Interstitial flows regulate collective cell migration heterogeneity through adhesion

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The migration behaviors of cancer cells are known to be heterogeneous. However, the interplay between the adhesion interactions, dynamical shape changes and fluid flows in regulating cell migration heterogeneity and plasticity during cancer metastasis is still elusive. To further quantitative understanding of cell motility and morphology, we develop a theory using stochastic quantization method that describes the role of biophysical cues in regulating diverse cell motility. We show that the cumulative effect of time dependent adhesion interactions that determine the structural rearrangements and self-generated force due to actin remodeling, dictate the super-diffusive motion of mesenchymal phenotype in the absence of flow. Interstitial flows regulate cell motility phenotype and promote the amoeboid over mesenchymal motility through adhesion interactions. Cells exhibit a dynamical slowing down of collective migration, with a decreasing degree of super-diffusion. Our findings, suggest a mechanism of Interstitial flow induced directed motion of cancer cells through adhesion, and provide the much needed insight into a recent experimental observation concerning the diverse motility of breast cancer cells.

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Collective cancer cell invasion, followed by local and distant metastasis, is a hallmark of cancer\cite{1}. Cancer metastasis is a multistep process, where tumor cells detach from primary tumor, invade through the interstitial extracellular matrix, intravasation of tumor cells into vascular vessels, extravasation of circulating tumor cells to peripheral tissues, and establish a secondary tumor at distant organ\cite{2–11}. Dynamics associated with invasion and metastasis, involve the collective cell migration regulated by biomechanical (e.g. cytokines secreted by cells and nutrients) and biophysical cues (e.g. fluid flows and ECM\cite{12–16}). Tumor cells reside in an extracellular matrix (ECM) containing interstitial fluid that transports nutrients and signaling molecules. The interstitial flow has been shown to affect the morphology and migration of cells such as fibroblasts, cancer cells, endothelial cells, and mesenchymal stem cells\cite{17}. Interstitial flows are particularly important for tumor cell invasion because it is elevated in tumor microenvironment due to the heightened interstitial fluid pressure as well as the abnormal angiogenic, lymphanogenic blood and lymphatic vessels\cite{13–16,18–20}. The flow speed associated with interstitial flows are in the order of a few micrometers per second in normal tissue\cite{21}. Two type of motility (e.g. amoeboid and mesenchymal) have been broadly categorized in cell migration in 3D architecture\cite{22,23}. Cells with aspect ratio smaller than 2.0 are considered rounded or amoeboid and cells with aspect ratio greater than 2.0 are considered elongated or mesenchymal (see fig.1)\cite{24–26}.

Recent experiment has demonstrated that interstitial flows regulate the cancer cell migration heterogeneity within a three dimensional biomatrix. Using a microfluidic model, authors show that breast cancer cells (MDA-MB-231) embedded in collagen matrix, exhibit both amoeboid and mesenchymal motility phenotype and interstitial flows promote amoeboid over mesenchymal motility of breast cancer cells\cite{27}.

How interstitial flows promote cancer cell invasion is largely unknown. The understanding of this process could help to develop drugs that inhibit the process and prevent cancer from metastasizing. How the biophysical forces modulate tumor cell migration heterogeneity and plasticity, and creates a complex spatiotemporal dynamical property during cancer metastasis is still elusive.

In this article, we develop a theory to describe how biophysical cues regulate the diverse collective cell motility. The cumulative effect arising from the non-equilibrium description of living cells using a time dependent mechanical interaction, and flows, lead to complex dynamics, which may have far reaching implications in our understanding of cancer metastasis. One of the major difficulties in the study of collective behavior of the cells far from equilibrium is the breakdown of a fluctuation-dissipation theorem (FDT); hence, independent diagrammatic expansions for the response function and the correlation function. The equilibrium distribution is not known and averages can be computed only for the statistical noise.

