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Macroscopic Transport Equations in Many-Body Systems from Microscopic Exclusion Processes in Disordered Media: A Review

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Describing particle transport at the macroscopic or mesoscopic level in non-ideal environments poses fundamental theoretical challenges in domains ranging from inter and intra-cellular transport in biology to diffusion in porous media. Yet, often the nature of the constraints coming from many-body interactions or reflecting a complex and confining environment are better understood and modeled at the microscopic level. In this paper we review the subtle link between microscopic exclusion processes and the mean-field equations that ensue from them in the continuum limit. We show that in an inhomogeneous medium, i.e., when jumps are controlled by site-dependent hopping rates, one can obtain three different nonlinear advection-diffusion equations in the continuum limit, suitable for describing transport in the presence of quenched disorder and external fields, depending on the particular rule embodying site inequivalence at the microscopic level. In a situation that might be termed *point-like* scenario, when particles are treated as point-like objects, the effect of crowding as imposed at the microscopic level manifests in the mean-field equations only if some degree of inhomogeneity is enforced into the model. Conversely, when interacting agents are assigned a finite size, under the more realistic extended crowding framework, exclusion constraints persist in the unbiased macroscopic representation.

Keywords: transport equations, nonlinear diffusion, macromolecular crowding, non-ideal fluids, stochastic processes

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1. INTRODUCTION

Diffusive transport is central in many areas of physics, chemistry, biology, and soft matter [1–4]. However, while the mathematics of diffusive processes in dilute and simple media is fairly well developed and understood [1], many interesting and relevant diffusive processes take place in strongly non-ideal conditions. These include a wealth of different highly dense media, from non-ideal plasmas [5] to biological membranes [6], media with complex topological structures, including porous media [7–9] and living cells [10, 11] and strongly confining environments [3, 12–16].

Crowding and confinement effects on diffusion-influenced phenomena still pose fundamental yet unanswered questions. Several computational [17] and experimental [18, 19] evidences exist of anomalous diffusion under dense crowded conditions [20]. Anomalous diffusion refers to phenomena that lead to a nonlinear growth of particles' mean square displacement. Deviation from the standard linear behavior arise, for example, when obstacles impede the motion of particles [17, 21, 22] or when distinguishable species compete for the available spatial resources [10, 23–27]. These conditions are certainly met when studying the molecular mobility inside a cell [28, 29]. Cells are occupied for over 30% of their volume by membrane delimited organelles and different sorts of cytoskeletal structures. In this respect, living cells behave much like fractal or otherwise disordered systems [30, 31]. However, strong evidences also exist in favor of normal (Brownian) diffusion, crowding, and confinement resulting in this scenario in (often nontrivial) modifications of the diffusion coefficient [10, 27, 32, 33]. Moreover, as shown in Galanti et al. [34], the effect of crowding can result in crossovers between normal and anomalous diffusion, leading to different descriptive scenarios which appear to depend on the selected initial conditions and on the specific time scale of observation.

Another related issue is that of diffusion-limited reactions [35], which are ubiquitous in many domains in biology and chemistry, touching upon problems such as association, folding and stability of proteins [13, 36] and bimolecular reactions in solution [37–41], including enzyme kinetics [42], but also the dynamics of *active* agents [43, 44]. Many theoretical studies have tackled these and related problems under different angles [13, 39, 42, 44–47]. Nevertheless, a full theoretical comprehension of transport in non-ideal media remains an elusive task, Fick's law itself and the very notion of effective diffusion coefficient being questionable in a disordered medium [31].

In this paper we review the subtle link between macroscopic transport equations, such as the diffusion equation, and microscopic processes, modeling the stochastic dynamics of some agents. For a classical and comprehensive account on diffusion in disordered media the reader can refer to Haus and Kehr [48]and references therein [49–56].

