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Optimal Noise Filtering in the Chemotactic Response of Escherichia coli

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Information-carrying signals in the real world are often obscured by noise. A challenge for any system is to filter the signal from the corrupting noise. This task is particularly acute for the signal transduction network that mediates bacterial chemotaxis, because the signals are subtle, the noise arising from stochastic fluctuations is substantial, and the system is effectively acting as a differentiator which amplifies noise. Here, we investigated the filtering properties of this biological system. Through simulation, we first show that the cutoff frequency has a dramatic effect on the chemotactic efficiency of the cell. Then, using a mathematical model to describe the signal, noise, and system, we formulated and solved an optimal filtering problem to determine the cutoff frequency that bests separates the low-frequency signal from the high-frequency noise. There was good agreement between the theory, simulations, and published experimental data. Finally, we propose that an elegant implementation of the optimal filter in combination with a differentiator can be achieved via an integral control system. This paper furnishes a simple quantitative framework for interpreting many of the key notions about bacterial chemotaxis, and, more generally, it highlights the constraints on biological systems imposed by noise.

Introduction

One of the thrusts of the new area of systems biology is the understanding that biological systems can be studied with many of the tools and theory that are used to analyze man-made systems [1,2]. Biological and engineered systems share many of the same features. One of these is the need to make decisions based on imperfect information about the environment, because the cell relies on noisy sensing [3–7]. The chemotaxis signaling pathway of Escherichia coli serves as an ideal vehicle for studying how biology copes with this form of uncertainty.

Bacteria traverse up gradients of chemical attractants in an efficient manner. This chemotactic behavior is universal in living organisms. Two basic chemotaxis strategies are spatial and temporal sensing [8]. In spatial sensing, cells compare spatial differences in chemical concentration (e.g., front versus back) to determine the direction of the gradient. In temporal sensing, cells detect temporal changes in chemical concentration as they move, thereby providing information about whether the course is favorable.

The classic work of Berg and colleagues, along with others, have conclusively demonstrated that E. coli employ a temporal sensing mechanism, engaging in a biased random walk consisting of alternating periods of straight runs and random tumbles (Figure 1A, [9]). When the concentration of chemoattractant (L) is increasing in time (dL/dt > 0), the bacteria tend to have longer runs (i.e., the probability of a tumble decreases), thus allowing the bacteria to move up the gradient. If the chemoattractant concentration is decreasing (dL/dt < 0), then the bacteria are more likely to reorient their direction by tumbling.

The sensing of the chemoeffectors in E. coli is performed by a two-component signal transduction pathway consisting of transmembrane receptors (MCPs, methyl-accepting proteins), receptor methylases (CheR), and demethylases (CheB) that regulate receptor activity, signal transducing histidine kinases, and downstream effectors (e.g., CheY) (Figure 1B, [10,11]). One hallmark of this signaling system is perfect or near-perfect adaptation to a persistent input stimulus, which is a consequence of the temporal differentiation effected by the signaling pathway [12]. It has been demonstrated that this perfect adaptation is robust to dramatic changes in component levels of the pathway, a robustness that can only be achieved through a special type of feedback control, integral feedback [12,13]. However, the adaptation time is quite sensitive to changes in component levels such as concentrations of CheB and CheR [13,14].

A major challenge of temporal sensing is accurately measuring changes in chemoattractant concentration (dL/dt) in the presence of noise. Fluctuations, such as those intrinsic to the ligand–receptor binding process, are amplified by this temporal differentiation. A traditional fix in engineering is to use a low-pass filter to remove the high-frequency noise from the lower-frequency signal; the E. coli signaling network implements such a mechanism (Figure 2). The key design criterion is to determine the appropriate cutoff frequency for the filter. In the time domain, this roughly corresponds to...
Synopsis

Bacterial motility involves successive periods of relatively straight runs, interspersed by tumbles—periods in which the bacteria are reoriented randomly. To move in the direction of chemical gradients—a process known as chemotaxis—cells modulate the duration of the runs. To ascertain whether the direction of the current run is desirable, cells continuously monitor temporal changes in the chemoattractant concentration. However, the decisions can only be based on imperfect information about the environment because binding noise implies that receptor occupancy is a limited measure of the chemoattractant concentration. Bacteria cope by filtering the sensed signal to reduce the effect of this binding noise. Through simulations, Andrews, Yi, and Iglesias demonstrate that there is a particular filter cutoff frequency that achieves optimal chemotaxis. Moreover, using a model of the sensing mechanism, the authors also compute the theoretically optimal system for estimating the chemoattractant concentration from the noisy receptor-occupancy signal. Andrews and colleagues show that these two filtering systems are closely matched, and that their frequency-dependent behavior corresponds to published experimental data. Their results highlight the constraints that noise places on cellular performance as well as demonstrating how cells have evolved to deal with this uncertainty in an optimal fashion.