We study the relevant continuum description of collective behavior of a colony of cells in the physical time scale, using stochastic quantization technique, originally proposed by Parisi and Wu\cite{28}. We show that the time de-
ependent adhesion interactions that determine the structural rearrangements, the long range hydrodynamic interactions among living cells, and self-generated force due to actin remodeling dictate the complex collective behavior, when a continuum description of the cellular colony is invoked, in the physical time scale. We find that cells exhibit both amoeboid and mesenchymal motility characterized by super-diffusive motion. The mean-square displacement (MSD) of the cells for the mesenchymal motility behaves as $t^\alpha$, with, $\alpha = 1.43$. The interstitial flows impair the collective migration with a gradually decreasing degree of super-diffusion and promote the amoeboid motility phenotype over mesenchymal motility. In the case of flow, the MSD exponent $\alpha = 1.2$, which reflects the dynamical slowing down of the spatiotemporal collective migration.

**Theory:** In the absence of flow, cells exhibit mesenchymal motility phenotype in 3D collagen matrix. Cells secreted fibronectin molecules into a fibrillar form, and form long lived adhesions with the collagen fibers, which trigger the downstream signaling that activates actin-network expansion and thus exhibit cell migration. 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 mesenchymal cell $i$ is $\frac{\partial \mathbf{r}_i}{\partial t} = -\sum_{j=1}^{N} \nabla U(\mathbf{r}_i(t) - \mathbf{r}_j(t)) + \eta_i(t) + f_0 \xi_i(t)$, where $U$ contains repulsive interactions with range $\lambda_1$, adhesion interactions with collagen matrix with range $\sigma_1$, and favorable attractive interactions between cells with range $\sigma$ and with strengths $\nu$, $g$ and $\kappa$ respectively. We use Gaussian potentials (see the Supplementary Information (SI) for details) in order to obtain analytical solutions. Needless to say that the conclusions would be valid for any short-ranged $U$. We assume that the adhesion strength is changing during the topological rearrangement via $a_i + (a_i - a_f) e^{-\lambda_1 t}$ [29]. $a_i$ and $a_f$ are initial and final interaction strengths ($a$ stands for $g$ and $\kappa$) and the time scale for changing the receptor-ligand interaction is given by $\lambda^{-1}$. The Gaussian white noise, satisfies $<\eta_i(t)\eta_j(t')> = 2D\delta_{ij}\delta(t - t')$. The mesenchymal cells are subject to a self-generated force of actin-network remodeling. The cells are, thus in addition subject to a random self-generated force with amplitude $f_0$. The randomness is modeled by an athermal noise $\xi(t)$, which is exponentially correlated over a time scale $\tau_p$. The statistics of the $\xi(t)$ is given by $<\xi(t)> = 0$, $<\xi(t)\xi(t')> = 0$ and $\xi(t)\xi(t') = b \exp[-|t-t'|/\tau_p]$, where $b$ is the dimensionless constant. The athermal noise in general does not obey the FDT.

In the presence of interstitial flow, cells exhibit amoeboid motility phenotype. The flows carried away the cell-secreted fibronectin molecules before they were assembled into fibrils and attached to the collagen fibers. The round shaped amoeboid cells extend their protrusions in all directions and form a short lived adhesions with collagen matrix. The amoeboid cells migrate through squeezeing the matrix when find a suitable path. We begin by considering the dynamics of a colony of cells in the presence of flow in a dissipative environment where inertial effects are negligible. Each cell experiences mechanical forces, such as adhesion, excluded volume interactions due to neighbors, and a random force characterized by Gaussian white noise. The equation of motion for single amoeboid cell $i$ is

$$\frac{\partial \mathbf{r}_i}{\partial t} = k_B T \sum_{j=1}^{N} \mu_{ij} \nabla \phi_j(\mathbf{r}_i, t), \mathbf{r}_j(t))$$