The purpose of our study is to contribute to the debate with a two-fold approach. One the one hand, we wish to understand in greater depth the delicate procedure of obtaining mean-field transport equations from microscopic, agent-based stochastic models. The idea is that sometimes it may prove simpler or more effective to describe a complex transport process (or a simple one occurring in a complex medium) at the microscopic level. On the contrary, it is sometimes better to deal with macroscopic equations. It is thus important to investigate how the two levels of description interface with each other. Furthermore, we will elaborate on the reasons why considerable information can be eventually lost when passing from the microscopic stochastic process to the macroscopic mean-field description, and draw attention on the distinct notions of *point-like* and *extended* crowding, this latter bearing potentially interesting applications, only partially explored in the relevant literature.

The paper is organized as follows. In Section 2 we discuss the general framework of simple exclusion processes (SEPs), which constitute the basic tool of the microscopic description, as well as the process of obtaining mean-field equations from SEPs in the continuum limit. We show that SEPs in inhomogeneous media can be constructed in apparently equivalent manners as for the site-dependence of the hopping rates. However, different advection-diffusion equations can ensue in the continuum limit, rendering this operation a rather subtle one in disordered systems [57]. Moreover, we show that the effect of crowding, enforced in the microscopic description through an excluded volume effect, is recognizable in the continuum limit only if some degree of inhomogeneity is introduced. In Section 3, we move a step forward and consider microscopic exclusion processes involving agents characterized by a *finite* size, as opposed to standard SEPs. In the last section we draw the conclusions and we summarize the different extent to which the crowding fine-tunes deviation from the classical picture.

2. FROM MICROSCOPIC PROCESSES TO MACROSCOPIC EQUATIONS

SEPs are space-discrete, agent-based stochastic processes modeling some kind of transport according to specific rules and bound to the constraint that no two agents can ever occupy the same site. SEPs occupy a central role in non-equilibrium statistical physics [58, 59]. While the first theoretical ideas underlying such processes can be traced back to Boltzmann's works [60], SEPs were introduced and widely studied in the 70s as simplified models of one-dimensional transport for phenomena like hopping conductivity [61] and kinetics of biopolymerization [5]. Along the same lines, the asymmetric exclusion process (ASEP), originally introduced by Spitzer [62], has become a paradigm in non-equilibrium statistical physics [63–66] and has now found many applications, such as the study of molecular motors [67], transport through nano-channels [68] and depolymerization of microtubules [69].

The most general SEP in one dimension is described by a stochastic jump process on a $1D$ lattice with inequivalent sites in the presence of a field

$$\begin{aligned} n_i(k+1) - n_i(k) &= z_{i-1}^{+} n_{i-1}(k)[1 - n_i(k)] \\ &\quad + z_{i+1}^{-} n_{i+1}(k)[1 - n_i(k)] \\ &\quad - z_i^{+} n_i(k)[1 - n_{i+1}(k)] \\ &\quad - z_i^{-} n_i(k)[1 - n_{i-1}(k)] \end{aligned} \tag{1}$$

Equation (1) is to be regarded as the update rule for a Monte Carlo process, where $n_i(k)$ is the occupancy of site i at time $t = k\Delta t$, which can be either zero or one. The quantities $z_i^{\pm}$ are variables which have the value 0 or 1 according to a random number ξ_i which has a uniform distribution between 0 and 1. By defining the jump probabilities $q_j^{\pm}$ ($j = i, i \pm 1$) one can formally write:

$$\begin{aligned} z_{i-1}^{+} &= \theta(\xi_i) - \theta(\xi_i - q_{i-1}^{+}) \\ z_{i+1}^{-} &= \theta(\xi_i - q_{i-1}^{+}) - \theta(\xi_i - q_{i-1}^{+} - q_{i+1}^{-}) \\ z_i^{+} &= \theta(\xi_i - q_{i-1}^{+} - q_{i+1}^{-}) - \theta(\xi_i - q_{i-1}^{+} - q_{i+1}^{-} - q_i^{+}) \\ z_i^{-} &= \theta(\xi_i - q_{i-1}^{+} - q_{i+1}^{-} - q_i^{+}) - \theta(\xi_i - 1) \end{aligned} \tag{2}$$

