Origin of superdiffusive behavior in a class of nonequilibrium systems

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Experiments and simulations have established that dynamics in a class of living and abiotic systems that are far from equilibrium exhibit superdiffusive behavior at long times, which in some cases (for example, an evolving tumor) is preceded by slow glass-like dynamics. By using the evolution of a collection of tumor cells, driven by mechanical forces and subject to cell birth and apoptosis, as a case study we show theoretically that on short timescales the mean-square displacement is subdiffusive due to jamming, whereas at long times it is superdiffusive. The results obtained by using a stochastic quantization method, which is needed because of the absence of the fluctuation-dissipation theorem, show that the superdiffusive behavior is universal and impervious to the nature of cell-cell interactions. Surprisingly, the theory also quantitatively accounts for the nontrivial dynamics observed in simulations of a model soap foam characterized by creation and destruction of spherical bubbles, which suggests that the two nonequilibrium systems belong to the same universality class. The theoretical prediction for the superdiffusion exponent is in excellent agreement with simulations for collective motion of tumor cells and dynamics associated with soap bubbles.

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I. INTRODUCTION

The collective movement of cells is a pervasive phenomenon in many processes in biology, ranging from tissue remodeling, which underlies embryonic morphogenesis, to wound repair and cancer invasion [1–6]. Consequently, there is considerable interest in understanding the dynamics associated with such processes. During migration, cells move as sheets, strands, clusters or ducts rather than individually, and use similar actin- and myosin-mediated protrusions and guidance by extrinsic chemotactic and mechanical cues just as in the motility of single cells [3,7–11]. Collective invasion during cancer progression, accompanied by the destruction of tissues and remodeling of the extracellular matrix, is also important in metastasis [7,8,12,13]. The dynamics of these processes are complicated because of an interplay of intercell adhesive interactions and the biology governing cell birth and apoptosis. The dynamical events involving cell birth and apoptosis implicitly generate active forces [14–16], thus driving the systems far from equilibrium. How the interplay of death-birth processes and cell-cell interactions in a growing tumor spheroid poise the cells for effective invasion into the surrounding matrix is poorly understood.

Complex dynamics in the systems mentioned above manifests itself as caging of a cell by surrounding cells and dynamic heterogeneity features that are reminiscent of supercooled liquids [17]. There are also some surprising departures from glass-like behavior, which is revealed by the superdiffusive behavior on long timescales. For example, experiments on tumor cells invading a collagen matrix [18] have shown that at long times (times exceeding the cell division time) the mean-square displacement of tumor cells, $\langle \Delta r^2(t) \rangle \sim t^{\alpha}$, exhibits superdiffusive behavior with $\alpha \approx 1.4 \pm 0.04$. Interestingly, rheology in completely unrelated synthetic materials (foams and mayonnaise) modeled as compressible spherical bubbles, which can be created or destroyed, also exhibit similar behavior. Simulations of such soft glassy materials [19] show that $\langle \Delta r^2(t) \rangle \sim t^{\alpha}$ at long times with $\alpha \approx 1.37 \pm 0.03$. Both tumor growth and ripening of bubbles are intrinsically nonequilibrium systems because cells (or bubbles) are born as a result of mitosis and also undergo apoptosis. Is there a common mechanism for the origin of superdiffusive behavior in these seemingly unrelated nonequilibrium systems and if so can the long-time universal behavior be explained theoretically?

Here, we answer the questions posed above in the affirmative by developing a theory to describe the nonequilibrium dynamics of collective cell migration. A brief sketch of the theory used to rationalize the results of simulations was given elsewhere [20]. Further developments, including the details, and plausible generality of the results are provided in this study. For concreteness, we develop the formalism in the context of tumor growth. Cells are modeled as deformable objects interacting with potentials that account for repulsive elastic forces and intercell adhesive attractions due to interactions between cadherins expressed on the cell surface. In addition, the cells could divide at a rate k_a, giving rise to daughter cells, and undergo apoptosis, at a rate k_b. Due to the death-birth processes (Fig. 1), cell-number conservation is violated, thus making it difficult to use standard methods to solve the stochastic equations describing the evolution of cell density. A similar scenario arises in the description of dynamics of chemotactic cells, in which cell division and death play an important role [10]. Because Gelimson and Golestanian were primarily interested in the long-time collective dynamics, they resorted to dynamical renormalization-group techniques to investigate the interplay of chemical signaling and cell growth. We follow a different route to study the relevant continuum description of collective behavior of a colony of cells in both the finite as well as in the long-time limit, using a stochastic quantization method introduced by Parisi and Wu [21] in the context of quantum field theory.

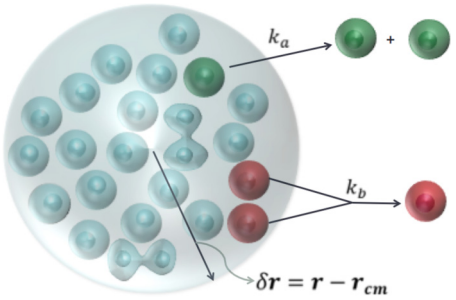

FIG. 1. Schematic of the dynamics associated with cell birth and death. Cell in green color divides into two cells with rate k_a and cells in red color undergo death with rate k_b. The invasion distance, $\delta\mathbf{r} = \mathbf{r} - \mathbf{r}_{\rm cm}$, is a measure of the extent of penetration of the tumor into the surrounding matrix.

The major results of this study are as follows: (i) The interplay between nonlinear terms that determine the intercellular interactions (adhesion and excluded volume repulsion, collectively referred to as mechanical interactions from now on) and death-birth processes are manifested in the dynamics that changes dramatically as the system evolves. At finite times, mechanical interactions with strong attraction between cells dominate over the effects cell birth and death, leading to glassy dynamics. The jammed cells exhibit subdiffusive motion at the intermediate timescales, where the mean-square displacement, $\langle \Delta r^2(t)\rangle$ increases sublinearly, as t^α with $\alpha = 0.8$. (ii) In the long-time limit (times exceeding the cell division time), the consequences of the birth-death processes dominate over the mechanical interactions, resulting in the fluidization of cells. Asymptotically, the cells exhibit superdiffusive motion, with $\langle \Delta r^2(t)\rangle \sim t^\alpha$ with the value of the universal exponent $\alpha = 1.33$, in three dimensions. The theoretical prediction is in excellent agreement with the simulation results [20] and a recent *in vitro* experiment of the three-dimensional growth of multicellular tumor spheroids [18]. (iii) Although the theory is set in the context of tumor growth, the present work also quantitatively describes the complex motion of bubbles in a foam in which bubble formation (birth) and collapse (death) occur.

