Steady-State Chemotactic Response in *E. 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 obtains, that depends subtly upon several aspects of the system—memory, correlation, and tumbling stochasticity in particular.

Chemotaxis refers to directed motion in response to chemical signals and has been extensively studied in the bacterium *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 the next run. Some amount of correlation between run duration and local bacterium density at the run’s starting point, which we took into account. All these effects yield a rich macroscopic behavior in the steady state that depends subtly upon the form of the single-bacterium response filter. In particular, (i) the usual bi-lobe 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 non-local dependence of the probability density upon the environment, due to the presence of memory in the dynamics; (iii) when tumble is non-instantaneous, 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, 6, 9]; specifically, correlations and tumble duration variability had been neglected in earlier treatments [1, 5, 6, 7, 8, 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 chemorepellent. Below, we discuss the differences in responses to ‘positive’ and ‘negative’ stimuli.) Run durations are Poissonian, with probability

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

(1)

to switch from run to tumble between times \( t \) and \( t + dt \) [3]. Here, \( F[c] \) 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 non-linearity, as
\[
\mathcal{F}[c] = \phi \left( \int_{-\infty}^{t} dt' R(t - t') c(t') \right),
\]
where the functions \( \phi(\cdot) \) and \( R(t) \) summarize the action of the biochemical machinery that processes input signals from the environment \( \tau \). If \( \phi(\cdot) \) is non-singular, it may be linearized, as
\[
\mathcal{F}_{\text{lin}}[c] = \int_{-\infty}^{t} dt' R(t - t') c(t'),
\]
where an additive constant is absorbed in a redefinition of \( \tau_0 \) (in Eq. (11)) and a multiplicative constant is absorbed in a rescaling of \( R(t) \). Experimental work \( \tau \) suggests instead a thresholding non-linearity \( \chi \), well fitted by the form
\[
\mathcal{F}_{\text{nl}}[c] = [\mathcal{F}_{\text{lin}}[c]]_+,
\]
where
\[
[x]_+ = \begin{cases} 
0 & \text{if } x \leq 0 \\
 x & \text{if } x > 0 
\end{cases}.
\]

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 \( R(t - t') \). These experiments yielded a bimodal shape for \( R(t - t') \), with a positive peak around \( t' \approx 0.5 \text{ sec} \) and a negative peak around \( t' \approx 1.5 \text{ sec} \). The negative lobe is shallower than the positive one and extends up to \( t' \approx 4 \text{ sec} \), beyond which it vanishes and to a good approximation satisfies \( \int_{-\infty}^{\infty} R(t') dt' = 0 \). The estimated value of \( \tau_0 \) is about 1 sec (see Fig. 1 for an illustration).

Tumble duration also is modulated stochastically, in close analogy to run duration behavior \( \tau \). Earlier theoretical work has mostly treated tumble as instantaneous \( \tau \). 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 comes short of a full description, the mere allocation of a non-vanishing duration to tumble brings in qualitative consequences, as discussed below.

The bi-lobe 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 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 \( \tau \) argues that a single-lobe, even punctual temporal filter, as \( R(t - t') = \chi \delta(t - t') \) with \( \chi \) 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 any addition of a negative contribution, akin to the bi-lobe shape measured experimentally, weakens the bias. The arguments developed in Ref. \( \tau \) concern the instantaneous dynamics of a bacterium and ignore the spatially varying buildup of probability in time; they apply, for example, to a transient situation in which the probability density is flat. Reference \( \tau \) contrasts transient and steady-state behavior 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. Finally, it argues that the typical bi-lobe shape of the linear filter, \( R(t) \), may derive from a constrained optimization involving transience and steady state. While Refs. \( \tau, \tau \) present a number of interesting ideas and go some length into explaining chemotaxis statistically, they make a number of limiting assumptions. First, they disregard the correlation between run duration and probability density in a given region. Second, they assume instantaneous tumble. Third, the constrained optimization in Ref. \( \tau \) is somewhat ad hoc.

