Fluctuations in Bacterial Suspensions Driven by Chemotaxis

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Abstract. Stochastic fluctuations in living systems create a spectacular variety of unique states far from equilibrium, which however remains largely unexplored regarding its underlying physics, especially when considering their instinctive responses to environmental stimuli. Here, by utilizing a molecular-dynamics model of bacterial chemotaxis, we present an investigation of tracer statistics in suspensions of chemotactic bacteria. Unlike Brownian motion in conventional media, the tracer particle performs a short-time ballistic but long-time Fickian diffusion with non-Gaussian dynamics. A phenomenological extension of Langevin equation accounts for the observed anomalous behaviors. Moreover, a violation of the Stokes-Einstein relation is identified regarding the size-dependence of particle diffusivity in bacterial suspensions. Our findings uncover the physical nature of stimulus-driven fluctuation statistics in bacterial fluids, and suggest a theoretical framework to deepen the understanding of the nonequilibrium statistical physics of active matter under external stimuli.

1. Introduction
Instinctive responses to external stimuli in living systems, which help organisms to realize adaptive behaviors in changing environments, ubiquitously affect the inner working and collective motion of complex biological fluids. Such responses of active matter can reconstruct the intrinsic irreversible nature of corresponding off-equilibrium dynamics, thereby leading to the emergence of intriguing and complex spatiotemporal behaviors [1,2]. Like the magnetoreception in bird migration for the acclimatization to climate [3], and Lévy walks in animal movements for optimal foraging [4], the intrinsic fluctuations and driven responses in living fluids allow a pivotal approach to reveal the novel statistical physics in nonequilibrium systems.

However, existing models and observations have focused predominantly on characterizing the natural fluctuations in living matter without stimulus responses [5, 6]. One typical system is the suspension of motile bacteria. A rich variety of intriguing fluctuation behaviors, such as enhanced diffusion [7], ratchet motors [8, 9], and violation of the fluctuation dissipation theorem [10], have been widely observed, demonstrating that bacterial suspensions are far from the conventional equilibrium media. However, the inner statistics of bacterial fluids under external stimuli, especially chemotaxis [11–15], has not been addressed yet. As chemotaxis is a basic but crucial living process of motile bacteria in response to chemical stimuli for adaptive behaviors [16], an in-depth insight into the fluctuation statistics with chemotactic effects is of essential importance in statistical and biological physics. [17–19]

2. Model
In this work, by utilizing a molecular-dynamics model of bacterial chemotaxis, we present the investigation of tracer statistics in suspensions of chemotactic bacteria, as depicted in Figure 1a. Both
the bacterial cell and the immersed chemoattractant-coated tracer are modeled by the sum of identical force centers with short-range interactions. The bacterial cell is modeled by a spherocylinder composed of three force centers located along the cell axis, with a diameter $\sigma$, a length $2\sigma$, and an orientation $\mathbf{e}$. The tracer particle is composed of $N$ force centers which are uniformly arranged as a circle. The radius of the tracer particle, $R$, satisfies

$$ R = \frac{\sigma}{2} \left( 1 + \frac{1}{\sin(2\pi/N)} \right) $$

(1)

The pair-repulsive forces between two force centers are chosen as $f(r) = Ar / r^{14}$ [8], with a cutoff distance $\sigma$. The resultant force $\mathbf{F} = \sum f(\mathbf{F}_m$ for particle and $\mathbf{F}_j$ for cell) acting on each force centers can thereby be calculated.

![Figure 1](image)

**Figure 1.** (a) The snapshot of the bacterial suspension in simulations. (b) Representative trajectory of the tracer particle tracked for 5000 s.

The motion of the tracer particle is governed by

$$ \dot{\mathbf{r}}_i = \mu \sum \mathbf{F}_m + \zeta_i, \quad \dot{\theta}_i = \mu \left( \sum r_m \times \mathbf{F}_m \right)_z + \xi_i, $$

(2)

where $\mathbf{r}_i$ and $\theta_i$ represent the position and orientation of the particle respectively. $(\cdots)_z$ denotes the $z$-component of the vector. $\zeta_i$ and $\xi_i$ are the Gaussian white noises.