The rest of the paper is organized as follows: In Sec. II we present the model and the theory used to understand the dynamics. This is followed in Sec. III, which describes the stochastic quantization method as the required theoretical technique to obtain the time-dependence of a number of observables that characterize the collective dynamics at intermediate and long times. The main results detailing the origin of subdiffusive motion at intermediate times and the universal superdiffusive dynamics at long times are contained in Sec. IV. This section also provides arguments for the generality of our results for similar universal behavior in abiotic nonequilibrium systems. Section V summarizes our findings. The technical details of the calculations are relegated to the three Appendixes.

II. THEORY

We consider the dynamics of a colony of cells in a dissipative environment where inertial effects are negligible. Each cell experiences systematic forces arising from mechanical interactions, and a Gaussian random force with white-noise spectrum. The equation of motion for a single cell i is $\frac{\partial \mathbf{r}_i}{\partial t} = -\sum_{j=1}^{N} \nabla U(\mathbf{r}_i(t) - \mathbf{r}_j(t)) + \eta_i(t)$, where U contains both repulsive interactions with range λ, and favorable attractive interactions between cells with range σ, with strengths v and κ, respectively. We use Gaussian potentials (see Appendix A for details) in order to obtain analytical solutions. Needless to say that the conclusions would be valid for any short-ranged U. The Gaussian white noise satisfies $\langle \eta_i(t)\eta_j(t')\rangle = 2D\delta_{ij}\delta(t-t')$. Let us consider the evolution of the density function for a single cell $\phi_i(\mathbf{r},t) = \delta[\mathbf{r} - \mathbf{r_i}(\mathbf{t})]$. A closed form of the Langevin equation for the density, $\phi(\mathbf{r},t) = \sum_i \delta[\mathbf{r} - \mathbf{r_i}(\mathbf{t})]$ may be obtained using the approach developed by Dean [22]. The time evolution of $\phi(\mathbf{r},t)$ is given by $\frac{\partial \phi(\mathbf{r},t)}{\partial t} = \nabla \cdot [\eta(\mathbf{r},t)\phi^{1/2}(\mathbf{r},t)] + \nabla \cdot [\phi(\mathbf{r},t)\int d\mathbf{r}'\phi(\mathbf{r}',t)\nabla U(\mathbf{r}-\mathbf{r}')] + D\nabla^2\phi(\mathbf{r},t)$. We extend the model phenomenologically by adding the source term that describes both cell birth and death as well as a noise term that breaks the cell-number conservation. The line of argument follows from the Doi–Peliti formalism [23–25], introduced in the study of reaction-diffusion processes.

The Langevin equation, for the time-dependent changes in the density, $\phi(\mathbf{r},t)$, is

$$\frac{\partial \phi(\mathbf{r},t)}{\partial t} = \nabla \cdot \left[\phi(\mathbf{r},t)\int d\mathbf{r}'\phi(\mathbf{r}',t)\nabla U(\mathbf{r}-\mathbf{r}')\right] + D\nabla^2\phi(\mathbf{r},t) + \bar{k}_b\phi(\mathbf{r},t)\left(\frac{k_a}{\bar{k}_b} - \phi(\mathbf{r},t)\right) + \nabla \cdot [\eta(\mathbf{r},t)\phi^{1/2}(\mathbf{r},t)] + \sqrt{k_a\phi + k_b\phi^2}f_\phi, \quad (1)$$

with f_ϕ satisfying $\langle f_\phi(\mathbf{r},t)f_\phi(\mathbf{r}',t')\rangle = \delta(\mathbf{r}-\mathbf{r}')\delta(t-t')$. The source term $g\phi(\phi_0 - \phi)$ [third term on the right-hand side of Eq. (1)], arises due to the cell death-birth processes (Fig. 1), with an effective growth rate $g = \bar{k}_b$, and carrying capacity $\phi_0 = \frac{k_a}{\bar{k}_b}$ (see Appendix B) [10,26]. The coefficient $(k_a\phi + \bar{k}_b\phi^2)^{1/2}$ is the strength of the noise due to number fluctuations, and is a function of density ϕ.

The absence of a fluctuation-dissipation theorem (FDT), due to the generation of active forces, makes this a far-from-equilibrium problem. Although dynamic renormalization-group methods could be used to solve Eq. (1) in the hydrodynamic limit [10], it would not capture the dynamics in the intermediate time regime. Our focus is to study the collective dynamics in a colony of tumor cells in both the intermediate- and long-time limits. Therefore, we solve Eq. (1) by treating the nonlinear terms as a perturbation, by adopting the stochastic quantization scheme [21,27,28], which allows us to calculate the form of the mean-square displacement (MSD) in the intermediate- as well as the long-time limit.

We assume that the density fluctuates around a constant value, which simplifies the multiplicative noise term [last term in Eq. (1)]. We write the density as $\phi(\mathbf{r},t) = \phi_0 + \phi_1(\mathbf{r},t)$ and perform a linear stability analysis in the Fourier space for the equation describing density fluctuations. The equation for

the density fluctuation becomes

$$\frac{\partial\phi_1(\mathbf{r},t)}{\partial t} = D\nabla^2\phi_1(\mathbf{r},t) + (k_a - 2\bar{k}_b\phi_0)\phi_1(\mathbf{r}',t) + \nabla\cdot\left[\phi_0\int d\mathbf{r}'\phi_1(\mathbf{r}',t)\nabla U(\mathbf{r}-\mathbf{r}')\right] + \nabla\cdot\left[\phi_1(\mathbf{r}',t)\int d\mathbf{r}'\phi_0\nabla U(\mathbf{r}-\mathbf{r}')\right] + \nabla\cdot\left[\phi_1(\mathbf{r},t)\int d\mathbf{r}'\phi_1(\mathbf{r}',t)\nabla U(\mathbf{r}-\mathbf{r}')\right] + \nabla\cdot\left[\eta(\mathbf{r},t)\phi_0^{1/2}\right] - \bar{k}_b\phi_1^2 + \sqrt{k_a\phi_0 + \bar{k}_b\phi_0^2}f_{\phi_1}. \tag{2}$$

In Fourier space, the above equation reads

$$\frac{\partial\phi_1(\mathbf{k},t)}{\partial t} = -[Dk^2 + \phi_0k^2U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0)]\phi_1(\mathbf{k}) + \int d\mathbf{q}(-\mathbf{q}\cdot\mathbf{k})U(\mathbf{q})\phi_1(\mathbf{q})\phi_1(\mathbf{k}-\mathbf{q}) - \bar{k}_b\int d\mathbf{q}\phi_1(\mathbf{q})\phi_1(\mathbf{k}-\mathbf{q}) + \eta'(\mathbf{k},t), \tag{3}$$

with $\langle\eta'(\mathbf{k},t)\eta'(-\mathbf{k},t')\rangle = (k_a\phi_0 + \bar{k}_b\phi_0^2 + 2D\phi_0k^2)\delta(t-t')$.

