Steady-State Chemotaxis in *Escherichia coli*

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The bacterium *E. coli* maneuvers itself to regions with high chemoattractant concentrations by performing two stereotypical moves: "runs," in which it moves in near-straight lines, and "tumbles," in which it does not advance but changes direction randomly. The duration of each move is stochastic and depends upon the chemoattractant concentration experienced in the recent past. We relate this stochastic behavior to the steady-state density of a bacterium population, and we derive the latter as a function of chemoattractant concentration. In contrast to earlier treatments, here we account for the effects of temporal correlations and variable tumbling durations. A range of behaviors is obtained that depends subtly upon several aspects of the system—memory, correlation, and tumbling stochasticity, in particular.

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Chemotaxis refers to directed motion in response to chemical signals. While many organisms perform chemotaxis, its phenomenology and biochemistry are best understood in *Escherichia coli* (*E. coli*) [1]. *E. coli* is confined to two stereotypical moves. When its flagellum motors turn counterclockwise (looking at the bacteria from the back), the bacterium moves in near-straight lines termed "runs," whose direction is limited by rotational diffusion. This motion is interrupted by periods of "tumble," which occur when the motors turn clockwise: The bacterium does not translate but instead rotates about itself in a random fashion and thus reinitializes the direction of the next run. Some amount of correlation between successive run directions yields an average angle shift of 68° [1], as compared with 90° in an uncorrelated case. Tumble durations are short, on the order of 0.1 s, with respect to runs which last about 1 s [2,3].

Bacteria modulate their whereabouts in response to their chemical environment. The small size ($\sim 2\ \mu$m) of *E. coli* rules out sensing spatial gradients: In the time it takes the bacterium to move by its own size, chemicals diffuse in a region 10 times larger [4]. Instead, *E. coli* relies upon temporal integration: It calculates spatial gradients by integrating chemical concentration over its recent history and modulating run and tumble durations accordingly. Much work has focused on this "algorithm," namely, on the filter of temporal integration and on its relation to the probability of run or tumble [1,5,6].

With knowledge of this stochastic algorithm, one would like to predict the distribution of trajectories of a bacterium or, equivalently, the behavior of a (noninteracting) population. Also, in particular, one would like to elucidate which aspects of the single-bacterium algorithm ensure population performance. Here we focus on the steady state, and we ask the following questions. Given a chemoattractant (or chemorepellant) concentration and a single-bacterium stochastic algorithm, what is the shape of the steady-state population density? How does it depend upon the details of the single-bacterium system, and which of these are qualitatively relevant?

Because of the single-bacterium stochasticity, the problem may be viewed as a biased random walk problem. The memory involved in temporal integration and the variable tumble duration, however, make the problem more difficult and more interesting. In particular, these induce correlations between run duration and local bacterium density at the run's starting point, which we take into account. All of these effects yield a rich macroscopic behavior in the steady state that depends subtly upon the form of the single-bacterium response filter and for which a simple description in terms of a Markovian biased random walker can be misleading. In particular, (i) the usual bilobe filters that turn temporal integration into spatial comparison may or may not lead to accumulation in favorable regions, depending upon their shape and the interplay of time scales [7,8]; (ii) correlations result in a nonlocal dependence of the probability density upon the environment, due to memory in the dynamics; (iii) when tumble is noninstantaneous, bacteria may aggregate in favorable regions in their tumbling phase. Surprisingly, this last effect occurs even for filters that are purely local in time. Our results are derived in one spatial dimension, as in Refs. [7,8], and fodder a long-standing debate [1,5–9]; specifically, correlations and tumble duration variability had been neglected previously [1,5–9].

E. coli climbs up chemical gradients by modulating run and tumble durations as a function of chemoattractant concentration c [1,3]. (Henceforth, we use the term "chemoattractant" indifferently to refer to both chemoattractant and chemorepellant. Below, we discuss the differences in responses to "positive" and "negative" stimuli.) Run durations are Poissonian, with probability

$$\frac{dt}{\tau(t)} = \frac{dt}{\tau_0}\{1 - \mathcal{F}[c]\} \tag{1}$$

to switch from run to tumble between times t and $t + dt$

[3]. Here $\mathcal{F}[c]$ is a functional of the chemical concentration $c(t')$ experienced by the bacterium at times $t' \leq t$; it results from a linear temporal filtering followed by a static rectification nonlinearity, as