where $\theta(\cdot)$ stands for the Heaviside step function and where we are assuming that $q^+_{i-1} + q^-_{i+1} + q^+_i + q^-_i = 1$. Note that the ordering of appearance of the $q^\pm_j$ in the above expressions is arbitrary. Equations (2) entail that $\langle z^\pm_j \rangle = q^\pm_j$, where $\langle \cdot \rangle$ indicates an average over many values of ξ_i, for a given configuration $\{n_i\}$. The above process is fully determined by the fields $q^\pm_i$, specifying the probability of jumping from site i to site $i+1$ (q^+_i) or to site $i-1$ (q^-_i) in a time interval Δt.

A (discrete-time) master equation for the above SEP can be obtained by averaging over many Monte Carlo cycles performed according to rule (1)

$$\begin{aligned} P_i(k+1) - P_i(k) = {} & q^+_{i-1}[P_{i-1}(k) - P_{i,i-1}(k)] \\ & + q^-_{i+1}[P_{i+1}(k) - P_{i,i+1}(k)] \\ & - q^+_i [P_i(k) - P_{i,i+1}(k)] \\ & - q^-_i [P_i(k) - P_{i,i-1}(k)] \end{aligned} \tag{3}$$

where we have defined the one-body and two-body site occupancy probabilities

$$P_i(k) = \langle\langle n_i(k) \rangle\rangle \tag{4}$$

$$P_{i,i\pm1}(k) = \langle\langle n_i(k) n_{i\pm1}(k) \rangle\rangle \tag{5}$$

Here $\langle\langle \cdot \rangle\rangle$ denotes averages over many independent Monte Carlo cycles performed until time $k\Delta t$, starting from the same initial condition. We emphasize that the same equation has been derived through a slightly different procedure by Richards in 1977 [61].

2.1. Mean-Field Equations

With the aim of deriving macroscopic transport equations from the microscopic stochastic process described by Equation (1), it is customary to assume a mean-field (MF) factorization,

$$\begin{aligned} P_{i,i\pm1}(k) \equiv {} & \langle\langle n_i(k) n_{i\pm1}(k) \rangle\rangle = \langle\langle n_i(k) \rangle\rangle \langle\langle n_{i\pm1}(k) \rangle\rangle \\ = {} & P_i(k) P_{i\pm1}(k) \end{aligned} \tag{6}$$

With the help of Equation(6), the master Equation (3) becomes

$$\begin{aligned} P_i(k+1) - P_i(k) = {} & q^+_{i-1} P_{i-1}(k)[1 - P_i(k)] \\ & + q^-_{i+1} P_{i+1}(k)[1 - P_i(k)] \\ & - q^+_i P_i(k)[1 - P_{i+1}(k)] \\ & - q^-_i P_i(k)[1 - P_{i-1}(k)] \end{aligned} \tag{7}$$

Nonlinear mean-field equations for exclusion process of this type have been used since the 70s to investigate one-dimensional transport in solids [70]. In fact, despite mean-field descriptions for the inhomogeneous ASEP are known to provide imperfect descriptions of certain non-equilibrium observables in one dimension, e.g., the current-density relation and critical exponents [71], continuum descriptions can be employed reliably to track the time-evolution of large-wavelength density fluctuations [34, 72–78]

2.2. Site-Dependent Rates: Three Jump Processes Yield Three Transport Equations

Let a be the lattice spacing and let us define a *reversal* probability ϵ_i, such that

$$q^+_i = Q_i \qquad q^-_i = Q_i - \epsilon_i \tag{8}$$

The condition (Equation 8) (with $\epsilon_i > 0$) amounts to considering a field introducing a bias in the positive x direction. In order to take the continuum limit $\lim_{a,\Delta t \to 0} P_i(k) = P(x,t)$, we must require

$$\lim_{a,\Delta t \to 0} \frac{Q_i a^2}{\Delta t} = D(x) \tag{9}$$

$$\lim_{a,\Delta t \to 0} \frac{\epsilon_i a}{\Delta t} = \nu(x) \tag{10}$$

Equation (9) defines the position-dependent diffusion coefficient, while Equation (10) defines the field-induced drift velocity. Note that we are assuming that the reversal probability vanishes linearly with a.

