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Brownian motion in a growing population of ballistic particles

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We investigate the motility of a growing population of cells in a idealized setting: we consider a system of hard disks in which new particles are added according to prescribed growth kinetics, thereby dynamically changing the number density. As a result, the expected Brownian motion of the hard disks is modified. We compute the density-dependent friction of the hard disks and insert it in an effective Langevin equation to describe the system, assuming that the inter-collision time is smaller than the timescale of the growth. We find that the effective Langevin description captures the changes in motility in agreement with the simulation results. Our framework can be extended to other systems in which the transport coefficient varies with time.

INTRODUCTION

The statistical description of the movement of living organisms enables their quantitative study. Notable examples include the study of animal migration [1] and the motion of bacteria [2]. Since more than a decade there has been increasing interest in self-propelled particles whose ability to provide their own propulsion results in systems where time-reversibility and energy conservation cannot always be satisfied [3, 4]. Furthermore, including interactions between organisms or with the environment can lead to the emergence of biological phase transitions and self-organization [5–7]. Besides sourcing energy for their own motion, another important characteristic of many such organisms is their ability to reproduce. This can under some circumstances impact the properties of motion of an active population, as the amount of interactions taking place will depend on the population density at a given time. One conspicuous example of such a system is a culture of motile cells on a spatially confined substrate. This type of in vitro setup is not uncommon, employed for example in the study of human cell migration [8, 9] related to tasks such as tissue growth [10], wound healing [11], and vascularization [12], as well as in studies concerning the migration of tumour cells in metastatic cancer [13]. In many such cases the motility of the individual cells is inextricably linked to the surrounding population growth, and measurements of related statistical quantities should be interpreted in the context of this dependence.

Here we introduce a simple parameter-free generalizable model for the averaged effect of growth in a system of repulsively interacting particles. Based on the notion of particles obstructing one another's paths, we adapt the Langevin equation for Brownian motion to include a dependence on the particle volume density. We show how this formalism effectively models the statistics of a 2D gas of hard-disks subject to particle number growth through comparison with stochastically seeded simulations of ballistically moving hard disks undergoing elastic interactions. Because this approach remains agnostic as to both the characteristics of the particles' motion between interactions as well as the mechanism by which the particle density varies, it is potentially applicable in any situation where there is an interest in studying properties of statistical motility in a population subject to density dynamics.

MODELING AND METHODS

Dynamical model

We consider a two-dimensional system of hard disks with diameter d and mass m. The disks interact through elastic collisions only and have ballistic trajectories in between. As the disks all have identical mass, this quantity plays no role and is set to $m = 1$. In this work, we are interested in properties of the hard disk system dependent on the confluency (the proportion of surface occupied by the particles)

$$c(t) = n(t)\pi d^2/4 , \quad (1)$$

where $n(t)$ is the number of particles per unit area at time t. Growth of the population is envisioned as the arrival of randomly spaced particles according to a predetermined growth curve which – in keeping with the model of a cell population in culture – we take to be the logistic curve

$$n(t) = \frac{kn_0 e^{\rho t}}{k + n_0(e^{\rho t} - 1)} \ , \tag{2}$$

with n_0 and k respectively the initial and the maximal particle densities, and ρ the rate of growth.

Diffusion coefficient for dilute hard disks

To estimate the motility at a given particle density n we compute the velocity autocorrelation function (VACF) of a single test particle:

$$\langle v(t) \cdot v(t+\tau) \rangle = \cos\theta(\tau)\, s(t)s(t+\tau) \ , \tag{3}$$