In the remainder of the paper, we proceed as follows. First, we write equations that govern the steady-state density of (non-interacting) bacteria (equivalently, the bacterium probability density); second, we derive the latter analytically in the linear model (Eq. (4)) and numerically in the non-linear model (Eq. (1)). We are after the density
\[
N(x) = N_R(x) + N_T(x),
\]
where \( N_i(x) \) is the number of bacteria lying between \( x \) and \( x + dx \) in the steady-state, and the subscripts \( R \) and \( T \) refer to run and tumble respectively. As a natural way to incorporate correlation, we borrow four intermediate quantities: \( n_{T-R}(x) \), the number of bacteria that switch from tumble to rightward run between \( x \) and \( x + dx \) per unit time; \( n_{T-R}(x) \), the number of bacteria that switch from tumble to leftward run between \( x \) and \( x + dx \) per unit time; \( n_{R-T}(x) \), the number of bacteria that switch from rightward run to tumble between \( x \) and \( x + dx \) per unit time; \( n_{R-T}(x) \), the number of bacteria that switch from leftward run to tumble between \( x \) and \( x + dx \) per unit time. The rightward and leftward fluxes are given by
\[
\partial_x j_+(x) = n_{T-R}(x) - n_{R-T}(x),
\]
\[
\partial_x j_-(x) = n_{T-R}(x) - n_{R-T}(x).
\]
If \( N_+(x) \) and \( N_-(x) \) are the densities of rightward and leftward running bacteria respectively, then \( j_+(x) =
so that Eq. (10) simplifies into

\[ \partial_x N_R(x) = \partial_x \left[ N_+ + N_- \right] \]

\[ = \frac{1}{v} \left[ n_{+ R - R}^x(x) - n_{+ R - T}^x(x) \right. \]

\[ - n_{- R - R}^x(x) + n_{- R - T}^x(x) \right] . \tag{10} \]

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, \( n_{+ R - R}^x(x) = (1 - q) n_{+ R - T}^x(x) + q n_{- R - T}^x(x) \) and \( n_{+ R - T}^x(x) = q n_{+ R - T}^x(x) + (1 - q) n_{- R - T}^x(x) \), so that Eq. (10) simplifies into

\[ \partial_x N_R(x) = \frac{2q}{v} [n_{+ R - T}^x(x) - n_{- R - T}^x(x)] . \tag{11} \]

Within our assumption of unmodulated tumble rate, in the steady state the density of tumbling bacteria, \( N_T(x) \), reads

\[ N_T(x) = \tau_T \left[ n_{+ R - T}^x(x) + n_{- R - T}^x(x) \right] . \tag{12} \]

As a final simplifying assumption, we posit that memory is erased at tumble-to-run switches. This assumption may not be validated by data,\(^2\), but it is unclear whether it improves or suppresses chemotaxis with respect to the no-erasure case. Equation (3) becomes

\[ F_{\text{lin}}[c] = \int_{t_0}^{t} dt' R(t - t') c(t'), \tag{13} \]

where \( t_0 \) is the time of last switch, and the run-to-tumble switch probability, \( dt/t(t, t_0) \), 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 \( dx/\tau v(x, y) \). We now have all the elements in hand to write the steady-state equations that govern density and keep track of correlations, as

\[ n_{+ R - T}^x(x) = \int_{-\infty}^{x} dy_n T_R^y(x, y) \rho_+(x, y), \tag{14} \]

\[ n_{- R - T}^x(x) = \int_{x}^{+\infty} dy_n T_R^y(x, y) \rho_-(x, y); \tag{15} \]

these express the fact that tumbling bacteria result from running bacteria that switch to tumbling mode. Here, \( \rho_+(x, y) dx \) and \( \rho_-(x, y) dy \) 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

\[ \rho_+(x, y) dx = \exp \left( \int_{y}^{x} dy' \frac{1}{v'(y', y)} \right) \frac{dx}{v'(x, y)}. \tag{16} \]

We choose to illustrate our results with steps of chemoattractant concentration, \( c(x) = \xi \theta(x) (\xi > 0) \), where \( \theta(x) \) denotes the Heaviside function. In the linear model, it is handy to focus upon singular response functions with \( R_{\Delta}(t) \propto \delta(t - \Delta/v) \), or equivalently in space coordinates, \( R_{\Delta}(x) = \chi_{\Delta} \delta(x \mp \Delta) \) (with a minus (plus) sign for rightward (leftward) runs). One can then derive solutions for more general cases as linear superpositions of solution for singular response functions. We treat the linear model perturbatively in the strength of bacterium response; specifically, we assume a regime with \( \alpha_{\Delta} \equiv \xi_{\Delta} \ll 1 \). (For \( \alpha_{\Delta} = 0 \), there is no chemotaxis.) Expanding Eq. (10) to first order in \( \alpha_{\Delta} \), we solve the steady-state Eqs. (14) and (15) for the intermediate quantities \( n_{\pm R - T}^{\pm} \). From these, we derive the incremental running and tumbling bacterium densities compared to the densities far to the left of the chemoattractant step: \( \delta N_{R}^{\pm}(x) \equiv N_{R}^{\pm}(x) - N_{R}^{\pm}(\infty) \) and \( \delta N_{T}^{\pm}(x) \equiv N_{T}^{\pm}(x) - N_{T}^{\pm}(\infty) \).