A pondering pause is required at this point before carrying out the continuum limit. In fact, a moment's thought is enough to realize that there are different ways one can enforce quenched disorder, corresponding to spatially varying hopping rates, in a jump process with the aim of modeling propagation in a inhomogenous medium. The master Equation (7) reflects only one of the possible choices. This observation has been made and thoroughly discussed in Painter and Sherratt [57]. In this paper the authors investigate the movements of cells capable of sensing strategies which depend on environmental factors.

To illustrate this interesting mathematical property, let us consider the jump from site i to site $i+1$. The probability of an agent taking an $i \to i+1$ leap can be equally well taken as (1) proportional to q^+_i, (2) proportional to q^+_{i+1} or (3) proportional to $(q^+_i + q^+_{i+1})/2$. All three cases correspond to the same space-dependent function $D(x)$ in the continuum limit, as prescribed by Equation (9). However, as we shall see in the following, depending on whether rule (1), (2), or (3) is chosen, one is led to totally different advection-diffusion equations in the continuum limit.

2.2.1. No-Exclusion Processes

In order to illustrate this subtle point, let us start with jump processes in the presence of quenched disorder but with no exclusion constraints on the allowed moves. Following the same reasoning that led us to Equation (7), it is not difficult to realize that the three possible choices (1), (2), and (3) referred above lead to the following master equations

$$\begin{aligned} P_i(k+1) - P_i(k) = {} & q^-_{i+1} P_{i+1}(k) + q^+_{i-1} P_{i-1}(k) \\ & - (q^+_i + q^-_i) P_i(k) \end{aligned} \tag{11}$$

$$\begin{aligned} P_i(k+1) - P_i(k) = {} & q^-_i P_{i+1}(k) + q^+_i P_{i-1}(k) \\ & - (q^+_{i+1} + q^-_{i-1}) P_i(k) \end{aligned} \tag{12}$$

$$P_i(k+1) - P_i(k) = \left(\frac{q^-_{i+1} + q^-_i}{2} \right) P_{i+1}(k)$$

$$
\begin{aligned}
&+\left(\frac{q^{+}_{i-1}+q^{+}_{i}}{2}\right)P_{i-1}(k)\\
&-P_i(k)\left[\left(\frac{q^{+}_{i+1}+q^{+}_{i}}{2}\right)+\left(\frac{q^{-}_{i-1}+q^{-}_{i}}{2}\right)\right]
\end{aligned}
\qquad (13)
$$

In the first case, Equation (11) (already obtained above), the rate for a given jump depends on the starting site, while the second, Equation (12), is the opposite, the rate depends on the index of the target site. The third case, Equation (13) is an intermediate, symmetric situation where jump rates are associated with *links* rather than with *nodes*. In the continuum limit $a, \Delta t \to 0$ one has

$$Q_{i\pm1} \approx Q(x) \pm \frac{\partial Q}{\partial x}a + \frac{1}{2}\frac{\partial^2 Q}{\partial x^2}a^2 + \dots \qquad (14)$$

$$\epsilon_{i\pm1} \approx \epsilon(x) \pm \frac{\partial \epsilon}{\partial x}a + \dots \qquad (15)$$

$$P_{i\pm1}(k) \approx P(x,t) \pm \frac{\partial P}{\partial x}a + \frac{1}{2}\frac{\partial^2 P}{\partial x^2}a^2 + \dots \qquad (16)$$

Therefore, recalling Equations (9) and (10), we have from Equations (11), (12) and (13), respectively,

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial J_1(x,t)}{\partial x} \qquad (17)$$

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial J_2(x,t)}{\partial x} \qquad (18)$$

