Adaptation and optimal chemotactic strategy for *E. coli*

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Extending the classic works of Berg and Purcell on the biophysics of bacterial chemotaxis, we find the optimal chemotactic strategy for the peritrichous bacterium *E. coli* in the high and low signal to noise ratio limits. The optimal strategy depends on properties of the environment and properties of the individual bacterium, and is therefore highly adaptive. We review experiments relevant to testing both the form of the proposed strategy and its adaptability, and propose extensions of them which could test the limits of the adaptability in this simplest sensory processing system. [S1063-651X(98)09104-1]

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I. INTRODUCTION

If placed in an inhomogeneous solution of a chemoattractant such as α-methyl-D,L aspartate, *E. coli* collect visibly in the regions of high concentration of the attractant [1,2]. There is a parallel phenomenon that occurs for chemorepellants where the bacteria collect in regions of low repellant concentration. The two phenomena are referred to as chemotaxis, and have been known in a variety of bacteria since the 1880s [3]. They constitute perhaps the simplest known example of sensory processing dependent behavior in a living organism. Actual sensory processing must be involved since, for *E. coli*, the chemoattractant need not be a substance that the bacterium can metabolize in any way, and it is known that the response to the chemoattractant relies on specific chemoreceptors on the outer membrane of the bacterium which bind chemoattractants and signal their occupancy to the interior of the cell through a phosphorylation cascade [1,4,5]. The manner in which the bacteria use this information to reach the regions of high chemoattractant concentration was first illuminated by Berg and Brown [6], who built a special microscope to track the motions of the individual bacteria. What they saw were stretches of motion at approximately 10μm/s with a slowly varying direction of orientation (termed ''runs'') separated by periods when the bacterium came to a stop and changed orientation very rapidly (referred to as ''tumbles''), before continuing on in another run. We now know that both of these characteristic motions of *E. coli*, and ultimately chemotaxis, are due to the rotation of the flagella [7–10]. *E. coli* typically have several flagella spread over their surfaces (this is what is meant by the designation ''peritrichous''), and runs result from counterclockwise rotation of all the flagella. For that direction of rotation, the flagella come together to form a ''bundle,'' and cooperate to propel the bacterium. Because the flagella are helical, the opposite sense of rotation has quite a different effect: the flagellar bundle comes apart, the bacterium is not propelled, and its orientation varies rapidly, but apparently randomly [6], resulting in a tumble. Chemotaxis results from the coordination of the tumbling times with the time dependence of the receptor occupancies, so that the bacteria change direction less often when they are headed in the direction of increasing chemoattractant [10–12]. The problem we will discuss in this work is the optimal strategy for coordinating these tumbles with the input from the chemoreceptors [13].

Clearly, for an optimal strategy to exist at all, a problem must be very highly constrained. The principle constraints which make this problem solvable are taken largely from the experimental literature on chemotaxis and motility of *E. coli*. First, as pointed out by Berg and Purcell [15] in this context, and as we will briefly discuss, due to rotational Brownian motion, *E. coli* cannot maintain an orientation for an extended period of time. Second, *E. coli* make no controlled changes of direction. It is obvious, given that they cannot maintain orientation that, for sensory processing reasons alone, they are incapable of turning in a specific direction [6,15]; however, a change of direction of a controlled magnitude is in principle possible. In practice, there is some evidence that the length of tumbles is affected by sensory input under some circumstances [16]; however, this is not believed to be important for chemotaxis under realistic conditions [6]. We therefore make the assumption that *E. coli* change direction by entering into ''tumbles'' which have have no characteristics which depend on sensory input. It seems likely that, in view of the limited use *E. coli* could make of steering capability given its orientation problems, this simple method of direction change was evolutionarily preferred because the cost associated with this capability are lower than those that a more developed steering capability would impose. In any case, we assume here that the tumbles are all identical, and effectively randomize the orientation of the bacteria over the course of a time $\tau_{\text{tumble}} \sim 0.15$ sec [17]. Finally, we assume that during runs the bacterium swims with a fixed speed v, independent of sensory inputs. This is known to be approximately true experimentally [6].

Taken together, these three constraints are sufficient to allow us to determine the optimal chemotactic strategy in the high signal to noise ratio limit for the following definition of

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optimality: we call a chemotactic strategy optimal if it maximizes the expectation value of $\langle \vec{v} \cdot \vec{\nabla} c \rangle$ for a static, uniform gradient. Here $\vec{v}$ is the swimming of the bacterium, and the average is over the time history of the bacterium's path. There are alternative definitions of optimality such as that of maximizing $\langle c \rangle$ or $\langle \vec{v} \cdot \vec{\nabla} c \rangle_r^2 / \langle \vec{v} \rangle_r^2$ (here the r subscript denotes an average only over the runs [18]), but we expect them to result in very similar optimal strategies provided they do not incorporate directly either (1) game-theoretic competition between bacteria, or (2) a complex structure of maxima and minima in the concentration so that gradient descent approaches, such as we are proposing, become trapped in local minima. The neglect of the latter possibility seems very reasonable for realistic environments; however, considerations like the former may well have played an important role in the evolution of *E. coli*. For example, the known pattern forming behaviors of *E. coli* and other chemotactic bacteria [14] demonstrate that the problem of chemotaxis has special properties in the presence of a depletable nutrient and/or large numbers of other bacteria. In fact, our choice of optimality is partly motivated by the consideration of competition. Maximizing $\langle \vec{v} \cdot \vec{\nabla} c \rangle$ for static, uniform gradients chooses the strategy that leads the bacterium to the attractant most rapidly, which is probably evolutionarily preferable to one that leads the bacterium there more slowly, but then results in the bacterium staying slightly closer to the region of maximal concentration.

Before discussing the strategy we obtain, let us first make a general remark on the nature of any optimal strategy: with the definition of optimality we have chosen, the strategy must consist of a deterministic algorithm for deciding when to tumble based on the history of chemoreceptor occupancy. For any given history, the bacterium's expected, future, average $\vec{v} \cdot \vec{\nabla} c$ is either raised or lowered by initiating a tumble at that particular moment; if it is raised the bacterium should tumble, and if it is lowered it should not. The stochastic nature of observed runs and tumbles should result (for an optimal strategy) entirely from the stochastic nature of the inputs (chemoreceptor bindings), not from any deliberate introduction of ''noise'' in the decision making on the part of the bacterium. In practice, a totally deterministic strategy at a fixed input requires an amplifier of arbitrary fidelity and gain to allow the inputs to drive the decision making apparatus, and is not realizable; however, the phosphorylation cascade seems capable, in practice, of providing sufficient gain and fidelity [4,5] that the tumbling would be effectively deterministic. A deterministic strategy is, however, in some conflict with the two state model proposed in Ref. [16] on experimental grounds, where the past history of the receptor occupancies is taken to modulate the rates with which the flagellar motors change their direction of rotation. In that strategy, it is not the states but the the rates for transitions between the states that are set for each flagellar motor, and they are all set separately, so that the only correlations between different flagella are rate-rate correlations. In that case, the strategy is actually stochastic even for fixed inputs to the chemoreceptors. However, in the limit that the rate modulations for going from running to tumbling are large (the rate is either ~ 0 or $\sim \infty$), the two state model has a strategy of the form we propose.

As mentioned above, in practice, a purely ''deterministic'' strategy for switching between two states is impossible and, to approach it, large variations in the rate of the above type could be used. The rate model is thus one possibility for a realistic process which approaches the optimal strategy, and may represent *E. coli*'s best effort to implement the optimal strategy. However, it should be noted that the evidence for the modulated rate model is not entirely conclusive. In particular, as we will see in our discussion of run and tumble statistics for the optimal strategies, the exponential tails present in the durations of run and tumble times are *not* uniquely explained by the rate model, as claimed in Ref. [16]. Further, there is a pronounced advantage that a deterministic strategy has when the problem of flagellar coordination is considered [19].