$$+ k_B T \sum_{j=1}^{N} \nabla \phi_i(\mu_{ij} + \eta_i(t) + f_0 \xi_i(t)).$$

The first term on the r.h.s. of Eq (1) is the effect of force acting on cell $j$ creates a hydrodynamic flow-field in the fluid, thereby entraining cell $i$. Where $U$ contains repulsive interactions with range $\lambda_1$, adhesion interactions with collagen matrix with range $\sigma_1$, and favorable attractive interactions between cells with range $\sigma$, and with strengths $\nu$, $g$, and $\kappa$ respectively (see the Supplementary Information (SI) for details). Second term in the Langevin equation is due to the spacial variation of the cell’s self motilities. It is introduced to compensate the flux caused by the position dependent random velocity contributions $\eta_i$, which are assumed to be Gaussian random vectors exhibiting hydrodynamic correlations according to fluctuation-dissipation theorem (FDT), $<\eta_i(t)\eta_j(t')> = 2k_B T \sum_{j=1}^{N} \mu_{ij}\delta(t - t')$. Hydrodynamic effects are incorporated via the mobility matrix $\mu_{ij}$, which is obtained from the Green’s function of Stokes equation as $8\pi \eta G^{(0)}_{\alpha\beta}(\mathbf{r}) = \frac{1}{2} \left( \delta_{\alpha\beta} + \frac{r_{\alpha}r_{\beta}}{r^2} \right)$. The time evolution of the density function for a single cell $\phi_i(\mathbf{r}, t) = \delta(\mathbf{r} - \mathbf{r}_i(t))$. A closed form Langevin equation for the density, $\phi(\mathbf{r}, t) = \sum_k \delta(\mathbf{r} - \mathbf{r}_k(t))$ can be obtained using standard approach [31]. The time evolution of $\phi(\mathbf{r}, t)$ is given by

$$\frac{\partial \phi(\mathbf{r}, t)}{\partial t} = \nabla \cdot \left( \phi(\mathbf{r}, t) \int d\mathbf{r}' \phi(\mathbf{r}', t) \mu_{ii} \nabla U(\mathbf{r} - \mathbf{r}') \right)$$

$$+ D \nabla^2 \phi(\mathbf{r}, t) + \nabla \cdot \left( \nabla \phi \right) + \left( \eta + \xi \right) \phi^{1/2}(\mathbf{r}, t).$$

Note that the density equation contains same information as N-body stochastic Langevin equations. This is an out of equilibrium problem characterized by the absence of fluctuation-dissipation theorem due to long range hydrodynamic term and self-generated force due to actin remodeling. Eq. (2) can be studied analytically by treating the non-linear terms using a perturbative approach, based on the stochastic quantization scheme [25] [32] [33].
Stochastic quantization approach: To understand the dynamics of collections of cells, we use the stochastic quantization method developed by Parisi-Wu in another context. The collective migration of cells described by Eq. (2) is an out of equilibrium problem characterized by the absence of FDT, which relates the correlation and response function in momentum space as $C = \frac{1}{2} \text{Im} G$. The usual analytic route to get the scaling solution of this problem, one can introduce a response field $\phi$. We need to calculate both the response function ($G = \langle \phi \phi \rangle$) and correlation function ($C = \langle \phi \phi \rangle$) because of the absence of a fluctuation dissipation relation. The key advantage of the present method is that we do not need to calculate both the correlation, and the response functions. The FDT is constructed in fictitious time introduced in fictitious time, one can obtain the correlation function, once the scaling of the problem. The FDT relation enables us to obtain the scaling solution of this problem, once the scaling of the response function is known. By taking the infinite limit in fictitious time, one can obtain the correlation function in real time. The scaling solution of the problem can be obtained by power counting analysis instead of doing renormalization group calculation.