Adaptation Times Affect Chemotaxis

In this paper, we use theoretical tools to study the effects of noise on the ability of a cell to chemotax and, more specifically, on how bacteria cope. We first use simulations to show that adaptation time (filter-cutoff frequency) affects the chemotactic performance of the cell and that there exists an optimal adaptation time that allows cells to chemotax the farthest. Having shown that the adaptation time can make a difference to chemotactic efficiency, we conjecture that this effect is predicated on the ability of the cell to estimate its environment accurately in the presence of noise. To test this, we use theoretical tools to determine which filter-cutoff frequency leads to optimal detection of temporal changes in the chemoattractant concentration. The signal to be estimated is ligand concentration, and noise arises from the discrete nature of ligand–receptor interactions during binding. We demonstrate that the theoretically obtained cutoff frequency for optimal estimation has the same dependence on external parameters (e.g., noise and rotational diffusion levels) as the adaptation time that achieves optimal chemotaxis in simulation, implying that optimal ligand estimation is necessary for optimal chemotaxis. Finally, we illustrate how integral feedback control, a known characteristic of the bacterial signaling network [12], implements robust temporal differentiation in which a first-order filter is in series with the differentiator. Thus, we show that the signal transduction pathway found in E. coli is an implementation of the optimal sensing mechanism we derive theoretically. This fact is further verified by quantitative comparison of our results with published models of the signaling network and experimental data.

Results

Adaptation Times Affect Chemotaxis

We first examined the effect of adaptation time on chemotaxis through simulation. To this end, we developed a model of the signal transduction network of E. coli (Materials and Methods). This model is based on the receptor-modification model of [17] and other more recent models that include receptor clustering and recreate the experimentally observed chemotactic behavior faithfully [18,19]. A simplified system consisting of a differentiator coupled to a first-order filter captures the primary features of this model: the cell averages the measurement of ligand over a period of
time, and then differentiates to determine the quality of the current run direction (Figure 2, Materials and Methods). This approximation of the signaling pathway allows us to adjust the filter’s cutoff frequency, mimicking the effect of changes in the concentrations of signaling components on adaptation time, while keeping other signaling characteristics constant (Figure 2B). The system’s gain was selected to reflect the gain of a model of the system. The simulations are 2-D and include the run/tumble decision, the motion of the bacterium, as well as the physical implementation of diffusion and noisy signaling. A 1-D linear gradient of attractant was applied, and the chemotactic performance was measured by the average migration distance up the gradient over a period of time. Other key parameters in our simulations were the rotational diffusion constant and the measurement noise variance (Materials and Methods).

Our simulations indicate a biphasic response: cells with a particular filter-cutoff frequency move farther up the chemotactant gradient than cells with either higher or lower frequency cutoffs (Figure 3A). Moreover, the range of frequencies for which optimal chemotaxis efficiency is observed was narrow (Figure 3B). For example, an approximately 2-fold increase in cutoff frequency from the optimal (from 3.4 to 7.0 rad/s) significantly decreased the distance traveled (249 ± 13 versus 169 ± 10 µm, SEM, \( p < 10^{-5} \) using Student’s t-test). Similarly, a 4-fold decrease in the cutoff frequency (from 3.4 to 0.8 rad/s) also reduced the distance traveled, though less significantly (213 ± 15 µm, SEM, \( p < 0.04 \)). These trends are also observed in signaling models that included higher order rolloff (Figure S1). These data illustrate that to achieve optimal chemotaxis, it is necessary to have optimal or near-optimal noise-filtering capabilities.

To determine how external parameters affect the optimal filtering conditions and how they relate to chemotaxis performance, we repeated our simulations for a wide range of binding noise levels and rotational diffusion coefficients (Figure 4A and 4B). In all cases the cells exhibited the same biphasic frequency dependence, indicating that the existence of an optimal filter-cutoff frequency was a robust feature of the network. However, the specific cutoff frequency at which optimal chemotaxis was achieved was parameter-dependent (see below).

Optimal Filtering in E. coli

The simulations above indicated the existence of specific adaptation times that lead to optimal chemotaxis, and that these adaptation times are dictated by the cutoff frequency of
a low-pass filter. To investigate this further, we used tools from estimation theory to deduce the optimal filter that best separates the true ligand concentration from the noise induced by ligand–receptor binding. We assumed that *E. coli* is swimming in an environment in which the concentration of the chemoattractant at point *z* is *L*(z). Moreover, the movement of the bacterium leads to a time-varying change in concentration in its neighborhood: *L*(z(0)) − *L*(z(t)) is the “signal” of the system—changes over time to determine whether the current swimming direction is favorable (dL/dt > 0) or unfavorable (dL/dt < 0). This determination and its effect on cell movement, achieved via the signal transduction network [20,21], leads the cell to new ligand concentrations *L*(z(t)), thus completing the feedback loop between the cell and its environment (Materials and Methods).

