Diffusion of tagged particles in a crowded medium

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Abstract – The influence of crowding on the diffusion of tagged particles in a dense medium is investigated in the framework of a mean-field model, derived in the continuum limit from a microscopic stochastic process with exclusion. The probability distribution function of the tagged particles obeys to a nonlinear Smoluchowski equation, where the force and diffusion terms are determined self-consistently by the concentration of crowders in the medium. Transient sub-diffusive or super-diffusive behaviors are observed, depending on the selected initial conditions, that bridge normal diffusion regimes characterized by different diffusion coefficients. These anomalous crossovers originate from the microscopic competition for space and reflect the peculiar form of the non-homogeneous force term in the governing equation. Our results strongly warn against the overly simplistic identification of crowding with anomalous transport *tout court*.

Introduction. – Diffusion is a fundamental process in nature that describes the spread of particles subject to random forces from regions of high density to regions of low density [1]. The hallmark of diffusive transport is the linear growth in time of the mean square displacement (MSD) of the spreading particles, $\langle \Delta R^2 \rangle \propto t$. This is a simple conclusion that follows directly from the law of conservation of matter (in the form of a continuity equation), when a simple constitutive equation is assumed, stating that the particle current is proportional to the concentration gradient. The latter law, known as the (first) Fick's law, can be regarded as a simple linear-response prescription, thus only appropriate to describe the relaxation of small density fluctuations.

Despite the fact that Fickean diffusion is generally appropriate to describe the spontaneous spatial rearrangement of particles in suspension, deviations are expected to occur in various situations of interest, *e.g.* if fixed obstacles are present (confinement) [2] or when different species compete for the available space at high concentration, a scenario often referred to in cellular biology as *macromolecular crowding* [3–13]. Despite the importance of crowding and confinement effects in diffusion-related mechanisms in chemistry and biology, there is no consensus on the mechanisms through which crowding and confinement fine-tune deviations from the classical Fickean picture. This lively debate is reflected by conflicting experimental reports in the literature concerning the mobility of biomolecules in the cytoplasm and extra-cellular matrix. Some authors maintain that crowding merely slows down transport by reducing the diffusion coefficient but does not alter the MSD exponent [5,12,14,15], while others [10,16–18] contend the identification of crowding in the cytoplasm with anomalous (typically sub-diffusive) transport [19–21], a feature observed in lateral diffusion in cellular membranes [22–24]. In this case one would have $\langle \Delta R^2 \rangle \propto t^\alpha$ with $\alpha < 1$ (sub-diffusion) or $\langle \Delta R^2 \rangle \propto t^\alpha$ with $\alpha > 1$ (super-diffusion). It is worthwhile to underline that

reports of anomalous transport connected to crowding are not limited to sub-diffusion. For example, super-diffusive behaviour has been recorded in the motion of endodermal Hydra cells [25], in the framework of a minimalistic model of random barriers in a percolation network as a tool to mimic diffusion in a crowded environment [26] and also in the case of driven crowded systems [27].

On the experimental side, it is interesting to remark that often claims of anomalous diffusion in three-dimensional crowded environments *in vitro* and *in vivo* rely on fluorescence recovery after photobleaching (FRAP) data that are analyzed through *ad hoc* modifications [17] of standard theories of fluorescence recovery [28,29]. However, to our knowledge no first-principle derivations of fluorescence recovery curves in the anomalous diffusion regime have yet been reported, analogous to the long-known equations derived in the context of normal diffusion [28,29]. Of course, other techniques exist to investigate particle mobility in complex media, such as single-particle tracking, which are less flawed by such problems. Interestingly, such techniques have uncovered anomalous transient regimes crossing over to normal diffusion in crowded and confining *milieux* [30]. The interested reader will find in ref. [31] a recent and exhaustive review of different measurements and simulations reporting anomalous transport in biological media.

As it is often the case, the truth probably reflects an intermediate picture. Possibly, complex (even multiple) crossovers are to be expected between anomalous and normal diffusion [30,32], or, alternatively, one needs to consider complex space- and geometry-dependent diffusion coefficients [33,34], as modeled, *e.g.*, by Fick-Jacobs [35] and related theories [36,37]. However, as it appears clear from the above recollection, the need for further, systematic investigation of transport in crowded and confining media is evident.