We now exploit the Parisi-Wu stochastic quantization scheme [28], and introduce a fictitious time $'\tau_f'$, and consider all variables to be functions of $'\tau_f'$, in addition to $k$ and $w$. A Langevin equation in $'\tau_f'$ space is,

$$\frac{\partial \phi_1(k, w, \tau_f)}{\partial \tau_f} = -\frac{\delta S}{\delta \phi_1(-k, -w, \tau_f)} + f_\phi_1(k, w, \tau_f), \quad (3)$$

with $f_{\phi_1} > 2 \delta(k + k') \delta(w + w') \delta(\tau_f - \tau_f')$. This ensures that as $\tau_f \rightarrow \infty$, the distribution function will be given by the action $S(k, w)$, because in the $\tau_f$-space a fluctuation dissipation theorem (FDT) is preserved. The action $S(k, w)$ can be obtained by writing down the probability distribution $P(f_{\phi_1}) \propto \exp[-\int_{k, w} \frac{1}{2} (\partial \phi_1)^2 + (f_{\phi_1} \phi_1)_{\omega} \frac{\delta S}{\delta \phi_1}(k, w)] = \exp[-S]$ corresponding to the noise term $f_{\phi_1}$, and the action $S(k, w)$ in terms of $\phi_1(k, w)$ with the help of Eq. (2). The expression for the $S$ is in the appendix.

We follow the procedure of obtaining scaling laws of the problem, which has been demonstrated in earlier works [32,33]. The dynamics of Eq. (3) requires only the calculation of response functions, the correlation functions in this dynamics are related to response function through FDT relation, i.e., in Fourier space, $C = \frac{1}{2} \text{Im} G$. We can obtain the scaling laws in real space and time in a straightforward fashion from the solution in the fictitious time $'\tau_f'$ space.

We obtain the following self-consistent equation for the self energy from the calculation of response function using Eq. (3):

$$\Delta \nu = \frac{D_0}{2\nu} \Sigma(k, \omega, \omega_{\tau_f}), \quad (4)$$

where, $\nu = D\mu(k) k^2 + \phi_0 k^2 \mu(k) g(\omega) U(k) + k^2 \mu(k)$, $D_0 = 2(D k^2 \phi_0 + (f \phi g^2 \xi(\omega)) \phi_0)$, and $\Sigma$ is the self-energy term, a two-loop contribution from the first order term containing two $\phi_1$ fields in Eq. (3) (first term in Fig. 3) will contribute in the scaling laws for the cell in the finite time. We use Eq. (13) for getting the scaling laws of both the amoeboid and mesenchymal cells phenotype.

Results: Mesenchymal motility: The mesenchymal cell phenotype forms long-lived integrin-based adhesions with the collagen matrix and migrate via either remodeling of actin network or degrading the matrix. The nonlinear term i.e. the adhesion interaction plays an important role in the complex dynamics of collective migration of mesenchymal cell phenotype. In a self consistent mode coupling theory, we now replace $\nu$ by $\Delta \nu$ in the self energy term $\Sigma(0, \omega, \omega_{\tau_f})$ in the first term in Fig (3), use $G \sim \omega_{\tau_f}^{-1}$ as from Eq. (3), and $C$, which follows from the FDT. In the absence of flow, $\mu = 1$. According to scale transformation, we know that $\omega \sim k^z$, $\omega_{\tau_f} \sim k^{4z-2}$, $G \sim k^{-4z+2}$, $C \sim k^{-8z+4}$ and the vertex factor $V \sim k^{2z}$. The self energy term in Fig. (3) can be written as $\Sigma(0, \omega, \omega_{\tau_f}) \sim \int d^d k \frac{\xi(\omega)}{2 \pi} \frac{\partial^2}{\partial \nu^2} VVGC$. By carrying out the momentum count of $\Sigma(0, \omega, \omega_{\tau_f})$, and using $\Delta \nu \sim k^z$, we find that $\Sigma(k, \omega, \omega_{\tau_f}) \sim k^{d+1-3z}$. Using Eq. (13) and $\nu / D_0 \sim k^z$, we have $k^{2z} \sim k^{1+4-3z}$, which leads to $z = \frac{d-4}{2}$. MSD exponent $\alpha = 2 / z = 10 / (d+4)$. In 3D, $\alpha = 1.43$, i.e., the mesenchymal cells undergo super-diffusion. The non-linear term arising from cell-cell adhesion that determines the dynamical shape change during cell motion and self-generated force, produce super-diffusive motion. The theoretical result is in excellent agreement with the recent experimental result using microfluidic model [29].

