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 intercollision 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.

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I. 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]. Over the past decades 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 [5–8]. 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 [9,10] related to tasks such as tissue growth [11], wound healing [12], and vascularization [13], as well as in studies concerning the migration of tumor cells in metastatic cancer [14]. 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 two-dimensional (2D) gas of hard disks subject to particle number growth through a 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 the properties of statistical motility in a population subject to density dynamics.

II. MODELING AND METHODS

A. Dynamical model

We consider a two-dimensional system where the Brownian particles are hard disks with diameter d and mass m each occupying a finite surface $\pi d^2/4$ (Fig. 1). The disks interact through elastic collisions only and have ballistic trajectories in between. As the disks all have identical mass, this

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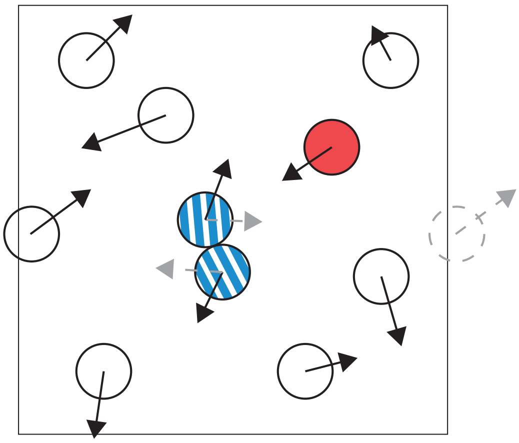

FIG. 1. Schematic illustration of the model. The particles (represented as circles) are hard disks of finite area moving at fixed speed in the periodic domain (the dashed grayed-out particle is reinserted at its periodic location). Their ballistic trajectories are interrupted by momentum-conserving collisions (blue semisolid circles). New particles (red solid circle) are inserted at random nonoccupied positions, with velocity given by the corresponding thermal distribution, and at times prescribed by the growth kinetics.

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 S occupied by the particles)

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

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. We limit ourselves to a confluency $c(t) \ll 1$, effectively considering a dilute regime for the collisional dynamics. This limitation is also necessary to make sure that new particles can be inserted easily in the system.

B. 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,

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

where $\mathbf{v}$ is the 2D velocity of a particle, the angle brackets indicate ensemble averaging, s is the norm of the particle's velocity vector (the particle speed), $\theta(\tau)$ is the angle between its velocities at t and $t+\tau$, and $\cdot$ 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 $\mathbf{v}(t)\cdot\mathbf{v}(t+\tau) = s(t)^2$. 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 modeled as a random uniformly distributed angle independent of the particle speed, such that the many-particle average $\langle\cos\theta(\tau)\rangle$ and thus $\langle \mathbf{v}(t)\mathbf{v}(t+\tau)\rangle_{\text{coll}}$ 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 modeled as a memoryless stochastic process, so that the intercollision time is given by the exponential distribution, $\mathbb{P}\{\text{no collision in } \tau\} = e^{-\lambda\tau}$ with $1/\lambda$ the average intercollision time. The VACF is thus

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

By integrating Eq. (4), we obtain through the Green-Kubo relation (see for instance the Ornstein-Uhlenbeck example in Ref. [15]) the spatial diffusion coefficient

$$\mathcal{D} = \frac{1}{2}\int_0^\infty \langle \mathbf{v}(t)\cdot\mathbf{v}(t+\tau)\rangle d\tau = \frac{\langle s(t)^2\rangle}{2\lambda} \tag{5}$$

(where the factor $1/2$ comes from the fact that we work in two spatial dimensions), so that in the absence of growth we expect a linear mean-squared displacement (MSD) in equilibrium: $\langle \mathbf{x}(t)^2\rangle = 4\mathcal{D}t$.

C. 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,

$$\frac{d\mathbf{v}(t)}{dt} = -\gamma\mathbf{v}(t) + \sqrt{2\eta}\,\xi(t), \tag{6}$$

where $\xi(t)$ is white noise [15],

$$\langle\xi(t)\rangle = 0 \quad \text{and} \quad \langle\xi_i(t)\xi_j(t')\rangle = \delta(t-t')\delta_{i,j}, \tag{7}$$

γ is the friction coefficient, and η is the noise intensity. Integration of Eq. (6) provides the autocorrelation function

$$\langle \mathbf{v}(t) \cdot \mathbf{v}(t+\tau)\rangle = \frac{2\eta}{\gamma}e^{-\gamma|\tau|}. \tag{8}$$