From the linear stability analysis, we find that the uniform density phase is stable if $\phi_0k^2U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0) > 0$ [Eq. (3)]. In this regime, mechanical interactions dominate over the cell birth-death and is the primary determinant of the dynamics of cells. In the opposite limit, when the active forces due to cell birth-death dominate, the cell colony grows rapidly. There is an instability at $\phi_0k^2U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0) = 0$, signaling a transition from subdiffusive to superdiffusive motion in the cell dynamics (see below). The Green's function G is given by

$$[G]^{-1} = -i\omega + Dk^2 + \phi_0k^2U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0) + \Sigma_\phi(\mathbf{k},\omega), \tag{4}$$

where $\Sigma_\phi(\mathbf{k},\omega) \sim \int \frac{d^d\mathbf{k}'}{(2\pi)^d}\frac{d\omega'}{2\pi}VVGC \sim \int \frac{d\mathbf{k}'}{(2\pi)^d}k'^{d-5}$, showing infrared divergence at the critical dimension $d_c = 4$. For $d > d_c$, scaling exponents are determined by linear theory and, for $d < d_c$, nontrivial exponents are governed by the nonlinear terms in Eq. (3).

To anticipate the consequences of nonlinearity, we introduce a change of scale $\mathbf{r} \to s\mathbf{r}$, $\phi \to s^\chi\phi$, and $t \to s^zt$ where χ is the exponent corresponding to the cell density fluctuations, and z is the dynamical exponent. The nonlinear term $(-\mathbf{q}\cdot\mathbf{k})U(\mathbf{q})\phi_1(\mathbf{q})\phi_1(\mathbf{k}-\mathbf{q})$ representing the cell-cell mechanical interactions scales as $s^{2\chi-2}$. The term $b\phi_1(\mathbf{q})\phi_1(\mathbf{k}-\mathbf{q})$, due to stochastic cell birth-death processes, scales as $s^{2\chi}$. In the long-time limit (times exceeding the cell division time), nonlinearity due to cell birth-death dominates over mechanical interaction. Therefore, in the long-time limit, scaling behavior is determined by the death-birth process, which implies that one expects universality in the scaling of the MSD in the long-time limit. These conclusions are supported by recent simulation results [20]. However, in the intermediate-time regime all the terms contribute to the time dependence of the MSD, $\langle\Delta r^2(t)\rangle$. By choosing the strength of the interactions, in such a way that the mechanical interactions dominate over death-birth term [first term in Eq. (1)], we can calculate $\langle\Delta r^2(t)\rangle$ as a function of t.

III. STOCHASTIC QUANTIZATION APPROACH

We now provide a theory in support of the arguments given above. As stated earlier, a major difficulty in studying the problem of collective behavior of cells far from equilibrium is the breakdown of the FDT. Therefore, independent diagrammatic expansions for the response function $\langle\tilde{\phi}_1\phi_1\rangle$ and the correlation function $\langle\phi_1\phi_1\rangle$ are necessary. The equilibrium distribution is unknown, and may not exist. Therefore, the averages can be computed only for the statistical noise. The usual analytic route employed in calculating the scaling exponents is to introduce a response field $\tilde{\phi}_1$ and compute the response function as $\langle\tilde{\phi}_1\phi_1\rangle$ and the correlation function as $\langle\phi_1\phi_1\rangle$. One can obtain the scaling solutions of the relevant problem by using dynamic renormalization-group (RG) scheme, as illustrated recently [10]. The novelty of our theory is that it successfully captures the growing phase of the tumor, which is not easily accessible in the perturbative calculation using the RG scheme [10]. Here, we develop a general theoretical formalism, in which scaling solutions can be obtained by a power counting analysis.

We now exploit the Parisi–Wu stochastic quantization scheme [21] and introduce a fictitious time "τ_f" and consider all variables to be functions of τ_f in addition to $\mathbf{k}$ and w. The Langevin equation in the τ_f variable is

$$\frac{\partial\phi_1(\mathbf{k},w,\tau_f)}{\partial\tau_f} = -\frac{\delta\mathcal{S}}{\delta\phi_1(-\mathbf{k},-w,\tau_f)} + f_{\phi_1}(\mathbf{k},w,\tau_f), \tag{5}$$

where f_{ϕ_1} satisfies $\langle f_{\phi_1}f_{\phi_1}\rangle = 2\delta(k+k')\delta(w+w')\delta(\tau_f-\tau_f')$. This ensures that, as $\tau_f \to \infty$, the distribution function will be given by $\mathcal{S}(\mathbf{k},w)$, because FDT holds in the τ_f variable. The correlation functions calculated by using Eq. (5) lead to the physical correlation functions of the original theory [Eq. (1)] in the $\tau_f \to \infty$ limit [28]. The action $\mathcal{S}(\mathbf{k},w)$ can be obtained by writing down the probability distribution corresponding to the noise term, which is given by

$$P(f_{\phi_1}) \propto \exp\left[-\int_{\mathbf{k},w}\frac{1}{2}f_{\phi_1}(\mathbf{k},w)f_{\phi_1}(-\mathbf{k},-w)\right] = \exp\left[-\frac{1}{2(k_a\phi_0 + \bar{k}_b\phi_0^2)}\int_{\mathbf{k},w}\mathcal{S}(\mathbf{k},w)\right]. \tag{6}$$

The action functional $\mathcal{S}(\mathbf{k},w)$ may be written in terms of $\phi_1(\mathbf{k},w)$ instead of $f_{\phi_1}(\mathbf{k},w)$, with the help of Eq. (2). The expression for the action $\mathcal{S}$ obtained by using Eq. (2) is

$$\mathcal{S} = \int\frac{d^d\mathbf{k}}{(2\pi)^d}\frac{dw}{2\pi}\frac{1}{2}\Big\{[-iw + Dk^2 + \phi_0k^2U(\mathbf{k})]\phi_1(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0)\phi_1(\mathbf{k})$$

$$- \int d\mathbf{q}(-\mathbf{q}\cdot\mathbf{k})U(\mathbf{q})\phi_1(\mathbf{q})\phi_1(\mathbf{k}-\mathbf{q}) + \bar{k}_b \int d\mathbf{q}\phi_1(\mathbf{q})\phi_1(\mathbf{k}-\mathbf{q})\Big\}$$
$$\times \Big\{[iw + Dk^2 + \phi_0 k^2 U(-\mathbf{k})]\phi_1(-\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0)\phi_1(-\mathbf{k})$$
$$- \int d\mathbf{q}(\mathbf{q}\cdot\mathbf{k})U(\mathbf{q})\phi_1(\mathbf{q})\phi_1(-\mathbf{k}-\mathbf{q}) + \bar{k}_b \int d\mathbf{q}\phi_1(\mathbf{q})\phi_1(-\mathbf{k}-\mathbf{q})\Big\}.$$