For run-and-tumble bacteria, the resultant force $\mathbf{F}_i$ and torque $T_i$ on the $i$th cell read

$$ \mathbf{F}_{B,i} = f_0 \mathbf{e}_i (1 - \epsilon_i) + \sum \mathbf{F}_j, \quad \mathbf{T}_{B,i} = T_i \mathbf{e}_i + \mathbf{e}_i \times \sum d_j \mathbf{F}_j, $$

(3)

where $\epsilon_i = 0$ for running state and 1 for tumbling state, and $d_j = (j - 2)\sigma / 2$. At each time step, the motile cell has a probability $\Gamma \Delta t$ to switch the running state into tumbling state and a probability $\Xi \Delta t \Gamma / \Delta t$ to switch the tumbling state into running state, where $\Delta t$ is the time interval. $f_0$ is a constant linear propelling force while $T_r$ is a random torque. The force coefficient $A$ is chosen to make two bacteria facing head to head on the same line being in equilibrium, that is: $A / \sigma = f_0 \rightarrow A = f_0 \sigma$. The velocity and angular velocity of the $i$th cell can be given by

$$ \dot{\mathbf{r}}_i = \Pi_i \cdot \mathbf{F}_{B,i} + \zeta_{B,T,i}, \quad \dot{\theta}_i = \left( \Omega_i \cdot \mathbf{T}_{B,i} \right)_z + \xi_{B,i}, $$

(4)
where \( \Pi_i = \mu_i e_i e_i + \mu_{ii} (1 - e_i e_i) \), \( \Omega_i = \mu_i^\parallel (1 - e_i e_i) \), \( \langle \xi_{B,T}^e(t) \xi_{B,R}^e(t') \rangle = 2 k_B T \Pi_i \delta(t - t') \), \( \langle \xi_{B,A}^e(t) \xi_{B,R}^e(t') \rangle = 2 k_B T \mu_i^\parallel \delta(t - t') \). Realistic physical value suitable for motile \textit{E.coli} cells [11, 17, 18], can be given as \( \sigma = 1.5 \mu m \), \( \mu_i = 60 \mu m/(pN \cdot s) \), \( \mu_{ii} = 53.544 \mu m/(pN \cdot s) \), \( \mu_i^\parallel = 20.242/(pN \cdot \mu m \cdot s) \), \( f_0 = 0.5 pN, \Xi = 10 s^{-1} \), and \( \Gamma = 1 s^{-1} \) (without chemotactic response). Numerical integration is performed with time interval \( \delta t = 10^{-4} s \).

The \textit{E.coli} chemotaxis pathway is briefly described in the following [13]. The average kinase activity \( p_{on} \) is given by the Monod-Wyman-Changeux (MWC) two-state model [12]:

\[
p_{on} = \frac{e^{-F_{os}}}{e^{-F_{os}} + e^{-F_{off}}} = \frac{1}{1 + e^F},
\]

where \( F = F_{on} - F_{off} \). For a cluster composed of \( N_r \) receptors, the total free-energy difference \( F = N_r f_m \), where \( f_m \) is given by

\[
f_m = \mathcal{E}(m) + \ln \left( \frac{1 + c/K_{off}}{1 + c/K_{on}} \right).
\]

Here \( \mathcal{E}(m) \) is taken to be linear in \( m \) as \( \mathcal{E}(m) = \alpha(m_0 - m) \). The kinetics of the methylation level follows

\[
\frac{dm}{dt} = k_{\parallel}(1 - p_{on}) - k_{\parallel}p_{on},
\]

where \( k_{\parallel} \) \( (k_{\parallel}) \) is the rate of methylation (de-methylation) for the inactive (active) receptors. The flagellar motor's probability \( \Gamma \) can be given as

\[
\Gamma = \Gamma_0 (p_{on} / p_{o})^H,
\]

where \( \Gamma_0 = 1 s^{-1} \) is the probability without chemotactic response, \( p_{o} \) is the kinase activity at steady-state, and \( H \) is the Hill coefficient of the motor response function. In our model, we use \( N_r = 6, K_{off} = 0.02 \text{mM}, K_{on} = 0.5 \text{mM}, \alpha = 1.7, m_0 = 1, k_{\parallel} = k_{\parallel} = 0.1/s \) (leading to \( p_{o} = 0.5 \)), and \( H = 10 \) [12,13].