Free swimming *E. coli* in the absence of gradients spend roughly a tenth of their time tumbling [6] while tethered bacteria [23] with a single flagellum rotate it clockwise nearly half of the time. Clearly, if the typical bacterium has five flagella, there must be significant conflict between the flagella in the absence of any signal. The formation of a coherent flagellar bundle 90% of the time requires some sort of coordination. Notice that no coordination can result from the signals to the flagella if the signals are independent, as the model of Ref. [16] predicts they should be at small signal to noise ratio, where the above numbers apply. At least one mechanism for the required coordination has been proposed [19], and it seems clear that some explanation is required, unless the data from tethered bacteria are taken to be unrepresentative. If the flagella are coordinated, then much of the self-induced ''noise'' implied by the stochastic nature of their individual biases will be eliminated by the pooling of their inputs: an effectively deterministic strategy will result. In fact, any ''deterministic'' strategy would have to result either from some sort of cooperativity effect (to reduce the noise inherent in the stochastic nature of the binding and unbinding of individual internal signaling molecules to receptors) or from sufficient amplification of the input signal to drive very large variations in the concentration of internal signaling molecule. Cooperativity is generally a more efficient and robust solution.

This solution could be supplied by either a coordination of the different flagella and a pooling of their signals, cooperative signaling to the individual flagella, or both. In fact, the protein FliM, which is believed to be responsible for translating the internal tumble signal [20], coming from the phosphorylated form of the protein CheY [21], is believed to be present in many (about 100) copies for each flagellar motor [22]. It is not known how many of these copies actually bind CheY, or how this binding is transduced into a tumble signal, but there is clearly great potential for cooperativity. For example, if the tumbling and/or running switch were whether more or less than 50 molecules of phosphorylated CheY were bound, then the behavior would be nearly deterministic even for moderate variations in the concentration of phosphorylated CheY.

In view of this, it is not clear that there is much difference in practice between a deterministic signal and stochastic signals to the individual motors or, perhaps, to the many individual CheY binding cites at each motor, since the results of pooling the stochastic signals might be nearly deterministic.

In so far as there is a difference, the deterministic strategy will lead to better performance, but may be an expensive capacity for *E. coli* to maintain.

We note that the ''response regulator'' model proposed in Ref. [24], in which the tumbles are induced by threshold crossing some functional of chemoreceptor binding histories, is of the appropriately deterministic type, and our optimal strategy will be a realization of this strategy where we specify, at a high signal to noise ratio, the correct threshold (with the functional being somewhat arbitrary). At a low signal to noise ratio, both the correct threshold and functional of the receptor histories will be determined, subject to certain assumptions about the receptor correlations. We will see that the statistics of runs and tumbles resulting in both cases are not inconsistent with the statistics observed experimentally, contrary to the claim of Ref. [16] that threshold crossing strategies, as opposed to rate modulation strategies, disagree with the data.

II. HIGH SIGNAL-TO-NOISE RATIO

Let us now begin with the ''high'' signal to noise ratio case, defined by the bacterium being able to measure the projection of the gradient of concentration of chemoattractant onto its swimming direction in a time much shorter than any other relevant time scale, in particular the time scale set by rotational diffusion. For an object undergoing rotational diffusion,

$$\langle \hat{n}(t)\cdot\hat{n}(0)\rangle = \exp(-2D_{\rm rot}t), \tag{1}$$

where $D_{\rm rot}$ is the rotational diffusion constant. For *E. coli* this is known empirically to be about 0.15 rad^2/s, implying a time scale for rotational Brownian motion of about 3 s. This is in rough agreement with what one expects for the case of a sphere of radius $r=1\ \mu$m in room-temperature water. There,

$$D_{\rm rot}\sim kT/\nu_{\rm rot}, \tag{2}$$

$$\nu_{\rm rot}\sim 8\pi\eta r^3 \sim 2.5\ \ 10^{-13}\ \text{cm}^2/\text{s}, \tag{3}$$

$$D_{\rm rot}\sim 0.16\ \text{rad}^2/\text{s}, \tag{4}$$

where T is the temperature, $\nu_{\rm rot}$ is the rotational drag on the sphere, and η is the viscosity of water. Note that, since we are at a low Reynolds number, the rotational diffusion which is disorienting the bacterium is Markovian; the bacterium's present orientation embodies *all* of its knowledge about the future and there is no need to keep track of an angular momentum. Because all of the information about the future is contained in the present orientation, or equivalently the bacterium's present knowledge of $\vec{v}\cdot\vec{\nabla}c$ obtained from the chemoreceptor histories, the optimal strategy in the high signal to noise ratio limit requires only the specification of a single number: a threshold X, which is the minimum value of $\vec{v}\cdot\vec{\nabla}c$ which the bacterium will tolerate before tumbling. Any processing strategy for the chemoreceptor histories that allows the determination of $\vec{v}\cdot\vec{\nabla}c$ rapidly compared to other time scales is acceptable. This makes this limit particularly simple to discuss.

To solve the high signal to noise ratio limit we need to make the assumption that each tumble is perfectly disorienting and totally randomizes the bacterium orientation. This is approximately true [6], and allows a full solution of this case. Our solution is interesting even though the bacterium may rarely, if ever, encounter a high signal to noise ratio environment because the optimal strategy can be solved for completely, and this gives us an idea what the low signal to noise ratio strategy is evolving toward as the signal to noise ratio is increased. In this limit there is still an interesting strategy, because the bacterium cannot steer, only reorient itself through stereotyped tumbles, each of which requires a finite amount of time. This finite time cost will be very important in determining the optimal strategy, and will result in the bacterium displaying a surprisingly large amount of ''optimism,'' by which we mean that bacteria which ''know'' they are not swimming directly up the gradient should choose to continue running because of the chance that rotational diffusion will improve their prospects faster than tumbling would.

Let us consider first the case where the bacterium is in a uniform gradient of chemoattractant and therefore has had time to measure the magnitude of $\vec{\nabla}c$. In this case, it can translate its knowledge of $\vec{v}\cdot\vec{\nabla}c$ directly into a knowledge of Θ, the angle between its motion and the concentration gradient, and the strategy consists of an angle at which the bacterium ''decides'' it is moving sufficiently in the wrong direction that it is worth taking the time and the risk of orienting even further in the wrong direction which a tumble will involve.

It is clear that the dimensionless number $D_{\rm rot}\tau_{\rm tumble}$ fixes Θ_c, and one would expect that, for small values of $D_{\rm rot}\tau_{\rm tumble}$, Θ_c would be small, vanishing like $(D_{\rm rot}\tau_{\rm tumble})^p$. In practice, $D_{\rm rot}\tau_{\rm tumble}\sim(0.15\ \text{s}^{-1})(0.15\ \text{s})\sim 0.02$, which is indeed small, and we might expect that Θ_c would also be small. However, we will see that this is not the case as $p=\frac{1}{6}$ and the prefactor between $(D_{\rm rot}\tau_{\rm tumble})^{1/6}$ and Θ_c is important. The correct value of Θ_c can be obtained from the following argument: the equilibrium distribution of the orientation of running *E. coli* for a specific choice of Θ_c can be obtained from solving the heat equation on the surface of a sphere with a perfectly absorbing boundary at Θ_c and a source term that deposits new *E. coli* uniformly over the allowed region at a rate that exactly cancels the current into the boundary at Θ_c. From the distribution, one can compute $\langle\vec{v}\cdot\vec{\nabla}c\rangle$ by first computing the average over the distribution of running *E. coli*, and then multiplying by the fraction of *E. coli* which are running. The latter is given by the integral of the distribution over the allowed region of the sphere divided by the current into the boundary of the allowed region times the average length of time between runs. The last factor is given by the average length of a tumble times a factor, $(1-[(\text{forbidden area})/4\pi])^{-1}$, which reflects the chance for a tumble to result in an orientation past Θ_c, in which case it will be followed immediately by another tumble. The relevant heat equation on the sphere reads

$$\frac{\partial \rho}{\partial t} = C + \frac{D_{\rm rot}}{\sin\Theta}\frac{\partial}{\partial \Theta}\left(\sin\Theta \frac{\partial \rho}{\partial \Theta}\right). \tag{5}$$