Interstitial flow induced amoeboid motility: In the presence of interstitial flow, cells exhibit amoeboid motility. The amoeboid cells form short lived adhesion with the collagen matrix. The time scale $\lambda^{-1}$ is small compared to the mesenchymal motility phenotype. In case of flow, the cells exhibit long range hydrodynamic interactions that determine the complex spatiotemporal dynamics of amoeboid cell phenotype. The self generating force of actin remodeling helps to propel in path finding fashion through collagen matrix. In a self consistent mode coupling theory, we now replace $\nu$ by $\Delta \nu$ in the self energy

![Fig. 2: Dashed line indicates the correlation function ($G_0 G_0^* \Sigma$) and solid line indicates the response function ($G_0$). Self-energy term ($\Sigma$) is obtained by contracting the two $\phi_1$ fields. First term is the two loop contribution from the first order term (contains two $\phi_1$ fields) in the fictitious time equation. Second one is the one loop contribution from second order term (contains three $\phi_1$ fields).](image-url)
term $\Sigma(0, \omega, \omega_f)$ in the first term in Fig.3, use $G \sim \omega_f^{-1}$ as from Eq. 4 and C, which follows from the FDT. According to scale transformation, we know that $\omega \sim k^z$, $\omega_f \sim k^{4z-2}$, $G \sim k^{-4z+2}$, $C \sim k^{-8z+4}$ and the vertex factor $V \sim k^{4z-2}$. The self energy term in Fig.3 can be written as $\Sigma(0, \omega, \omega_f) \sim \int \frac{d^d k}{(2\pi)^d} \frac{d\omega}{2\pi} \frac{d\omega_f}{2\pi} VVG_C$. By carrying out the momentum count of $\Sigma(0, \omega, \omega_f)$, and using $\Delta \nu \sim k^z$, we find that $\Sigma(k, \omega, \omega_f) \sim k^{d+z}$. Using Eq. 13 and $\nu/D_0 \sim k^{3z-2}$, we have $k^{4z-2} \sim k^{d+z}$, which leads to $z = \frac{d+2}{2}$. MSD exponent $\alpha = 2/z = 6/(d+2)$. In 3D, $\alpha = 1/2$, i.e., the amoeboid cells undergo superdiffusion. The non-linear term due to long-range hydrodynamic interactions among cells in addition with self-generated force, produce super-diffusive motion for amoeboid cell phenotype. The decrease of MSD exponent determines the dynamical slowing down of initial collective migration of mesenchymal cell phenotype. Therefore, interstitial flows impair the cells ability to spread by sweeping away the adhesion molecules with the flow and making the cells as amoeboid phenotype with short-lived adhesion with the collagen fiber. The cells migrate via squeezing through the pore of the collagen fiber when find a suitable path. The theoretical result is in excellent agreement with the recent experimental result using microfluidic model.

Conclusion: In the present contribution, using a new theoretical framework, we provide insight into the dynamics of a colony of cancer cells driven by physical cues. The theory reveals that the interstitial flows regulate cancer cell morphology and motility phenotypes, emphasizing the role of fluid flows in regulating cancer cell migration heterogeneity. The conventional practice in dealing with this out of equilibrium problems is to use a set of fictitious fields called response fields, which provide a field theoretic prescription for the response function. In contrast, we propose the introduction of a fictitious time in which a FDT is valid, and thereby only correlation functions need to be calculated. Our approach greatly simplifies the evaluation of scaling exponents. We find that the non-linear term in the density evolution equation arising from mechanical interactions along with self generating force due to actin remodeling, determine the scaling behavior for the collective migration of cells. In the absence of flow, cells exhibit collective migration of mesenchymal motility phenotype induced by time dependent interaction potentials that determine the structural rearrangement during their path generating migration through collagen matrix. In contrast, the cells exhibit the amoeboid motility in the presence of flow and exhibit a dynamical slowing down of directed migration, with a gradually decreasing degree of super-diffusion. The long-range hydrodynamic interactions among cells in the presence of interstitial flow, determines the collective migration of cells through collagen matrix in a path finding fashion. The theoretical framework introduced here provides evidence of interstitial flow directed collective motion heterogeneity and could explain the invasion of cancer cells under interstitial flow, observed in a recent experiment. The theory introduced here could help us understand how cancer cells spread by invading adjacent tissues involved in metastasis.