where v is the 2D velocity of a particle, the brackets indicate ensemble averaging, s is the norm of the particle's velocity vector – the particle speed – and $\theta(\tau)$ the angle between its velocities at t and $t+\tau$. $\cdot$ is the scalar product. If the particle moves undisturbed in the short time τ, then $\theta(\tau) = 0$, $s(t+\tau) = s(t)$, and thus $v(t) \cdot v(t+\tau) = s^2(t)$. If on the other hand the particle undergoes a collision in this time, the autocorrelation will depend on the form of the interaction. Assuming isotropic interactions, there will be a class of systems for which $\theta(\tau)$ can be modelled as a random uniformly distributed angle independent of the particle speed, such that the many particle average $\langle \cos\theta(\tau) \rangle$ and thus $\langle v(t)v(t+\tau) \rangle_{\text{coll}}$ vanishes. Then for a large ensemble only those particles which have not yet collided will contribute to the VACF. For a system in thermal equilibrium the occurrence of collisions may reasonably be modelled as a memoryless stochastic process, so that the inter-collision time is given by the exponential distribution: $\mathbb{P}\{\text{no collision in } \tau\} = e^{-\lambda\tau}$ with $1/\lambda$ the average inter-collision time. The VACF is thus

$$\langle v(t) \cdot v(t+\tau) \rangle = \left\langle s^2(t) \right\rangle e^{-\lambda\tau} \ . \tag{4}$$

By integrating Eq. (4), we obtain the spatial diffusion coefficient $\mathcal{D} = \left\langle s^2(t) \right\rangle \lambda^{-1}/2$, so that in absence of growth we expect a linear mean squared displacement in equilibrium: $\left\langle x(t)^2 \right\rangle = 4\mathcal{D}t$.

Effective Langevin dynamics

We establish here the link between the diffusion coefficient computed in the previous section and the Langevin equation (LE) in two dimensions:

$$\frac{\mathrm{d}v(t)}{\mathrm{d}t} = -\gamma v(t) + \sqrt{2D}\xi(t) \ , \tag{5}$$

where $\xi(t)$ is white noise [14]:

$$\langle \xi(t) \rangle = 0 \quad \text{and} \quad \langle \xi_i(t)\xi_j(t') \rangle = \delta(t-t')\delta_{i,j} \ , \tag{6}$$

γ is the friction coefficient and D is the noise intensity. Integration of Eq. (5) provides the autocorrelation function

$$\langle v(t) \cdot v(t+\tau) \rangle = \frac{2D}{\gamma} e^{-\gamma\tau} \ . \tag{7}$$

For $\tau = 0$ we find the second moment of the speed

$$\left\langle s(t)^2 \right\rangle = 2D/\gamma \ . \tag{8}$$

Inserting this back into Eq. (7) and comparing with Eq. (4), we see that the autocorrelation functions for the Brownian particle and the ensemble of interacting particles are in fact equal upon identification of $\lambda = \gamma$. We use this correspondence to interpret the Langevin dynamics of Eq. (5) as an averaged description of the particle paths in the interacting ensemble, with the expected time between collisions encoded in the Brownian friction coefficient as $1/\gamma$. For the simple dynamical model of hard disks, we can now estimate the friction and noise intensity directly from the physical parameters so that – in equilibrium – we can use Eq. (5) without fitting any parameter. For a particle density n, the mean inter-collision time is related to the mean free path l, which in turn can be coupled to the density (with $\sigma = 2d$ the collisional cross section) [15]:

$$l = \frac{\langle s \rangle}{\gamma} = 1/\sqrt{2}\sigma n \ . \tag{9}$$

At equilibrium, the speed distribution can be shown to approach the Rayleigh distribution [4] with mean

$$\langle s \rangle = \sqrt{D\pi/2\gamma} \ , \tag{10}$$

and the fluctuation-dissipation relation dictates the relation between γ and D

$$k_B T = D/\gamma \ . \tag{11}$$

Thus combining Eqs. (9), (10), and (11), we may write the coefficients in the Langevin equation in terms of the particle density and system temperature:

$$\begin{cases} \gamma = \sqrt{\pi k_B T}\, \sigma n \\ D = k_B T \gamma \end{cases} \tag{12}$$

and we obtain the diffusion coefficient

$$\mathcal{D} = D/\gamma^2 = \sqrt{k_B T/\pi}\, (\sigma n)^{-1} \ . \tag{13}$$

Up to this point we have silently assumed that the particle density of the system is constant, both in the derivation of the velocity autocorrelation as well as in the assumption of an equilibrium speed distribution. It is however worth investigating to what extent Eq. (12) holds if the particle density varies slowly. For example, we might envision a population of cells undergoing divisions, where the growth rate is slow enough that many collisions occur in between mitotic events. If then the equilibrium assumption remains adequate, the LE in Eq. (5) can be used with time-dependent coefficients $\gamma(t)$ and $D(t)$ to obtain statistical properties of the particles subject to the growth function $n(t)$.