C can be fixed by the requirement that ρ vanish at Θ_c. The resulting, unnormalized solution is

$$\rho(\Theta) = \ln\left(\frac{\cos\Theta/2}{\cos\Theta_c/2}\right), \tag{6}$$

$$C = D_{\rm rot}/2. \tag{7}$$

Both C and ρ can be multiplied by an arbitrary, common factor since we have not yet imposed any normalization. The ''current'' into the boundary is given by

$$J_{\rm loss} = 2\pi C(1-\cos\Theta_c), \tag{8}$$

while the integral of ρ is given by

$$2\pi\int_0^{\Theta_c} d(-\cos\Theta)\rho(\Theta) = \pi\left[\cos\Theta_c - 1 - 4\ln\left(\cos\frac{\Theta_c}{2}\right)\right]. \tag{9}$$

The expectation value of $\vec{v}\cdot\vec{\nabla}c$ is given by

$$\langle \vec{v}\cdot\vec{\nabla}c\rangle = v|\vec{\nabla}c|\frac{\sin^4\frac{\Theta_c}{2}}{2D_{\rm rot}\tau_{\rm tumble} - 2\left(\sin^2\frac{\Theta_c}{2} + 2\ln\cos\frac{\Theta_c}{2}\right)}. \tag{10}$$

In general, the maximum can be found numerically, but for the special case of $D_{\rm rot}\tau$ small, where one expects small Θ_c, one can expand the trigonometric functions to find, for $x = \Theta_c/2$,

$$\langle \vec{v}\cdot\vec{\nabla}c\rangle \sim v|\vec{\nabla}c|\frac{480x^4 - 80x^6 + 6x^8 + \cdots}{15\,360 D_{\rm rot}\tau_{\rm tumble} + 480x^4 + x^8 + \cdots}. \tag{11}$$

Anticipating the result that $D_{\rm rot}\tau_{\rm tumble} \propto x^6$, and expanding again, one finds that the derivative vanishes for

$$x \sim \sqrt[6]{6 D_{\rm rot}\tau_{\rm tumble}}, \tag{12}$$

$$\Theta_c \sim 2\sqrt[6]{6 D_{\rm rot}\tau_{\rm tumble}}. \tag{13}$$

Already for $D_{\rm rot}\tau_{\rm tumble} \sim 0.01$, Θ_c is not small (the above formula is valid only if it is small and would predict $\sim 0.4\pi$ already at this point). The value of Θ_c obtained from numerically finding the value which maximizes the return in depicted in Fig. 1. It rises very rapidly to the vicinity of $\pi/2$, where it remains for all reasonable values of $D_{\rm rot}\tau_{\rm tumble}$, until ultimately the behavior for very large $D_{\rm rot}\tau_{\rm tumble}$ is given by

$$\Theta_c = \pi - \sqrt{2/D_{\rm rot}\tau_{\rm tumble}}. \tag{14}$$

We see that, under a broad range of circumstances, the optimal strategy is essentially to continue if one is moving into regions of higher concentrations of attractant, and to reorient if one is moving into regions of lower concentration of attractant. The bacterium should be surprisingly tolerant of moving in the directions that are far from perfectly aligned with $\vec{\nabla}c$, even if it has perfect information as to how far off course it is. In fact, the fraction of time the bacterium spends tumbling, f, is not ~ 1, as one would naively expect, but rather is given by

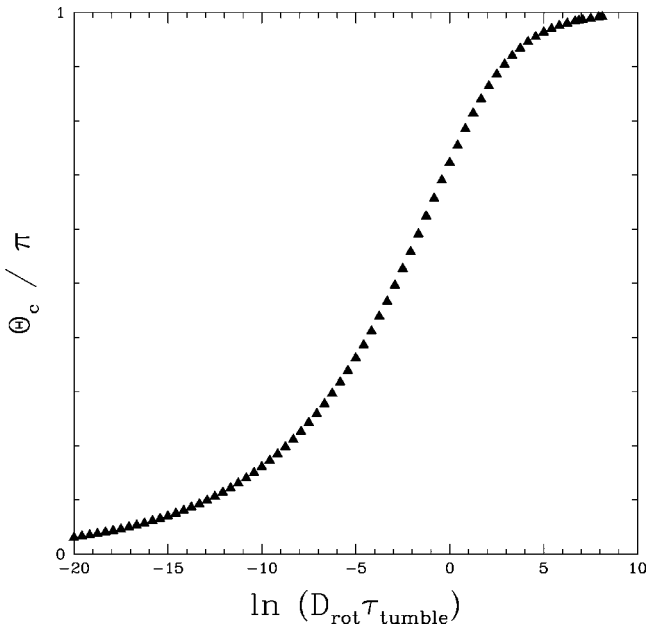

FIG. 1. Plot for the high signal to noise ratio case of the optimal angle at which the bacterium should initiate tumbles as a function of the product of its rotational diffusion constant, $D_{\rm rot}$, and the duration of the disorienting tumbles, $\tau_{\rm tumble}$.

$$f = \frac{\tau_{\rm tumble}J_{\rm loss}}{\left(1 - \frac{\text{forbidden area}}{4\pi}\right)\int 2\pi d(-\cos\Theta)\ \rho(\Theta) + \tau_{\rm tumble}J_{\rm loss}} \tag{15}$$

$$= \frac{2D_{\rm rot}\tau_{\rm tumble}}{\cos\Theta_c - 1 - 4\ln\left(\cos\frac{\Theta_c}{2}\right) + 2D_{\rm rot}\tau_{\rm tumble}} \tag{16}$$

$$\sim \frac{5D_{\rm rot}\tau_{\rm tumble}}{1 + 5D_{\rm rot}\tau_{\rm tumble}} \tag{17}$$

$$\sim 0.1, \tag{18}$$

where we have used $\Theta_c \sim \pi/2$ and $D_{\rm rot}\tau_{\rm tumble} \sim 0.02$. High frequency noise added to the thresholded quantity will make the bacterium even more tolerant of a signal indicating that it is swimming the wrong direction.

Before discussing noise, we first mention what strategy is appropriate if the bacterium is, for some reason, such as being in a spatially nonuniform gradient, unable to estimate the magnitude of the gradient, and therefore the absolute angle between its present orientation and the gradient. First, note that, for the appropriate value of $D_{\rm rot}\tau_{\rm tumble}$, the critical angle is close to $\pi/2$ so that, approximately, only the sign of $\vec{v}\cdot\vec{\nabla}c$ is important and the ignorance about $|\vec{\nabla}c|$ is unimportant. In so far as it is important, the optimal strategy in the

absence of information about $|\vec{\nabla}c|$, depends on the *a priori* probability $P(|\vec{\nabla}c|)$ and is therefore somewhat nonuniversal, depending strongly on the statistics of the bacterium's environment (it should consequently also be highly adaptive). In particular, the optimal strategy is now to choose a value of $s_{\rm critical}=\vec{v}\cdot\vec{\nabla}c$ at which to tumble, and the optimal value can be chosen by maximizing

$$\langle \vec{v}\cdot\vec{\nabla}c\rangle \sim \int d(|\vec{\nabla}c|)P(|\vec{\nabla}c|)R\left[\Theta_c=\arccos\left(\frac{s_{\rm critical}}{|\vec{\nabla}c|}\right)\right], \tag{19}$$

where $R(\Theta_c)$ is defined by the right hand side of Eq. (10). The quantity to be maximized corresponds to the average of the previously calculated return over the actual strategies that will result from a given choice $s_{\rm critical}$. Clearly, as $P(|\vec{\nabla}c|)$ becomes sharply peaked, this reduces to the case where $|\vec{\nabla}c|$ may be taken to be known, in which case, as we have seen, $s_{\rm critical}\sim 0$; when the uncertainty in $|\vec{\nabla}c|$ is large, the bacterium should select an even smaller $s_{\rm critical}$. The exact details depend on $P(|\vec{\nabla}c|)$ in the environment to which the bacterium is adapted.

