

## Statistical Mechanics of Interacting Run-and-Tumble Bacteria

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We consider self-propelled particles undergoing run-and-tumble dynamics (as exhibited by *E. coli*) in one dimension. Building on previous analyses at drift-diffusion level for the one-particle density, we add both interactions and noise, enabling discussion of domain formation by “self-trapping,” and other collective phenomena. Mapping onto detailed-balance systems is possible in certain cases.

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Several species of bacteria, including *Escherichia coli*, perform self-propulsion by a sequence of “runs”—periods of almost straight-line motion at near-constant speed ( $v$ )—punctuated by sudden and rapid randomizations in direction, or “tumbles,” occurring stochastically with rate  $\alpha$ . It is no surprise that the resulting class of random walk gives a diffusive relaxation of the number density at large scales [1]. The resulting diffusion constant  $\sim v^2/\alpha$  is vastly larger than that of nonswimming particles undergoing pure thermal motion at room temperature. Therefore, apart from, e.g., the upper limit it imposes on the duration of a straight run (set by rotational diffusion), true Brownian motion can usually be ignored.

Because bacterial diffusion is *not* thermal, the steady-state probability density cannot be written as  $p_s \propto \exp[-H/k_B T]$ , with  $H$  a Hamiltonian, even for a single diffuser. The physicist’s intuition can easily be led astray: for instance, Refs. [2–4] address models (of chemotaxis) comprising noninteracting particles in 1D, with no external forces, but  $v(x)$ ,  $\alpha(x)$  functions of position  $x$ . Instead of a uniform density, as would arise with *any* force-free detailed-balance dynamics, one finds  $p_s(x) \propto 1/v(x)$  [2].

Here we extend previous analyses of run-and-tumble motion to the many-particle level, addressing the roles of noise and interactions. These determine, for instance, the dynamic correlator of run-and-tumble bacteria, which is measurable by light scattering at low density [5] and at higher density, in principle, by particle-tracking microscopy [6]. Additionally, particles for which  $v$ ,  $\alpha$  depend on the local density (either via thermodynamic interactions such as depletion [7] or kinetic effects such as collision-induced tumbles) could show collective phenomena such as domain-formation or flocking. Such effects have previously been addressed within models where a self-propelled particle responds vectorially to the velocity of its neighbors, by direct sensing or passive hydrodynamics [8–10]. Below, we shall find, for run-and-tumble dynamics, similar effects in even simpler cases when only the *speed* of a particle is density-dependent.

In making the transition from a single particle to many, most bacterial modeling approximates the number density by a simple replacement  $\rho = Np$  [3,4]. But even for non-interacting particles,  $\rho$  (unlike  $p$ ) is a fluctuating quantity,

and a full statistical mechanics must compute noise terms for  $\rho$ . As seen below, these are not *ad hoc*, but follow from the run-and-tumble dynamics directly.

To allow relatively rigorous progress we work in 1D throughout. For  $d > 1$ , although good descriptions exist at the one-particle level [3,4], we leave many-body effects to future work. To avoid unwieldy equations for the probability flux  $J$ , we assume that, in units where run-and-tumble parameters such as  $v$ ,  $\alpha$  are  $O(1)$  quantities, spatial gradients of these and of  $J$  are  $\ll 1$ . (We show below that this was also implicit in [3].) This restriction also judiciously avoids complicated memory effects arising from the time-retarded response function of bacteria [1,11] that can lead to much reduced universality [12].

We start below with the microscopic dynamics of a single particle. We show how, on large scales, its probability density is governed by a drift-diffusion equation, whose Langevin counterpart we then extend to describe the time evolution of the particle density in an assembly of interacting run-and-tumble particles. We then illustrate some dramatic consequences of these interactions and finally address the role of external fields such as gravity.

Let us define  $R(x, t)$ ,  $L(x, t)$  the probability of finding a single run-and-tumble particle at  $x, t$  in a right- or left-moving state [13], respectively. With discrete run speeds  $v_{R,L}$  and  $R \leftrightarrow L$ , and interconversion rates  $\alpha_{R,L}/2$  that depend on  $x$ , we have (with prime denoting  $\partial_x$ )

$$\dot{R} = -(v_R R)' - \alpha_R R/2 + \alpha_L L/2 \quad (1)$$

$$\dot{L} = (v_L L)' + \alpha_R R/2 - \alpha_L L/2 \quad (2)$$

$$\dot{p} = -J'. \quad (3)$$

Equation (3) sums (1) and (2), to relate the single-particle probability density  $p \equiv R + L$  to its current  $J \equiv v_R R - v_L L$ . Noise is not present in (1) and (2), which already represent an exact master equation for the dynamics of one particle.

