Pathway-Based Mean-Field Model for Escherichia coli Chemotaxis

Guangwei Si,1,2 Tailin Wu,1 Qi Ouyang,1,2,* and Yuhai Tu3,2,†

1The State Key Laboratory for Artificial Microstructures and Mesoscopic Physics, School of Physics, Peking University, Beijing 100871, China
2Center for Quantitative Biology and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China
3IBM T.J. Watson Research Center, P.O. Box 218, Yorktown Heights, New York 10598, USA

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We develop a mean-field theory for Escherichia coli chemotaxis based on the coupled spatiotemporal dynamics of the cell population and the mean receptor methylation level field. This multiscale model connects the cells’ population level motility behavior with the molecular level pathway dynamics. It reveals a simple scaling dependence of the chemotaxis velocity on the adaptation rate in exponential gradients. It explains the molecular origin of a maximum chemotaxis velocity. Simulations of our model in various spatiotemporal stimuli profiles show quantitative agreements with experiments. Moreover, it predicts a surprising reversal of chemotaxis group velocity in traveling wave environments. Our approach may be used to bridge molecular level pathway dynamics with cellular behavior in other biological systems.

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To understand the behavior of living organisms from the underlying interactions of biomolecules is one of the main goals of modern biological sciences. The problem is challenging as there are many scales (time and space) spanning from molecules to behaviors. Here, we develop a multiscale modeling approach to describe the population level behavior of Escherichia coli (E. coli) chemotaxis based on the underlying signaling pathway dynamics. We show that our model not only leads to insight into the molecular origins of important chemotaxis behavior, it also allows us to predict novel chemotaxis behavior in complex environments.

The swimming behavior of an E. coli cell follows an alternating run and tumble pattern [1] with a bias toward higher (lower) concentration of attractant (repellent) which results in the cell’s chemotaxis behavior [2,3]. At the population level, such biased-random-walk motion has been described by a drift-diffusion equation, proposed by Keller and Segel (KS) [4]. The KS equation and its variants can explain experiments in slowly varying environments phenomenologically (see Ref. [5] for a review), but it fails to account for bacterial chemotaxis behavior in fast-changing environments as demonstrated in recent microfluidic experiments [6].

Great progress has been made in understanding the molecular mechanism of the E. coli chemosensory system in the past decades (see [7] for a recent review). The membrane bound methyl-accepting chemoreceptor protein (MCP) receptors can bind with the chemoeffector molecules (ligands). Ligand binding causes conformational changes of MCP and modulates the kinase activity of the histidine kinase CheA. The activated CheA then phosphorylates the response regulator CheY, and the phosphorylated CheY-P controls the switching probability of the flagellar motor between its counterclockwise (CCW) and clockwise (CW) rotational states, which causes the run and tumble motions, respectively. The bacterial chemosensory system adapts by the relatively slow receptor methylation and demethylation processes catalyzed by two enzymes CheR and CheB, respectively. The receptor methylation level, due to its slow dynamics, serves as the cell’s memory, which the cell uses to compare with its current environment to decide whether to run or tumble.

Recently, the dynamics of the signaling pathway has been measured quantitatively [8–11], which has led to the development of predictive models for the signaling pathway [12–16]. Here, we develop a pathway-based mean field theory (PBMFT) for bacterial chemotaxis by incorporating the molecular-level signaling dynamics, in particular the slow adaptation dynamics of the MCP receptors, to understand the population-level behavior of the cells.

For convenience, we develop our model in one dimension by considering the movement of a single cell in the + or − direction with a constant velocity \( v_0 \). A swimming cell tumbles with a frequency \( z_t \) and chooses a random new direction. The tumbling frequency \( z_t \) depends on the receptor activity \( a \), which is a function of the chemoattractant concentration \( L \) and the receptor methylation level \( m \). The dynamics of \( m \) is governed by \( dm/dt = F(a) \), where \( F(a) \) is the methylation rate function (see [16,17] for detail). The rotational diffusion effect can be treated as an additional directional change, which leads to a total effective tumbling frequency \( \overline{z} = z_t[a(m, [L])] + z_\theta \), where \( z_\theta \) is a constant rotational diffusion coefficient of the cells. The average run time is \( \overline{z}^{-1} \), and the average running distance is \( v_0\overline{z}^{-1} \).