Let us now discuss, in the case of a sharply peaked $P(|\vec{\nabla}c|)$, the introduction a small amount of high frequency, Gaussian noise to the bacterium's information about Θ. By the noise being small we mean that its magnitude is much less than that of the signal $v|\vec{\nabla}c|$, and by high frequency we mean that the characteristic time for $\vec{v}\cdot\vec{\nabla}c$ to vary due to diffusion ($\sim\Theta_c^2/D_{\rm rot}$) is much larger than the noise time constant, $\tau_{\rm noise}$, defined by

$$\tau_{\rm noise}=\sqrt{\frac{\int d\omega\, N(\omega)}{\int d\omega\ \omega^2 N(\omega)}}. \tag{20}$$

Here $N(\omega)$ is the two-sided power spectrum of the noise so that the mean-squared magnitude of the noise, $\langle\eta^2\rangle$, is given by

$$\langle\eta^2\rangle=\int_{-\infty}^{\infty}\frac{d\omega}{2\pi}N(\omega). \tag{21}$$

Such noise might arise inside the cell, involving the thresholding mechanism itself or the phosphorylation cascade, or it might come from the fluctuations in receptor occupancy if the cell does not completely low pass filter the receptor inputs. To compensate for the noise the optimal strategy for the bacterium is to set its threshold, X, on the input, $\vec{v}\cdot\vec{\nabla}c+\eta$, where η is the noise, slightly lower than in the noiseless case where without noise $X=v\ \cos\Theta_c|\vec{\nabla}c|$. To determine X note that the rate at which $\vec{v}\cdot\vec{\nabla}c+\eta$ crosses the threshold, X, in one direction is given by [25]

$$r(\Theta)=\frac{\tau_{\rm noise}^{-1}}{2\pi}\exp\left(-\frac{(X-v\ \cos\Theta|\nabla c|)^2}{2\langle\eta^2\rangle}\right). \tag{22}$$

The ideal value of X can then be computed by converting our previous heat equation with a perfectly absorbing boundary into one with heat absorption at angle Θ given by $\rho(\Theta)R(\Theta)$. For $v\ \cos\Theta|\nabla c|>X$, $R(\Theta)$ is given by $r(\Theta)$, and for $v\ \cos\Theta|\vec{\nabla}c|<X$, by $(2\pi\tau_{\rm noise})^{-1}$. Treating the tumble rate as heat absorption in this way is exact if the tumbling is a modulated Poisson process. This is true in the limit $\tau_{\rm noise}\to 0$ (a sensible answer in this limit also requires $\langle\eta^2\rangle\to 0$), but the treatment is approximate for noise with a finite correlation time. However, we are interested in the short correlation time limit and the approximation is justified. In this limit, the heat effectively cannot penetrate into the region where

$$(v\ \cos\Theta|\vec{\nabla}c|-X)^2<2\langle\eta^2\rangle\ln(D_{\rm rot}\tau_{\rm noise}); \tag{23}$$

equivalently,

$$\Theta>\arccos\left(\frac{X}{v|\vec{\nabla}c|}+\sqrt{\frac{2\langle\eta^2\rangle|\ln(2\pi D_{\rm rot}\tau_{\rm noise})|}{v^2|\vec{\nabla}c|^2}}\right). \tag{24}$$

It is important to realize that, at this point, the tumbling rate is rapidly increasing because the value of the argument of the exponential, $\sim|\ln(2\pi D_{\rm rot}\tau_{\rm noise})|$ for small $\tau_{\rm noise}$, is large and so is its derivative with respect to Θ. The point effectively specifies the location of an absorbing ''wall,'' and, therefore, we are back to the case where our original analysis applies and the optimal strategy is one which chooses X so that Θ lies at the Θ_c of the noiseless problem; this can be done by choosing the threshold to be at $v\ \cos\Theta_c|\vec{\nabla}c| -\sqrt{[2\langle\eta^2\rangle|\ln(2\pi D\tau_{\rm noise})|]}$. The threshold has been moved further from $v|\vec{\nabla}c|$ because the noise results in tumbles being triggered prematurely. Thus the bacterium should be even more tolerant of an input signal, which indicates that it is swimming in the wrong direction than we observed that it should be in the noiseless case.

At this point it is worth making a few remarks about the statistics of the runs and tumbles in the high signal to noise ratio case. For simplicity, let us consider the noiseless case with known $|\vec{\nabla}c|$. The bacteria emerge from tumbles with random orientations, and for some tumbles the orientation immediately after a tumble is past the critical allowed orientation and they immediately tumble again. This will lead to a renormalization of the effective tumble length in this model from $\tau_{\rm tumble}$ to $\tau_{\rm tumble}[2/(1-\cos\Theta_c)]$; however, the tumble durations will continue to be purely exponentially distributed, if they were initially exponentially distributed, as they are found to be experimentally. Meanwhile, if we average over all the bacteria which do not immediately tumble to find the statistics of run durations, we find these are also roughly exponentially distributed. To see this, recall that the heat equation we solved to get $\rho(\Theta)$ is of the form

$$\frac{\partial\rho}{\partial t}-\hat{L}\rho=C, \tag{25}$$

where $\hat{L}$ is a linear operator, and we impose the boundary condition $\rho(\Theta>\Theta_c)=0$. This could have been solved by solving for the orthonormal eigenfunctions $f_\lambda(\Theta)$ of $\hat{L}$, which vanish at Θ_c, then re-expressing the linear source term, C, as a sum of these:

$$C=\sum_{\lambda} c_{\lambda} f_{\lambda}(\Theta), \tag{26}$$

$$c_{\lambda}=C\int_{0}^{\Theta_c} d(-\cos\Theta) f_{\lambda}(\Theta). \tag{27}$$

Then we have

$$\rho(\Theta)=\sum_{\lambda} a_{\lambda} f_{\lambda}(\Theta), \tag{28}$$

$$a_{\lambda}=-\frac{c_{\lambda}}{\lambda}. \tag{29}$$

The distribution of intertumble intervals is then proportional to $\Sigma_{\lambda} c_{\lambda} e^{-\lambda t}$. The eigenfunctions for a general Θ_c are hypergeometric functions ${}_2F_1(-\nu,\nu+1;1;\zeta)$, where $\zeta=\frac{1}{2}(1-\cos\Theta)$ [26], and solving the boundary condition is in general impossible. However, for the special case $\Theta_c=\pi/2$, the eigenfunctions are those Legendre polynomials, $P_n(\cos\Theta)$, which vanish at $\pi/2$. The eigenvalues are $Dn(n+1)$, where all odd n are allowed. The smallest eigenvalue is $2D$, and the tail is therefore of the form e^{-2Dt}. The next highest eigenvalue is $12D$, and the coefficient in front of it at $t=0$, c_{12D}, is $\frac{7}{48}$ of the contribution from the $n=1$ term, so the approach to exponential decay of the form e^{-2Dt} is very rapid. This is consistent with the fact that the mean duration of a run is, in general, given by $[\cos\Theta_c-1-4\ln\cos(\Theta_c/2)]/[D_{\rm rot}(1-\cos\Theta_c)]$, which for $\Theta_c=\pi/2$ gives $[(2\ln 2-1)/D]\sim 0.38D^{-1}$. This is only slightly smaller than $\frac{1}{2}D^{-1}$ because of the inclusion of the higher n terms. Roughly half of the shift is accounted for already by the inclusion of the $n=3$ term.