The diffusive limit is found by a second time differentiation, elimination of  $R, L$  and their derivatives, and setting  $\ddot{p} \rightarrow 0$  [3,4]. The outcome can always be viewed as a time-local “constitutive” relation  $J = J[p(x)]$  for use with the continuity equation (3).  $J$ , though linear in  $p$ , need not be local in space; in fact, setting  $\ddot{p} = 0$  (which implies

$J = 0$ ) gives the differential equation (with  $2\nu \equiv \nu_L + \nu_R$  and  $2\alpha \equiv \alpha_L + \alpha_R$ ):

$$(1 + \xi_1)J + \xi_2 J' = \mathcal{J} \quad (4)$$

$$\mathcal{J} \equiv -\mathcal{D}p' + \mathcal{V}p; \quad \mathcal{D} \equiv \nu_R \nu_L / \alpha \quad (5)$$

$$\mathcal{V} \equiv (\alpha_L \nu_R - \alpha_R \nu_L) / 2\alpha - \nu(\nu_R \nu_L / \nu)' / \alpha \quad (6)$$

$$\xi_1 \equiv [\nu_R(\nu_R / \nu)' - \nu_L(\nu_L / \nu)'] / 2\alpha \quad (7)$$

$$\xi_2 \equiv (\nu_R - \nu_L) / \alpha. \quad (8)$$

An explicit nonlocal form  $J[p]$  is readily found from (4). By neglecting  $J'$  in (4), we instead obtain the local form  $J = \mathcal{J} / (1 + \xi_1)$  which is valid as long as  $\mathcal{V} / \mathcal{D}$  is itself small, a condition that must anyway hold if our diffusion-drift description is to avoid large  $p$  gradients in the flux-free steady state  $p_s(x)$ . The latter obeys  $\mathcal{V} / \mathcal{D} = (\ln p_s)'$ , which follows exactly from (1) and (2). Our local approximation reduces to that of Schnitzer [3] on further neglecting  $\xi_1$ . While the latter maintains  $p_s$  exactly, by retaining  $\xi_1$  we extend this exactness to *all* steady states ( $J' = 0$ ).

We thus write as an optimal local approximation

$$\dot{p} = -J'; \quad J = -Dp' + Vp, \quad (9)$$

with  $D \equiv \mathcal{D} / (1 + \xi_1)$  and  $V \equiv \mathcal{V} / (1 + \xi_1)$ .

To analyze the more complex physics arising at many-body level, we first exactly recast (9) as an Ito-Langevin process for a trajectory  $x_i(t)$ :

$$\dot{x}_i = A(x_i) + C(x_i)L_i(t), \quad (10)$$

with  $L_i(t)$  unit-variance Gaussian white noise,  $C^2 = 2D$ ,  $A = V + \partial D / \partial x_i$ , and  $C, A$  evaluated at the start of each time increment [14]. The latter (Ito) prescription eases the extension to many particles  $x_i(t)$  whose parameters  $\nu_{R,L}, \alpha_{R,L}$  depend on position, not only explicitly as in (10), but also implicitly via the particle density. The latter is formally constructed as  $\rho(x) = \sum_i \rho_i(x) = \sum_i \delta(x - x_i)$ ; a coarse-grained version (compatible with a gradient expansion) is found by choosing a smoothed function for  $\rho_i(x)$ . Within Ito's formulation [14], no further account need now be taken of the time dependence of  $\rho$ : despite interactions, the random displacements  $C(x_i)L_i(t)\delta t$  depend only on the *preceding*  $\rho(t)$  and are statistically independent of each other [15].