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I. SUPPLEMENTARY INFORMATION: INTERSTITIAL FLOWS REGULATE COLLECTIVE CELL MIGRATION HETEROGENEITY THROUGH ADHESION

A. Short-range interaction

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

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

where \( \nu \) and \( \kappa \) are the strengths of excluded volume and attractive interactions, respectively.

In addition, the cell surface-ECM interactions \( U_s \), determining the configuration-dependent forces experienced by the cells: \( U_s = -\frac{g}{(2\pi \sigma_0)^{3/2}} e^{-\frac{(r - r_0)^2}{2\sigma_0^2}} \). The potential term \( U_s \) describes the cell surface-collagen interactions as a function of \( r_0 \), the average distance between cell and collagen. Cells interact with the collagen through receptor-ligand interactions, described by short range potential. Mesenchymal cells form long-lived adhesion with collagen. We assume the adhesion strength is changing during the topological rearrangement via, \( a_f + (a_i - a_f)e^{-\lambda t}. \) \( a_i \) and \( a_f \) are initial and final interaction strengths and the time scale of changing the receptor-ligand interaction is given by \( \lambda^{-1} \). Where \( a \) stands for \( g \) and \( \kappa \). In contrast, amoeboid cells form short lived adhesion with the collagen, i.e., the time scale for the adhesive interaction \( \lambda^{-1} \), is small compared to mesenchymal cells.

B. Density equation

To simplify the multiplicative noise term (last term in Eq. (2) in the main text), we assume that the density fluctuates around a constant value. Hence, we define the density using \( \phi(r, t) = \phi_0 + \phi_1(r, t) \), and expand Eq.(1) in the main text in \( \frac{\partial}{\partial \phi_0} \) up to the lowest order in non-linearity. In Fourier space, the equation for the density fluctuation becomes,

\[ \frac{\partial \phi_1(k, t)}{\partial t} = -(Dk^2 \mu(k) + \phi_0 k^2 a(\omega) \mu(k)) U(k) + k^2 \mu(k) \phi_1(k) + \int dq (-q \cdot k) \mu(q) U(q) a(\omega) \phi_1(q) \phi_1(k - q) + f_{\phi_1}, \]

with \( f_{\phi_1} \phi_1 \geq Dk^2 \mu_0 + k^2 \xi(\omega) \phi_0 \). Where, \( \xi(\omega) = \frac{2\sigma_r}{1 + \frac{\omega^2}{\omega_r^2}} \). The Greens function \( G \) is given by,

\[ [G]^{-1} = -i\omega + Dk^2 \mu(k) + \phi_0 k^2 a(\omega) \mu(k) U(k) + k^2 \mu(k) + \Sigma(k, \omega), \]

where, \( a(\omega) = \frac{1}{\lambda + i\omega} \), and \( \Sigma(k, \omega) \) is the self energy term contributed from non-linear adhesion interactions.
C. Stochastic quantization technique

We now exploit the Parisi-Wu stochastic quantization scheme \cite{T1,CW,CW77}, and introduce a fictitious time $\tau_f$, and consider all the variables to be functions of $\tau_f$. A Langevin equation in $\tau_f$ space is,

$$\frac{\partial \phi_1(k, w, \tau_f)}{\partial \tau_f} = -\frac{\delta S}{\delta \phi_1(-k, -w, \tau_f)} + f_{\phi_1}(k, w, \tau_f), \quad (8)$$