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial x} \qquad (19)$$

where

$$J_1(x,t) = -D(x)\frac{\partial P(x,t)}{\partial x} + \left[v(x) - \frac{\partial D(x)}{\partial x}\right]P(x,t) \qquad (20)$$

$$J_2(x,t) = -D(x)\frac{\partial P(x,t)}{\partial x} + \left[v(x) + \frac{\partial D(x)}{\partial x}\right]P(x,t) \qquad (21)$$

$$J(x,t) = -D(x)\frac{\partial P(x,t)}{\partial x} + v(x)P(x,t) \qquad (22)$$

We see that the stochastic processes (11) and (12) correspond to diffusion with drift (or, equivalently, in an external potential). The drift velocity comprises two contributions: the difference between the right-bound and left-bound jump rate fields and a contribution arising from the spatial variation of the diffusion coefficient. Interestingly, the latter term has the opposite sign depending on whether jumps at the microscopic level are controlled by the rates evaluated at the start or target sites. This means that in these cases, even a symmetric jump process results in diffusion with drift. Conversely, considering symmetrized jump rates does not result in the appearance of such additional term in the drift velocity. Working in this setting one hence recover the standard diffusion equation.

2.2.2. Enforcing the Excluded-Volume Constraint

We can now come back to our original aim, i.e., taking the continuum limit of the master Equation (1). It is now clear that, if we want to consider an inhomogeneous medium, we must not restrict to the prescription leading to Equation (1), but we must also consider the other two kinds of processes described above in the absence of exclusion. Extending the reasoning that led us to Equation (1) and recalling Equations (12) and (13), the three master equations with excluded-volume constraints read

$$
\begin{aligned}
P_i(k+1)-P_i(k) &= [q^{-}_{i+1}P_{i+1}(k)+q^{+}_{i-1}P_{i-1}(k)][1-P_i(k)]\\
&\quad -P_i(k)\{q^{+}_{i}[1-P_{i+1}(k)]\\
&\quad +q^{-}_{i}[1-P_{i-1}(k)]\}
\end{aligned}
\qquad (23)
$$

$$
\begin{aligned}
P_i(k+1)-P_i(k) &= [q^{-}_{i}P_{i+1}(k)+q^{+}_{i}P_{i-1}(k)][1-P_i(k)]\\
&\quad -P_i(k)\{q^{+}_{i+1}[1-P_{i+1}(k)]\\
&\quad +q^{-}_{i-1}[1-P_{i-1}(k)]\}
\end{aligned}
\qquad (24)
$$

$$
\begin{aligned}
P_i(k+1)-P_i(k) &= \left(\frac{q^{-}_{i+1}+q^{-}_{i}}{2}\right)P_{i+1}(k)[1-P_i(k)]\\
&\quad +\left(\frac{q^{+}_{i-1}+q^{+}_{i}}{2}\right)P_{i-1}(k)[1-P_i(k)]\\
&\quad -\left(\frac{q^{+}_{i+1}+q^{+}_{i}}{2}\right)P_i(k)[1-P_{i+1}(k)]\\
&\quad -\left(\frac{q^{-}_{i-1}+q^{-}_{i}}{2}\right)P_i(k)[1-P_{i-1}(k)]
\end{aligned}
\qquad (25)
$$

The mean field limit $a, \Delta t \to 0$ of the above master equations is readily obtained by introducing as above the Taylor expansions of $q(x)$ and $P(x,t)$. By doing this, we find

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial \mathcal{J}_1(x,t)}{\partial x} \qquad (26)$$

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial \mathcal{J}_2(x,t)}{\partial x} \qquad (27)$$