A particularly interesting approach to model transport in complex media is to derive macroscopic equations as mean-field approximations of suitable microscopic stochastic processes. In this way, the microscopic constraints imposed by complex environmental factors are *naturally* incorporated in the transport equations [38–42]. For example, in ref. [43] we derived a modified nonlinear equation suitable for describing the mean-field limit of a persistent random walk in a dense environment.

The idea is to move from a space-discrete simple exclusion process specifying the competition for space at the microscopic level. This is an agent-based stochastic model bound to the condition that no two agents can occupy the same site [44–46]. In certain limits, the governing equations obtained through such procedure can be also viewed as nonlinear diffusion equations derived from generalized free-energy functionals [47]. In one-dimensional systems, this setting is also known as *single-file* diffusion [48–51], a well-studied problem [2,50,52–55] which is known to display anomalous transport and other interesting features,

such as violation of the Einstein relation and persistent effects determined by the initial conditions [56].

In this paper we consider the diffusion of tagged particles immersed in a densely populated *milieu* of co-evolving agents, hereafter the *crowders*, as a primer for most fluorescence-based single-molecule tracking experiments. Following an approach inspired from ref. [43], we derive a system of partial differential equations for the mean-field densities of both the tagged particles and the crowders. For the sake of simplicity, we provide the mathematical details of our derivation in one dimension and only report the equations in arbitrary dimension, leaving the details of these in the supplemental online material in ref. [57]. We stress that our focus is not on the one-dimensional case, where, despite exact formulations of hydrodynamic equations exist [58] along with approximate but successful mean-field approaches [58,59], the validity of mean-field descriptions is known to break down in certain cases, such as the prediction of phase diagrams [60], the effects of boundaries [61]. The paper is organized as follows. In the next section we introduce our model and work out the system of coupled mean-field transport equations. Then, we study the spreading of an initially localized collection of tagged particles in one and two dimensions with different starting configurations of the crowders as possible realizations of feasible and interesting experiments. Finally, we summarize our results and stress the important conclusions reported in this paper.

The microscopic model and its mean-field limit. – To simplify the discussion, let us consider a one-dimensional problem. As we will show in the following, the $1D$ derivation can be readily extended to higher dimensions (see supplemental material in ref. [57]) without altering the ensuing physical picture. Let us consider a one-dimensional lattice of spacing a. Each site can be occupied by either a crowder or a tagged particle. We denote with the binary variables $m_i(k)$ and $n_i(k)$ the *occupancies* of site i at time $t = k\Delta t$ for the tagged and crowding particles, respectively. Hence $m_i(k), n_i(k)$ can be either zero or one depending on whether site i is occupied or not by the respective particle.

The stochastic process that governs jumps of the tagged particles can be cast in the following form:

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

Equation (1), and its analogue for species $n_i(k)$, can be regarded as the update rule for a simple Monte Carlo process. If the target site is occupied by either a crowder or a tagged particle, the move cannot occur. The quantities $z_i^\pm$ are variables that take the value 0 or 1 depending on a random number ξ_i uniformly distributed between 0 and 1. By considering homogeneous jump probabilities, $q_j^\pm = q$

$$
\begin{aligned}
\rho_i(k+1) - \rho_i(k) ={}& q\left(\rho_{i-1}(k) + \rho_{i+1}(k)\right)\left[1 - \rho_i(k)\right]\left[1 - \phi_i(k)\right] \\
& - q\,\rho_i(k)\left[2 - (\rho_{i-1}(k) + \rho_{i+1}(k)) - (\phi_{i-1}(k) + \phi_{i+1}(k)) + \phi_{i+1}(k)\rho_{i+1}(k) + \phi_{i-1}(k)\rho_{i-1}(k)\right], \\
\phi_i(k+1) - \phi_i(k) ={}& w\left(\phi_{i-1}(k) + \phi_{i+1}(k)\right)\left[1 - \phi_i(k)\right]\left[1 - \rho_i(k)\right] \\
& - w\,\phi_i(k)\left[2 - (\phi_{i-1}(k) + \phi_{i+1}(k)) - (\rho_{i-1}(k) + \rho_{i+1}(k)) + \phi_{i+1}(k)\rho_{i+1}(k) + \phi_{i-1}(k)\rho_{i-1}(k)\right], \quad (3)
\end{aligned}
$$