with $< f_{\phi_1} f_{\phi_1} > = 2\delta(k + k')\delta(w + w')\delta(\tau_f - \tau'_f)$. Because FDT is valid in the fictitious time it follows that as $\tau_f \to \infty$, the distribution function will be given by the action $S(k, w)$. The action $S(k, w)$ can be obtained by writing down the probability distribution $P(f_{\phi_1}) \propto \exp[-\int \frac{d^d k}{(2\pi)^d} 2\pi \int \frac{d^d \mu}{(2\pi)^d} f_{\phi_1}(k, w) f_{\phi_1}(-k, -w)] = \exp[-S]$ corresponding to the noise term $f_{\phi_1}$ in Eq. (6), and the action $S(k, w)$ in terms of $\phi_1(k, w)$ using Eq. (6). The expression for the action $S$ obtained using Eq. (6) is,

$$S = \int \frac{d^d k}{(2\pi)^d} \int \frac{d^d \mu}{(2\pi)^d} \int \frac{d^d \xi}{(2\pi)^d} \left(\int d\omega \phi_1(q) \phi_1(q) \phi_1(k-q) \left\{ -i\omega + \left( Dk^2 \mu + \phi_0 k^2 a(\omega) U(k) + k^2 \mu(k) \right) \phi_1(k) + \int d\omega (-q \cdot k) \mu(q) a(\omega) U(q) \right\} \left\{ -i\omega + \left( Dk^2 \mu - \phi_0 k^2 a(\omega) U(k) + k^2 \mu(k) \right) \phi_1(-k) + \int d\omega (-q \cdot -k) \mu(q) a(\omega) U(q) \right\} \phi_1(q) \phi_1(-k-q) \right) \right)$$

D. Greens function for density equation

The correlation functions, calculated from Eq. (5), lead to the required correlation functions of the original theory, in the $\tau_f \to \infty$ limit. In order to obtain the scaling laws, it suffices to work at arbitrary $\tau_f$. It is obvious from Eq. (8) that in the absence of the non-linear terms, the Greens function $G^{(0)}$ is given by,

$$[G^{(0)}]^{-1} = -i\omega_{\tau_f} + \frac{1}{2(Dk^2 \mu + \phi_0 k^2 \mu a(\omega) U(k) + k^2 \mu(k))^2} \left[ \omega^2 + Dk^2 \mu(k)^2 + \phi_0 k^2 \mu(k) a(\omega) U(k) + k^2 \mu(k) \right]$$

where $\omega_{\tau_f}$ is the frequency corresponding to the fictitious time $\tau_f$. As is customary, the effect of non-linear terms, can be included perturbatively leading to the Dyson’s equation

$$[G]^{-1} = [G^{(0)}]^{-1} + \Sigma(k, \omega, \omega_{\tau_f}) \quad (10)$$

Here, we are concerned with the behavior of $\Sigma(k, \omega, \omega_{\tau_f})$, which becomes non-linear when expanded to second order. We note that the contribution comes from two different sources (1) a one-loop contribution from the second order term (containing three $\phi_1$ fields) in Fig. (8) (second term in Fig. 3) and (2) a two-loop contribution from the first order term (containing two $\phi_1$ fields) in Fig. (8) (first term in Fig. 3). The contribution arising from the term containing three $\phi_1$ fields, in Eq. (8) can be readily obtained by contracting two of the $\phi_1$ fields. The second order term coming from 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. 3), coming from the two-loop contribution in Eq. (8), which is significant. The correlation function is given by the FDT as $C = \frac{1}{\omega_{\tau_f}} \text{Im}G$. With these observations, Eq. (10) can be written as,

$$[G]^{-1}(k, \omega, \omega_{\tau_f}) = -i\omega_{\tau_f} + \frac{1}{2(D_0)} [\omega^2] + \frac{1}{2(D)} [\nu_{eff}^2], \quad (11)$$

\[\Sigma = \left\{ \begin{array}{c}
\Sigma_1(k, \omega, \omega_{\tau_f}) + \Sigma_2(k, \omega, \omega_{\tau_f}) \end{array} \right\}