Chemical stimuli are generated by the coated portion of the immersed tracer particle. For the full-coated particle, the concentration field \( c \) only depends on the center-to-center distance, \( r \), between cell and particle, and satisfies

\[
\frac{\partial c(r,t)}{\partial t} = \epsilon \nabla^2 c(r,t) - kc(r,t).
\]

By performing the Laplace transform, the analytic solution of Eq. (9) can be given by

\[
c = \frac{c_0 R}{2r} \left( e^{-\sqrt{\epsilon}(r-R)} \operatorname{erfc} \left( \frac{r-R-2\sqrt{\epsilon t}}{2\sqrt{\epsilon t}} \right) + e^{\sqrt{\epsilon}(r-R)} \operatorname{erfc} \left( \frac{r-R+2\sqrt{\epsilon t}}{2\sqrt{\epsilon t}} \right) \right),
\]

where \( \operatorname{erfc}(x) = \frac{2}{\sqrt{\pi}} \int_x^\infty e^{-t^2} dt \) is the complementary error function. Using \( \epsilon = 500 \mu m^2/s \) [12,13] and \( k = 10 s^{-1} \) [20], the time evolutions of \( c \) at different \( r \) can be obtained. It can be found that \( c \) reaches the steady-state value within 0.05s, thereby approximately leading to a stationary concentration field at each instance, i.e., \( \partial_t c \equiv 0 \) [21]. Thus, Eq. (9) can be reduced to a time-independent form as follow:
\[ \nabla^2 c(r) = \frac{k c(r)}{\epsilon}, \quad (11) \]

with boundary conditions \( c(R) = c_0 \) and \( c(\infty) = 0 \). Hence, by solving Eq. (11), the field \( c \) for the full-coated tracer particle follows:

\[ c(r) = \frac{c_0 R}{r} e^{-\sqrt{k/\epsilon} (r-R)}. \quad (12) \]

### 3. Results and discussions

The bacterial suspension is modeled by a two-dimensional box \( L \times L \) (\( L = 200 \mu m \)) with periodic boundary conditions (Figure 1a). \( N = 1200 \) bacterial cells with number density \( \phi = N / L^2 = 0.03 / \mu m^2 \) are considered. First, we systematically investigate the effects of chemical stimuli on the mean square displacements (MSDs) of the tracer particle with a radius \( R = 6.50 \mu m \) for a wide range of coating concentrations \( c_0 \). The MSD \( \langle \Delta r^2(t) \rangle \) is defined by

\[ \langle \Delta r^2(t) \rangle = \langle |x(t) - x(0)|^2 \rangle, \quad (13) \]

where \( x(t) \) is the position vector of the tracer particle and \( \langle \cdots \rangle \) denotes the time and ensemble average. 20 independent runs are performed for each parameter set. As shown in Figure 2a, the motion of tracer particle is found to be short-time superdiffusive, i.e., \( \langle \Delta r^2(t) \rangle \sim t^\gamma \) with diffusion exponent \( \gamma > 1 \), and becomes Fickian (\( \gamma = 1 \)) at long time scales. To rationalize this intuitively, we use the term \( \pi_b \) to describe the collisional forces exerted by bacterial cells. The interactions between the tracer particle and solvent are described by the term \( \pi_T \). Therefore, the motion of tracer can be theoretically governed by the following Langevin equation:

\[ \dot{x}(t) = \pi_b(t) + \pi_T(t). \quad (14) \]

Here, \( \pi_T \) is the Gaussian white noise satisfying \( \langle \pi_T(t) \rangle = 0 \) and \( \langle \pi_T(t) \pi_T^T(t') \rangle = 2D \delta(t-t') \), where \( D \) is the intrinsic diffusivity of the tracer particle and \( I \) is the identity matrix. Considering the space symmetry, the collisional forces of bacterial forces are statistically uniform, i.e., \( \langle \pi_b(t) \rangle = 0 \). However, the superdiffusive motion of tracer suggests that the \( \pi_b(t) \) at different times should not be temporally uncorrelated. We assume that the autocorrelation function of \( \pi_b(t) \) is in an exponential form, given by:

\[ \langle \pi_b(t) \pi_b^T(t') \rangle = 1 - \frac{\lambda}{\tau} e^{-|t-t'|/\tau}, \quad (15) \]

where \( \lambda \) is the noise intensity and \( \tau \) is the characteristic time of collisional forces. Under this assumption, the theoretical expression of MSD can be calculated via

\[ \langle \Delta r^2(t) \rangle = \int_0^t dt_1 \int_0^t dt_2 \langle \dot{x}(t_1) \cdot \dot{x}(t_2) \rangle. \quad (16) \]