In practice, the cell can only determine an estimate of *L*(z(t)) based on the number of receptor–ligand complexes on the cell surface. Moreover, this estimate is corrupted by the presence of noise. Sources of noise include: (i) stochastic binding dynamics of ligand to receptor (ligand binding noise [22]), and (ii) counting fluctuations associated with the diffusion of a small number of ligand molecules into a finite volume (ligand diffusion noise [15,23,24]). We assume that the concentration of ligand-bound receptor complexes is *C*(t) + *v*(t) where *C*(t) is the concentration of receptor complexes in the absence of noise and *v*(t) is a noise term due to ligand–receptor binding. We now ask the following question: from a signal processing perspective, what is the optimal filtering mechanism that best estimates *L*(z(t)) from the noisy observation *C*(t) + *v*(t)? To answer this, we first made several assumptions about the cell’s environment.

We assumed a 2-D environment with linear ligand gradient *g* (μM/μm). Then dL/dt = ∂L/∂z ∂z/∂t = g cos(θ(t)), where *z* is cell position, *g* is the magnitude of the cell’s velocity, and θ(t) is the orientation of the cell at time *t* with respect to the gradient. We treated θ(t) as a zero-mean white random process with variance 2*D*t, where *t* is an average length of a bacterial run, and *D* is the rotational diffusion coefficient. This implies that dL(t)/dt = w(t), where *w*(t) is a white random process with variance *g*²*u²*var(cos(θ(t))). Thus, changes in the signal *L*(z(t)) of the system are affected by rotational diffusion: larger *D* yields greater signal fluctuations.

The optimal estimate of *L*(t) given the observed signal *C*(t) + *v*(t) can be found using the Kalman filter, an algorithm developed to detect and separate signals in the presence of random, unwanted noise, that is used widely in engineering navigation and guidance systems [25,26]. We computed the optimal estimator numerically for the state *L*(z(t)) under the assumption that *C* + *v* is observed (Materials and Methods). The optimal estimator is a low-pass filter: at low frequencies, the system response does not depend on frequency; at higher frequencies, a frequency-dependent dropoff, inversely proportional to frequency, and characteristic of a first-order low-pass filter, is seen (Figure 4C). Moreover, there was good agreement between the theoretical optimal cutoff frequency for ligand estimation and the filter-cutoff frequency required for optimal chemotaxis in the simulations. We repeated this computation for a range of noise levels and rotational diffusion coefficients. There was a striking similarity in the observed trends. For example, the optimal cutoff frequency for both chemotaxis and ligand estimation decreases as the level of binding noise in the system increases (Figure 4D). In contrast, increasing the level of rotational diffusion in the simulations led to higher optimal cutoff frequencies for chemotaxis; a trend that was also consistent with the cutoff frequency of the optimal ligand estimator (Figure 4E). This consistency between the theory and simulations argues that optimal ligand concentration estimation as defined by the Kalman filter is necessary for optimal chemotaxis in our simulations.

To investigate the dependence of the optimal cutoff frequency for chemoattractant estimation on environmental conditions, we repeated our computations for different levels...
of mean ligand concentration and varying spatial concentration gradients (Figure 5). In all cases the frequency response of the optimal filter was that characteristic of a first-order low-pass filter. However, the cutoff frequencies varied from one condition to another. In particular, cutoff frequencies increased with increasing chemoattractant gradients, but decreased as the mean level of ligand increased. These variations suggest that chemotactic signaling systems need to be tuned to their environment for optimal estimation of the environment.

Quantitative Comparisons to Experimental Observations

We next determined the degree to which the cutoff frequencies of the optimal filter for chemoattractant estimation matched the frequency-dependent behavior observed experimentally. To this end we used published data describing the behavior of the *E. coli* chemotactic system [20,27], adjusted to comprise only the primary filtering component by removing the differentiator and the phosphorylation cascade modeled in [28] (Materials and Methods). Additionally, we used our full model of the *E. coli* signaling pathway as a proxy for the wild-type *E. coli* chemotaxis behavior. We linearized the model (valid for moderately large step changes in ligand, Materials and Methods) and computed the corresponding low-pass filter component to compare with our theoretical results. Linearizations of other models [17] also revealed similar low-pass filtering characteristics (Materials and Methods). Interestingly, the cutoff frequencies observed from the experimental data and calculated from the model matched reasonably well the theoretical optimal value for a particular gradient and ligand concentration (Figure 6A). This agreement suggests that the chemotaxis signal transduction pathway in *E. coli* is acting as an optimal filter. It should also be noted that other experimental evidence suggests lower cutoff frequencies (adaptation times on the order of several minutes) [13]. This may be due to strain differences or saturation of the methylation machinery from large ligand stimulants.