$$\mathcal{F}[c] = \phi\left[\int_{-\infty}^{t} dt' R(t-t')c(t')\right], \tag{2}$$

where the functions $\phi(\cdot)$ and $R(t)$ summarize the action of the biochemical machinery that processes input signals from the environment [1]. If $\phi(\cdot)$ is nonsingular, it may be linearized, as

$$\mathcal{F}_{\text{lin}}[c] = \int_{-\infty}^{t} dt' R(t-t')c(t'), \tag{3}$$

where an additive constant is absorbed in a redefinition of τ_0 [in Eq. (1)] and a multiplicative constant is absorbed in a rescaling of $R(t)$. Experimental work [3] suggests instead a thresholding nonlinearity [9], fitted by the form

$$\mathcal{F}_{\text{nlin}}[c] = [\mathcal{F}_{\text{lin}}[c]]_+, \tag{4}$$

where $[x]_+ = 0$ for $x \leq 0$ and $[x]_+ = x$ for $x > 0$.

The response filter $R(t-t')$ was measured in classic experiments on wild-type bacteria, in which puffs of chemoattractant were presented to a single bacterium, effectively replacing $c(t')$ by a delta function which allowed one to resolve for $R(t-t')$ [1,3]. These experiments yielded a bimodal shape for $R(t-t')$, with a positive peak around $t' \simeq 0.5$ s and a negative peak around $t' \simeq 1.5$ s (see Fig. 1, inset). The negative lobe is shallower than the positive one and extends up to $t' \simeq 4$ s, beyond which it vanishes and to a good approximation satisfies $\int_0^\infty R(t')dt' = 0$. The estimated value of τ_0 is about 1 s.

Tumble duration is also modulated stochastically, in close analogy to run duration behavior [3]. Earlier theoretical work has mostly treated tumble as instantaneous [7–9]. We treat tumble duration as a Poisson variable with rate $1/\tau_T$, but, for the sake of simplicity, we ignore any dependence of the latter upon the chemical environment. While this falls short of a full description, the mere allocation of a nonvanishing duration to tumble yields new qualitative consequences, as discussed below.

The bilobe shape of the response filter points to a simple mechanism: It enables the bacterium to perform a coarse-grained temporal derivative of the chemical concentration that it experiences. If the gradient is positive, then the run duration tends to increase; if the gradient is negative, then the run duration tends to decrease [in the linear case of Eq. (3)] or is unmodulated [in the threshold-linear case of Eq. (4)]. However, the connection between simple arguments such as this and quantitative results is far from immediate. Reference [7] argues that a single-lobe, even punctual, temporal filter, such as $R(t-t') = \chi\delta(t-t')$ with χ *positive*, leads to a net bias toward increasing chemoattractant concentration. In fact, the analysis suggests that the response is strongest if the filter is local in time, with $t' = 0$, and that a *delayed* response ($t' > 0$) or

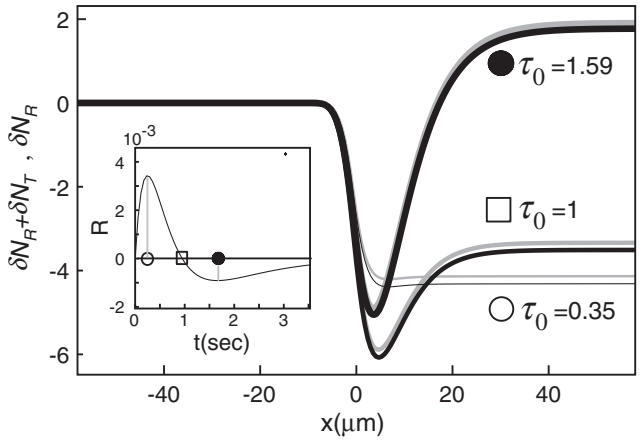

FIG. 1. Numerical results in the nonlinear model with $c(x) = 10^{-3}\theta(x)$. All quantities are given in arbitrary units. To obtain $\delta N_R(x)$ and $\delta N_T(x)$, Eqs. (13) and (14), for the nonlinear model, were solved iteratively on a computer, using a discrete lattice of size 800, with $v = 10$ μm/s, $q = 0.4$, $\tau_T = 0.58$ s, and $dx = 0.05$ μm. The results were uniformly rescaled for convenience, and we display the region in which the bacterium density varies, about $x = 0$, the location of the chemoattractant step. Three different values of τ_0 (in seconds) are indicated. The correspondence between the bacterium density and the value of τ_0 is indicated by the solid and open symbols in the figure and the inset. The response function, illustrated in the inset, was chosen as $R(t) = [14.1t\exp(-14.1t) - 1.7t\exp(-0.4t)]$, which satisfies $\int_0^\infty R(t)dt = 0$.