Accordingly, we can read Eq. (10) as the Ito-Langevin equations for many interacting particles  $i = 1, \dots, N$ , with  $A = A(x, [\rho])$  and  $C = C(x, [\rho])$  [16]. From these, the Ito-Langevin equation for the collective density  $\rho(x)$  is found by standard procedures [17], as follows. Ito's theorem [14] states that for any function  $f(x_i)$  of one variable

$$\dot{f}(x_i) = (A + CL_i)\partial f / \partial x_i + (C^2/2)\partial^2 f / \partial x_i^2 \quad (11)$$

$$= \int \rho_i(x, t)[(A + CL_i)f' + Df'']dx. \quad (12)$$

Integrating (12) by parts and using the identity  $\dot{f}(x_i) = \int \dot{\rho}_i(x, t)f(x)dx$  gives

$$\dot{\rho}_i = -(A\rho_i)' + (D\rho_i)'' - (L_i C\rho_i)'. \quad (13)$$

Summing on  $i$  we obtain for the collective density [16]

$$\dot{\rho} = -(A\rho)' + (D\rho)'' - \sum_i (CL_i\rho_i)' = -J'_C \quad (14)$$

$$J_C = \rho\{V + [\delta/\delta\rho]D\} - D\rho' + (2D\rho)^{1/2}\Lambda, \quad (15)$$

with  $\langle \Lambda(x, t)\Lambda(x', t') \rangle = \delta(t - t')\delta(x - x')$  [17–19]. In (15),  $\rho$  is to be read as a coarse-grained, locally smooth field. Again by standard methods (but avoiding any appeal to detailed balance) [20] the Fokker-Planck equation for the many-body probability  $\mathcal{P}[\rho]$  then follows as

$$\dot{\mathcal{P}} = \int dx \frac{\delta}{\delta\rho(x)} \partial_x \left[ \rho V - D\partial_x \rho - D\rho \left( \partial_x \frac{\delta}{\delta\rho(x)} \right) \right] \mathcal{P} \quad (16)$$

Allowing that  $V, D$  are now functionals of  $\rho$ , we next seek conditions under which we can map (16), or equivalently (10), onto a thermal system with detailed balance. (Clearly we require no macroscopic flux,  $\langle J_C \rangle = 0$ .) In such a system, forces derive from an excess free energy  $\mathcal{F}_{\text{ex}}[\rho]$ , diffusion and mobility matrices obey the Einstein relation  $D_{ij} = \mu_{ij}$ , and steady-state probability obeys  $\mathcal{P}_s[\rho] \propto e^{-\mathcal{F}[\rho]}$  with  $\mathcal{F}[\rho] = \mathcal{F}_{\text{ex}} + \int \rho(\ln \rho - 1)dx$ . (We set  $k_B T = 1$  without loss of generality.) Since in (10) the  $L_i$  for different particles are independent,  $D_{ij}$  is diagonal [15]. Hence the required condition is simply

$$V([\rho], x) / D([\rho], x) = -[\delta \mathcal{F}_{\text{ex}}[\rho] / \delta \rho(x)], \quad (17)$$

where the right-hand side represents the force (i.e., excess chemical potential gradient) on a particle at  $x$ .

For 1D noninteracting particles, (17) always holds, with  $\mathcal{F}_{\text{ex}} = \int F(x)\rho(x)dx$  and  $F(x) = \int V(x')/D(x')dx'$ . For instance, when  $\nu_L = \nu_R = \nu(x)$  and  $\alpha_L = \alpha_R = \alpha(x)$ , one has [3,4]  $F(x) = \ln \nu(x)$  so that the mean steady-state density obeys  $\rho_s(x) = \rho_s(0)\nu(0)/\nu(x)$ . For interacting particles, existence of  $\mathcal{F}_{\text{ex}}$  is not generic even in 1D, as the configuration space is  $Nd$ -dimensional. Nonetheless, some interesting cases do admit an  $\mathcal{F}_{\text{ex}}$ . In particular, whenever  $V = (s_1(\rho))'$  and  $D = s_2(\rho)$ , with  $s_{1,2}$  depending locally on  $\rho$  only, then  $V/D$  satisfies (17) with  $\mathcal{F}_{\text{ex}} = \int s_3(\rho)dx$  and  $s_3(\rho)$  obeying  $s_2 d^2 s_3 / d\rho^2 = ds_1 / d\rho$ .