We computed the cutoff frequencies of the model for a wide range of chemoattractant gradients and mean concentrations...
and compared these with the theoretically derived optimal estimator cutoff frequencies (Figure 6B). We found that the two sets did not intersect for all ligand-gradient combinations. However, we did find a range of combinations in which the model filter matches the optimal cutoff frequency (Figure 6C). Remarkably, this combination exhibits an approximately linear dependency (slope 0.184 μM⁻¹, R² = 0.97), suggesting that the filtering characteristic of E. coli is optimized for environments where the relative gradient of chemoattractant is constant. This dependency on the relative gradient is reminiscent of earlier results in other organisms, including amoebae [29–31] and yeast (S. Paliwal et al., unpublished data), that focused on chemoattractant gradient sensing.

Discussion

Previously, Berg and others have argued that the choice of a time over which the bacterium integrates the observed signal to determine the tumbling decision balances the need to average fluctuations in the measurement of ligand levels with the ability to track rapid changes in direction caused by rotational diffusion of the cell [32]. We have constructed a simple mathematical framework to capture these ideas. The notion of integration time, or adaptation time, is captured by the cutoff frequency of the filter that attenuates stochastic disturbances in the sensing mechanism. Using simulations, we demonstrated that chemotactic efficiency is quite sensitive to this filter-cutoff frequency (Figure 3). In particular, we showed that there is a frequency for which optimal chemotaxis can be achieved, and that this frequency is dependent on external parameters (Figure 4).

Next, using theoretical tools, we computed the filter that best estimates the ligand concentration in the face of noisy ligand–receptor complexes. We found strong agreement between the cutoff frequencies associated with optimal chemotaxis and optimal chemoattractant estimation (Figure 4D and 4E).

The optimal cutoff frequency for chemoattractant estimation represents the averaging time that best compromises the tradeoff between noise attenuation and signal amplification. This is illustrated in Figure 7A, which highlights the contributions of the noise and signal power spectral densities (PSDs) to this tradeoff. As binding noise increases, the noise PSD shifts upward, and the optimal cutoff frequency (ω_cf) decreases, thus yielding a longer time over which to average ligand measurements so that the additional noise may be attenuated. This trend was seen in the chemotaxis simulations.
It should be noted that while we have considered binding fluctuations as the measurement noise that results solely from the stochastic dynamics of ligand–receptor interactions, the total noise that contributes to uncertainty in ligand measurement also depends on ligand diffusion [15,24]. Diffusion of ligand molecules in the environment affects their interaction with receptors positioned on the cellular membrane and provides a physical limitation to the accuracy of cell measurements. Estimates of the variance of measurement uncertainty due to ligand diffusion yield measurement fluctuations on the order of $10^{-5}$ μM^2 [15,24]. The variance in the amount of bound receptor complexes due to binding dynamics can be quantified at steady state and is on the order of 0.1 μM^2 [4,33]. Thus, the binding-dynamics noise component overwhelms any uncertainty from ligand diffusion and so we only consider noise from ligand–receptor dynamics in our analysis. However, ligand diffusion provides a limit (the perfect sensor limit) which restricts the degree to which the optimal filter cutoff frequency can increase in response to decreasing binding-dynamics noise (Figure 4D).

We have shown that a low-pass filter is necessary for optimal chemotactic performance of the bacterial system in the presence of noise. Integral control provides an important unifying theme in this work. An integral feedback control system implements a differentiator in combination with a first-order low-pass filter (Figure 7B). This implementation is robust because the central properties of this differentiator depend only on the integral feedback controller (e.g., receptor methylation/demethylation dynamics) and not on the rest of the system (e.g., phosphorylation dynamics of cascade, interaction of CheY-P with motor, etc.). Furthermore, in the context of integral feedback control, the connection between the kinetics of receptor methylation/demethylation, adaptation time, integration time, and the filter breakpoint becomes apparent. Indeed, one can view robust perfect adaptation as a consequence of robust temporal sensing realized via integral control.