Because of the singular response function and the discontinuity in chemoattractant density at \( x = 0 \), our solutions have singular points at \( x = \pm \Delta \). We find, for \( x < -\Delta \),

\[ \delta N_{R}^{\pm}(x) = \delta N_{T}^{\pm}(x) = 0; \tag{17} \]

for \( -\Delta \leq x \leq \Delta \),

\[ \delta N_{R}^{\pm}(x) = -2aq \frac{\alpha_{\Delta}(x + \Delta)}{v^{2} \tau_{0}} e^{-\Delta/v \tau_{0}}, \tag{18} \]

\[ \delta N_{T}^{\pm}(x) = -a \frac{\alpha_{\Delta} \tau_{T}}{v \tau_{0}} \left( 1 + 2q \frac{(x + \Delta)}{v \tau_{0}} \right) e^{-\Delta/v \tau_{0}}. \tag{19} \]

for \( x > \Delta \),

\[ \delta N_{R}^{\pm}(x) = -4aq \frac{\alpha_{\Delta} \Delta}{v^{2} \tau_{0}} e^{-\Delta/v \tau_{0}}, \tag{20} \]

\[ \delta N_{T}^{\pm}(x) = -a \frac{\alpha_{\Delta} \tau_{T}}{v \tau_{0}} \left( 1 + 4q \frac{\Delta}{v \tau_{0}} \right) e^{-\Delta/v \tau_{0}} \]

\[ = \left( 2 + \frac{v \tau_{0}}{2q \Delta} \right) \frac{\tau_{T}}{\tau_{0}} \delta N_{T}^{\pm}(x); \tag{21} \]

here \( a \) is a positive constant that sets the overall density of bacteria. From Eq. (20), running bacteria accumulate to the right if \( \alpha_{\Delta} < 0 \), as long as the ‘response memory’ is non-vanishing (\( \Delta \neq 0 \)). Accumulation is strongest for \( \Delta = v \tau_{0} \)\(^{i} \) e.\( \), when the response memory, \( \Delta/v \), is comparable to the typical run duration, \( \tau_{0} \). 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. (21) implies that \( \delta N_{R}^{\pm} \) is dominated by \( \delta N_{T}^{\pm} \). 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 (with \( \Delta = 0 \))—a possibility overlooked in earlier work that treat tumble as instantaneous.
In this tumbling-dominated regime, bacteria accumulate at favorable tumbling sites while the uniformly populated runs serve as a way to explore potentially favorable tumbling positions.

![Graph](image)

**FIG. 1:** Numerical results in the non-linear model with $c(x) = 10^{-7} \theta(x)$. All quantities are given in arbitrary units. To obtain $\delta N_R(x)$ and $\delta N_I(x)$, Eqs. (14-15), for the non-linear model, were solved iteratively on a computer, using a discrete lattice of size 800, with $v = 10 \mu m$, $q = 0.4$, $\tau_T = 10/17\tau$ and $dx = 0.05 \mu m$. 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 $\tau_0$ (in seconds) are indicated in the figure. The correspondence between the bacterium density and the value of $\tau_0$ is indicated by the solid and open symbols, in both figure and inset in which the response function is illustrated. The functional form of the response function was chosen as $R(t) = (240t \exp(-200t/17) - 29.4t \exp(-7t/17))/17$ which satisfies $\int_0^\infty R(t)dt = 0$.

Our analysis suggests that bacteria accumulate in favorable regions if the impulse response function is negative. As remarked in Ref. [3], this conclusion is paradoxical in view of experimental measurements, which yield a bi-lobe response function [3]. For comparable positive and negative lobes, chemotaxis ought to work best if the negative lobe is peaked around a time $\tau_0$ 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 non-linear model (Eq. (4)) for a step of chemoattractant concentration. We use a bi-lobe response function similar to the experimental one and derive the steady state density of bacteria for three different values of $\tau_0$. According to Fig. 1, accumulation in favorable regions occurs when $\tau_0$ 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 $\tau_0$, bacteria feel the negative peak only rarely and accumulation occurs in unfavorable regions. This picture agrees with our analytical results in the linear model.

Curiously, the experimental value $\tau_0$ generally quoted ($\sim 1$ sec) 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 rational 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 rational for a bi-lobe response function is the resulting ‘adaptive’ mechanism of mean subtraction.

In sum, 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 non-local function of the chemoattractant density (see Eqs. (15-18) 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 [3]. Our approach also predicts a regime in which bacteria accumulate favorably, even in the case of memory-less 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 bi-lobe 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.

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