Combining Eq. (14)- (16), we can obtain

\[ \langle \Delta r^2(t) \rangle = 4Dt + 4\lambda \left( t + \tau e^{-t/\tau} - \tau \right) \quad (17) \]

in the two-dimensional geometry. For a timescale \( t << \tau \), the tracer performs a superdiffusive motion with \( \langle \Delta r^2(t) \rangle = 2\lambda t^2 / \tau + 4Dt \) using Taylor series expansion. On the other hand, for a large timescale \( t >> \tau \), Fickian diffusion with \( \langle \Delta r^2(t) \rangle = (4\lambda + 4D)t \) can be obtained. Therefore, we reveal that the temporal correlation of collisional forces of bacteria results in the short-time ballistic but long-time Fickian diffusion of the tracer particle.
Next we turn to the inner dynamics of the diffusion of tracer particle. A normal diffusion process in one dimension should satisfy the diffusion equation, given by

$$\frac{\partial G_x(r,t)}{\partial t} = D \frac{\partial^2 G_x(r,t)}{\partial r^2},$$

(18)

where $G_x(r,t)$ is the self-part of the van Hove correlation function. With the initial condition $G_x(r,t = 0) = \delta(r)$, $G_x(r,t)$ follows the Gaussian form:

$$G_x(r,t) = \frac{1}{\sqrt{4\piDt}} \exp\left(-\frac{r^2}{4Dt}\right).$$

(19)

That is, the particle displacements are Gaussian distributed. However, in recent years, numerous experimental and simulation results indicate that non-Gaussian diffusion is more prevalent than expected. The non-Gaussian features of these diffusions call for a general perspective and corresponding physical descriptions. A straightforward but effective way to quantify the heterogeneity of a non-Gaussian diffusion, is to examine the ratio defined as $\langle \Delta r^4(t) \rangle / \langle \Delta r^2(t) \rangle^2$. Through comparing the ratio of the realistic diffusion with that of the Gaussian one, the deviation from the Gaussian form of the diffusion can be quantitatively identified. A non-Gaussian parameter $\alpha_{2,k}(t)$ is thereby defined for this purpose, where $k$ is the space dimensionality. In one dimension, we can obtain that

$$\langle \Delta r^2(t) \rangle = \int_{-\infty}^{\infty} r^2 G_1(r,t)\,dr = 2Dt,$$

(20)

$$\langle \Delta r^4(t) \rangle = \int_{-\infty}^{\infty} r^4 G_1(r,t)\,dr = 3(2Dt)^2,$$

(21)

for the Gaussian diffusion. Thus, we can define the non-Gaussian parameter $\alpha_2(t)$ in one dimension as follow:

$$\alpha_2(t) = \frac{\langle \Delta r^4(t) \rangle}{3\langle \Delta r^2(t) \rangle^2} - 1.$$

(22)
A larger $|\alpha_1(t)|$ indicates a more heterogeneous dynamics of the diffusion, and $\alpha_2(t) = 0$ when the diffusion follows the Gaussian statistics.

As shown in Figure 2b, we show the time dependences of non-Gaussian parameters $\alpha_2(t)$ for a wide range of $c_0$. The dramatic departure of $\alpha_2(t)$ from 0 at short times shows the emergence of non-Gaussian statistics and a violation of central limit theorem (CLT). A perspective of such violation is that the environmental noise is strongly correlated during the characteristic time interval of athermal collisions [22], thereby making the sum of noises unable to converge in a Gaussian form as CLT describes at that time scale. However, the temporal correlation of collisional forces of bacteria cannot directly lead to a non-Gaussian statistics. One famous instance is the Ornstein-Uhlenbeck (OU) process $\dot{z}(t) = \pi_{OU}(t)$, where noise $\pi_{OU}$ is also exponentially correlated $\langle \pi_{OU}(t) \pi_{OU}(t') \rangle = \frac{\lambda}{\tau} e^{\frac{|t-t'|}{\tau}}$ but Gaussian distributed. By solving the corresponding master equation, the probability distribution $p(z,t)$ can be explicitly given with an initial condition $p(z,0) = \delta(z)$, written in a Gaussian form as