Although we do not believe that high signal to noise ratio limit applies to the experiments of Refs. [6,11,16], we should point out that the exponential tails observed for the run distributions are consistent with the statistics of runs and tumbles observed there. The fact that our procedure for ending runs is essentially of the threshold crossing type does not imply that the distributions of run durations have a power law tail. This contradicts the claims of Ref. [16], in which power law tails were found for the threshold crossings *of a random walk,* and argued to be typical for threshold crossing processes. A random walk is a very special case, since there is no finite correlation time for the displacement. Threshold crossing a variable with a finite correlation time results in a tail for intervals between crossings that is generally exponential. The decay constant is roughly given by $\tau_{\rm correlations}^{-1}|\ln(\text{prob. no crossings in } \tau_{\rm correlations})|$, and only for divergent or vanishing $\tau_{\rm correlations}$ should nonexponential tails result. Thus there is not, in general, any *a priori* conflict between response regulator models and the statistics of runs and tumbles.

III. LOW SIGNAL TO NOISE RATIO STRATEGY

How should the bacterium make use of the information available to it in a small signal to noise ratio limit? As in the high signal to noise ratio case, the optimal strategy is a deterministic algorithm for generating tumbles based on the chemoreceptor binding histories. In this case, however, the bacterium will not tumble at a fixed angle, because it cannot determine its orientation with respect to the gradient accurately. Instead, it will tumble when the output of some filtering of the chemoreceptor histories crosses some threshold, which indicates that it is headed sufficiently in the wrong direction [27]. The problem of the optimal strategy is to determine the filter $F(t)$ and the threshold. This problem will be soluble for two different assumptions about the nature of the tumbles. First, we will treat the case of completely disorienting tumbles of finite duration ($\tau_{\rm tumble}$), as for the high signal to noise ratio case, and then the case of instantaneous tumbles which do not completely disorient the bacteria.

Let us introduce some notation. In the low signal to noise ratio limit, the filtering should be linear and, we denote the filtered output by $\nu(t)$, defined by

$$\nu(t)=\int_{0}^{\infty} dt' F(t')\dot{c}(t-t'), \tag{30}$$

where $c(t)$ is an instantaneous concentration inferred from the fraction of occupied receptors, $\phi(t)$. Defining the concentration at which half of the chemoreceptors will bind the attractant as $c_{1/2}$, we have

$$c(t)=\frac{\phi(t)}{1-\phi(t)} c_{1/2}. \tag{31}$$

It is convenient to regard $\dot{c}(t)$ as the sum of two terms,

$$\dot{c}(t)=\vec{v}(t)\cdot\vec{\nabla}c+\dot{\eta}(t), \tag{32}$$

and denote their contributions to $\nu(t)$ by

$$s(t)=\int_{0}^{\infty} dt' F(t') v(\vec{t})\cdot\vec{\nabla}c, \tag{33}$$

$$n(t)=\int_{0}^{\infty} dt' F(t')\,\dot{\eta}(t). \tag{34}$$

The η term represents the fluctuations in the chemoreceptor occupancy associated with the stochastic binding of attractant molecules to receptors.

Now let us compute the ''return'' $\langle\vec{v}\cdot\vec{\nabla}c\rangle$ to be maximized. For this, we anticipate the result that the characteristic time constant of the filtered ''noise,'' $n(t)$, is short compared to that of the filtered ''signal,'' $s(t)$ (see the Appendix). We take the ''noise'' to be Gaussian since it is a linearly filtered version of the noise in the chemoreceptors, and is expected to be approximately Gaussian via the central limit theorem as there are many ($\sim$3000 [15]), weakly correlated (see the Appendix) receptors, each making small contributions to the total noise.

In this case, the rate at which the filtered output $f(t)$ crosses the threshold X is given by

$$r(s)=\frac{\tau_n^{-1}}{2\pi}\exp\left(-\frac{(X-s)^2}{2\langle n\rangle^2}\right), \tag{35}$$

with τ_n defined by

$$\tau_n = \sqrt{\frac{\langle n^2 \rangle}{\langle \dot{n}^2 \rangle}}. \tag{36}$$

The trajectory of a bacterium emerging from a tumble at time $t=0$ is therefore weighted by

$$w(t,\{s\}) = e^{-\int_0^t dt' r[s(t')]}. \tag{37}$$

The return on the strategy is then given by

$$\langle \vec{v} \cdot \vec{\nabla} c \rangle = \frac{\langle \int dt' \vec{v}(t') \cdot \vec{\nabla} c \; w(t',\{s\}) \rangle}{\tau_{\text{tumble}} + \langle \int dt' w(t',\{s\}) \rangle}, \tag{38}$$

where the numerator is the product of the magnitude of the concentration gradient and the mean distance swum up the gradient in a run, and the denominator is the mean time required for a run.

Let us begin with the computation of the denominator. The typical length of a trajectory is given by

$$\tau_{\text{run}} = \left\langle \int dt' w(t',\{s\}) \right\rangle. \tag{39}$$

This can be computed to lowest order in the signal to noise ratio more or less straightforwardly; the only caveat is that while $s(t)$ is formally proportional to the gradient of concentration, there is the possibility that the coefficient of proportionality could diverge if the filter F has a long tail. In fact, $s(t)$ can be partitioned into two pieces: one coming from the contribution to the integral from times in the not too distant past, i.e., not much longer ago than the rotational diffusion time $[\int_0^{\sim \tau} dt' F(t') \vec{v}(t-t') \cdot \vec{\nabla} c$, where $\tau = (2D_{\text{rot}})^{-1}]$, and another piece coming from the remainder of the integral $[x \equiv \int_{\sim \tau}^{\infty} dt' F(t') \vec{v}(t-t') \cdot \vec{\nabla} c]$. Only the second piece can avoid being small for small concentration gradient, and only if $F(t)$ decays slowly at long times. In this case, this term yields a contribution to $s(t)$ which is effectively static, and is distributed in a Gaussian way since it is essentially the sum of many independent contributions from $s(t)$ stretching far into the past [recall that $\vec{v}(t)$ decorrelates on a time scale that is of order $(2D_{\text{rot}})^{-1}$]. The mean value of this contribution $\langle x \rangle$ is zero and

$$\langle x^2 \rangle = \frac{\tau_{\text{run}}}{\tau_{\text{run}} + \tau_{\text{tumble}}} \left\langle \int dt' \int dt'' F(t') F(t'') \times \vec{v}(t-t') \cdot \vec{\nabla} c \vec{v}(t-t'') \cdot \vec{\nabla} c \right\rangle \tag{40}$$

$$= \frac{\tau_{\text{run}}}{\tau_{\text{run}} + \tau_{\text{tumble}}} \frac{2v^2 |\vec{\nabla} c|^2}{3\gamma} \int dt' F^2(t'), \tag{41}$$

where we have assumed that

$$\langle \vec{v}(t) \vec{v}(0) \rangle \propto e^{-\gamma |t|}, \tag{42}$$

and also assumed a low signal to noise ratio. For the case where each tumble completely disorients the bacterium, γ is given at zeroth order in the concentration gradient by

$$\gamma = \tau_{\text{run}}^{-1} + 2D_{\text{rot}}. \tag{43}$$

This second contribution x to $s(t)$ can be thought of as a contribution to the noise, since it is uncorrelated with the present orientation of the bacterium. In fact, since it and the occupancy noise are both Gaussian, it can be integrated out. Let us therefore switch to using s to refer only to the first part, since that is the part which actually does contain the signal. Then we find that

$$\langle r(s) \rangle_{x = \text{second part of s}} = \int \frac{dx}{\sqrt{2\pi \langle s^2 \rangle}} \frac{\tau_n^{-1}}{2\pi} \exp\left(- \frac{x^2}{2\langle s^2 \rangle} \right) \times \exp\left(- \frac{(X-s-x)^2}{2\langle n^2 \rangle} \right) \tag{44}$$

$$= \frac{\tau_{n'}^{-1}}{2\pi} \exp\left(- \frac{(X-s)^2}{2\langle n'^2 \rangle} \right), \tag{45}$$

where n' is a new effective noise whose statistics are those of the original noise n plus a static contribution x. Thus

$$\langle n'^2 \rangle = \langle n^2 \rangle + \langle x^2 \rangle, \tag{46}$$

$$\tau_{n'} = \sqrt{\frac{\langle n'^2 \rangle}{\langle \dot{n}^2 \rangle}}. \tag{47}$$