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial \mathcal{J}_3(x,t)}{\partial x} \qquad (28)$$

where

$$
\begin{aligned}
\mathcal{J}_1(x,t) &= -[1-P(x,t)]\frac{\partial}{\partial x}[D(x)P(x,t)] - D(x)P(x,t)\frac{\partial P(x,t)}{\partial x}\\
&\quad + v(x)P(x,t)[1-P(x,t)]
\end{aligned}
\qquad (29)
$$

$$
\begin{aligned}
\mathcal{J}_2(x,t) &= P(x,t)\frac{\partial}{\partial x}\{D(x)[1-P(x,t)]\}\\
&\quad - D(x)[1-P(x,t)]\frac{\partial P(x,t)}{\partial x}\\
&\quad + v(x)P(x,t)[1-P(x,t)]
\end{aligned}
\qquad (30)
$$

$$\mathcal{J}_3(x,t) = -D(x)\frac{\partial P(x,t)}{\partial x} + v(x)P(x,t)[1-P(x,t)] \qquad (31)$$

We see that even in the case of excluded-volume interactions, the mean-field equations can be cast in the form of continuity equations with suitably defined currents given by Equations (29), (30) and (31). We note that, as it happens with the symmetric exclusion process without quenched disorder, the microscopic exclusion constraint disappears in taking the continuum limit of the master Equation (25) in the absence of external fields, which yields a transport equation, Equation (28), identical to its counterpart with no exclusion, Equation (19) in the case $v(x) \equiv 0$.

Equations (26), (27) and (28) are nonlinear advection-diffusion equation, appropriate for describing the continuum limit of a microscopic exclusion process occurring on a lattice of inequivalent sites in the presence of a field. It is interesting to note that in the case of equivalent sites, which translates to a constant diffusion coefficient, the diffusive parts become linear, i.e., the microscopic exclusion rule is *lost* in the diffusive part. In the case of zero field, one then simply recovers the ordinary diffusion equation for the three jump processes, which, as it is widely known, can be derived from a microscopic jump process with no exclusion rules. This curious observation has been first reported by Huber [70]. If both the diffusion coefficient and the drift velocity are constant, Equations (26), (27) and (28) all reduce to

$$\frac{\partial P}{\partial t} = D\nabla^2 P - v\frac{\partial}{\partial x}[P(1-P)] \tag{32}$$

an equation already obtained recently in Simpson et al. [78].

Equations (26), (27) and (28) contain the single-particle probability field $P(x, t)$, which is a number between zero and one. The value $P = 1$ should correspond to the maximum density ρ_M allowed in the system. Thus, more *physical* equations can be obtained by introducing the agent density

$$\rho(x, t) \equiv \rho_M P(x, t) = \frac{\phi_M}{v_1(\sigma/2)} P(x, t) \tag{33}$$

where

$$v_1(r) = \frac{(\pi^{1/2} r)^d}{\Gamma(1 + d/2)} \tag{34}$$

is the volume of a d-dimensional sphere[1] of radius r and ϕ_M is the maximum packing fraction for systems of d-dimensional hard spheres, $\phi_M = 1$ $(d = 1)$, $\phi_M = \pi/\sqrt{12} \approx 0.907$ $(d = 2)$ and $\phi_M = \pi/\sqrt{18} \approx 0.740$ $(d = 3)$ [79]. With these definitions, and using a more general vector notation, Equations (26), (27) and (28) become

$$\frac{\partial \rho(x, t)}{\partial t} = -\nabla \cdot \mathcal{J}_1(x, t) \tag{35}$$

$$\frac{\partial \rho(x, t)}{\partial t} = -\nabla \cdot \mathcal{J}_2(x, t) \tag{36}$$

$$\frac{\partial \rho(x, t)}{\partial t} = -\nabla \cdot \mathcal{J}_3(x, t) \tag{37}$$

with

$$\begin{aligned}\mathcal{J}_1(x, t) = &-\left(1 - \frac{\rho}{\rho_M}\right)\nabla[D(x)\rho(x, t)] - D(x)\left(\frac{\rho}{\rho_M}\right)\nabla\rho(x, t) \\ &+ v(x)\rho(x, t)\left(1 - \frac{\rho}{\rho_M}\right)\end{aligned} \tag{38}$$

$$\begin{aligned}\mathcal{J}_2(x, t) = &\ \rho(x, t)\nabla\left[D(x)\left(1 - \frac{\rho}{\rho_M}\right)\right] \\ &- D(x)\left(1 - \frac{\rho}{\rho_M}\right)\nabla\rho(x, t) \\ &+ v(x)\rho(x, t)\left(1 - \frac{\rho}{\rho_M}\right)\end{aligned} \tag{39}$$

$$\mathcal{J}_3(x, t) = -D(x)\nabla\rho(x, t) + v(x)\rho(x, t)\left(1 - \frac{\rho}{\rho_M}\right). \tag{40}$$