For example, consider a translationally invariant dynamics in which  $\nu_{R,L}, \alpha_{R,L}$  at  $x$  depend on  $\rho(x), \rho'(x), \dots$ , with even parity:  $\rho(x) \leftrightarrow \rho(-x)$  induces  $\alpha_L(x), \nu_L(x) \leftrightarrow \alpha_R(-x), \nu_R(-x)$ . Then  $[\delta \mathcal{F}_{\text{ex}}[\rho] / \delta \rho(x)]' = \Psi + [\ln(\nu_R \nu_L / \nu)]'$ , where  $\Psi \equiv (\alpha_R \nu_L - \alpha_L \nu_R) / 2\nu_R \nu_L$ . On symmetry grounds,  $\Psi$  must vanish when all odd derivatives of  $\rho$  do so; thus to leading order in gradients we can write  $\Psi = (\psi(\rho))'$ . Likewise  $\nu_{R,L} - \nu \propto \pm \rho'$  so we can write  $[\ln(\nu_R \nu_L / \nu)]' = [\ln \nu(\rho)]'$  to leading order. Thus we recover  $\mathcal{F} = \int f(\rho)dx = \int [\rho(\ln \rho - 1) + f_{\text{ex}}(\rho)]dx$ , with

$$f_{\text{ex}}(\rho) = \int_0^\rho [\psi(u) + \ln v(u)] du. \quad (18)$$

To leading order in gradients, this system is then equivalent to a system of Brownian particles at  $k_B T = 1$ , with mobility matrix  $D_{ij} = \delta_{ij} v^2(\rho(x_i)) / \alpha(\rho(x_i))$ , and a local free energy density  $f(\rho)$ . Thus, according to mean-field theory [18], whenever

$$\frac{d^2 f}{d\rho^2} = \frac{1}{\rho} + \frac{d}{d\rho} [\psi(\rho) + \ln v(\rho)] < 0 \quad (19)$$

the system is locally unstable toward spinodal decomposition into domains of unequal density  $\rho$ . Also, it is globally unstable to noise-induced (nucleated) phase separation whenever  $\rho$  lies within a common-tangent construction on  $f(\rho)$  [18,19]. In particular, for  $\psi = 0$  (left-right symmetry), any system with  $dv/d\rho < -v/\rho$  is liable, by the above reasoning, to undergo phase separation. Since one result of finite tumble duration is effectively to reduce  $v$  [13], a strong enough tendency for the duration of tumbles to increase with density may have similar effects.

In practice, of course, the very existence of a thermodynamic mapping in this (strictly 1D) system ensures that the bulk phase separation predicted by mean-field theory is replaced by Poisson-distributed alternating domains of mean size  $\propto e^\Delta$ . Here  $\Delta$  is a domain-wall energy, fixed by gradient terms—if these remain compatible with the existence of  $\mathcal{F}_{\text{ex}}$  (which is not guaranteed). To gain a first estimate of such gradient terms (retaining  $\psi = 0$ ) we choose a model where, in a uniform system,  $v(\rho) = v_0 e^{-\lambda\rho}$  with  $\lambda$  a constant. Now we argue that the dependence  $v$  on  $\rho$  is somewhat nonlocal, sampling  $\rho$  on scales  $\gamma$  of order the run distance,  $v/\alpha$ , which is  $O(1)$  in our units. We therefore write for the nonuniform case  $v = v(\tilde{\rho})$  where  $\tilde{\rho} = \rho + \gamma^2 \rho''$ . (A linear term is forbidden by symmetry.) Thus  $\delta \mathcal{F}_{\text{ex}} / \delta \rho(x) = \ln v = \ln v_0 - \lambda(\rho + \gamma^2 \rho'')$  and

$$f_{\text{ex}}(\rho, \rho') = \rho \ln v_0 + \lambda[-\rho^2 + \gamma^2 \rho'^2] / 2. \quad (20)$$

The resulting  $f(\rho)$  is very familiar [19], and locally unstable for all  $\rho \geq 1/\lambda$ . A stable dense phase is however regained if  $v(\rho)$  saturates at large  $\rho$ . Suppose, e.g.,  $v = v_0 \exp[-\lambda\varphi \arctan(\rho/\varphi)]$ , which falls as  $v_0 e^{-\lambda\rho}$  before approaching  $v_{\text{sat}} = v_0 \exp[-\lambda\varphi\pi/2]$  at  $\rho \gg \varphi$ . So long as  $\varphi > 2/\lambda$ , a window of phase separation is maintained in mean field. Notably, some of the gradient terms arising from (the above form of) nonlocality now violate our thermodynamic mapping. However, if one ignores such violations,  $\Delta$  is found to be large, and domain formation accordingly pronounced, whenever  $\varphi \gg 1$ .