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

$$\langle s(t)^2\rangle = 2\eta/\gamma. \tag{9}$$

Inserting this back into Eq. (8) 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. (6) 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. (6) without fitting any parameter. In the dilute regime, we can express the mean intercollision time as a function of the mean free path l, which in turn can be coupled to the particle density n (with $\sigma = 2d$

the collisional cross section) [16],

$$l = \frac{\langle s \rangle}{\gamma} = 1/\sqrt{2}\sigma n. \tag{10}$$

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

$$\langle s \rangle = \sqrt{\eta\pi/2\gamma}, \tag{11}$$

and the fluctuation-dissipation relation dictates the relation between γ and η,

$$k_B T = \eta/\gamma. \tag{12}$$

Thus combining Eqs. (10)–(12), we may write the coefficients in the Langevin equation in terms of the particle density and system temperature,

$$\gamma = \sqrt{\pi k_B T}\sigma n, \quad \eta = k_B T\gamma. \tag{13}$$

Using the derivations above and Eqs. (5) and (9), we obtain the spatial diffusion coefficient

$$\mathcal{D} = \eta/\gamma^2 = \sqrt{k_B T/\pi}\,(\sigma n)^{-1}. \tag{14}$$

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. (13) 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. (6) can be used with time-dependent coefficients $\gamma(t)$ and $\eta(t)$ to obtain statistical properties of the particles subject to the growth function $n(t)$.

While solving the LE with time-dependent coefficients is difficult, we can also investigate the validity of an overdamped approximation, which corresponds to taking $\frac{d*}{d\mathbf{v}(t)}t = 0$. This permits a straightforward solution of the LE, as the corresponding Fokker-Planck equation is simply the diffusion equation with time-dependent diffusion coefficient Eq. (14). This can be solved in the usual manner and results in the MSD,

$$\langle \mathbf{x}(t)^2 \rangle = 4\int_0^t \mathcal{D}(t')dt'. \tag{15}$$

D. 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 $k_B T$. 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

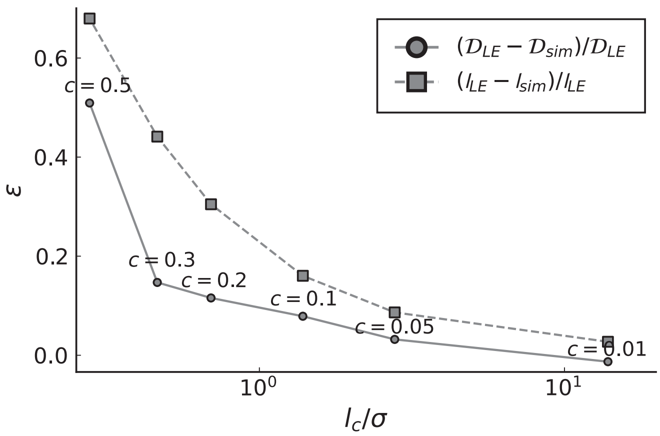

FIG. 2. The relative errors on the diffusion coefficient $\mathcal{D}$ predicted by Eq. (14) and the mean intercollision distance l predicted by Eq. (10) with respect to simulations at fixed density, as a function of the ratio of the intercollision distance to the collisional cross section. The simulations consisted of 2000 individual particles for each confluency investigated.

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 $\sqrt{2k_B T}$ to ensure the system evolves isothermally [17]. To compare simulation results of the density-varying system with the Langevin model (13) we compute stochastic realizations of the equation with the SOSRI algorithm [18] using the JULIA package DifferentialEquations.jl [19].

III. 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 $c \leqslant 0.1$, whereas for higher particle densities the error grows as the available volume is increasingly occupied (Fig. 2). The origin of this error can be found in our assumption of independent collisions with a well-defined mean free path (10), 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.

When population growth is introduced the particle density increases and the Langevin parameters γ and η 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