Simulations

To test the validity of this approach we also study the hard disk system with event-driven simulations. We place the disks in a periodic domain and assign random initial velocities such that the average kinetic energy per particle is k_BT. Due to the randomness of the initial velocity distribution the system will generally present a nonzero center-of-mass drift, which we remove before initiating dynamics. The simulation then proceeds in an event-driven manner. At the start of each increment, all particles are moved according to their current velocity. Next, potential collisions (detected as overlapping surfaces) are identified and sorted in order of occurrence. Collisions are then performed successively – with newly occurring overlaps being similarly detected, timed, and added to the queue – until all overlaps have been treated. Population growth is implemented by the introduction of new particles at random positions in the simulation area and fixed times according to the growth curve in Eq. (2). Newly birthed particles are added with initial speed $\sqrt{2k_BT}$ to ensure the system evolves isothermally [16]. To compare simulation results of the density-varying system with the Langevin model (12) we compute stochastic realizations of the equation with the SOSRI algorithm [17] using the Julia package DifferentialEquations.jl [18].

MODEL RESULTS

For systems where the particle density remains fixed, we find the accuracy of the Langevin model to depend on the confluency. The predicted diffusion coefficient agrees well with simulations of the hard-disk particle dynamics for $c \leq 0.1$, whereas for higher particle densities the error grows as the available volume is increasingly occupied (Figure 1). The origin of this error can be found in our assumption of independent collisions with a well defined mean free path (9), which gives a poor representation of the hard-disk system when its value approaches the order of the collisional cross section. In the low density limit the model's validity is principally restricted by the timescale of interest, since if the characteristic collision time $1/\gamma$ is larger than the timescale the individual particle motion is effectively ballistic and Brownian motion does not apply. However for a large number of particles the ensemble statistics remained in agreement even for the lowest density investigated ($c = 0.01$) at a timescale of a hundredth of the characteristic time.

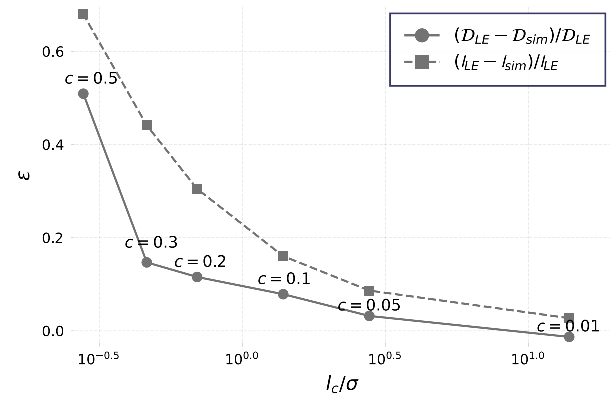

Figure 1. The relative errors on the diffusion coefficient $\mathcal{D}$ predicted by Eq. (13) and the mean inter-collision distance l predicted by Eq. (9) with respect to simulations at fixed density, as a function of the ratio of the inter-collision distance to the collisional cross section. The simulations consisted of 2000 individual particles for each confluency investigated.

When population growth is introduced the particle density increases and the Langevin parameters γ and D are no longer constant in time. We investigate the validity of the density-dependent model with respect to the hard-disk system under isothermal growth by simulating the addition of particles at randomly distributed positions at a rate prescribed by the growth function. As an illustrative example we consider the case of logistic growth (2) for different rate parameters ρ, shown in Figure 2. We observe that as the density rises the inter-collision times decreases, resulting in a relative decrease of the diffusive motion during the growth period, whereas once the maximal population density is reached the diffusion regains a linear character. As intended, the Langevin prediction shows good agreement with the particle simulations in the quasi-equilibrium parameter regime (Figure 2), where the rate of growth is smaller than the time between collisions. Interestingly, the model maintains similar accuracy even if the growth rate is significantly higher as a growth rate of up to 25 times the inter-collision time was tested.