3. EXTENDED CROWDING

In the previous section we described how to derive macroscopic mean-field equations starting from microscopic master equations which account for exclusion effects. In our description we did not take into account size and shape of the agents by prescribing that each molecule occupies a single lattice site and can not move if the target site is already occupied by another particle. To recover a macroscopic continuous description, we performed the limit for vanishing lattice spacing. This strategy amounts to considering agents of vanishing size in the continuum limit. We term this peculiar situation in the macroscopic world *point-like crowding*. As we have shown in the previous section, considerable microscopic information is lost in the continuum limit with point-like agents. The point-like characterization has to be the reason why the mean-field approximation loses the memory of the microscopic exclusion constraint and the diffusion equation is recovered for equivalent sites in the absence of a field. Starting from these premises, we set to work in the *extended crowding* framework, where the finite size of the particles is explicitly accounted for. Operating within this scenario, the exclusion constraint shall be detectable in the mean-field limit even for unbiased motion and homogeneous domain. A reason for employing the *extended crowding* philosophy is that in many biological contexts one has to model the interaction between agents displaying complicated shapes, which are not well represented by spherical particle occupying a single lattice site. Biological macromolecules diffusing in the cytoplasm, or even proliferating cells, for example, are often elongated and rod-shaped, a property that inspired the derivation of microscopic models using *hard rods* as the individual units [80, 81]. This is for example the case of the human peritoneal mesothelial cells modeled in Simpson et al. [80] as hard rods of aspect ratio equal to four. Moreover, when modeling the interaction between multiple species diffusing in the same environment, the differences in shape and dimension of the agents do have an influence on the extent of the collective motion.

The first model for the diffusion of extended particles with exclusion interactions on a one-dimensional lattice was described in Schönherr and Schütz [82] for a general process involving symmetric, as well as asymmetric, hopping dynamics of the rods (the theory is named L-ASEP). Referring to rods of length L, where L has to be interpreted as the aspect ratio between the dimensions of the elongated agent, the authors derive a mean-field equation for the one-dimensional exclusion process. In the absence of a field and for equivalent sites the equation for the

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[1] We emphasize that we use the general terminology of d-dimensional hard spheres. Obviously, these are hard rods in one dimension and hard disks in two.

density of particles reads

$$\frac{\partial \rho}{\partial t} = D_0 \frac{\partial^2}{\partial x^2}\left[\frac{\rho}{1-(L-1)\rho}\right]. \tag{41}$$

The previous equation shows that, at least in one dimension, the extended-crowding procedure yields a modified diffusion term even in the absence of external fields or spatial inhomogeneities. By defining a density-dependent diffusion coefficient, which has to be regarded as a collective diffusivity $D(\rho) = D_0/[(1-(L-1)\rho]^2$, eq. (41) can be reformulated as a nonlinear transport equation:

$$\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x}\left[D(\rho)\frac{\partial \rho}{\partial x}\right]. \tag{42}$$

The nonlinear diffusion Equation (41) has been derived through an ingenious but complicate change of variables based on a quantitative mapping between the L-ASEP and the zero-range process [82]. However, it is interesting to note that it can be regarded as the local-density approximation (LDA) of a simple general property of one-dimensional exclusion processes. As pointed out in 1967 by Lebowitz and Percus [83] concerning bulk properties:

”*For many purposes, however, adding a finite diameter does not introduce any new complications; it merely requires the replacement in certain expressions of the actual volume per particle ρ^{-1} by the reduced volume $\rho^{-1} - \sigma$, i.e., $\rho \to \rho/(1-\sigma\rho)$.*”