$$p(z,t) = \exp \left( -\frac{z^2}{2\sigma(t)} \right) / \sqrt{2\pi\sigma(t)},$$

(23)

where $\sigma(t) = \lambda(1+te^{-t/\tau})$. Hence, the OU process is governed by CLT, quite different from the tracer statistics where the displacement distribution is strongly non-Gaussian (Figure 2b). Therefore, unlike $\pi_{OU}$, $\pi_\theta$ must be a non-Gaussian (athermal) noise, as predicted by the aforementioned perspective.

![Figure 3](image.png)

**Figure 3.** (a) Effective diffusion coefficients $D_{eff}$ at various $c_0$ for tracer particles with $R = 3.65\mu m$ and $6.50\mu m$ respectively. (b) Red scatters: size dependence of $D_{eff}$ at $c_0 = 0.01\text{mM}$ in the bacterial suspension. The blue dashed line shows the predictions of Stokes-Einstein relation [Eq. (27)] for different $R$ in the equilibrium media (water).

One physically motivated interpretation of such non-Gaussianity is that, such distribution is described by the convolution of Gaussian, independently diffusive processes [23]], which can be described by:

$$G_r(r,t) = \int P(D) \cdot g(r|D) \cdot dD$$

(24)

where $P(D)$ is the effective distribution of diffusivities, which reflects physically the temporal correlation of microscopic fluctuations, and $g(r|D) = 1/\sqrt{4\pi D t} \exp(-r^2/4Dt)$. Therefore, $G_r(r,t)$ in bacterial suspensions can be approximated by a steepest descent analysis to:
In the limit of constant $\partial \ln(P(D))/\partial D$, $G_s(r,t)$ is exponential whereas it is closer to Gaussian when $\partial \ln(P(D))/\partial D$ is a strong function of $D$. In physical terms, the more heterogeneous the dynamics is in regimes of large amplitude, the closer to exponential the displacement distributions are anticipated to be. Such phenomena also indicate that the fluctuations in bacterial suspensions should be colored, i.e., temporally correlated.

Furthermore, the size dependence of particle diffusivity is systematically investigated. Here, the effective diffusion coefficient $D_{\text{eff}}$ of the tracer particle is defined by the MSD at long-time scales, given by:

$$D_{\text{eff}} = \lim_{t \to \infty} \langle \Delta r^2(t) \rangle / 4t$$

Such parameter gives a quantitative description of tracer particle activities. As shown in Figure 3a, the value of $D_{\text{eff}}$ increases monotonically with $c_0$, as a consequence of the more frequent collisions of bacterial cells at high coating concentrations. As described by the well-known Stokes-Einstein relation, the diffusivity of a spherical particle with radius $R$ in a conventional media with viscosity $\eta$ is given by

$$D_{\text{eff}} = \frac{k_BT}{6\pi\eta R}$$

indicating that a larger size should lead to a smaller particle diffusivity. However, it can be found that tracer particle with larger size performs a more enhanced mobility at same $c_0$ in the bacterial suspension. For instance, as shown in Figure 3b, $D_{\text{eff}}$ at $c_0 = 0.01\text{mM}$ dramatically increases with the rising $R$. That is, the size dependence of $D_{\text{eff}}$ demonstrates an anomalous violation of the Stokes-Einstein relation.

Conclusion
In summary, by utilizing a molecular-dynamics model of bacterial chemotaxis, we present an investigation of tracer statistics in suspensions of chemotactic bacteria. Unlike Brownian motion in conventional media, the tracer particle performs a short-time ballistic but long-time Fickian diffusion with non-Gaussian dynamics. A phenomenological extension of Langevin equation accounts for the observed anomalous behaviors. Moreover, a violation of the Stokes-Einstein relation is identified regarding the size-dependence of particle diffusivity in bacterial suspensions. The results could provide a significant advance in revealing the underlying physics of anomalous diffusion in active systems. Our findings uncover the physical nature of stimulus-driven fluctuation statistics in bacterial fluids, and suggest a theoretical framework to deepen the understanding of the nonequilibrium statistical physics of active matter under external stimuli.

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