Although rigor is now exhausted, the physics seems reasonable: we know [2–4] that for an imposed  $v = v(x)$  particles accumulate in regions of low  $v$ . Thus with  $dv/d\rho$  sufficiently negative, “self-trapping” of high-density, slow-moving domains can be expected. To investigate whether this scenario arises, we have simulated Eq. (10) for the above conditions and indeed observed the predicted

spinodal dynamics (Fig. 1). Moreover, if we create a fully phase-separated initial state, this shows prolonged stability when the mean density lies between the predicted binodals; outside these, it collapses to uniformity. Thus the self-trapping scenario appears valid despite violations of our thermodynamic mapping at gradient level. Equations (14) and (15) generalize obviously to  $d > 1$ , where they would lead to genuine phase separation under similar conditions. However, an adequate local approximation relating  $A$ ,  $C$  to run-and-tumble parameters remains to be established, and the range of validity of the diffusive limit is unknown. In  $d > 1$  additional physics also enters, such as hydrodynamic interactions which are only partially accounted for by our use of a density-dependent velocity field [10].

Finally, let us consider a translationally invariant system with no density dependence of  $\alpha$  nor of  $v$ , but where  $v_{L,R}$  are biased by some colloidal interaction  $H_{\text{int}}$ . That is,  $v_{R,L}(x) = v \pm v_T$ , with  $v_T = -\mu_T [\delta H_{\text{int}} / \delta \rho(x)]'$  and  $\mu_T$  the mobility (inverse friction) [7]. To first order in small  $v_T$  we then have  $V = v_T$  and  $D = v^2/\alpha$ . The latter swamps any small thermal contribution ( $D_T = k_B T \mu_T$ ), so that (10) and (16) are, to this order, equivalent to a thermodynamic system with  $H_{\text{int}}$ , but at enhanced temperature  $k_B T_{\text{eff}} \approx D/\mu_T$ . Correlators such as  $\mathcal{S}(q, t' - t) \equiv \langle \rho_q(t) \rho_{-q}(t') \rangle$  follow, although in many cases  $T_{\text{eff}}$  may be so large that these approach the noninteracting limit,  $\mathcal{S}(q, t) = N \exp[-Dq^2 t]$  [21]. A similar expansion shows  $T_{\text{eff}}$  also to control sedimentation equilibrium under weak enough gravity ( $H = H_{\text{int}} + mg \int \rho(x) x dx$ ).

For the chosen  $\rho$ -independent  $v$  and  $\alpha$ , this effective temperature picture is intuitively clear and appealing. Nonperturbatively, however,  $\mathcal{V} = v_T + (v_T^2)'/\alpha$  and  $\mathcal{D} = (v^2 - v_T^2)/\alpha$ . Since  $v_T = v_T[\rho]$ , Eq. (17) no longer holds: the effective temperature concept breaks down as soon as the colloidal or gravitational interactions are non-infinitesimal. (This is true even within the gradient expansion, which itself fails at  $v_T/v \approx 1$ .) Perhaps instructive is the exactly solved case of *noninteracting* sedimentation,

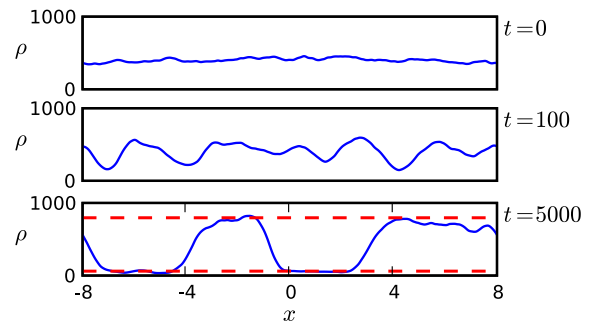


FIG. 1 (color online). Spinodal-like behavior of 6400 interacting particles within the region where  $d^2 f / d\rho^2 < 0$ . In the numerics,  $\tilde{\rho}$  is defined by convolution of  $\rho$  with a smooth function of finite range  $\pm 1/2$ ; we set  $v_0 = 2.5$ ,  $\lambda = 0.01$ ,  $\varphi = 250$ . The box length is 16, with periodic boundary conditions, and the mean density is 400. Dashed lines show the common-tangent densities ( $\rho = 60; 800$ ).