any addition of a *negative* contribution, akin to the bilobe shape measured experimentally, *weakens* the bias. The arguments developed in Ref. [7] concern the instantaneous dynamics of a bacterium. Reference [8] contrasts transient and steady-state behaviors and argues that, while a positive filter is most favorable for climbing chemical gradients in an initial transient phase, a negative filter is favorable for steady-state accumulation in advantageous regions. References [7,8] make a number of limiting assumptions; mainly, they disregard the correlation of run duration and probability density and assume instantaneous tumble.

In the remainder of this Letter, we proceed as follows. First, we write equations that govern the steady-state density of (noninteracting) bacteria (equivalently, the bacterium probability density); second, we derive the latter analytically in the linear model [Eq. (3)] and numerically in the nonlinear model [Eq. (4)]. To the best of our knowledge, this is the most complete treatment of steady-state models to date, which includes the nonlinearity typically ignored. We are after the density

$$N(x) = N_R(x) + N_T(x), \tag{5}$$

where $N_i(x)dx$ is the number of bacteria lying between x and $x + dx$ and the subscripts R and T refer to run and tumble, respectively. To incorporate correlation, we borrow four intermediate quantities: $n_+^{T\to R}(x)dx$, the number of bacteria that switch from tumble to a *rightward* run between x and $x + dx$ per unit time; $n_-^{T\to R}(x)dx$, the num-

ber of bacteria that switch from tumble to a *leftward* run between x and $x + dx$ per unit time; $n_+^{R\to T}(x)dx$, the number of bacteria that switch from a *rightward* run to tumble between x and $x + dx$ per unit time; $n_-^{R\to T}(x)dx$, the number of bacteria that switch from a *leftward* run to tumble between x and $x + dx$ per unit time. The rightward and leftward fluxes are given by

$$\partial_x j_+(x) = n_+^{T\to R}(x) - n_+^{R\to T}(x), \tag{6}$$

$$\partial_x j_-(x) = n_-^{T\to R}(x) - n_-^{R\to T}(x). \tag{7}$$

In the steady state, $n_+^{T\to R}(x) + n_-^{T\to R}(x) = n_+^{R\to T}(x) + n_-^{R\to T}(x)$, which amounts to the usual condition $\partial_x[j_+(x) + j_-(x)] = 0$. If $N_+(x)$ and $N_-(x)$ are the densities of rightward and leftward running bacteria, respectively, then $j_+(x) = vN_+(x)$ and $j_-(x) = -vN_-(x)$, and the density of running bacteria $N_R(x)$ obeys

$$\partial_x N_R(x) = \partial_x[N_+(x) + N_-(x)] \tag{8}$$

$$= \frac{1}{v}[n_+^{T\to R}(x) - n_+^{R\to T}(x) - n_-^{T\to R}(x) + n_-^{R\to T}(x)]. \tag{9}$$

Tumbling bacteria retain some memory of their recent run direction; we call q the probability that a tumble causes a run direction change and treat it as a parameter in our model. Thus, $n_+^{T\to R}(x) = (1-q)n_+^{R\to T}(x) + qn_-^{R\to T}(x)$ and $n_-^{T\to R}(x) = qn_+^{R\to T}(x) + (1-q)n_-^{R\to T}(x)$, so that Eq. (9) simplifies into

$$\partial_x N_R(x) = \frac{2q}{v}[n_-^{R\to T}(x) - n_+^{R\to T}(x)]. \tag{10}$$