![FIG. 3: Dashed line indicates the correlation function (G_{eff}) and solid line indicates the response function (G_0). Self-energy term (Σ) is obtained by contracting the two $\phi_1$ fields. First term is the two loop contribution from the first order term (contains two $\phi_1$ fields) in the fictitious time equation. Second one is the one loop contribution from second order term (contains three $\phi_1$ fields).]
where $D_0 = 2(Dk^2\mu\phi_0 + (f_0^2k^2\xi(\omega))\phi_0))$, and $\tilde{D}$ is defined by
\[
\frac{1}{2(D)}[\nu_{eff}^2] = \frac{1}{2(D_0)}(\nu)^2 + \Sigma(k, \omega, \omega_{\tau})
\]
with $\nu = D\mu(k)k^2 + \phi_0k^2\mu(k)a(\omega)U(k) + k^2\mu(k)$. Expanding $\nu_{eff}$, $\tilde{D}$ about $\nu$ and $D_0$, respectively, and noting that the renormalization of $\nu$ dominates, we get
\[
\nu_{eff} \simeq \nu + \frac{D_0}{2\nu} \Sigma(0, \omega, \omega_{\tau}),
\]
or,
\[
\Delta \nu = \frac{D_0}{2\nu} \Sigma(0, \omega, \omega_{\tau}).
\]

E. Scaling exponents

In a self consistent mode coupling theory, we now replace $\nu$ by $\Delta \nu$ in the self energy term $\Sigma(0, \omega, \omega_{\tau})$ in the first term in Fig. (3), use $G \sim \omega_{\tau}^{-1}$ as from Eq. (10) and $C$, which follows from the FDT. According to scale transformation, we know that $\omega \sim k^z$, $\omega_{\tau} \sim k^{4z-2}$, $G \sim k^{-4z-2}$, $C \sim k^{-8z+4}$ and the vertex factor $V \sim k^{4z-2}$. The self energy term in Fig. (4) can be written as $\Sigma(0, \omega, \omega_{\tau}) \sim \int \frac{d^d k'}{(2\pi)^d} \frac{d\omega'}{2\pi} VVGC$. By carrying out the momentum count of $\Sigma(0, \omega, \omega_{\tau})$, and using $\Delta \nu \sim k^z$, we find that $\Sigma(k, \omega, \omega_{\tau}) \sim k^{d-z}$. Using Eq. (13) and $\nu/D_0 \sim k^{3z-2}$, we have $k^{4z-2} \sim k^{d+z}$, which leads to $z = \frac{d+2}{2}$. Where, $\nu \sim a(\omega) \approx \omega = k^z$ and use $\lambda^{-1}$ is small because in the case of flow, cells are amoeboid phenotype with short lived adhesion with collagen fiber. MSD exponent $\alpha = 2/z = 6/(d+2)$. In 3D, $\alpha = 1.2$, i.e., the amoeboid cells undergo super-diffusion.

F. The expression for $\Sigma(1, \omega, \omega_{\tau})$

\[
\Sigma(k, \omega, \omega_{\tau}) = \frac{2}{(Dk^2\mu\phi_0 + (f_0^2k^2\xi(\omega))\phi_0))} \int \frac{d^d k'}{(2\pi)^d} \frac{d\omega'}{2\pi} V(k, \omega, k', \omega') G(k', \omega', \omega_{\tau}) C(k - k', \omega - \omega', \omega_{\tau} - \omega')
\]
where vertex term, $V(k, \omega, k', \omega') = \{i\omega + Dk^2\mu(k) + \phi_0k^2\mu(k)a(\omega)U(k) + k^2\mu(k)\} \{(-k' \cdot k)\mu(k')a(\omega)U(k')\} + \{i\omega' + Dk'^2\mu(k') + \phi_0k'^2\mu(k')U(k') + k'^2\mu(k')\} \{(-k' \cdot k)\mu(k)a(\omega)U(k)\} + \{i\omega' + Dk'^2\mu(k') + \phi_0k'^2\mu(k')a(\omega)U(k')\} + \{k'^2\mu(k')\} \{(-k' \cdot (k - k'))\mu(k - k')a(\omega)U(k - k')\}$

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