where  $v_T = -\mu_T mg$ . This gives in steady state a Boltzmann-like exponential density,  $\rho_s(x) = \rho(0)e^{-\kappa x}$ , whose spatial decay rate  $\kappa = -v_T \alpha / (v^2 - v_T^2)$  is, however, nonlinear in  $g$  [22]. On increasing  $g$ , the density profile collapses to zero height, not when  $g \rightarrow \infty$  but when  $v_T(g) \rightarrow v$ . Although cut off by other physics (such as true Brownian motion) this finite- $g$  singularity occurs because for  $|v_T| > v$ ,  $L$  and  $R$  particles move in the same direction: a steady state of zero flux is clearly then impossible. Strong colloidal forces may likewise create absorbing states whose local “escape velocity” exceeds  $v$ . This conclusion would alter if  $v$  represented not a fixed value but the mean of a distribution extending (as in a truly thermal system) to unlimited speeds. Existence of a strict upper limit to the speed of self-propelled particles could thus be an important factor in their physics.

In summary, by considering the passage from local run-and-tumble to drift-diffusion dynamics at large scales, we have elucidated the roles of both noise and interactions. When the mean run speed  $v$  is a sufficiently decreasing function of local density (or tumble time  $\tau$  sufficiently increasing [13]), purely kinetic interactions could cause “self-trapping” of domains in 1D, suggestive of bulk phase separation in higher dimensions. For particles interacting not by kinetic but by conventional thermodynamic forces (creating local drift velocities superposed on a density-independent run-and-tumble dynamics), such a mapping gives, perturbatively, an effective temperature set by the ratio of the run-and-tumble diffusivity to the thermodynamic mobility. However, this mapping breaks down as soon as the drift velocities  $v_T$  arising from the interactions become a significant fraction of the run speed  $v$ . For  $|v_T| > v$ , and in the absence of true Brownian motion, absorbing states are possible.

Because of the progress it allows, we have focused above on those exceptional cases that, despite nonequilibrium interactions and noise, admit a thermodynamic mapping. Accordingly, large areas of parameter space remain unexplored; these could harbor many further interesting forms of collective nonequilibrium behavior.

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 [13] We take tumbles as instantaneous, but a finite mean duration  $\tau$  is similar to setting  $(v, \alpha) \rightarrow (v, \alpha)/(1 + \alpha\tau)$ . Indeed, for Poissonian tumble durations and  $v_R, \alpha_R = v_L, \alpha_L$  the stated diffusive limit is thereby recovered, on neglect of all second-order time derivatives.  
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 [15] Velocity-dependent forces, such as hydrodynamic interactions, would change this; see also [10].  
 [16] We have  $A(x_i, [\rho]) = V(x_i, [\rho]) + \partial D(x_i, [\rho])/\partial x_i$ , whose second term is found by the chain rule as  $\{D'(x) + [\delta/\delta\rho(x)]D(x)\}_{x=x_i}$ , and leads directly to the  $(\delta/\delta\rho)'D$  term in (15). This vanishes whenever  $D(x_i, [\rho])$  can be written  $D = \tilde{D}(x_i, [\rho - \rho_i(x)])$ , which excludes self-density interaction.  
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 [18] Omitting the noise term from (15) as in [3,4] amounts to a dynamic mean-field theory (MFT),  $J_C[\rho] = J_C(x, [\langle\rho\rangle])$ , which loses the statistical mechanics of fluctuations and thus of activated phenomena such as nucleation. Static MFT instead finds the global extremum of  $\mathcal{F}[\rho]$ , allowing access to nucleated phase separations [19]. The thermodynamic mappings reported below include all noise terms and are therefore not contingent on either MFT. In some further cases, not explored here, such mappings can be made within dynamic MFT but are then violated by fluctuations.  
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 [21] These results hold only at diffusive scales,  $qv/\alpha \ll 1$ , whereas the opposite limit is more easily reached in scattering experiments [5].  
 [22] Noninteracting particles in a quadratic potential,  $v_\tau = -kx$ , obey  $\rho_s(x) = \rho_0|1 - k^2x^2/v^2|^{\alpha/2k-1}$ , which is even further from Boltzmann form.