With the action given above, we obtain the Langevin equation using Eq. (5) for $\phi_1(\mathbf{k}, \omega, \tau_f)$:

$$\frac{\partial\phi_1(\mathbf{k},\omega,\tau_f)}{\partial\tau_f} = -\frac{1}{\left(k_a\phi_0 + \bar{k}_b\phi_0^2 + Dk^2\right)}[\omega^2 + \{Dk^2 + \phi_0 k^2 U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0)\}^2]\phi_1(\mathbf{k},\omega,\tau_f) - \frac{1}{\left(k_a\phi_0 + \bar{k}_b\phi_0^2 + Dk^2\right)}$$
$$\times \int_{\mathbf{k}',\omega'} [\{i\omega + Dk^2 + \phi_0 k^2 U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0)\}\{(-\mathbf{k}'\cdot\mathbf{k})U(\mathbf{k}') - \bar{k}_b\}$$
$$+ \{i\omega' + Dk'^2 + \phi_0 k'^2 U(\mathbf{k}') - (k_a - 2\bar{k}_b\phi_0)\}\{(-\mathbf{k}'\cdot\mathbf{k})U(-\mathbf{k}) - \bar{k}_b\}$$
$$+ \{i\omega' + Dk'^2 + \phi_0 k'^2 U(\mathbf{k}') - (k_a - 2\bar{k}_b\phi_0)\}\{(-\mathbf{k}'\cdot(\mathbf{k}-\mathbf{k}'))U(\mathbf{k}-\mathbf{k}') - \bar{k}_b\}]$$
$$\times \phi_1(\mathbf{k}',\omega')\phi_1(\mathbf{k}-\mathbf{k}',\omega-\omega') + f_\phi(\mathbf{k},\omega,\tau_f) + \text{higher order terms}. \tag{7}$$

To obtain the scaling laws for the MSD, it suffices to work at arbitrary τ_f. It follows from Eq. (7) that, in the absence of the nonlinear terms, the Green's function $G^{(0)}$ is given by $[G^{(0)}]^{-1} = -i\omega_{\tau_f} + \frac{1}{2(k_a\phi_0+\bar{k}_b\phi_0^2)}[\omega^2 + \{Dk^2 + \phi_0 k^2 U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0)\}^2]$, where ω_{τ_f} is the frequency corresponding to the fictitious time τ_f. The effect of nonlinear terms can be included perturbatively, leading to the Dyson's equation

$$[G]^{-1} = [G^{(0)}]^{-1} + \Sigma\left(\mathbf{k},\omega,\omega_{\tau_f}\right), \tag{8}$$

where the self-energy $\Sigma(\mathbf{k},\omega,\omega_{\tau_f})$ contains the nonlinear contributions to the bare Green's function (see Fig. 2). The expression for $\Sigma(\mathbf{k},\omega,\omega_{\tau_f})$ is given by

$$\Sigma\left(\mathbf{k},\omega,\omega_{\tau_f}\right) = \frac{2}{\left(k_a\phi_0 + \bar{k}_b\phi_0^2 + Dk^2\right)^2}\int_{\mathbf{k}',\omega',\omega'_{\tau_f}} [\{i\omega + Dk^2 + \phi_0 k^2 U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0)\}$$
$$\times \{(-\mathbf{k}'\cdot\mathbf{k})U(\mathbf{k}') - \bar{k}_b\} + \{i\omega' + Dk'^2 + \phi_0 k'^2 U(\mathbf{k}') - (k_a - 2\bar{k}_b\phi_0)\}\{(-\mathbf{k}'\cdot\mathbf{k})U(-\mathbf{k}) - \bar{k}_b\}$$
$$+ \{i\omega' + Dk'^2 + \phi_0 k'^2 U(\mathbf{k}') - (k_a - 2\bar{k}_b\phi_0)\}\{[-\mathbf{k}'\cdot(\mathbf{k}-\mathbf{k}')]U(\mathbf{k}-\mathbf{k}') - \bar{k}_b\}]$$
$$\times [\{i\omega + Dk^2 + \phi_0 k^2 U(\mathbf{k}) - (k_a - 2\bar{k}_b\phi_0)\}\{[-(\mathbf{k}-\mathbf{k}')\cdot\mathbf{k}]U(\mathbf{k}-\mathbf{k}') - \bar{k}_b\}$$
$$+ \{i(\omega-\omega') + D(\mathbf{k}-\mathbf{k}')^2 + \phi_0(\mathbf{k}-\mathbf{k}')^2 U(\mathbf{k}-\mathbf{k}') - (k_a - 2\bar{k}_b\phi_0)\}\{[-(\mathbf{k}-\mathbf{k}')\cdot\mathbf{k}]U(-\mathbf{k}) - \bar{k}_b\}$$
$$+ \{i(\omega-\omega') + D(\mathbf{k}-\mathbf{k}')^2 + \phi_0(\mathbf{k}-\mathbf{k}')^2 U(\mathbf{k}-\mathbf{k}') - (k_a - 2\bar{k}_b\phi_0)\}\{[-(\mathbf{k}-\mathbf{k}')\cdot(\mathbf{k}')]U(\mathbf{k}') - \bar{k}_b\}]$$
$$\times G(\mathbf{k}',\omega',\omega'_\tau)C(\mathbf{k}-\mathbf{k}',\omega-\omega',\omega_{\tau_f}-\omega'_\tau). \tag{9}$$

We are mainly interested in the behavior of $\Sigma(\mathbf{k},\omega,\omega_{\tau_f})$ when expanded to second order in nonlinearity. The contributions arise from two sources (1) a one-loop contribution from the second-order term (containing three ϕ_1 fields) in Eq. (7) (second term in Fig. 2) and (2) a two-loop contribution from the first-order term(containing two ϕ_1 fields) in Eq. (7) (first term in Fig. 2). The contribution arising from the term containing three ϕ_1 fields, in Eq. (7), can be readily obtained by contracting two of the ϕ_1 fields. The second-order contribution due to the one-loop contribution in Eq. (8) does not have any new momentum dependence. Hence, it is the second-order contribution (first term in Fig. 2) arising from the two-loop contribution in Eq. (8) which is relevant. The correlation function is given by the FDT as $C = \frac{1}{\omega_{\tau_f}}\text{Im}G$. With these observations, Eq. (8) can be written as