Within our assumption of an unmodulated tumble rate, the steady-state density of tumbling bacteria $N_T(x)$ reads

$$N_T(x) = \tau_T[n_+^{R\to T}(x) + n_-^{R\to T}(x)]. \tag{11}$$

As a final, simplifying assumption, we posit that memory is erased at tumble-to-run switches. This assumption may not be validated by data [3], but it is unclear whether it improves or suppresses chemotaxis with respect the no-erasure case. Equation (3) becomes

$$\mathcal{F}_{\text{lin}}[c] = \int_{t_0}^{t} dt' R(t-t')c(t'), \tag{12}$$

where t_0 is the time of the last switch, and the run-to-tumble switch probability $dt/\tau(t, t_0)$ is now a function of both t and t_0. Alternatively, this probability can be expressed in terms of the initial and final positions of the run, y and x, respectively, as $dx/v\tau(x, y)$. We now have all of the elements in hand to write the steady-state equations that govern density and keep track of correlations, as

$$n_+^{R\to T}(x) = \int_{-\infty}^{x} dy n_+^{T\to R}(y)\rho_+(x, y), \tag{13}$$

$$n_-^{R\to T}(x) = \int_{x}^{+\infty} dy n_-^{T\to R}(y)\rho_-(x, y); \tag{14}$$

these express the fact that tumbling bacteria result from running bacteria that switch to tumbling mode. Here $\rho_+(x, y)dx$ and $\rho_-(x, y)dx$ are probabilities that a bacterium, which tumbled last at y, tumbles again between x and $x + dx$ (and not before), for $x > y$ and $x < y$, respectively. These probabilities are given by

$$\rho_\pm(x, y)dx = \exp\left[\mp \int_y^x dy' \frac{1}{v\tau(y', y)}\right]\frac{dx}{v\tau(x, y)}. \tag{15}$$

We treat the linear model perturbatively in the strength of bacterium response. Our results are presented for steps of chemoattractant concentration $c(x) = \xi\theta(x)$ ($\xi > 0$), where $\theta(x)$ denotes the Heaviside function, and singular response functions with $R_\Delta(t) \propto \delta(t - \Delta/v)$ or, equivalently in spatial coordinates, $R_\Delta(x) = \chi_\Delta\delta(x \mp \Delta)$ [with a minus (plus) sign for rightward (leftward) runs]. The linear approximation is valid in a regime with $\alpha_\Delta \equiv \xi\chi_\Delta \ll 1$ [1]. (For $\alpha_\Delta = 0$, there is no chemotaxis.) Our solution serves as the Green's function of the problem: One can derive solutions for general chemoattractant concentrations and response functions by a suitable superposition of solutions for singular response functions and step concentrations. Furthermore, while it is straightforward to show that the conclusions for, say, a linear chemoattractant profile are similar to those that we present below, results are easier to interpret for a step chemoattractant profile. Expanding Eq. (15) to first order in α_Δ, we solve the steady-state equations [Eqs. (13) and (14)] for the intermediate quantities $n_\pm^{R\leftrightarrow T}$. Because of the singular response function and the discontinuity in chemoattractant density at $x = 0$, our solutions have singular points at $x = \pm\Delta$. One finds that $n_\pm^{R\leftrightarrow T}$ is piecewise constant for $x < -\Delta$, $-\Delta < x < \Delta$, and $x > \Delta$. From these we derive the incremental running and tumbling bacterium densities compared to the densities far to the left of the chemoattractant step: $\delta N_{R,T}^\Delta(x) \equiv N_{R,T}^\Delta(x) - N_{R,T}^\Delta(-\infty)$. The derivation is outlined in the supplementary material [10].

We find, for $x < -\Delta$,

$$\delta N_R^\Delta(x) = \delta N_T^\Delta(x) = 0; \tag{16}$$

for $-\Delta \le x \le \Delta$,

$$\delta N_R^\Delta(x) = -2aq\frac{\alpha_\Delta(x + \Delta)}{v^2\tau_0}e^{-\Delta/v\tau_0}, \tag{17}$$

$$\delta N_T^\Delta(x) = -a\frac{\alpha_\Delta\tau_T}{v\tau_0}\left(1 + 2q\frac{\Delta + x}{v\tau_0}\right)e^{-\Delta/v\tau_0}; \tag{18}$$

and for $x > \Delta$,

$$\delta N_R^\Delta(x) = -4aq\frac{\alpha_\Delta\Delta}{v^2\tau_0}e^{-\Delta/v\tau_0}, \tag{19}$$

$$\delta N_T^{\Delta}(x) = -a\frac{\alpha_\Delta \tau_T}{v\tau_0}\left(1+4q\frac{\Delta}{v\tau_0}\right)e^{-\Delta/v\tau_0} = \left(1+\frac{v\tau_0}{q\Delta}\right)\frac{\tau_T}{\tau_0}\,\delta N_R^{\Delta}(x); \quad (20)$$