Hereafter, we switch to using n to refer to the effective noise rather than using n'. We are now also in a position to state our definition of the signal to noise ratio, $\mathcal{R}_{\text{SN}}$:

$$\mathcal{R}_{\text{SN}} = \frac{9 \langle s \vec{v} \cdot \vec{\nabla} c \rangle^2}{v^2 |\vec{\nabla} c|^2 \langle n^2 \rangle}. \tag{48}$$

The result is implicitly a function of the filtering scheme and the tumbling rate; however, one generally expects the signal to noise ratio to be proportional to $v^2 |\vec{\nabla} c|^2 / \langle \eta \eta \rangle$. In fact, anticipating our results for the optimal filter and tumbling rate, we find that, in the low signal to noise ratio limit,

$$\mathcal{R}_{\text{SN}} = \frac{v^2 |\vec{\nabla} c|^2 (1 + \bar{r} \tau_{\text{tumble}})}{N(8D_{\text{rot}} + 4D_{\text{rot}} \bar{r} \tau_{\text{tumble}} - \bar{r} - 3\bar{r}^2 \tau_{\text{tumble}})(2D_{\text{rot}} + \bar{r})^2}, \tag{49}$$

where

$$\langle \eta(t) \eta(t') \rangle = \frac{N}{2\tau_{\text{bare}}} \exp(-|t-t'|/\tau_{\text{bare}}) \tag{50}$$

$$\sim N \delta(t-t'). \tag{51}$$

We now consider the return at lowest order in the signal to noise ratio. To zeroth order in the concentration gradient, r is constant over a run, and is given by

$$\bar{r} = \frac{\tau_n^{-1}}{2\pi} \exp\left(- \frac{X^2}{2\langle n^2 \rangle} \right) \tag{52}$$

and the mean run length is just $\bar{r}^{-1}$ and the denominator of the return expression [Eq. (38)] is just $\tau_{\text{tumble}} + \bar{r}^{-1}$.

The numerator of Eq. (38) can also be computed to lowest order in the signal to noise ratio. The redefinition of the ''signal'' and the effective noise that we used for calculating the mean run length is also appropriate here, so we continue to use s to refer only to the contribution from the recent past. We expand w appearing in the numerator to lowest order in s, to find

$$\left\langle \int dt' \vec{v}(t') \cdot \vec{\nabla} c \; w(t', \{s\}) \right\rangle$$

$$\sim v^2 |\vec{\nabla} c|^2 \int_0^\infty dt' \left\langle \cos\Theta(t') \frac{\partial}{\partial (v \nabla c)} \times \exp\left(- \int_0^{t'} r(t'') dt'' \right) \right\rangle \tag{53}$$

$$\sim v^2 |\vec{\nabla} c|^2 \frac{\partial \bar{r}}{\partial X} \int_0^\infty dt' e^{-\bar{r} t'} \int_0^{t'} dt'' \int_0^{t''} dt''' F(t''') \times \langle \cos\Theta(t') \cos\Theta(t'' - t''') \rangle \tag{54}$$

$$\sim \frac{(-X) v^2 |\vec{\nabla} c|^2}{3 \langle n^2 \rangle (2 D_{\rm rot} + \bar{r})} \times \int_0^\infty F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t'''], \tag{55}$$

where we have used

$$\frac{\partial \bar{r}}{\partial X} = - \frac{\bar{r} X}{\langle n^2 \rangle}. \tag{56}$$

The return is therefore given by

$$\langle \vec{v} \cdot \vec{\nabla} c \rangle = \frac{\bar{r} (-X) v^2 |\vec{\nabla} c|^2}{3 \langle n^2 \rangle (2 D_{\rm rot} + \bar{r})(1 + \bar{r} \tau_{\rm tumble})} \times \int_0^\infty dt''' F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t'''] \tag{57}$$

$$\equiv - \frac{v^2 |\vec{\nabla} c|^2}{3} \frac{X}{\langle n^2 \rangle} f(\bar{r}) \times \int_0^\infty dt''' F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']. \tag{58}$$

To maximize the return we require that $\partial \langle \vec{v} \cdot \vec{\nabla} c \rangle / \partial X = 0$ and $\delta \langle \vec{v} \cdot \vec{\nabla} c \rangle / \delta F(t) = 0$ [28].

For the X equation, we require

$$\frac{1}{X} - \frac{1}{\langle n^2 \rangle} \frac{\partial \langle n^2 \rangle}{\partial X} + \left(\frac{\partial \ln f(r)}{\partial r} - \frac{\int_0^\infty dt''' t''' F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']}{\int_0^\infty dt''' F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']} \right) \frac{\partial \bar{r}}{\partial X} = 0, \tag{59}$$

$$\frac{X^2}{\langle n^2 \rangle} = \left(\frac{2 D_{\rm rot} - \bar{r}^2 \tau_{\rm tumble}}{(1 + \bar{r} \tau_{\rm tumble})(2 D_{\rm rot} + \bar{r})} - \frac{\bar{r} \int_0^\infty dt''' t''' F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']}{\int_0^\infty dt''' F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']} \right)^{-1}, \tag{60}$$

where we have neglected subleading terms in the signal to noise ratio.

Now we need to set up the filter equation and solve the two simultaneously. For the filter equation we need to know

$$\frac{\delta \bar{r}}{\delta F(t)} = \frac{1}{2} \left(\frac{\bar{r}}{\langle n^2 \rangle} \right) \left(\frac{X^2 - \langle n^2 \rangle}{\langle n^2 \rangle} \frac{\delta \langle n^2 \rangle}{\delta F(t)} - \tau_n^2 \frac{\delta \langle \dot{n}^2 \rangle}{\delta F(t)} \right). \tag{61}$$

We will also need to know $\delta \langle n^2 \rangle / \delta F(t)$ and $\delta \langle \dot{n}^2 \rangle / \delta F(t)$, for which we need to specify the nature of the bare noise, η. We take $\langle \eta \rangle = 0$ and

$$\langle \eta(t) \eta(t') \rangle = \frac{N}{2 \tau_{\rm bare}} \exp(- |t - t'| / \tau_{\rm bare}) \tag{62}$$

$$\sim N \delta(t - t'), \tag{63}$$

since the bare noise time constant is much shorter than any other time scale in the problem (see the Appendix). In this case,

$$\frac{\delta \langle n^2 \rangle}{\delta F(t)} \sim -2 N \ddot{F}(t) + \frac{4 v^2 |\vec{\nabla} c|^2}{3 (1 + \bar{r} \tau_{\rm tumble})(2 D_{\rm rot} + \bar{r})} F(t), \tag{64}$$

$$\frac{\delta \langle \dot{n}^2 \rangle}{\delta F(t)} \sim 2 N \frac{\partial^3}{\partial t^3} F(t), \tag{65}$$

where these equations are valid for regions where F is slowly varying compared to the bare noise time and to leading order in the signal to noise ratio. The filter equation is given by

$$0 = \left(\frac{\partial \ln f(r)}{\partial \bar{r}} - \frac{\int_0^\infty dt''' t''' F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']}{\int_0^\infty dt''' F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']} \right) \frac{\delta \bar{r}}{\delta F(t)} - \frac{1}{\langle n^2 \rangle} \frac{\delta \langle n^2 \rangle}{\delta F(t)} + \frac{\exp[-(2 D_{\rm rot} + \bar{r}) t]}{\int_0^\infty F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']}, \tag{66}$$

$$\frac{\exp[-(2 D_{\rm rot} + \bar{r}) t]}{\int_0^\infty F(t''') \exp[-(2 D_{\rm rot} + \bar{r}) t''']} = \frac{1}{\langle n^2 \rangle} \frac{\delta \langle n^2 \rangle}{\delta F(t)} - \left(\frac{\langle n^2 \rangle}{\bar{r} X^2} \right) \frac{\delta \bar{r}}{\delta F(t)}. \tag{67}$$