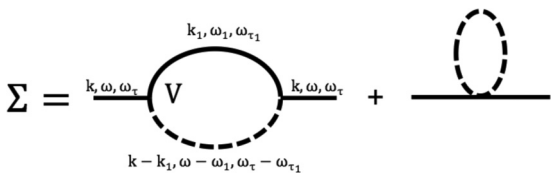

FIG. 2. Dashed line indicates the correlation function $G_0 G_0^*$ and solid line indicates the response function G_0. The self-energy term Σ is obtained by contracting the two ϕ_1 fields. The first term is the two-loop contribution from the first-order term (contains two ϕ_1 fields) in the fictitious time equation in Eq. (7). The second term gives the one-loop contribution from second-order term (contains three ϕ_1 fields).

$$[G]^{-1}\left(\mathbf{k},\omega,\omega_{\tau_f}\right) = -i\omega_{\tau_f} + \frac{1}{2(D_0)}[\omega^2] + \frac{1}{2(\bar{D})}\left[\nu_{\text{eff}}^2 k^4\right], \tag{10}$$

where $D_0 = k_a\phi_0 + k_b\phi_0^2$ and $\bar{D}$ is defined as

$$\frac{1}{2(\bar{D})}\left[\nu_{\text{eff}}^2 k^4\right] = \frac{1}{2(D_0)}(\nu k^2)^2 + \Sigma\left(\mathbf{k},\omega,\omega_{\tau_f}\right), \tag{11}$$

with $\nu = D + \phi_0 U(\mathbf{k})$. In the intermediate time, the strength of the interactions is such that $\phi_0 k^2 U(\mathbf{k})$ dominates over $(k_a - 2k_b\phi_0)$. We obtain Eq. (11) by neglecting the term $(k_a - 2\bar{k}_b\phi_0)$ in the Green's function equation [Eq. (10)] in the finite-time regime. Expanding $\nu_{\rm eff}$ and $\bar{D}$ about ν and D_0, respectively, and noting that the renormalization of ν dominates, we write

$$\nu_{\rm eff}k^2 \simeq \nu k^2 + \frac{1}{2\nu k^2}\Sigma\big(\mathbf{k},\omega,\omega_{\tau_f}\big),$$
$$\text{or } \Delta\nu k^2 = \frac{1}{2\nu k^2}\Sigma\big(\mathbf{k},\omega,\omega_{\tau_f}\big). \tag{12}$$

The two-loop contribution from the first-order term (containing two ϕ_1 fields) in Eq. (7) will contribute to the scaling laws in the intermediate as well as in the long-time limit (see below).

IV. RESULTS

A. Subdiffusive motion

In the spirit of self-consistent mode coupling theory, we replace ν by $\Delta\nu$ in the self-energy term $\Sigma(\mathbf{k},\omega,\omega_{\tau_f})$. We use G from Eq. (8), and an expression for C follows from the FDT. According to scale transformation, we know $\omega \sim k^z$, $\omega_\tau \sim k^{2z}$, $G \sim k^{-2z}$, $C \sim k^{-4z}$, and the vertex factor $V \sim k^{z+2}$. The self-energy term (Fig. 2), can be written as $\Sigma(\mathbf{k},\omega,\omega_{\tau_f}) \sim \int \frac{d^d\mathbf{k}'}{(2\pi)^d}\frac{d\omega'}{2\pi}\frac{d\omega'_\tau}{2\pi}VVGC$. By carrying out the momentum count of $\Sigma(\mathbf{k},\omega,\omega_{\tau_f})$, and keeping in mind that $\Delta\nu k^2 \sim k^z$, we find that $\Sigma(\mathbf{k},\omega,\omega_{\tau_f}) \sim k^{d-z+4}$. Using Eq. (12), we have $k^z \sim k^{d-z+2}$, which leads to $z = 1 + \frac{d}{2}$.

The single-cell mean-square displacement behaves as

$$\langle[r(t) - r(0)]^2\rangle \sim t^{2/z} = t^\alpha. \tag{13}$$

In three dimensions, $\alpha = \frac{4}{5} = 0.8$, implying that a labeled cell undergoes subdiffusive motion, which is one characteristic feature of glassy systems. If cell-cell interaction is modeled as $U_1 = U_0/\cosh^2(r/a)$ instead of a Gaussian, we obtain $\alpha = \frac{4}{6} = 0.57$, implying subdiffusive behavior. Although subdiffusive behavior is preserved at intermediate times, the scaling exponents depend on the form of interaction potential, which shows that the intermediate behavior of $\langle\Delta r^2(t)\rangle$ is nonuniversal. The subdiffusive behavior is a consequence of jamming of cells.

We also investigated how the jamming regime depends on the cell-cell adhesion strength, κ. The form of the interaction potential is shown in Eq. (A1) of Appendix A. We define the time-dependent order parameter in terms of the function $\langle Q(t)\rangle \equiv \int dr_1 dr_2 \langle\phi(r_1,0)\phi(r_2,t)\rangle\delta(r_1 - r_2)$, measuring the number of "overlapping" cells in two configurations separated by a time interval t. In Fourier space,

$$\langle Q(t)\rangle = \int_{\mathbf{k},w}\langle\phi_1(\mathbf{k},w)\phi_1(-\mathbf{k},-w)\rangle e^{iwt}$$
$$= \int_{\mathbf{k}}\frac{1}{\frac{\Sigma(\mathbf{k})}{\kappa k^2}}\exp\left[-t\frac{\Sigma(\mathbf{k})}{\kappa k^2}\right] = \int_{\mathbf{k}}\tilde{S}(\mathbf{k},t), \tag{14}$$

where the second line is obtained by using the mode-coupling approximation. The dynamic structure factor $\tilde{S}(\mathbf{k},t)$ decays exponentially [Eq. (14)] from which it follows that the relaxation time depends linearly on the adhesion strength κ. For small value of κ, $\tilde{S}(\mathbf{k},t)$ decays rapidly and, for large κ, the relaxation time increases substantially, leading to a stronger caging effect, which results in the extremely slow relaxation of the dynamic structure factor [17,29].