The theory and simulations offer several important predictions. First, the activities of the receptor methylase CheR and the demethylase CheB determine the breakpoint of the chemotactic differentiator. For example, increasing the level/activity of CheR causes the breakpoint to shift to larger frequencies and, correspondingly, shorter adaptation times. This trend is observed in the experimental results of [13] and the model of [14]. More importantly, if, as we theorize, _E. coli_ has evolved towards an optimal filter, then moving the breakpoint by altering the methylation/demethylation dynamics should cause impaired chemotaxis performance. Based on our results, we predict that these cells could not chemotax as far up a gradient as cells with wild-type expressions of CheB and CheR. Second, we expect the optimal breakpoint to depend on certain environmental/cellular conditions. In particular, optimal cutoff frequencies may differ by an order of magnitude depending on mean cellular conditions. In particular, optimal cutoff frequencies may differ by an order of magnitude depending on mean cellular conditions. In particular, optimal cutoff frequencies may differ by an order of magnitude depending on mean cellular conditions. In particular, optimal cutoff frequencies may differ by an order of magnitude depending on mean cellular conditions.
correlating the frequency-dependent responses of both mutant and wild-type cells under varying environmental conditions to their chemotactic efficiency. Another issue for future study is the effect of the filter gain. Because the aim of this work is establishing the existence of an optimal low-pass filter for chemoattractant estimation and chemotaxis, we have focused on frequency dependencies and the optimal cutoff frequency and neglected optimal filter gains.

Finally, our results also highlight the fragile nature of the chemotaxis system by demonstrating how sensitive chemotactic performance can be to changes in adaptation times. In fact, the experiments that definitively showed that the property of adaptation was robust also demonstrated that the adaptation times were not: changes in CheB and CheR expression levels cause significant changes in adaptation time [13,14]. As stated above, our results predict that these cells would not chemotax as efficiently, and point towards a potential fragility of the system [34]. However, recent experimental results demonstrate that within a population of cells there is large variability in behavior and that this is proportional to the probability of the state being inactive (active).

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where we have assumed that all of the microstates in the configuration are equally probable. Moreover, we assume that the energy difference of each ligand-unbound-bound process is equal regardless of the receptor, thus allowing us to drop the index \( n \).

Only inactive states may be methylated, and only active states may be demethylated. Thus, a state with \( j \) sites methylated is (further) methylated at a rate

\[
\gamma^\text{M}j = \gamma^\text{M}(1 - p^\text{un}(j))
\]

where \( \gamma^\text{M} \) is the methylation rate constant. The demethylation rate of a state with \( j \) sites methylated is

\[
\gamma^\text{D}j = \gamma^\text{D}p^\text{un}(j).
\]

In general (with obvious exceptions for \( R^0 \), \( RL^0 \), \( RLM^0 \), and \( RLNM^0 \)), the differential equations describing the rate of change of concentration of states \( R^j \) and \( RL^j \) are

\[
\frac{dR^j}{dt} = -b^L + k_M^L + k_M^U(R^j)(RL^j) + b^L + k_M^U(j - 1)R^{-1}
\]

\[
+ k_M^L(j + 1)RL^{-1}
\]

\[
\frac{dRL^j}{dt} = -(b^L + k_M^L + k_M^U(j)(RL^j) + b_M^L \times R^j + k_M^U(j - 1)RL^{-1}
\]

\[
+ k_M^L(j + 1)RL^{-1}.
\]

Total activity of the cluster is

\[
A = \sum_{j=0}^{NM} p^\text{un}(j)(RL^j + p^\text{un}(j)(RL^j).
\]

Model validation. We compared a variety of different response characteristics of the model to those observed experimentally (Figure 9). Step increases in chemoattractant induce an initial transient decrease in receptor activity, corresponding to an increase in the probability of counterclockwise (CCW) flagella rotation, that decays exponentially to its pre-stimulus steady-state level (Figure 9A). This behavior is consistent with responses observed experimentally [13,20,27] and in previously published models [14,17,21,35–37]. The response to impulses of chemoattractant exhibit an initial spike in CCW probability followed by a decrease below the pre-stimulus level that then increases exponentially back to the pre-stimulus level (Figure 9B). Step and impulse responses agree closely with experimentally observed responses from [27]. Step-decreases in chemoattractant induce a response similar to step-increases with an initial increase.
A model from [17], linearized about a ligand input of fraction of receptors in the cluster always having a nonzero probability of
This sensitivity response closely matches data from the
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pass characteristics consistent with observations in [27].
(D) For step inputs, normalized peak activity of the model (1 – decreases) with increasing change in attractant concentration. Adapta-
(C) The initial response to addition (removal) of attractant increases (red dots show data from Figure 1 of [27]).
return to its pre-stimulus level) and response magnitude increase
with increasing step size and are asymmetric with respect to positive
and negative steps (Figure 9C, [17]). The peak activity response to step inputs exhibits high sensitivity to the size of the step (Figure 9D), as has been observed experimentally [38,39], and is seen in other
published models [18,19,35,36,40]. Sensitivity of our model closely matches that of [36].
The model parameters used are N = 4, M = 4, k_r = 0.01 μM^{-1} ms^{-1}, k_a = 1 μm, γ_r = 1.2 s^{-1}, and γ_a = 2 γ_r. Free energy differences used are given in Table 1.
Model linearization and frequency response. We implemented the model as an S-Function in Matlab, version 7 (Mathworks, http:// www.mathworks.com), and linearized it using the linmod command. The linearization is valid for even moderately large step changes in ligand concentration (Figure 10). We compared the frequency response of the linearization (Figure 9E) as well as the Barkai-Leibler model [17] (Figure 9F) to experimentally observed frequency responses [20,27]. All frequency responses exhibited low-pass characteristics: low-frequency input components are “passed” through the system and high-frequency input components are attenuated.
For a meaningful quantitative comparison with experimental data, we need to adjust for the fact that the models include only the receptor methylation/demethylation dynamics, but the experimental data measures the system response in terms of motor biases and so contain the dynamics of the phosphorylated CheA, CheY, CheZ, and FliM-bound CheY. To determine the contribution of these elements to the overall frequency response, we used a linearization of the differential equation model for these elements [28]. Finally, because we are primarily interested in the low-pass filtering characteristics, we also accounted for the differentiation. The adjustment was made by combining a system with the same frequency response as in [20] in series with an integrator (to remove the differentiator) and the inverse of the transfer function obtained from a linearization of the phosphorylation cascade modeled in [28] (to remove the phosphorylation cascade that directly affects motor rotation).
The frequency response of the system exhibits characteristics of a differentiator coupled with a first-order low-pass filter; thus, the model of the E. coli signaling network may be approximated by a system with Laplace transform of the form \( \frac{k}{(s + k)} \) where \( k \) is the bandwidth of the system. The ability of this simple linear system to recreate the response of the model is further verified in Figure 2.