Define \( P^\pm(m, x, t) \) as the probability density of the cells with methylation level \( m \) in the “+” direction. The
The master equation for \( P^\pm \) has three contributions: cell migration in position \( x \), methylation dynamics in \( m \) space, and directional switch caused by tumbling,

\[
\begin{align*}
\frac{\partial P^+}{\partial t} & = -\frac{\partial (v_0 P^+)}{\partial x} - \frac{\partial [F(a) P^+]}{\partial m} - \frac{Z}{2} (P^+ - P^-), \\
\frac{\partial P^-}{\partial t} & = \frac{\partial (v_0 P^-)}{\partial x} - \frac{\partial [F(a) P^-]}{\partial m} + \frac{Z}{2} (P^+ - P^-).
\end{align*}
\]

(1)

One key insight is that the methylation dynamics are slow relative to the cell’s tumbling rate \( z \). Therefore, cells moving in different directions can have different methylation levels. Here, we neglect the higher order moments of \( m \) and approximate \( P^\pm \) as \( \delta \) functions in \( m \),

\[
P^\pm(m, x, t) = P^\pm_m(x, t) \delta (m - M^\pm(x, t)),
\]

(2)

where \( M^+ \) and \( M^- \) are the average methylation levels of the cells swimming in the + and − direction, respectively.

We define the population-weighted average of \( M^+ \) and \( M^- \) as \( M(x, t) \) and their difference as \( 2\Delta M = M^+ - M^- \) (see Supplemental Material \[18\] for details). Let \( Z(= z_m - M) \) denote the tumbling rate at \( m = M \). Since the direction of motion is randomized during each tumbling event, \( \Delta M \) can be approximated as the methylation level difference in the mean methylation field \( M(x, t) \) over the average run length \( v_0 Z^{-1} \),

\[
\Delta M \approx -\frac{\partial M}{\partial x} Z^{-1} v_0.
\]

(3)

in which the effect of receptor methylation during the relatively short run time \( Z^{-1} \) is neglected.

The cell density \( \rho \) and cell flux \( J \) are defined from \( P^\pm \),

\[
\rho(x, t) = P^+_m + P^-_m, \quad J(x, t) = v_0 (P^+_m - P^-_m).
\]

By subtracting the two equations in Eq. (1) and integrating with respect to \( m \) we obtain the equation for \( J \),

\[
\frac{\partial J}{\partial t} = -v_0^2 \frac{\partial \rho}{\partial x} - Z J - v_0 \frac{\partial Z}{\partial M} \Delta M \rho.
\]

Since typical time scales of interest for population dynamics are much longer than the average run time \( Z^{-1} \) (∼1 s) of individual cells, we can make the quasiequilibrium assumption \( \partial J/\partial t \approx 0 \), which leads to

\[
J = -v_0^2 Z^{-1} \frac{\partial \rho}{\partial x} - v_0^2 \frac{\partial Z^{-1}}{\partial M} \frac{\partial M}{\partial x} \rho.
\]

(4)

The two terms in Eq. (4) represent the passive diffusion flux and the active chemotaxis flux, respectively. Intuitively, cells swimming up or down the chemoeffect gradient have different methylation levels (measured by \( \Delta M \)), which leads to the difference in average run time \( \langle \Delta M \rangle_T \) and the chemotaxis drift velocity \( v_0 \frac{\Delta M}{Z^{-1}} \).

Unlike the KS equation which assumes that chemotaxis is driven directly by the concentration gradient, our model shows that chemotaxis is controlled by the dynamics of the receptor methylation level \( M \).

By adding the two equations in Eq. (1) and integrating with respect to \( m \) we obtain the dynamics of \( \rho \),

\[
\frac{\partial \rho}{\partial t} = -\frac{\partial J}{\partial x}.
\]

(5)

which is simply due to the conservation of cells. The dynamic equation for \( M \) can be obtained by multiplying the two equations in Eq. (1) by \( m \), adding the equations, and integrating with respect to \( m \),

\[
\frac{\partial M}{\partial t} = F - \frac{J}{\rho} \frac{\partial M}{\partial x} + \frac{1}{\rho} \frac{\partial}{\partial x} \left( v_0^2 Z^{-1} \frac{\partial M}{\partial x} \right).
\]

(6)

The first term in the right-hand side of Eq. (6) represents the intracellular receptor (de)methylation dynamics. The second and the third terms represent the advective and the diffusive transport of \( M \), respectively. Detailed derivations can be found in the Supplemental Material \[18\].

