$ and $D_0 = \lim_{\rho \to 0} D(\rho)$. The steady-state Smoluchowski equation in spherical coordinates reads then

$$\nabla \cdot \vec{J} = -\frac{\beta D_0}{r^2} \frac{d}{dr} \left[ r^2 \frac{d \rho}{d\rho(r)} + \frac{d \Pi(\rho)}{d\rho(r)} \right] = 0 \quad (3)$$

with the boundary conditions $\rho(R_s + R_p) = 0$ and $\lim_{r \to \infty} \rho(r) = \rho_\infty$. Integrating the equation that defines the encounter rate, namely $\kappa/(4\pi r^2) = J(r)$, in the interval $[R_s + \infty)$ with $J(r) = [\vec{J}] = \beta D_0 [d\rho(r)/dr] [d \Pi(\rho)/d\rho]$ one obtains

$$\frac{\kappa}{\kappa_S} = \frac{\beta \Pi(\rho_\infty)}{\rho_\infty}, \quad (4)$$

where $\beta \Pi(\rho_\infty)/\rho_\infty = Z(\phi)$ is the compressibility factor.
As it is clearly shown in Fig. 3, the progressive structuration of the system bears the clear signature of the radial distribution function $g(r)$ of a hard-sphere liquid at intermediate densities. This effect is by no mean trivial, as $g(r)$ provides a measure of spatial correlations in the reference frame of a moving particle. Here, translational symmetry is broken by the sink, which causes the emergence of a denser layer near the absorber, triggering the onset of stationary density waves.

The simultaneous onset of density oscillations and rate falloff observed upon reducing $R_s$ suggests that the organized accumulation of particles is the consequence of a competition among the particles diffusing in the proximity of the sink. In this regard, it is important to note that, $\Delta$ being a constant, the particles compete for the sink at a distance from the absorber that depends on the size of the diffusers only, and not on the size of the latter.

In order to emphasize the connection between the increasing structuration of the liquid and the slowing down of the encounter process it is possible to regard the onset of density fluctuations as marking the appearance of an effective potential between the sink and individual particles. Within such representation, the accumulation of particles at $\Delta$ will act on a freely diffusing particle as an energy barrier $\tilde{V}(r) = f(r; \phi, R_p)$ [Fig. 4(a)], whose height should depend parametrically on both the bulk concentration $\phi$ and the sink size $R_s$, to account for the increasing structuration of the density profile for large values of $\phi$ and small values of $R_s$. In general, in the presence of an interaction potential $V(r)$, the Smoluchowski rate reads [23],

$$\frac{\kappa}{\kappa_S} = \left[ R \int_0^\infty \frac{e^{\tilde{V}(r)}}{r^2} \, dr \right]^{-1}. \quad (5)$$

It is possible to generalize Eq. (5) in order to account for the effects of crowding by noting that finite densities imply $\kappa \propto \beta \Pi(\rho_\infty)$, as shown by Eq. (4), instead of $\kappa \propto \rho_\infty$, as from Eq. (1) (free particles). As a consequence, we may write

$$\frac{\kappa}{\kappa_S} = \frac{\beta \Pi(\rho_\infty)}{\rho_\infty} \left[ R \int_0^\infty \frac{e^{\tilde{V}(r)}}{r^2} \, dr \right]^{-1}. \quad (6)$$

It is reasonable to assume that the height $V$ of the potential energy barrier reflects the excess pressure that accumulates in the vicinity of the sink with respect to the ideal case as the packing fraction increases. As a consequence, we assume

$$\beta \tilde{V} = c \frac{\Pi(\eta) - \Pi_{id}(\eta)}{\Pi_{id}(\eta)} = c[Z(\eta) - 1], \quad (7)$$

where $\eta$ is related to the local density at a distance $\Delta$ [Fig. 4(b)] and $\Pi_{id}(\rho) = \beta \rho$ is the ideal gas pressure. For simplicity, we take $\eta = \rho_s(\Delta)$ which introduces the dependence on $R_s$ in the effective potential.

Remarkably, a one-parameter fit of Eq. (6) to the numerical data accounts extremely well for both the $\phi$ and $R_s$ dependence of the rate [Fig. 4(c)] with a single best-fit value of the floating parameter ($c = 3.75$) for $0 < \phi < 0.52$ and $1/30 < R_s < 8/3$, thus substantiating our theoretical analysis. Despite its simplicity, this approach seems to capture the essence of the problem, namely, a density-weighted competition among the particles diffusing around the sink. Diffusion-limited reactions in crowded environments are thus the result of a subtle combination of the

![FIG. 3 (color online). Structuration of the density profiles under crowding. The profiles are plotted at increasing bulk packing fraction $\phi$ for $R_s = 2/3$ (left) and $R_s = 1/30$ (right). Structuration is enhanced in the case of the smaller sink, but the liquid gets structured at approximately the same distance $\Delta$ from the contact distance $R_s + R_p$ in the two cases. The density oscillations are in phase with the radial distribution function $g(r)$ of a hard-sphere liquid at intermediate densities.](image1)

![FIG. 4 (color online). Effective-potential description of diffusion-limited reactions under crowding. The effective potential $V(\phi, R_s)$ (a) accounts for the accumulation of particles at distance $\Delta$, resulting in the oscillations in the density profiles (b). The solid lines in panel (b) are plots of the Smoluchowski profiles (1), emphasizing the $R_s$ dependence of the density at $\Delta$. (c) The one-parameter fits obtained through Eq. (6) are in excellent agreement with the numeric results for all values of $R_s$, providing a quantitative link between the drop in the rate and the onset of stationary density oscillations.](image2)
liquid properties of the diffusers with the underlying long-range Smoluchowski description.

As a first extension of our numerical scheme to more complicated diffusion-limited reactions [4, 8, 24], we investigated the effects of introducing a finite amount of nonreacting hard-sphere impurities ($I$) in the system. We found that an infinitesimal fraction ($x = 1/2000$) is sufficient to slow down considerably the reaction with respect to the one-component case (Fig. 5). While at low crowding the rate and the density profiles are insensitive to the presence of nonreacting particles, an accumulation of the latter rate and the density profiles are insensitive to the presence of an absorbing boundary is reported for a system that is still in a liquidlike state.

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*Present address: Centre de Biophysique Moléculaire (CBM-CNRS), Rue Charles Sadron, 45071 Cedex 2 Orléans, France.

[24] Details of the simulations reported in a forthcoming study.

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**FIG. 5** (color online). Encounter rate versus fraction of nonreacting impurities $x$ for $R_s = 2/3$. Inset: the density profile for impurities $\phi_1(r)$ for $x = 1/2000$. 

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\frac{\kappa}{\kappa_s} \begin{cases} 0 & \phi < 0.18 \\ 10^4 & \phi > 0.35 \end{cases}
\]  

\[x = 0, 1/100, 1/2000\] 

\[\phi_1 = 0.18, \phi_2 = 0.33, \phi_3 = 0.45\]