Environmental model. To study the effect of adaptation time on chemotaxis, we developed a computational model of a chemotaxing cell in Simulink version 6.2 by Mathworks, available by contacting the authors; see Figure 11A. We describe the major components of the model here.

Environment. Bacteria are assumed to chemotax in a 2-D (x,y) plane. The ligand concentration at a position \( z = (x,y) \) is \( L(z) = \text{max}(g_{x}x + L_{0}) \) where the gradient changes along the x direction with slope g_x and \( L_{0} \) is a constant initial ligand concentration at \( z = 0 \). At each simulation step, the concentration of ligand at the bacterium’s current location is calculated as \( L(z) \). In the absence of rotational and translational diffusion, cells are assumed to move at a constant velocity of 20 μm/sec. Fluctuations in receptor occupancy are modeled in the simulation by an additive noise term to the concentration. This contribution is assumed normal with distribution \( \mathcal{N}(0,\sqrt{\text{variance}}) \) where \( \text{variance} \) is the binding dissociation constant, \( k_{a} \) and \( k_{r} \) are the on and off rates, respectively, and \( R_{T} \) is the total number of receptors [4,35]. As demonstrated by Berg, even when running the cell cannot maintain a straight path for long because of the effects of rotational diffusion [41]. Rotational diffusion is implemented through an additive stochastic component to the bacterium’s heading at each simulation step. This component is assumed normal with distribution \( \mathcal{N}(0,2\sigma_{D_{t}}) \) where \( D_{t} \) is the rotational diffusion coefficient and \( \sigma_{D_{t}} \) is the sample time of the simulation [41]. Translational diffusion is implemented through a diffusion coefficient and an additive noise term to the velocity of the bacterium. In the latter, \( \sigma_{D_{t}} \) appears in the denominator because translational diffusion affects position with a variance of \( 2\sigma_{D_{t}} \), and we are adding a velocity component. The diffusion coefficients used in simulation are \( D_{t} = 0.16 \text{ radians}^{2} \text{sec}^{-1} \) and \( D_{t} = 2.2 \times 10^{-6} \text{ m}^{2} \text{sec}^{-1} \) [41].

Signal transduction. The signal transduction pathway in E. coli takes the form of a differentiator coupled with a low-pass filter (see above). We therefore implement the signaling network in simulation with the differentiator function \( k_{a}(s + k) \) with gain \( k \) and cutoff frequency \( 1/k \). We assume the system takes ligand as its input and outputs the phosphorylated form of CheY (CheYp) and that this is a linearization of the actual network about a ligand input concentration \( L_{0} \) and a steady state CheYp concentration of 3 μM [42]. Linearizations of the model suggest a gain of \( k \approx 0.05 \), which we use in our simulations. While other gains were found to potentially affect the cutoff frequency optimal for chemotaxis, the existence of an optimal cutoff frequency and the qualitative characteristics of our results, such as

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**Figure 9.** Validation of E. coli Signaling Network Model

(A) Response of the E. coli signaling network model is plotted for a 0.1- mM step increase in chemotactant concentration from 0.2 mM at 10 s. For comparison with experimental data, activity from the model is converted to the probability of CCW flagella rotation by means of a Hill function (Materials and Methods). A transient response after an initial increase in CCW probability adapts to the pre-stimulus level. Adaptation times are similar to experimentally obtained data [20,27] (red dashed line shows data from Figure 2 of [27]).