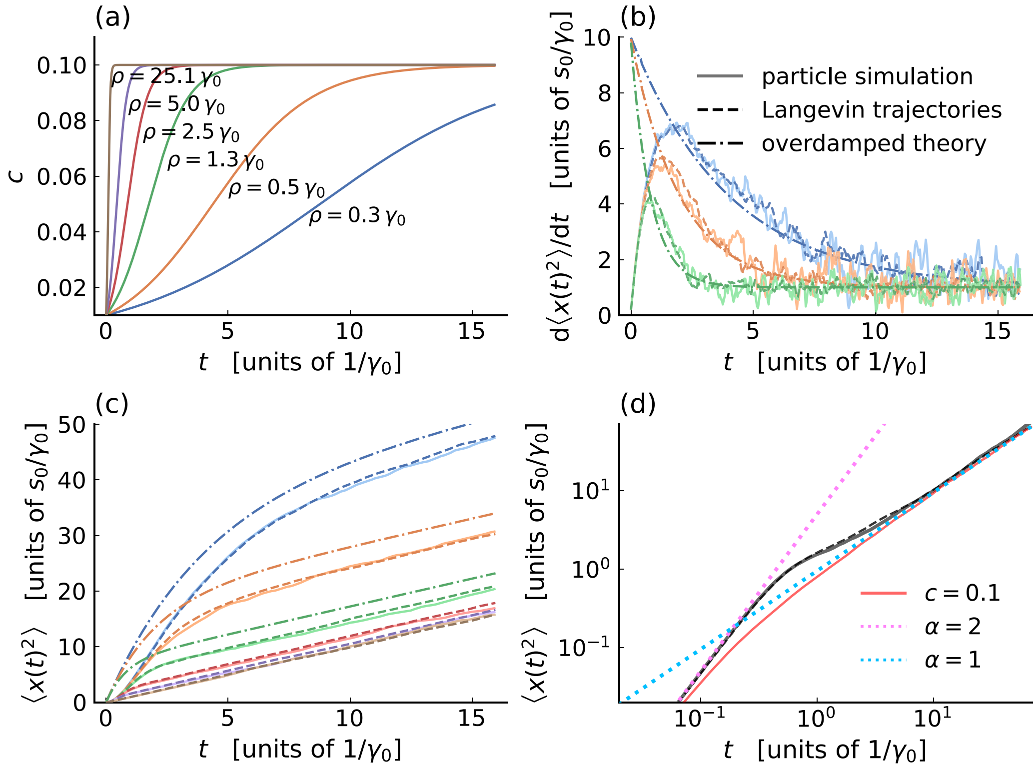

FIG. 3. Dynamics of particles in populations with density subject to the logistic growth function (2). Results for different growth rates ρ are shown in populations with initial confluency $c = 0.01$ (1000 particles) and maximal capacity $c = 0.1$ (10 000 particles). Time and distance are presented in units of the average intercollision time for the initial density $1/\gamma_0$ and the average intercollision distance s_0/γ_0. (a) Confluency over time. (b) Derivative of the MSD obtained from particle simulations (solid lines), simulations of the LE (dashed lines), and predicted by the overdamped approximation (dashed-dotted lines), for the slowest growth rates used in (a), increasing from top to bottom. (c) MSD under all simulated growth rates for particle simulations [same legend as (b); for clarity, the overdamped prediction is not shown for the highest growth rates]. (d) Log-log plot of the MSD under growth rate $\rho = 5.0\gamma_0$, compared to a simulation at fixed confluency $c = 0.1$ (solid red line). Additional trendlines (dotted) $f_\alpha(t) \propto t^\alpha$ are shown to illustrate motion type: $\alpha = 1$ adheres to classical diffusion, whereas $\alpha = 2$ implies ballistic motion.

ρ, shown in Fig. 3(a). We observe that as the density rises the intercollision time decreases, resulting in a decreasing variation of the particle MSD during the growth period and thus apparent subdiffusive motion [Figs. 3(b)–3(d)]. Once the maximal population density is reached, the slope of the MSD becomes constant. Such a linear limit of the functional form of the MSD for large times is an indicator of classical diffusion [Figs. 3(c) and 3(d)].

As intended, simulations of the LE show good agreement with the particle simulations in the quasiequilibrium parameter regime [Fig. 3(c)], where the rate of growth is smaller than the time between collisions. Furthermore, the overdamped approximation of Eq. (15) agrees well with the subdiffusive variation of the MSD, however, as to be expected it does not capture the initial short-time ballistic motion [Fig. 3(b)], resulting in an eventual overestimation of the displacement [Fig. 3(c)]. Interestingly, the LE model maintains similar accuracy even if the growth rate is significantly higher, as a growth rate of up to 25 times the intercollision time was tested.

IV. 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 η 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 intercollision distance that—with the assumption of memoryless collisions—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 intercollision 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 nonlinear, reflecting the changing dynamic parameters. Comparing statistics from numerical simulations of the density-dependent LE with the particle simulations showed agreement up to the highest growth rates investigated. The good correspondence at such growth rates comes as a surprise, considering the equilibrium assumptions used to derive the LE. We can think of a number reasons why this is the case, such as the fact that we insert particles from a thermal distribution at random locations, thus not promoting spatial inhomogeneity, and the dilute nature of the gas. However, we have no formal explanation to elucidate this matter.