B. Long-time superdiffusion

In the long-time limit, the effects of nonlinearity due to death-birth dominate over mechanical interactions. Following the same procedure outlined above, we obtain the self-consistent mode coupling equation of the form $\Delta\mu = \frac{1}{2\mu}\Sigma(\mathbf{k},\omega,\omega_{\tau_f})$ in the hydrodynamic limit, with $\mu = (k_a - 2\bar{k}_b\phi_0)$. We now replace μ by $\Delta\mu$ in the self-energy term $\Sigma(\mathbf{k},\omega,\omega_{\tau_f})$ (Fig. 2), use G in Eq. (8), and C is calculated by using the FDT. The scale transformation for all the variables is the same as before except that the vertex factor $V \sim k^z$. By noting that $\Delta\mu \sim k^z$, we find $\Sigma(\mathbf{k},\omega,\omega_{\tau_f}) \sim \int \frac{d^d\mathbf{k}'}{(2\pi)^d}\frac{d\omega'}{2\pi}\frac{d\omega'_\tau}{2\pi}VVGC \sim k^{d-z}$. The self-consistent equation $\Delta\mu = \frac{1}{2\mu}\Sigma(\mathbf{k},\omega,\omega_{\tau_f})$ produces the dynamic exponent $z = d/2$. Therefore, asymptotically $\alpha = 1.33$, implying that the MSD exponent is greater than unity, which implies that collective motion leads to superdiffusive behavior. The calculated value of α is in excellent agreement with both the value obtained from simulations [20] and experimental results [18].

C. Invasion distance

Recently, the movement of the fibrosarcoma cells at the boundary of a growing spheroid pushing against a collagen matrix was measured by using imaging techniques [18]. The dynamics was quantified by using the invasion distance (Fig. 1), which is defined as the average distance from the center of mass of the tumor to the cells at the periphery, $\delta\mathbf{r}(t) = \langle\mathbf{r}_b - \mathbf{r}_{\rm CM}\rangle$, where $\mathbf{r}_b$ is the position of the cell at the boundary, and $\mathbf{r}_{\rm CM} = (1/N)\sum_i \mathbf{r}_i$, with N being the number of cells. It was found that $\langle\delta\mathbf{r}(t)\rangle \sim t^{1/z} = t^\xi$ with $\xi = 0.8$ [18]. By using our theory we find that $\langle\delta\mathbf{r}(t)\rangle \sim t^{2/3}$. The calculated and measured values of ξ are in fair agreement. If the dynamics were purely diffusive, as would be the case for a homogeneously distributed sample of individual cells, then ξ would be 0.5. The departure from this value is another indication of superdiffusion in this nonequilibrium system. The time-dependent structure factor $\tilde{S}(\mathbf{k},t)$ in this case decays exponentially as $\exp[-t\frac{\Sigma(\mathbf{k})}{\mu}]$, implying that the relaxation time depends linearly on the birth rate [20].

D. Dynamics of soft material and growing tumor are similar

Interestingly, the dynamics of certain soft glassy materials and the collective migration of cells have a common feature in that the underlying dynamics of these systems are governed by the birth and death processes. For the soft foam, Hwang and coworkers [19] used a model for Ostwald ripening for the bubbles, which can be recast as the reaction $X + X \to X$, which is identical to the apoptosis process used in tumor evolution. This process produces the nonlinearity $(k_b\phi^2)$ in both the problems. The present theory shows that this nonlinear term determines the scaling behavior in the long-time limit. From the theory presented above we conclude that both $\langle\Delta r^2(t)\rangle$

must have the same scaling behavior. Our theory predicts the general feature that birth-death-driven dynamics should lead to superdiffusive behavior with a universal dynamical exponent in the long-time limit. Thus, asymptotically, MSD scaling is impervious to the interaction details between the constituent objects in the nonequilibrium systems. Based on the calculation of $\langle \Delta r^2(t) \rangle$ for cells in tumors we surmise that the mean-square displacement for bubbles should increase as t^α at long times with the same exponent, $\alpha \approx 1.33$. Remarkably, this value is in accord with the simulation results reported elsewhere [19].

V. CONCLUSION

In summary, using a new theoretical framework, we have provided insights into the dynamics of a colony of tumor cells driven by an interplay of mechanical interactions and stochastic death-birth processes. The breakdown of number conservation, resulting from the stochastic death-birth process, makes the dynamics far from equilibrium, characterized by the absence of FDT. The introduction of a fictitious time in which FDT is valid allows us to calculate the response functions from which the correlation functions can be obtained by using the FDT. This new approach greatly simplifies the calculation of the scaling exponents. Nonlinear terms in the density evolution equation, arising from mechanical interactions determine the scaling behavior in the intermediate time. Strong cell-cell adhesion interactions lead to the glass-like caging behavior characterized by subdiffusive motion in the intermediate time. Stochastic death-birth processes determine the scaling in the long-time limit, which is independent of the mechanical interactions, as long as they are short ranged. In the long-time limit, the dynamics shows superdiffusive motion, leading to fluidization of the colony of cells. Our theory shows that the universal long-time behavior would arise in any systems in which the cells (or particles) are born and undergo apoptosis. These dynamical processes, surely relevant in many biological processes, produce active forces of sufficient magnitude to fluidize the dynamics of jammed cells at long times. It is this mechanism that apparently is also operative in soft glassy materials [19], that produces the unexpected superdiffusion in this abiotic system. As a consequence of the fundamental similarity between these completely distinct problems, we assert that, asymptotically, the cells in an evolving tumor and bubbles in a soap foam have precisely the same underlying dynamics at long times. In other words, these nonequilibrium systems belong to the same universality class. It would be most interesting to explore if the mechanism proposed to explain the origin of superdiffusion is present in other nonequilibrium systems as well. Finally, the theory presented here could help us to understand how cancer spreads by invading adjacent tissue involved in metastasis [30].

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APPENDIX A: SHORT-RANGE INTERACTION

To obtain the dynamics of an evolving collection of cells, we use the following simplified form for cell-cell interaction:

$$U(\mathbf{r}(i)-\mathbf{r}(j)) = \frac{\upsilon}{(2\pi\lambda^2)^{3/2}} e^{-\frac{[\mathbf{r}(i)-\mathbf{r}(j)]^2}{2\lambda^2}} - \frac{\kappa}{(2\pi\sigma^2)^{3/2}} e^{-\frac{[\mathbf{r}(i)-\mathbf{r}(j)]^2}{2\sigma^2}}, \tag{A1}$$

where υ and κ are the strengths of excluded volume and attractive interactions, respectively.