here a is a positive constant that sets the overall density of bacteria. From Eq. (19), running bacteria accumulate to the right if $\alpha_\Delta < 0$, as long as the "response memory" is nonvanishing ($\Delta \neq 0$). Accumulation is strongest for $\Delta = v\tau_0$, i.e., when the response memory Δ/v is comparable to the typical run duration τ_0. We note also that accumulation vanishes if $q = 0$; indeed, in this case bacteria do not change their run direction after tumble and, hence, behave roughly as if there were no tumbles whatsoever. As typically $\tau_T \ll \tau_0$ (experimentally, for *E. coli*, $\tau_T \approx \tau_0/10$), Eq. (20) implies that δN_T^{Δ} is dominated by δN_R^{Δ}. However, the reverse occurs in the particular case with small response memory $\Delta/v < \tau_T/2$, i.e., when the typical tumble duration exceeds the response memory. In this case, bacteria may accumulate to the right (if $\alpha_\Delta < 0$) *even for a response function purely local in time* (i.e., with $\Delta = 0$)—a possibility overlooked in earlier studies that treat tumble as instantaneous. In this tumbling-dominated regime, bacteria accumulate at favorable tumbling sites, while the uniformly populated runs serve to explore favorable tumbling positions.

Our analysis suggests that bacteria accumulate in favorable regions if the impulse response function is negative. As remarked in Ref. [8], this is paradoxical in view of experimental measurements, which yield a bilobe response function [3]. For comparable positive and negative lobes, chemotaxis ought to work best if the negative lobe is peaked around a time τ_0 in the past and fail if it is relegated much beyond in the past. We illustrate this issue in Fig. 1, where we plot solutions of the *nonlinear* model [Eq. (4)] for a step of chemoattractant concentration (shown for comparison with the analytical solution of the linear model). (Similar conclusions apply for a linear chemoattractant profile—see Fig. 1 in the supplementary material [10]). We use a bilobe response function similar to the experimental one and derive the steady-state density of bacteria for three different values of τ_0. According to Fig. 1, accumulation in favorable regions occurs when τ_0 is comparable to the time of the negative peak in the response function (top curve in Fig. 1, labeled by a disk symbol). For smaller values of τ_0, bacteria feel the negative peak only rarely and accumulate in unfavorable regions. This picture agrees with analytical results in the linear model.

Curiously, the experimental value τ_0 generally quoted ($\sim$1 s) falls between the two peaks of the response function and, in our model, does not lead to favorable accumulation (intermediate curve in Fig. 1, labeled by an open square). This conclusion may be modified for a different shape of the response function, less similar to the experimental one—for example, one with a very deep negative lobe. Obviously, there are a number of constraints and performance requirements which we have not considered and which inform the shape of the single-bacterium filter. For example, a rationale for a response function that is spread out in time instead of narrowly peaked is the resulting robustness with respect to input noise, and a rationale for a bilobe response function is the resulting "adaptive" mechanism of mean subtraction.

In summary, we have introduced steady-state equations that govern bacterium density in chemotactic response to a chemoattractant profile. The solutions present a rich behavior which depends in a subtle manner on the details of the model. We find that the bacterium density is a nonlocal function of the chemoattractant density [see Eqs. (17)–(20) and Fig. 1]. This feature of the steady state is a direct consequence of the presence of memory in the dynamics and emerges in a proper treatment of correlations; earlier studies which ignore correlations find local solutions [8]. Our approach also predicts a regime in which bacteria accumulate favorably, even in the case of memoryless dynamics, in the tumbling state. Most earlier studies treat tumble as instantaneous. We treated tumble duration as a homogeneous Poisson process. In experiments, tumble duration seems to be influenced by the recent past in much the same way as run duration is but with a bilobe response function that is more narrowly peaked and sign-inverted [3]. Roughly, we may say that tumbles tend to be shorter in favorable regions and longer in unfavorable regions. If so, chemotactic response may be weakened by this effect, with respect to the homogeneous tumble case. Finally, the sensitivity of the solutions points to the need for further experimental studies. By gently changing parameters, experiments may explore different qualitative behaviors.

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[10] See EPAPS Document No. E-PRLTAO-100-046824 for analytical derivation and a figure pertaining to linear chemoattractant profiles. For more information on EPAPS, see http://www.aip.org/pubservs/epaps.html.