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. A generalization to three spatial dimensions would be straightforward, the main difference in the derivation being that the Maxwell-Boltzmann distribution must be taken for the particle speeds. Furthermore, the inclusion of external forces can be achieved by introducing their relevant potentials in the LE. The consideration of more complicated interaction effects—such as for example aligning forces [8] or particle-generated flow fields in a background fluid [20]—likely presents a greater challenge, as the method described here exploits a simple statistical uniformity of interactions, i.e., the particle's direction of motion following a collision modeled as a uniform distribution. Nevertheless, such interactions can in principle be included through multiparticle potentials in the LE, for which various analysis procedures exist in the literature (see, for example, Refs. [6,20], or [7]). Finally, the application of the LE derived 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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[1] K. Pearson and J. Blakeman, *A Mathematical Theory of Random Migration*, Vol. 15 (Dulau and Company, London, 1906).
[2] H. C. Berg, *Random Walks in Biology* (Princeton University Press, Princeton, NJ, 1983).
[3] M. E. Cates, Diffusive transport without detailed balance in motile bacteria: Does microbiology need statistical physics? Rep. Prog. Phys. **75**, 042601 (2012).
[4] P. Romanczuk, M. Bär, W. Ebeling, B. Lindner, and L. Schimansky-Geier, Active Brownian particles, Eur. Phys. J.: Spec. Top. **202**, 1 (2012).
[5] Y. Fily and M. C. Marchetti, Athermal Phase Separation of Self-Propelled Particles with No Alignment, Phys. Rev. Lett. **108**, 235702 (2012).
[6] J. Tailleur and M. E. Cates, Statistical Mechanics of Interacting Run-and-Tumble Bacteria, Phys. Rev. Lett. **100**, 218103 (2008).
[7] J. Stenhammar, A. Tiribocchi, R. J. Allen, D. Marenduzzo, and M. E. Cates, Continuum Theory of Phase Separation Kinetics for Active Brownian Particles, Phys. Rev. Lett. **111**, 145702 (2013).
[8] T. Vicsek, A. Czirók, E. Ben-Jacob, I. Cohen, and O. Shochet, Novel Type of Phase Transition in a System of Self-Driven Particles, Phys. Rev. Lett. **75**, 1226 (1995).
[9] M. Lintz, A. Muñoz, and C. A. Reinhart-King, The mechanics of single cell and collective migration of tumor cells, J. Biomech. Eng. **139**, 021005 (2017).
[10] P.-H. Wu, D. M. Gilkes, and D. Wirtz, The biophysics of 3D cell migration, Annu. Rev. Biophys. **47**, 549 (2018).
[11] C. J. Weijer, Collective cell migration in development, J. Cell Sci. **122**, 3215 (2009).
[12] P. Friedl and D. Gilmour, Collective cell migration in morphogenesis, regeneration and cancer, Nat. Rev. Mol. Cell Biol. **10**, 445 (2009).
[13] W. Risau, Mechanisms of angiogenesis, Nature (London) **386**, 671 (1997).
[14] K.-C. Lin, G. Torga, Y. Sun, R. Axelrod, K. J. Pienta, J. C. Sturm, and R. H. Austin, The role of heterogeneous environment and docetaxel gradient in the emergence of polyploid, mesenchymal and resistant prostate cancer cells, Clin. Exp. Metastasis **36**, 97 (2019).
[15] C. W. Gardiner, *Handbook of Stochastic Methods for Physics, Chemistry, and the Natural Sciences*, 3rd ed., Springer Series in Synergetics (Springer, Berlin, 2004).
[16] S. Chapman and T. G. Cowling, *The Mathematical Theory of Non-uniform Gases: An Account of the Kinetic Theory of Viscosity, Thermal Conduction and Diffusion in Gases*, 3rd ed. (Cambridge University Press, Cambridge, U.K., 1990), pp. 87–88.
[17] The simulation code, written with the JULIA programming language, is available at https://github.com/natevmp/particle-crowding.
[18] C. Rackauckas and Q. Nie, Stability-optimized high order methods and stiffness detection for pathwise stiff stochastic differential equations, in *2020 IEEE High Performance Extreme Computing Conference (HPEC)* (IEEE, New York, 2020), pp. 1–8.
[19] C. Rackauckas and Q. Nie, Differentialequations.jl—a performant and feature-rich ecosystem for solving differential equations in JULIA, J. Open Res. Softw. **5**, 15 (2017).
[20] A. Baskaran and M. C. Marchetti, Statistical mechanics and hydrodynamics of bacterial suspensions, Proc. Natl. Acad. Sci. U.S.A. **106**, 15567 (2009).