for $j = i, i \pm 1$, one can formally write

$$
\begin{aligned}
z_{i-1}^{+} &= \theta(\xi_i) - \theta(\xi_i - q), \\
z_{i+1}^{-} &= \theta(\xi_i - q) - \theta(\xi_i - 2q), \\
z_{i}^{+} &= \theta(\xi_i - 2q) - \theta(\xi_i - 3q), \\
z_{i}^{-} &= \theta(\xi_i - 3q) - \theta(\xi_i - 4q), \quad (2)
\end{aligned}
$$

where $\theta(x)$ is the Heaviside step function and we are assuming $q \leq 1/4$. Equations (2) entail $\langle z_j^{\pm} \rangle = q$, where $\langle \dots \rangle$ denotes an average over many values of ξ_i for a fixed configuration $\{n_i, m_i\}$. The above process is entirely determined by the jump probabilities q, which we here assume constant and homogeneous.

A (discrete-time) master equation can be obtained by averaging over many Monte Carlo realizations performed according to the rule (1) and starting from the same initial condition (we denote this average by $\langle\langle \dots \rangle\rangle$). Introducing the one-body occupancy probabilities $\rho_i(k) = \langle\langle m_i(k) \rangle\rangle$ and $\phi_i(k) = \langle\langle n_i(k) \rangle\rangle$ and assuming a mean-field factorization for the two-body and three-body correlations, one finds the following equation:

see eq. (3) *above*

where w denotes the jump probability associated with crowders' motion. To proceed in the analysis, we assume that the concentration of tagged particles is small, $\rho_i \ll 1$. We therefore approximate eqs. (3) as

$$
\begin{aligned}
\rho_i(k+1) - \rho_i(k) ={}& q\left(\rho_{i-1}(k) + \rho_{i+1}(k)\right)\left[1 - \phi_i(k)\right] \\
& - q\rho_i(k)[2 - (\phi_{i-1}(k) + \phi_{i+1}(k))], \\
\phi_i(k+1) - \phi_i(k) ={}& w\left(\phi_{i-1}(k) + \phi_{i+1}(k) - 2\phi_i(k)\right). \quad (4)
\end{aligned}
$$

Note that the microscopic exclusion constraint is lost in the equation for ϕ_i, the crowders occupancy probability. Tagged particles are in fact highly diluted and thus interfere negligibly with the diffusive motion of the crowders.

Let us now move to the continuum. We do so formally by letting $\rho(x,t) = \lim_{a,\Delta t \to 0} \rho_i(k)$ and $\phi(x,t) = \lim_{a,\Delta t \to 0} \phi_i(k)$. In addition we must require $\lim_{a,\Delta t \to 0} qa^2/\Delta t = D_\rho$ and $\lim_{a,\Delta t \to 0} wa^2/\Delta t = D_\phi$, where D_ρ and D_ϕ denote the diffusion coefficients of the tagged particles and the crowders, respectively. Making use of the above definitions, one readily obtains the continuum limit of eqs. (4)

$$
\begin{aligned}
\frac{\partial \phi}{\partial t} &= D_\phi \frac{\partial^2 \phi}{\partial x^2}, \\
\frac{\partial \rho}{\partial t} &= D_\rho \frac{\partial}{\partial x}\left\{\frac{\partial}{\partial x}\left[(1-\phi)\rho\right] + 2\rho\frac{\partial \phi}{\partial x}\right\}. \quad (5)
\end{aligned}
$$

The mean-field density of crowders ϕ evolves in time following a standard diffusion equation. On the contrary, the density ρ obeys a nonlinear Smoluchowski equation where the density of crowders plays the role of an external potential, which embodies the excluded-volume rules imposed at the microscopic level. In the annexed supplemental material [57] we give an alternative derivation of eqs. (5), following a perturbative calculation inspired by van Kampen system size expansion [62]. We note that the equation for the evolution of ρ has also been derived in ref. [63] for a constant non-homogeneous background field $\phi(x)$.