Taken together, Eqs. (5) and (6) \([\text{with } J \text{ given in Eq. (4)}]\) define the PBMFT model for \( E. \text{coli} \) chemotaxis. The intracellular adaptation dynamics and the motor response are characterized by the two functions \( F \) and \( z \). As shown in \[16\], to maintain accurate adaptation, \( F \) should only depend strongly on activity \( a \) with a fixed point \( F(a_0) = 0 \) and \( F'(a_0) < 0 \). The exact form of \( F(a) \) was measured recently \[11\] with a large linear region near \( a = a_0 \), which is what we use here,

\[
F(a) = k_R (1 - a/a_0),
\]

(7)

where \( k_R \) is the methylation rate. The receptor activity \( a \) is a function of the methylation level \( M \) and the chemottractant concentration \( [L] \). In the standard two-state model \[12, 14\]

\[
a(m, [L]) = (1 + \exp[N e(m_m, [L])])^{-1},
\]

(8)

where \( N \) is the number of tightly coupled receptors in the MCP cluster. There are two contributions to \( e \) from receptor methylation and ligand binding,

\[
e(m_m, [L]) = -a(m_m - m_0) + f_0([L]),
\]

\[
f_0([L]) = \ln(1 + [L]/K_l)/(1 + [L]/K_A).
\]

(9)

The switching frequency of a flagellar motor from CCW to CW is \( z_t = \tau^{-1}(a/a_0)^H \) with \( H(=10) \) the large Hill coefficient \[9\] and \( \tau \) the average switching time at \( a = a_0 \). Combining \( z_t \) with the rate \( z_\theta \) of directional fluctuation due to rotational diffusion, we express the rate of total directional change as

\[
z = z_\theta + \tau^{-1}(a/a_0)^H.
\]

(10)

When the external time scales are much longer than the adaptation time, or \( k_R \to \infty \), Eq. (6) is dominated by the methylation rate \( F(a) \), and all cells can adapt to their preferred activity \( a = a_0 \). The constant value of \( a \) in space
leads to \( \frac{\partial M}{\partial x} = \frac{1}{\alpha} \frac{\partial f_0}{\partial x} \), which by using in Eq. (4) and then Eq. (5), we derive the KS chemotaxis equation,
\[
\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x} \left( \mu_0 \frac{\partial \rho}{\partial x} - \frac{\partial}{\partial x} \left( \chi_0 \rho \frac{\partial f_0}{\partial x} \right) \right),
\]  
where the diffusion coefficient \( \mu_0 \) and the chemotaxis coefficient \( \chi_0 \) are determined directly from the signaling pathway parameters
\[
\mu_0 = \frac{v_0^2}{\tau + \tau'}, \quad \chi_0 = \frac{v_0^2 \tau^{-1}}{(\tau + \tau^{-1})^2} HN(1 - a_0). \tag{12}
\]
Equation (12) clearly shows that both the receptor cooperativity \( (N) \) and the motor level ultrasensitivity \( (H) \) lead to high chemotaxis coefficient.

To verify our model, we compute the cell’s steady state profiles for various linear attractant gradients. Our PBMFT model, with all the parameters obtained from independent microscopic experiments, agrees quantitatively with the experimental measurements \[19\]. See Fig. S1 in the Supplemental Material \[18\] for details.

For \( K_I \ll [L] \ll K_A, f_0([L]) = \ln([L]/K_I) \), Eq. (11) shows that \( E. coli \) chemotaxis is log-sensing. Specifically, in an exponential gradient \( [L] = [L]_0 \exp(G x) \), the drift velocity \( v_d = \chi_0 \frac{\ln([L])}{\tau a} = \chi_0 G \) increases linearly with \( G \). However, \( v_d \) can not increase forever. As shown in single cell based simulations, \( v_d \) reaches its maximum \( v_{d,\text{max}} \), and \( v_{d,\text{max}} \) for \( G \) larger than a characteristic gradient \( G_c \). Furthermore, both \( G_c \) and \( v_{d,\text{max}} \) are controlled by the adaptation rate \( k_R \) \[17,20\]. Here, we investigate the dependence of \( v_d \) on \( G \) and \( k_R \) analytically by solving the PBMFT.