In that sense, the quantity $\rho/[1-(L-1)\rho]$ is recognized as an effective density in Ferreira and Alcaraz [84] within the analysis of the velocity of finite sized particles which occupy L units of lattice spacing in one dimension. By performing the substitution

$$\rho(x,t) \to \frac{\rho(x,t)}{[1-(L-1)\rho(x,t)]}$$

in Fick’s law, one recovers (41). Point-like crowding in the mean field approximation corresponds to systems of fully penetrable spheres, while extended-size crowding yields a transport equation suitable for systems of totally impenetrable (hard) objects. We stress that the case of point-like crowding is recovered for agents of aspect ratio $L = 1$. The discussion above which leads to Equation (41) applies to one dimensional systems. Starting from this setting, one can raise the question whether similar arguments might be employed to obtain a modified nonlinear equation accounting for excluded volume effects in the diffusion of hard spheres in two and three dimensions. Unfortunately, the strategy used to recover Equation (41) in Schönherr and Schütz [82] can not be employed to provide a description of the extended crowding in higher dimensions. Several other models have been proposed for two and three dimensional domains [76, 80, 85], starting from stochastic processes enforced with different microscopic rules. Depending on the shape of the agents (hard rods or hard spheres), on the prescribed hopping rules, on the allowed mechanisms for changing the orientation of the agents (rotation or reptation), and on the mean field assumptions made to recover the macroscopic picture, different equations are derived for the density of extended particles in higher dimensions. All models yield however the same qualitative behavior at low densities, suggesting that the diffusion coefficient should increase linearly with the concentration amount.

4. SUMMARY AND DISCUSSION

Crowding and confinement certainly affect diffusion-driven phenomena, and potentially impact a large plethora of distinct applications. Particularly relevant is the study of mobility inside the cell: the complex cellular environment is in fact populated by obstacles and compartments, which impede the particles flowing. Moreover, the cytoplasm is quite densely packed, different molecular species competing for the available spatial resources. Given these premises, it is important to elaborate on plausible theoretical pictures that enable one to adequately capture the constraints imposed by many-body interactions or reflecting the specificity of the embedding, confining environment.

In this paper, we have reviewed a general framework allowing to obtain macroscopic transport equation accounting for excluded volume effects starting from microscopic stochastic exclusion processes. The aim of this procedure is to derive mean-field equations suitable for describing transport processes in many-body systems in highly non-ideal conditions. Two strategies can be identified to carry out this task. The first route, termed *point-like* crowding, leads from standard SEPs to the mean-field Equations (35), (36) and (37). For a homogenous medium in the absence of a field these reduce to a simple diffusion equation, which is why this scenario can be dubbed *point-like* crowding. Only for inequivalent sites and/or in the presence of a field the microscopic exclusion constraint does survive in the mean-field limit. Different is the case of multiple species [86] or recognizable agents [34], where cross-terms appear in the mean field limit due to the fact that particles are made distinguishable. In general, we can state that crowding reflects in the macroscopic limit of the point-like description only if some degree of inhomogeneity is enforced at the microscopic level. Moreover, we have highlighted that in the presence of quenched disorder, i.e., inequivalent sites, there are (at least) three different ways to assign the site dependence of the hopping rates. These correspond to different microscopic stochastic processes and lead to as many different nonlinear advection-diffusion equations in the continuum limit.

The second strategy, named *extended-crowding*, takes inspiration from a modified microscopic exclusion process in one dimension involving extended agents, the so-called L-ASEP [82]. Qualitatively similar equations for the continuous density are found in higher dimensions at moderate concentrations for different shapes of the individual units. Remarkably, for extended objects characterized by a finite size, the blueprint of the crowding persists at the macroscopic level, even for systems defined on homogeneous domains and without external potentials. This observation marks a clear distinction between the two approaches to which we alluded above and points to the potential interest of the extended crowding setting, which, to the best of our knowledge, remains to be largely explored.

AUTHOR CONTRIBUTIONS

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

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