DISCUSSION

We have shown how a 2D system of ballistic hard-disk particles subject to population level density dynamics can be modeled by an effective Brownian Langevin equation, in which the friction γ and force intensity D are made to depend explicitly on the particle density of the system. This parameter-free dependence is obtained by employing a classic model for the mean inter-collision distance that – with the assumption of memoryless colli-

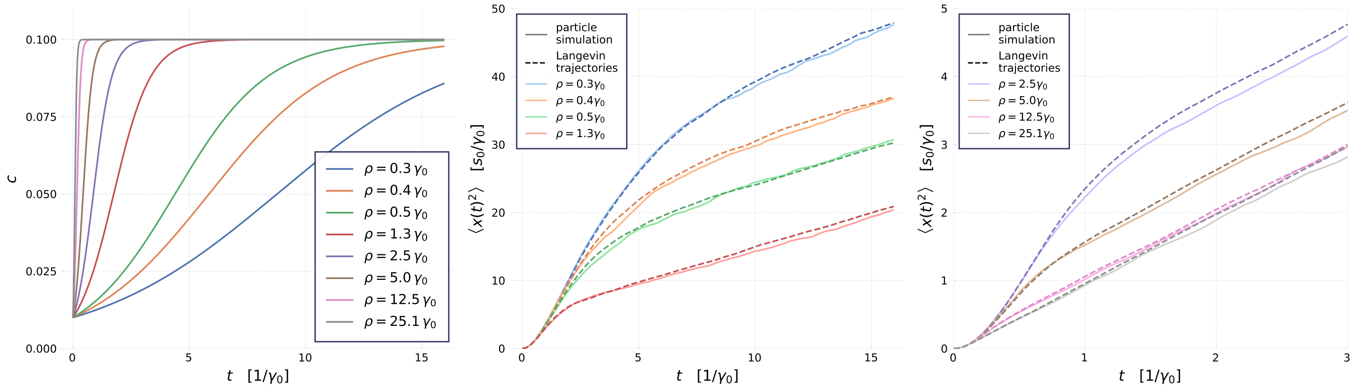

Figure 2. Dynamics of particles in populations with density subject to the logistic growth function (2). Results for different growth rates ρ are shown in populations with initial confluency $c = 0.01$ (1000 particles) and maximal capacity $c = 0.1$ (10'000 particles). Time and distance are presented in units of the average inter-collision time for the initial density $1/\gamma_0$ and the average inter-collision distance s_0/γ_0. Left: confluency over time. Middle/right: mean squared displacement obtained from simulations of the LE and measured from particle simulations, for growth rates that are slow (middle) and fast (right) compared to the inter-collision time.

sions – arises in the velocity autocorrelation function of the LE. By comparison with simulations of the system, we showed the model to be accurate up to a confluency of around 0.1. For higher densities we found the error on the mean inter-collision distance to grow rapidly with confluency, implying that the LE could potentially remain accurate under a different model for the free path lengths.

To test the validity of the LE in the case of a dynamically varying density – where the assumption of thermal equilibrium is in principle no longer valid – we investigated a model system where new particles are added according to a logistic growth function. The mean-squared displacement under these conditions becomes non-linear, reflecting the changing dynamic parameters. Comparing statistics from numerical simulations of the density dependent LE with the particle simulations showed agreement up to relatively high growth rates.

While the specific system studied here may appear restrictive, it is illustrative of the potential for modeling the effect of stochastically occurring interactions within a density-varying population as an effective random walk. The application of the LE described here need not be constrained to the case of ballistically moving particles, as it can simply be added to the LE of more complex motions, serving as a population effect on the movement of individual particles. With growing interest in biological systems where proliferation is present, this approach provides a useful alternative to modeling interactions directly.

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