We look for a steady state solution (ansatz) with constant \( \rho, J, a \) in space and time. The requirement of constant \( a \) leads to a steady state profile for \( M: \frac{\partial M}{\partial x} = \alpha^{-1} \frac{\partial f_0}{\partial a} = \frac{G}{\alpha} \). By applying this expression of \( \partial M/\partial x \) in Eqs. (4) and (6), we obtain two simple equations,
\[
v_d = \chi(a) G, \tag{13}
\]
\[
F(a) = \frac{v_d}{G} = \frac{\chi(a)}{\alpha}. \tag{14}
\]
Equation (13) shows that \( v_d \) is proportional to \( G \) with an activity dependent mobility \( \chi(a) \),
\[
\chi(a) = HN v_0^2 \tau^{-1} (1 - a) \left( \frac{a}{a_0} \right)^H (\tau + \tau^{-1} \left( \frac{a}{a_0} \right)^H \right)^{-2}. \tag{15}
\]
Equation (14) results from equating the intrinsic methylation rate to the methylation transport rate in steady state. Equations (13) and (14) are solved to determine the dependence of \( v_d \) and \( a \) on \( G \) and \( k_R \). The results are shown in Fig. 1(a).

Remarkably, Eqs. (13) and (14) are invariant under the transformation \( F \rightarrow y F, v_d \rightarrow y^{1/2} v_d \), and \( G \rightarrow y^{1/2} G \). Setting \( y = k_R^{-1} \), we obtain the scaling relation
\[
\frac{v_d}{\sqrt{k_R}} = S \left( \frac{G}{\sqrt{k_R}} \right).
\]
with a \( k_R \) independent function \( S \). Indeed, all the curves in Fig. 1(a) collapse under this scaling transformation as shown in Fig. 1(b). Thus, both \( v_{d,\text{max}} \) and \( G_c \) scale as \( k_R^{1/2} \). Results from the signaling pathway-based \( E. coli \) chemotaxis simulator (SPECS) \[17\] in two dimensions also collapse with exactly the same scaling law [Fig. 1(b)].

The origin of the maximum chemotaxis velocity can be understood from our model. For small \( G \ll G_c \), \( a \approx a_0 \), \( \chi(a) \approx \chi_0 \), and \( v_d = \chi_0 G \) increases linearly with \( G \). As \( G \) increases, a decrease from \( a_0 \), leading to a longer run time \( t_r = \tau(a_0/a)^H \) and a larger chemotaxis mobility \( \chi(a) \). However, as \( t_r \) becomes comparable with the rotational diffusion time \( t_\theta = \tau_0^{-1} \), a further decrease in \( a \) lowers \( \chi(a) \) due to the Brownian reorientation of the cell. Indeed, for \( G \gg G_c \), \( a \approx 0 \), our model [Eqs. (7) and (14)] shows that \( F(a) = k_R \), and \( v_d = a k_R/G \), which decreases with \( G \). The maximum \( v_d \) is approached when \( t_r \) becomes comparable with \( t_\theta \). For large \( t_r \), higher order terms neglected in our model become relevant, which may explain the quantitative difference between the PBMFT and the SPECS results for large \( G \) [Fig. 1(b)]. However, regardless of the quantitative form of the \( v_d \) dependence on \( G \), it is clear that \( v_{d,\text{max}} \) is controlled by rotational diffusion. This is also verified by the dependence of \( v_{d,\text{max}} \) on \( \tau_\theta \) in both PBMFT and SPECS (see Fig. S2 in the Supplemental Material \[18\]).