First, consider the behavior of the filter for times large compared to $(2D_{\rm rot}+\bar{r})^{-1}$. In this case the left hand side of Eq. (67) is negligible. Further, the contribution to $\delta\bar{r}/\delta F(t)$ from the $\delta\langle\dot{n}^2\rangle/\delta F(t)$ is small, provided that F is slowly varying in this region. So the filter equation requires that

$$\frac{\delta\langle n^2\rangle}{\delta F(t)}=0, \tag{68}$$

$$\ddot{F}(t)=\frac{2v^2|\vec{\nabla}c|^2}{3N(1+\bar{r}\tau_{\rm tumble})(2D_{\rm rot}+\bar{r})}F(t). \tag{69}$$

The absolute scale of the filter is arbitrary given the definition of X used in Eq. (59), so we may take

$$F(t)\sim\exp\left(-\sqrt{\frac{2v^2|\vec{\nabla}c|^2}{3N(1+\bar{r}\tau_{\rm tumble})(2D_{\rm rot}+\bar{r})}}\,t\right). \tag{70}$$

The filter thus has an extremely long tail determined by the square root of the signal to noise ratio.

The behavior for intermediate times, times of order $(2D_{\rm rot}+\bar{r})^{-1}$, is more complicated. Now we must retain the exponential term in Eq. (67); however, the term in $\delta\bar{r}/\delta F$ coming from $\delta\langle\dot{n}^2\rangle/\delta F(t)$ is still negligible, and we may also neglect the term in $\delta\langle n^2\rangle/\delta F(t)$ that vanishes with the signal to noise ratio. In this case we have

$$\left(\frac{1}{2\langle n^2\rangle}+\frac{1}{2X^2}\right)\frac{\delta\langle n^2\rangle}{\delta F(t)}=\frac{\exp[-(2D_{\rm rot}+\bar{r})t]}{\int_0^\infty dt'''F(t''')\exp[-(2D_{\rm rot}+\bar{r})t''']}, \tag{71}$$

$$\exp[-(2D_{\rm rot}+\bar{r})t]=\left(\frac{1}{\langle n^2\rangle}+\frac{1}{X^2}\right)N\ddot{F}(t)\int_0^\infty dt'''F(t''')\times\exp[-(2D_{\rm rot}+\bar{r})t''']. \tag{72}$$

This requires that

$$F(t)=A+Bt+C\,\exp[-(2D_{\rm rot}+\bar{r})t]. \tag{73}$$

Matching the filter onto the result for long times requires that $A=1$ and $B=0$, while $F(0)=0$ requires $C=-1$, unless F were to vary very rapidly in the short time region, which is clearly not optimal because of the additional contribution to the noise that would result. In this case, $C=-1$ imposes a self-consistency condition. Equation (72) requires that

$$\left(\frac{1}{\langle n^2\rangle}+\frac{1}{X^2}\right)=\frac{2}{N(2D_{\rm rot}+\bar{r})}, \tag{74}$$

where we have assumed that the very short time contribution to $\int_0^\infty dt'''F(t''')\exp[-(2D_{\rm rot}+\bar{r})t''']$ is negligible. The contribution to $\langle n^2\rangle$ from the the intermediate and long time parts of the filter is $[N(2D_{\rm rot}+\bar{r})]/2$ so that there must be a short time contribution to $\langle n^2\rangle$ given by

$$\langle n^2\rangle_{\rm short\ times}=\frac{N^2(2D_{\rm rot}+\bar{r})^2}{4X^2-2N(2D_{\rm rot}+\bar{r})}. \tag{75}$$

The short time behavior of the optimal, low signal to noise ratio filter depends on the characteristics of the bare noise. The short time equation for the optimum filter is

$$2\left(\int_0^\infty dt'''F(t''')\exp[-(2D_{\rm rot}+\bar{r})t'''\right)^{-1}=\left(\frac{1}{X^2}+\frac{1}{\langle n^2\rangle}\right)\frac{\delta\langle n^2\rangle}{\delta F(t)}+\tau_n^2\frac{1}{X^2}\frac{\delta\langle\dot{n}^2\rangle}{\delta F(t)}, \tag{76}$$

where

$$\frac{\delta\langle n^2\rangle}{\delta F(t)}=\frac{2}{\tau_{\rm bare}}F(t)-\frac{1}{\tau_{\rm bare}^2}\int_0^\infty dt'F(t')\exp(-|t-t'|/\tau_{\rm bare}), \tag{77}$$

$$\frac{\delta\langle\dot{n}^2\rangle}{\delta F(t)}=-\frac{2}{\tau_{\rm bare}^3}F(t)-\frac{2}{\tau_{\rm bare}}\ddot{F}(t)+\frac{1}{\tau_{\rm bare}^4}\int_0^\infty dt'F(t')\exp(-|t-t'|/\tau_{\rm bare}). \tag{78}$$

For small $\tau_{\rm bare}$, we may neglect the left hand side of Eq. (76), and the equation is the solution for a filter of the form

$$F(t)\sim A[1-\exp(-t/\tau_{\rm bare})], \tag{79}$$

where A must be chosen so that

$$\tau_n=\tau_{\rm bare}\sqrt{1+\frac{X^2}{\langle n^2\rangle}}. \tag{80}$$

This requires

$$A=2\tau_{\rm bare}(2D_{\rm rot}+\bar{r})\,\frac{N(2D_{\rm rot}+\bar{r})}{2X^2-N(2D_{\rm rot}+\bar{r})}. \tag{81}$$

This choice of A must also fulfill the self-consistency equation from intermediate times, [Eq. (72)]. A straightforward calculation demonstrates that, to leading order in the signal to noise ratio, both self-consistency requirements are satisfied by this choice of A in the limit of small $\tau_{\rm bare}$. We thus arrive at the final form of the filter:

$$F(t)=\left(1+2\tau_{\rm bare}(2D_{\rm rot}+\bar{r})\,\frac{N(2D_{\rm rot}+\bar{r})}{2X^2-N(2D_{\rm rot}+\bar{r})}\right)\times\exp\left(-\sqrt{\frac{2v^2|\vec{\nabla}c|^2}{3N(1+\bar{r}\tau_{\rm tumble})(2D_{\rm rot}+\bar{r})}}\,t\right)-2\tau_{\rm bare}(2D_{\rm rot}+\bar{r})\,\frac{N(2D_{\rm rot}+\bar{r})}{2X^2-N(2D_{\rm rot}+\bar{r})}\exp\left(-\frac{t}{\tau_{\rm bare}}\right)-\exp[-(2D_{\rm rot}+\bar{r})t]. \tag{82}$$