A derivation analogous to the one described above can be repeated in higher dimensions (see supplemental material), leading to a straightforward generalization of eq. (5),

$$
\begin{aligned}
\frac{\partial \phi(\mathbf{x},t)}{\partial t} &= D_\phi \nabla^2 \phi(\mathbf{x},t), \\
\frac{\partial \rho(\mathbf{x},t)}{\partial t} &+ \nabla \cdot \mathbf{J}(\mathbf{x},t) = 0, \quad (6)
\end{aligned}
$$

where $\mathbf{J} = -D_\rho\{\nabla[(1-\phi)\rho] + 2\rho\nabla\phi\}$ is the total (osmotic plus force) current for the tagged species. In the following section the above equations are integrated numerically, both in one and two dimensions. As we shall demonstrate, the *effective* force term leads to the emergence of sub-diffusive or super-diffusive transients in the dynamics of the tagged species, depending on the chosen initial conditions.

Sub- and super-diffusive transients. – In order to monitor the dynamics of the tagged species, we follow the time evolution of the mean square displacement (MSD) $\mu_2(t)$

$$
\mu_2(t) = \int \rho(\mathbf{x},t)|\mathbf{x} - \langle \mathbf{x} \rangle|^2 \, \mathrm{d}^n\mathbf{x}, \quad (7)
$$

where $\langle \mathbf{x} \rangle = \int \rho(\mathbf{x},t)\mathbf{x}\,\mathrm{d}^n\mathbf{x}$ and n denote the dimension. It is well known that the MSD scales linearly with time for unobstructed diffusion, while a sub-linear growth of the MSD is often interpreted as a direct manifestation of the microscopic competition for available space in crowded media. As we shall prove in the following, this is an overly simplistic picture, as more complex scenarios can easily be obtained by direct integration of eqs. (5), where nonlinear MSDs emerge only as *transient* regimes. We are particularly interested in a specific class of initial condition, symmetric in the domain of definition, so that $\langle \mathbf{x} \rangle = 0$.

Let us first illustrate the one-dimensional case. At time $t = 0$, the tagged species is localized at the origin, while
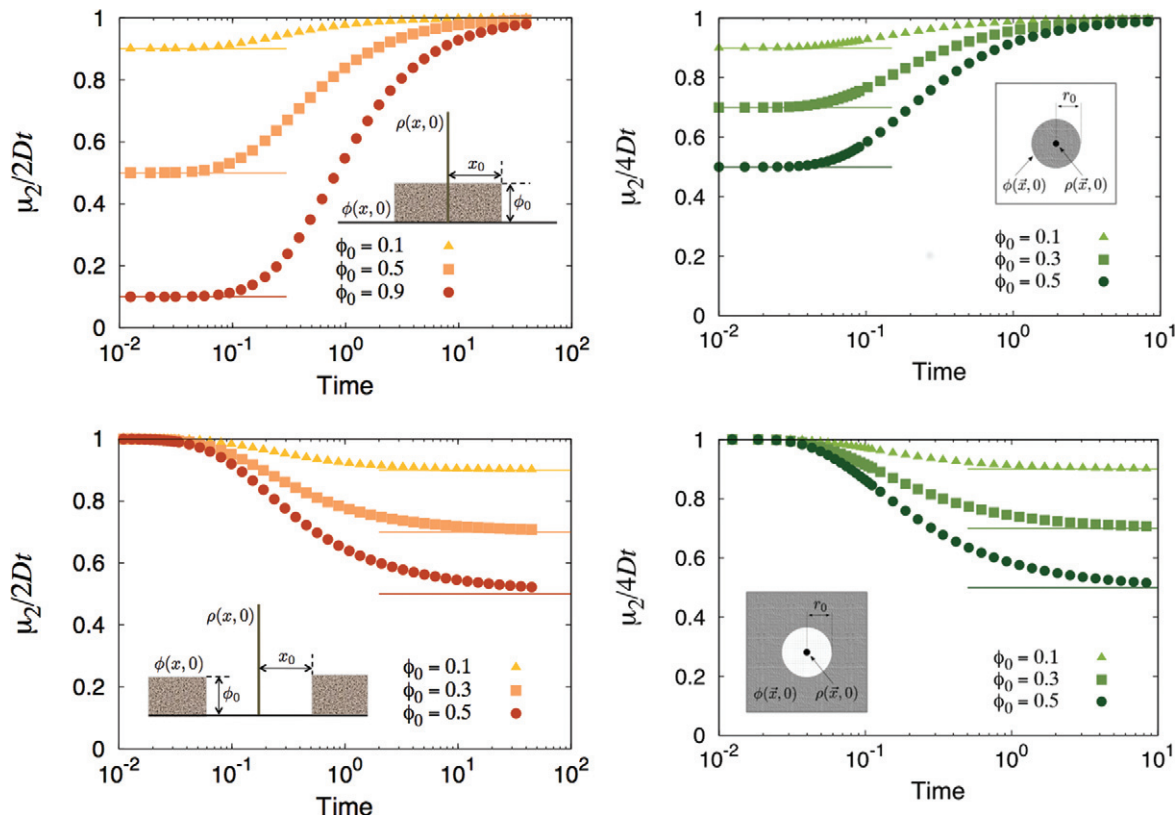
Fig. 1: (Color online) Rescaled MSD of the tagged species as function of time for different crowding strengths in $1D$ (left panels) and $2D$ (right panels). Time is expressed in units of $\tau_1 = x_0^2/2D$ ($1D$) and $\tau_2 = r_0^2/2D$ ($2D$).