In natural environments, chemical signals can vary in both space and time. Recent microfluidic experiments and SPECS simulations have shown strong evidence for frequency-dependent chemotactic responses \[6,17\], which cannot be explained by the KS type equations. Here, we
FIG. 2 (color online). Chemotactic behavior in traveling wave attractant. (a) The average velocity of bacteria $v_d$ in traveling wave environment for different wave speeds $u$. $v_d$ reverses its direction at $u = u_c$. The parameters used are: $[L_0] = 500 \mu$M, $[L_1] = 100 \mu$M, $\lambda = 800 \mu$m. (b) The $M$ and $M^*$ profiles in the comoving frame for $u = 8 \mu$m/s labeled in (a). (c) The corresponding $dM/dx$ and $\chi$ profiles. The regions with $dM/dx < 0$ are shaded in (b) and (c).

apply the PBMFT to study the chemotaxis behavior in spatial-temporal varying environments. The first case is the chemotaxis behavior in response to oscillatory spatial gradients where the attractant profile between the two control points mimics a standing wave as done in recent experiments [6]. We solve the PBMFT numerically and compute the phase shifts of the center of mass of the cells relative to the ligand concentration for different oscillation frequencies $\omega$. The PBMFT confirms the existence of a phase shift that increases with $\omega$ and becomes significant as $\omega$ becomes comparable with $E. coli$’s adaptation rate. The quantitative agreement with the experiments (see Fig. S3 in the Supplemental Material [18]) validates the PBMFT model.

Next, we consider a traveling attractant concentration wave $[L] = [L_0] + [L_1] \sin(\frac{2\pi}{\lambda}(x - ut))$ in a circular channel with a wave speed $u$ and a wavelength $\lambda$ equal to the circumference of the channel. We investigate the $E. coli$ chemotactic behavior for different wave speeds $u$. Naively, one may expect that the average bacteria motion follows the direction of the attractant wave. Surprisingly, simulations of the PBMFT show that $v_d$ reverses sign when $u$ is larger than a critical value $u_c$. This means that cells migrate in the direction opposite to the attractant wave speed for $u > u_c$. The SPECS simulations confirm the reversal of $v_d$ in response to traveling wave stimuli [Fig. 2(a)].

The origin of this counterintuitive phenomenon can be understood from analysis of our PBMFT model. For small wave velocity $u < u_c$, cells can catch up with the attractant wave and stay near the (moving) peak of the attractant profile [see Fig. S4(a) in the Supplemental Material [18]]. Essentially, when the frequency $\omega \equiv u/\lambda$ is low, the internal variable field $M(x, t)$ has enough time to adapt to its target value $M^*(x, t) = m_0 + a^{-1} \ln(1 + [L]/K_D)/(1 + [L]/K_A)$ to maintain $a = a_0$. Indeed, our study shows that $M = M^*$ in this low wave speed regime [see Fig. S4(b) in the Supplemental Material [18]].

For large $u > u_c$, however, the cells can no longer follow the attractant wave. When $\omega$ becomes comparable to the internal adaptation rate, a significant reduction in the amplitude of $M$ and a phase lag between $M$ and $M^*$ develops, as shown in Fig. 2(b). Since the cells cannot follow the peak of the attractant wave, the cell density $\rho$ is almost uniform in space [see Fig. S4(c) in the Supplemental Material [18]], so $v_d$ is dominated by the chemotactic drift term in Eq. (4): $J/\rho = \chi dM/dx$. In Fig. 2(c), we plot the spatial dependence of the mobility $\chi$ and the methylation gradient $dM/dx$. In most of the region with $dM/dx > 0$, we have $M \gg M^*$ due to the phase shift between $M$ and $M^*$, which leads to a large activity $a \gg a_0$ and, consequently, a “tumbly” behavior with small chemotactic mobility $\chi$, as shown in Fig. 2(c). On the other hand, for most of the region [shaded in Figs. 2(b) and 2(c)] with $dM/dx < 0$, we have $M \ll M^*$, which leads to a small activity $a \ll a_0$, and consequently normal to smooth swimming behavior with larger $\chi$ (the dip of $\chi$ near $x = 200 \mu$m in Fig. 2(c) is caused by rotational diffusion).

The asymmetry of $\chi$ in the regions with positive and negative $dM/dx$ leads to an average negative drift speed. This asymmetry is essentially caused by the phase shift in the internal variable $M$ with respect to the external driving field $[L]$, which occurs in the high wave speed regime.

In summary, our model shows quantitative agreements with existing experiments and predicts novel chemotactic behavior, which is being tested in ongoing experiments in our lab. Our work provides a good example of bridging molecular mechanisms with population-level behaviors. This integrative multiscale approach may be used to study other biological systems, such as quorum sensing and biofilm formation [21].

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*qi@pku.edu.cn
†yuhai@us.ibm.com