APPENDIX B: NONLINEAR TERM ARISING FROM BIRTH-DEATH PROCESS

We consider a minimal model to study the interplay between stochastic cell growth and annihilation processes leading to apoptosis and use it to derive a Langevin-type equation for logistic growth. We use the Doi–Peliti formalism [23,24,31] in order to derive an expression for the density dependence of the noise strength that describes cell-number fluctuations. The birth reaction $X \xrightarrow{k_a} X + X$ occurs at the rate constant k_a for each cell, and the backward reaction (annihilation or apoptosis) $X + X \xrightarrow{k_b} X$ occurs at rate k_b (see Fig. 1 in the main text). The master equation for this process is written as

$$\frac{\partial P(X_i,t)}{\partial t} = k_a[(X_i-1)P(X_i-1,t) - X_iP(X_i,t)] + k_b[X_i(X_i+1)P(X_i+1,t) - X_i(X_i-1)P(X_i,t)], \tag{B1}$$

where $P(X_i,t)$ is the probability of finding X_i particles at time t, and k_b is taken to be the apoptosis rate of distinct pairs of cells. The central idea of the Doi–Peliti formalism [23,24,31] is the introduction of a single vector $|\psi(t)\rangle$, which is a collection of a series of infinite number of $P(X_i,t)$:

$$|\psi(t)\rangle = \sum_{X_i=0}^{\infty} P(X_i,t)|X_i\rangle. \tag{B2}$$

Using Eq. (B2), the master equation in Eq. (B1) can be written in a compact form,

$$\frac{\partial}{\partial t}|\psi(t)\rangle = -L(c^\dagger, c)|\psi(t)\rangle, \tag{B3}$$

where

$$L(c_i^\dagger, c_i) = k_a\left(c_i^{\dagger 2} - c_i^\dagger\right)c_i + k_b\left(c_i^\dagger - c_i^{\dagger 2}\right)c_i^2. \tag{B4}$$

The bosonic creation operator $c_i^\dagger$ and annihilation operator c_i obey

$$[c_i, c_i^\dagger] \equiv c_ic_i^\dagger - c_i^\dagger c_i = 1, \tag{B5}$$

where [.,.] is the commutator, and the actions of the creation and annihilation operators for the ket vectors $|n\rangle$ are defined as, $c_i^\dagger|X_i\rangle = |X_i+1\rangle$, $c_i|X_i\rangle = X_i|X_i-1\rangle$.

The Schrödinger-like equation [Eq. (B3)] for the evolution of the state of the system may be integrate to find

$$|\psi(t)\rangle = e^{-Lt}\,|\psi(0)\rangle, \tag{B6}$$

with the initial state $|\psi\rangle = e^{\bar{X}_0 \sum_i (c_i^\dagger - 1)}|0\rangle$. The initial configuration for the master equation is an independent Poisson distribution at each site,

$$P(\{X_i\};0) = \Pi_i P_0(X_i) = \Pi_i e^{-\bar{X}_0} {X_0}^{-X_i}/X_i!, \tag{B7}$$

with mean initial input and output concentrations $\bar{X}_0$.

Our goal is to compute averages and correlation functions with respect to the configurational probability $P(\{X_i\};t)$, which is accomplished by using the projection state $\langle\mathcal{P}| = \langle 0|\Pi_i e^{c_i}$, for which $\langle\mathcal{P}|0\rangle = 1$ and $\langle\mathcal{P}|c_i^\dagger = \langle\mathcal{P}|$, since $[e^{c_i}, c_j^\dagger] = e^{c_i}\delta_{ij}$. The average value of an observable $A(\{X_i\})$ is

$$\langle A(t)\rangle = \sum_{\{X_i\}} A(\{X_i\})P(\{X_i\};t), \tag{B8}$$

from which the statistical average of an observable can be calculated by using

$$\begin{aligned}\langle A(t)\rangle &= \langle\mathcal{P}|A(\{c_i^\dagger, c_i\})|\psi(t)\rangle \\ &= \langle\mathcal{P}|A(\{c_i^\dagger, c_i\})e^{-H(\{c_i^\dagger\},\{c_i\})t}|\psi(0)\rangle.\end{aligned} \tag{B9}$$

We follow a well-established route in quantum many-particle theory [32] and derive a field theory representation by constructing a path integral equivalent of the time-dependent Schrödinger equation [Eq. (B3)] based on coherent states [31]. These are defined as right eigenstates of the annihilation operators, $c_i|\alpha_i\rangle = \alpha_i|\alpha_i\rangle$, with complex eigenvalues α_i. The coherent states satisfy $|\alpha_i\rangle = \exp(\frac{1}{2}|\alpha_i|^2 + \alpha_i\alpha_i^\dagger)|0\rangle$, the overlap integral $\langle\alpha_j|\alpha_i\rangle = \exp(-\frac{1}{2}|\alpha_i|^2 - \frac{1}{2}|\alpha_j|^2 + \alpha_j^*\alpha_i)$, and the completeness relation $\int \Pi_i d^2\alpha_i|\{\alpha_i\}\rangle\langle\{\alpha_i\}| = \pi$. After splitting the temporal evolution [Eq. (B3)] into infinitesimal increments, inserting the completeness relation at each time step, and with additional manipulations, we obtain an expression for the configurational average,

$$\langle A(t)\rangle \propto \int \Pi_i d\alpha_i d\alpha_i^* A(\{\alpha_i\})e^{-\mathcal{S}[\alpha_i^*,\alpha_i]}. \tag{B10}$$

The exponential statistical weight is determined by the action

$$\mathcal{S}[\alpha_i^*, \alpha_i] = \sum_i \left[\int_0^{t_f} \left\{\alpha_i^*(t)\frac{\partial\alpha_i(t)}{\partial t}\right\} + L(\alpha_i^*, \alpha)\right]dt. \tag{B11}$$

Finally, by taking the continuum limit using $\sum_i \to a_0^{-d}\int d^dx$, a_0 is a lattice constant, $\alpha_i(t) \to \phi(x,t)$ and $\alpha_i(t) \to a_0^d\phi(x,t)$, the expectation value is represented by a functional integral,

$$\langle A(t)\rangle \propto \int \Pi_i \mathcal{D}[\phi^*,\phi]A(\{\phi\})e^{-\mathcal{S}[\phi^*,\phi]}, \tag{B12}$$

with an effective action

$$\mathcal{S}[\phi^*, \phi] = \int_0^{t_f} \left[\left\{\phi^*(t)\frac{\partial\phi(t)}{\partial t}\right\} + L(\phi^*, \phi)\right]dt. \tag{B13}$$

In the Hamiltonian [Eq. (B4)], $c^\dagger$ is replaced by the field variable ϕ^*, and the c operator becomes ϕ.