(B) Response to a positive (+0.2 mM) chemotactant impulse of width 0.5 s is also consistent with experimentally observed behavior [20,27] (red dots show data from Figure 1 of [27]).

(C) The initial response to addition (removal) of attractant increases (decreases) with increasing change in attractant concentration. Adaptation times for attractant addition are longer than that for removal as observed [17].

(D) For step inputs, normalized peak activity of the model (1 – \( \Delta A/\Delta A_{w} \), where \( \Delta A \) is the change in activity from steady-state level \( A_{w} \)) exhibits sensitivity to the size of the step (red line with dots is a guide to the eye). This sensitivity response closely matches data from the “small lattice” model of [36] (blue line with triangles is a fitted sigmoid function). The blue dashed line indicates experimental data from [27] as plotted in Figure 4 of [36] (MeAsp input concentration of [27] is adjusted to that of aspartate that yields an equivalent receptor occupancy). As discussed in [36], the nonzero baseline of our model for large step inputs is due to a fraction of receptors in the cluster always having a nonzero probability of being active.

(E,F) Frequency responses of the E. coli signaling network model and the model from [17], linearized about a ligand input of \( L_{0} = 1 \) μM, reveal low-pass characteristics consistent with observations in [27].

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decrease in CCW probability instead of an increase (Figure 9C). Both the adaptation time (the time required for the step response to return to its pre-stimulus level) and response magnitude increase with increasing step size and are asymmetric with respect to positive and negative steps (Figure 9C, [17]). The peak activity response to step inputs exhibits high sensitivity to the size of the step (Figure 9D), as has been observed experimentally [38,39], and is seen in other
published models [18,19,35,36,40]. Sensitivity of our model closely matches that of [36].
the dependence of the optimal cutoff frequency on external parameters, was independent of the gain. 

Running bias. It is known that the probability of an individual flagellum rotating clockwise, which induces tumbling, or CCW, which leads to runs, is a Hill function of CheYp concentration [42]. The parameter \( K_c \) is determined using steady-state values of CheYp and a CCW flagellar rotation bias of 3 \( \mu M \) and 0.64, respectively [42]. We assume the majority of a cell’s flagella must be rotating CCW for running to occur. Thus, we calculate the probability of running of the entire bacteria as

\[
B = \frac{N}{N_o} \prod_i (1-b)^{N_i-1},
\]

where \( N \) is the total number of flagella and \( n \) is the minimum number of CCW-rotating individual flagella needed for running [21]. In our simulations, \( N = 8 \) and \( n = 5 \). The decision at each simulation step of whether to run or tumble is made in the “Run decision” simulation block as a function of the current run/tumble state and the flagellar rotation bias that is output from the signaling network. This block essentially determines the probability of running given the current state of the system so that the overall probability of running is given by the bias and the expected run and tumble lengths match those seen in the literature. To achieve this, we use the following analysis. Let \( p \) be the run bias, \( p_1 \) be the run bias given that the cell is already running, and \( q_2 \) be the tumble bias given that the cell is already tumbling. The expected run length in number of simulation steps is:

\[
RL = \left( \frac{n + 1}{N} \right) (1-p) = \frac{1}{1-p}.
\]

Similarly, the expected tumble length is:

\[
TL = \frac{1}{1-q_2}.
\]

Therefore, the expected run bias is:

\[
p = \frac{RL}{RL + TL} = \frac{p_1}{1-p_1} = \frac{p}{1-p}.
\]

Suppose that \( p \) and \( q_2 \) are fixed. Then, solving for \( p_1 \) yields:

\[
p_1 = 1 - (1-q_2) (1-p)/p = 1 - TL/RL.
\]

This can then be converted to a value of \( q_2 \): \( q_2 = 1 - TL/RL \), which leads to

\[
p_1 = 1 - (1-q_2) (1-p)/p = 1 - TL/RL = 1 - \frac{1}{1-q_2}.
\]

The probabilities \( p_1 \) and \( q_2 \) are then used to determine at a given simulation step whether the next time step should consist of a run or a tumble.

The tumbling angle \( \theta \) was assumed to follow the probability density function \( f(\theta) = \frac{1}{\sqrt{2\pi}} \cos(\theta)/2, -\pi \leq \theta \leq \pi \) [43]. This distribution gives mean tumbling angles of 65° with standard deviation 43° that match the experimentally determined angles closely (68° and 38°, respectively [9]).