the crowders populate a compact domain also centered at the origin. In formulae, $\rho(x,0) = \delta(x)$, where $\rho(\cdot)$ is Dirac delta, and $\phi(x,0) = \phi_0 \left[\theta(x + x_0) - \theta(x - x_0)\right]$, with $\phi_0 \in [0,1]$ gauging the crowding strength (see inset in the upper-left panel of fig. 1). From here on, as a further simplification, we assume $D_\rho = D_\phi = D$.

Figure 1 shows the rescaled MSD of the tagged species as a function of time as obtained by integrating eqs. (5) numerically. At short times, the tagged species is immersed in the almost uniform sea of surrounding crowders. Since ϕ is approximately constant, the tagged particles diffuse normally with an effective diffusion coefficient equal to $D(1 - \phi_0)$. In the long-time limit, the crowders are evenly spread over the one-dimensional support (which we imagine closed but very large so as to neglect boundary effects). Consequently, the density ϕ is small and its contribution can be neglected in the Smoluchowski equation for the evolution of ρ (zero force). Again, we recover normal diffusion, but with a larger diffusion coefficient D. In short, the rescaled MSD $\mu_2/2Dt$ is close to $(1 - \phi_0)$ at short times and converges asymptotically to 1. The two regimes of normal diffusion appear bridged by a super-diffusive crossover.

It is remarkable, and to some extent counter-intuitive, that a super-diffusive transient is found in a model accounting for crowding in the absence of driving. In fact, excluded-volume interactions among diffusing agents are customarily believed to lead to slower-than-diffusive

spread of concentrations. We observe that the time duration of the super-diffusive transient increases quadratically with x_0, the width of the initial density of crowders.

Of course, the origin of the observed dynamics can be traced back to the force term in the current of tagged particles. The effective force $F(x,t) = -\partial\phi(x,t)/\partial x$ induced by the crowders acts as a systematic bias in the evolution of the density ρ. Initially, ρ evolves freely, as $\phi(x,t) \simeq \phi_0$ for all values of x where ρ is non-zero. Then, after a time of the order of $\tau \propto x_0^2$, the support of ρ extends to a domain where it is no longer possible to assume $\phi(x,t)$ constant. In particular, $\partial\phi(x,t)/\partial x < 0$ for $x > 0$ and $F(x,t) < 0$ when $x < 0$, which implies $F(x,t) > 0$, hence a force-induced *boost* over the osmotic current. The mean-field force, which stems from the microscopic competition for space between crowders and tagged particles, pulls the distribution ρ away from the origin, stretching the right (left) tail towards the direction of positive (negative) x. This leads to the super-diffusive transient shown in fig. 1.