The action in Eq. (B13) encodes the stochastic master-equation kinetics through four independent fields (ϕ^*, ϕ). With this formulation, an immediate connection can be made to the response functional formulation by using the Janssen–De Dominicis formalism for the Langevin equations [33,34]. In this approach, the response field enters at most quadratically in the pseudo-Hamiltonian, which may be interpreted as an average over Gaussian white noise. With this in mind, we apply the nonlinear Cole–Hopf transformation [35,36] in order to obtain the quadratic terms in auxiliary fields, $\phi^* = e^{\bar{\phi}_I}$, $\phi = e^{-\bar{\phi}_I}\phi_I$, to the action in Eq. (B13). The Jacobian for this variable transformation is unity, and the local particle density is $\phi^*\phi = \phi_I$. We obtain the following Hamiltonian:

$$L = -\bar{k}_b\bar{\phi}\phi\left(\frac{k_a}{k_b} - \phi\right) + \bar{\phi}^2\left[\frac{k_a}{2}\phi + \bar{k}_b\frac{\phi^2}{2}\right], \tag{B14}$$

where $\bar{k}_b = a_0^d k_b$. In the above equation, the exponential term has been expanded to second order. The rate equation is obtained through $\delta\mathcal{S}/\delta\bar{\phi}\,|_{\bar{\phi}=0} = 0$. The terms quadratic in the auxiliary field $\bar{\phi}$ encapsulate the second moment of the Gaussian white noise with zero mean.

We arrive at an expression for the action for a colony of tumor cells, governed by the dynamics illustrated in Fig. 1 in the main text, in the continuum description,

$$\begin{aligned}S[\bar{\phi}, \phi] = \int dt \Bigg\{&\bar{\phi}\left[\frac{\partial\phi}{\partial t} - \bar{k}_b\phi\left(\frac{k_a}{\bar{k}_b} - \phi\right)\right] \\ &+ \bar{\phi}^2\left[\frac{k_a}{2}\phi + \bar{k}_b\frac{\phi^2}{2}\right]\Bigg\}.\end{aligned} \tag{B15}$$

The term $\bar{k}_b\phi(\frac{k_a}{\bar{k}_b} - \phi)$ gives the source term for cell birth-death. The coefficient of $\bar{\phi}^2$ gives the expression for noise correlation in the Langevin description, which breaks the cell-number conservation and plays a crucial role in the dynamical behavior of the collection of cells.

APPENDIX C: EFFECTIVE DIFFUSION COEFFICIENT

The emergence of superdiffusion may be rationalized by considering movement of a labeled cell as a diffusive process with an effective time-dependent diffusion coefficient. In the spirit of mode-coupling theory, we write $D_{\text{eff}}k^2 \sim k^z$, where D_{eff} is the effective diffusion coefficient of the cell. In the real time, D_{eff} scales as $t^{\frac{2-z}{z}}$. Using the Langevin equation of the form $\dot{y} = \sqrt{D_{\text{eff}}(t)}\eta_y$, where $\langle\eta_y(t)\eta_y(t')\rangle = 2\delta(t-t')$, we obtain the mean-square displacement, $\langle\Delta y^2\rangle \sim \int D_{\text{eff}}(t)dt \sim t^{2/z}$.

In the homogeneous state, the evolution of cells is given by

$$\frac{\partial\phi_1(\mathbf{r},t)}{\partial t} = D\nabla^2\phi_1(\mathbf{r},t) + \nabla\cdot\left[\eta(\mathbf{r},t)\phi_0^{1/2}(\mathbf{r},t)\right]. \tag{C1}$$

We assume that Eq. (C1) is invariant under the scale transformations, $\mathbf{r} \to s\mathbf{r}$, $\phi \to s^\chi\phi$, and $t \to s^z t$ where χ is the exponent corresponding the cell density fluctuations, and z is the dynamical exponent. With these transformations, Eq. (C1) becomes

$$\begin{aligned}\frac{\partial\phi_1(\mathbf{r},t)}{\partial t} &= Ds^{z-2}\nabla^2\phi_1(\mathbf{r},t) \\ &\quad + s^{-d/2+z/2-\chi-1}\nabla\cdot\left[\eta(\mathbf{r},t)\phi_0^{1/2}(\mathbf{r},t)\right].\end{aligned} \tag{C2}$$

To find the critical exponents z and χ, we require that Eq. (C1) must be invariant under the scale transformations. Thus, to ensure scale invariance, each term on the right-hand side of Eq. (C2) must be independent of s, which implies that $z = 2$ and $\chi = -d/2$. Under these conditions, the cells undergo normal diffusion with MSD $\sim t$.

In the growing phase, $\phi_1(\mathbf{r}, t)$ satisfies

$$\frac{\partial \phi_1(\mathbf{r},t)}{\partial t} = D\nabla^2\phi_1(\mathbf{r},t) + (k_a - 2\bar{k}_b\phi_0)\phi_1(\mathbf{r}',t) - \bar{k}_b\phi_1^2 + \nabla\cdot\left[\eta(\mathbf{r},t)\phi_0^{1/2}(\mathbf{r},t)\right] + \sqrt{k_a\phi_0 + \bar{k}_b\phi_0^2}f_\phi, \tag{C3}$$

which is obtained by neglecting interaction between cells.

Using the same scale transformation as before, we obtain

$$\frac{\partial \phi_1(\mathbf{r},t)}{\partial t} = Ds^{z-2}\nabla^2\phi_1(\mathbf{r},t) + s^z(k_a - 2\bar{k}_b\phi_0)\phi_1(\mathbf{r}',t) - s^{\chi+z}\bar{k}_b\phi_1^2 + s^{-d/2+z/2-\chi-1}\nabla\cdot\left[\eta(\mathbf{r},t)\phi_0^{1/2}(\mathbf{r},t)\right] + s^{-d/2+z/2-\chi}\sqrt{k_a\phi_0 + \bar{k}_b\phi_0^2}f_\phi. \tag{C4}$$

To ensure scale invariance, one would expect that the right-hand side of Eq. (C4) must be independent of s. However, this procedure provides five scaling relations for two exponents z and χ, thereby overdetermining them. To get the correct values of the exponents, the coefficients must also change under scaling. By using the stochastic quantization scheme mentioned in the main text, we find $z = 3/2$ in the long-time limit. The effective diffusion coefficient D_{eff} scales as $t^{1/3}$, thereby, MSD scales as $t^{4/3}$, implying that at long times the motion is superdiffusive.

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