The combined signal transduction and environmental model exhibits several traits observed in cells. The exponential shape of the run/tumble distributions is characteristic of a Poisson distribution and is similar to interval distributions found experimentally [44] and in previous models [57] (Figure 1B and 1C). Recent results suggest that, although average run and tumble distributions of a population may exhibit Poisson characteristics, distributions for individual cells may adhere to a power law [5]; however, we assume Poisson characteristics to be a reasonable description of cellular behavior for our purposes. The ability to navigate up a gradient of chemotactant is evident in that cells travel farther along the x-axis (the direction of the gradient) as time progresses (Figure 1D). Furthermore, a larger slope in the gradient of ligand concentration increases the success of the bacteria in swimming in the x direction. 

Optimal filter derivation. To determine the optimal filter for extracting the signal from the noisy measurement, we used Kalman filter theory. The Kalman filter is an algorithm, used widely in engineering navigation and guidance systems, developed to detect and separate signals in the presence of random, unwanted noise [25,26]. General Kalman filtering theory is provided in Protocol S1, and here we present a model of bacterial chemotaxis for the purpose of obtaining accurate chemotactant estimates using the Kalman filter. Let the state of the system during chemotaxis be

\[
\begin{align*}
x(t) &= \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} = \begin{pmatrix} L(t) \\ C(t) \end{pmatrix},
\end{align*}
\]

where \( L(t) \) is ligand concentration and \( C(t) \) is the concentration of bound receptor complexes resulting from ligand-receptor binding. The differential equation describing the binding reaction (without noise) is

\[
\frac{dC}{dt} = -k_c C + k_r (R_T - C)L_c,
\]

which can be linearized about an average ligand concentration \( L_0 \) and a steady-state receptor-complex concentration \( C_0 \) to give

\[
\frac{dC}{dt} = A_c C + B_c L
\]

with \( A_c \) and \( B_c \) constant. Because

\[
\frac{dL}{dt} = \frac{\partial L}{\partial x_2} = g \cos(\theta(t)) = w(t),
\]

and, if we assume the cell measures \( y(t) = C(t) + v(t) \) where the binding noise \( v(t) \) is a zero-mean, white random process with variance \( R_T L_c K_{dL}^2 (K_{dL} + L_c)^2 \) [4,33], then we have the linear system

\[
\begin{align*}
\frac{dx}{dt} &= \begin{pmatrix} 0 & 0 \\ B_c & A_c \end{pmatrix} x + \begin{pmatrix} 0 \\ w \end{pmatrix},
\end{align*}
\]

\[
y = \begin{pmatrix} 0 & 1 \end{pmatrix} x + v.
\]

For simplicity, we assume \( \theta(t) \) is a white-noise process with variance \( 2D_T \tau \) where \( \tau \) is an average run length and \( D_T \) is the rotational

| M | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| \( f(p) \) (m) | \( \infty \) | 1 | 0 | \(-1\) | \(-20\) |
| \( f(q) \) (m) | \( \infty \) | 1 | 0 | \(-20\) |
Figure 11. Model of Bacterial Chemotaxis

(A) The chemotaxis simulation assumes the following feedback interaction between the bacteria and its environment: 1) the external environment affects the sensing model through the external ligand concentration $L$ and incorporates the effect of binding noise; 2) ligand concentration is determined by the location of the cell in the environment (the spatial location $z$); 3) spatial location is determined by integrating the velocity and angle, which incorporates the effect of rotational diffusion and the “run/tumble” decisions; and 4) the run/tumble decisions are based on the signaling mechanism’s response (that is, the filter + differentiation) to the measured ligand concentration.

(B,C) Validation of chemotaxis model histograms of tumble (B) and run (C) durations for an unstimulated ($g = L_0 = 0$) E. coli with a simulation time of 2,000 s. Both distributions exhibit characteristics of a Poisson process.

(D) Average simulation results of 500 runs of a bacteria swimming in a gradient of ligand concentration with varying chemoattractant slopes.

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diffusion coefficient. This means that \( w \) is a (nonzero mean) white noise process with variance \( g^2 u^2 \var(cv\cos(\theta) t) \). The fact that \( w \) has nonzero mean can be accounted for by including an input \( u(t) \) and redefining \( w \); however, this does not affect the cutoff frequency of the optimal filter.

Our results are obtained by computing the optimal filter for the above system using the kalman function from the Control System Toolbox version 6.2 in Matlab. The variance of \( \cos(\theta) \) is approximated numerically in Matlab using an average run length of \( \tau = 1 \) s.

Supporting Information

Figure S1. Effect of Filter Rolloff
Simulations of chemotactic performance for varying cutoff frequencies were repeated for filters with \( \tau = 0 \), \( \tau = 0.1 \), and \( \tau = 0.2 \), respectively. Higher-order filters do not affect the existence of an optimal cutoff frequency, although the cutoff frequency does decrease. Also, performance is greatest with the first-order filter, possibly due to increased phase delay with the higher-order filters.

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