A dual situation can be imagined yielding a sub-diffusive transient. To this end, let us consider the crowders to be initially distributed uniformly in a (large) one-dimensional domain of size $2L$. At time $t = 0$, the crowders that populate a segment of width $2x_0$, centered around the origin, are removed from the system. This amounts to considering the initial distribution $\phi(x,0) = \phi_0 \left[1 - \theta(x + x_0) + \theta(x - x_0)\right]$ (see inset in the bottom left panel of fig. 1). At short times, the

diffusion of tagged particles is not affected by the crowders. The rescaled MSD $\mu_2/2Dt$ is hence approximately equal to one and stays constant over a finite time window of order x_0^2/D. At long times, the crowders will have approximately relaxed to the uniform concentration $\phi_L = \phi_0(1 - x_0/L)$. Hence, the tagged particles will find themselves diffusing in a uniform medium with a reduced diffusion coefficient $D(1 - \phi_L)$. The bottom panel of fig. 1 confirms our reasoning, as the rescaled MSD $\mu_2/2Dt$ is seen to decrease monotonously, interpolating between the initial plateau $\mu_2/2Dt = 1$ and the final value $\mu_2/2Dt = (1 - \phi_L) < 1$. In this case, one thus observes a sub-diffusive crossover. In fact, in this case $\partial\phi(x,t)/\partial x > 0$, for $x > 0$, which implies $F(x,t) < 0$, *i.e.* an effective force that opposes the osmotic thrust to delocalization.

Let us now turn to considering the spreading of tagged particles in two dimensions. To this end, we consider a straightforward generalization of the initial conditions discussed above, as exemplified by the cartoons reported in fig. 1 (right panels). Sub and super-diffusive transients are again observed depending on the initial conditions, in stringent analogy with what observed in one dimension. Along the same lines, the observed behavior can be rationalized in terms of the effective force on the tagged species caused by the crowders. In this case, the total radial current is $J_r = -D\{\nabla_r[(1 - \phi)\rho] + 2\rho\nabla_r\phi\}$. Again, we see that an effective force in the radial direction $F = 2\nabla_r\phi$ arises when the tagged particles diffuse into regions of changing density of crowders, yielding a current boost (super-diffusive crossover) or a drop (sub-diffusive crossover) depending on the initial conditions.

In the online supplemental material [57] we compare the mean-field prediction with the results of Monte Carlo simulations of the spreading of an initially localized tagged particle in two dimensions. As it can be appreciated from fig. 1 in the online supplemental material, the agreement is excellent, confirming the soundness of the mean-field approach.

Conclusion. – The study of molecular diffusion under crowded conditions represents a particularly crucial topic for its applications to cellular biology. At high density, particles diffusion is impeded and excluded-volume effects may no longer be ignored. In this paper we have considered the diffusive dynamics of an ensemble of inert particles, the *tagged* species, immersed in a crowded background of co-evolving agents. This is a quite general scenario, which can be invoked to describe different experimental conditions. The tagged particles are assumed to be sufficiently diluted, a working hypothesis that allows us to neglect their feedback on the crowders. As a consequence, the continuum density of the tagged species is governed by a nonlinear Smoluchowski equation, where the diffusion coefficients and the external potential are self-consistently determined by the time-dependent concentration of crowders.

In the background, the crowders are undisturbed and undergo normal diffusion.

Working within this framework, we have shown that transient sub-diffusive as well as super-diffusive regimes can emerge, depending on the specific initial conditions. When the crowders are uniformly dispersed in the container, but removed from an isolated patch where the tagged species is initially confined, a sub-diffusive scaling for the mean square displacement is observed. This crossover regime persists within a finite, possibly very long time window. On the contrary, if the tagged agents are trapped inside a uniform patch of crowders inside a much larger, otherwise empty container, excluded-volume interactions produce an effective force term in the current of tagged particles, that accelerates their spread with respect to the osmotic current. We observe that crowding is rather often associated with anomalous slowing down of transport, *i.e.* sub-diffusion. It is therefore surprising that the dynamical interference between crowders and tagged particles may result in super-diffusive dynamics for certain choices of the initial condition. The situations described above can be easily recreated in laboratory experiments, by initially confining the particles, including those whose evolution is to be tracked, within a finite portion of the available space.

In summary, our results prove that both super-diffusion and sub-diffusion transients can occur as a result of crowding in one and higher dimensions in the absence of driving, depending on the initial conditions. These findings strongly warn against the simplistic identification of crowding with anomalous transport *tout court*.

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