Notice that, as expected based on Berg and Purcell's original arguments [15], the time scale of the filter is set primarily by the rotational diffusion time of the bacterium. Our filter is also similar to that found in Ref. [18], where a different criterion for optimality was used. However, the

long time behavior found here is somewhat different from that of Ref. [18], and from that expected based on the arguments of Ref. [15]. We find that, in the low signal to noise ratio limit, a temporal filter extending for significantly longer than the rotational diffusion time is optimal. For weak signal strengths some useful information is gained from averaging in measurements made much longer ago than the rotational diffusion time scale, and thus the optimal filter includes these times. This is not what one would have naively expected based on the arguments of Ref. [15]. A similar effect was found in Ref. [18], where the tail of of the optimal filter was found to extend to infinitely long times; however, that result was obtained in the strictly zero signal case, rather than in the limit of small signal as for our filter. We find that it holds only for the case of strictly zero signal to noise ratio (either for our definition of optimality or that used in Ref. [18]), and that, for a finite signal to noise ratio, the optimal filter involves an additional time scale, $\sqrt{3N(1+\bar{r}\tau_{\rm tumble})(2D_{\rm rot}+\bar{r})/(2v^2|\vec{\nabla}c|^2)}$, depending on the rotational diffusion time *and* the signal to noise ratio. The tail of the filter decays on this time scale, which diverges with the inverse of the square root of the signal to noise ratio, but is of the same order as the rotational diffusion time for finite signal strengths (where the calculations considered here are not strictly valid but should be qualitatively correct). Our results therefore unify the conclusions of Refs. [15] and [18]: for moderate signal strengths, Berg and Purcell's argument that the filtering time scale will be of the order of the rotational diffusion time will be correct, but at a low signal to noise ratio a new, extremely long, averaging time scale is optimal.

To compare Eq. (82) to experimental results on the filtering strategies used by the bacteria, we require the equations which determine $\bar{r}$, X, $\langle n^2\rangle$, and τ_n. These are given by Eq. (52),

$$X=\sqrt{\langle n^2\rangle\,\frac{2(1+\bar{r}\tau_{\rm tumble})(2D_{\rm rot}+\bar{r})}{4D_{\rm rot}-3\bar{r}-5\bar{r}^2\tau_{\rm tumble}}}, \tag{83}$$

$$\langle n^2\rangle=\left(\frac{2}{N(2D_{\rm rot}+\bar{r})}-X^{-2}\right)^{-1}, \tag{84}$$

and Eq. (80), respectively. We can combine Eqs. (83) and (84) to obtain

$$X=\sqrt{\frac{N}{2}(2D_{\rm rot}+\bar{r})\,\frac{8D_{\rm rot}+4D_{\rm rot}\bar{r}\tau_{\rm tumble}-\bar{r}-3\bar{r}^2\tau_{\rm tumble}}{4D_{\rm rot}-3\bar{r}-5\bar{r}^2\tau_{\rm tumble}}}, \tag{85}$$

$$\langle n^2\rangle=\frac{N}{4}\,\frac{8D_{\rm rot}+4D_{\rm rot}\bar{r}\tau_{\rm tumble}-\bar{r}-3\bar{r}^2\tau_{\rm tumble}}{1+\bar{r}\tau_{\rm tumble}}. \tag{86}$$

The remaining equations must be solved numerically, and for the typical values [6]

$$\tau_{\rm tumble}\sim 0.15\ {\rm s}, \tag{87}$$

$$2D_{\rm rot}\sim 0.3\ {\rm s}^{-1}, \tag{88}$$

$$\tau_{\rm bare}\sim 1\ {\rm ms}, \tag{89}$$

the resulting $\bar{r}$ is

$$\bar{r}\sim 0.17\ {\rm s}^{-1}. \tag{90}$$

This value depends only very weakly on the poorly known $\tau_{\rm bare}$ and the experimentally measurable $\tau_{\rm tumble}$ [29]. It depends strongly on $D_{\rm rot}$ and also on the assumption that each tumble totally disorients the bacterium. For this reason it is worth considering the problem of tumbles which are not perfectly disorienting.

The low signal to noise ratio is also solvable for tumbles which do not perfectly disorient the bacterium in the limit of vanishing $\tau_{\rm tumble}$. If we define

$$z=1-\langle\hat{v}_{\rm before}\hat{v}_{\rm after}\rangle \tag{91}$$

then we find that the return [Eq. (10)] becomes

$$\langle\vec{v}\cdot\vec{\nabla}c\rangle=\frac{v^2|\vec{\nabla}c|^2}{3}\,\frac{X}{\langle n^2\rangle}\,\frac{z\bar{r}}{2D_{\rm rot}+z\bar{r}}\times\int_0^\infty dt\ F(t)\exp[-(2D_{\rm rot}+\bar{r})t]. \tag{92}$$

In this case, all of the arguments for the case of perfectly disorienting tumbles go through as before except that (1) the return is scaled by z, (2) $\bar{r}$ must be replaced everywhere by $z\bar{r}$, and (3) $\tau_{\rm tumble}$ is to be set equal to zero everywhere. Roughly, the resulting optimal value of $\bar{r}$ will be $1/z$ larger. Experimentally, it appears that $z\sim\frac{1}{2}$ [6], and for this value we find

$$\bar{r}\sim 0.37\ {\rm s}^{-1}. \tag{93}$$

IV. COMPARISON WITH EXPERIMENTS

Many of the features we would expect in the behavior of bacteria implementing the optimal strategy are directly comparable to the observations of Refs. [6] and [30], where the behavior of free swimming *E. coli* in spatial and temporal gradients of various chemoattractants, as well as in the absence of such gradients, was studied. In Ref. [6], free swimming *E. coli* in the absence of gradients were found to have a distribution of run times that was approximately exponential with a time constant of about 0.85 s. The distribution of run times could be made almost perfectly exponential by rescaling the run times by the mean run times of the individual bacteria. This form for the distribution of run times for an individual bacterium is in agreement with the form we find in the low signal to noise ratio limit, the relevant limit in this case. The fact that the time constant is different for different bacteria is also a natural for the optimal strategy, because the bacteria differ in their rotational diffusion constants, and, therefore, different bacteria should choose different rates for initiating tumbles. It would be very useful to see if differences in the rotational diffusion constants of individual bacteria correlate with their different tumbling rates, a question not investigated in Ref. [6]. Assuming that the disorientation due to tumbling remains fixed, the tumbling rate from the optimal low signal to noise ratio strategy

should be roughly proportional to the rotational diffusion constant, if the bacteria are pursuing the optimal, adaptive strategy.

Whatever the nature of the correlations between rotational diffusion and rates of tumble initiation, the mean rate of tumbling observed, $\sim 1.2\ s^{-1}$, is anomalously large. It is a factor of 3 larger than the rate we would expect even if we take into account the correlation between orientations before and after tumbles reported in Ref. [6]. It is possible that there is significant error in either the value of D_{rot} or of z that we have used, and it would be of great value to have precise experimental determinations of these from tracking experiments, since they are both experimentally directly measurable. However, a factor of 3 appears to be too large to be the result of inaccuracies in these values, and Ref. [6] quotes a mean change in orientation from the beginning to the end of a run of only 23°, implying that the bacteria really do run for times significantly shorter than the time which disorients them. In the low signal noise ratio limit this is not optimal; however, this behavior may be the result of the experiments involving bacteria *in the absence of any chemoattractant*, rather than merely in the absence of gradients. In fact, bacteria in a uniform solution of 10^{-4} molar serine have an exponential run distribution with a time constant that is roughly three times longer than was found in the absence of serine [6]. This agrees rather well with the value expected for the optimal strategy, however, it should be noted that a uniform concentration of aspartate, a different chemoattractant, was not found to have the same effect. Clearly it would be desirable to have more tracking work done in uniform or nearly uniform solutions of chemoattractant that are as similar as possible to the natural environment of *E. coli* in order to settle this question. This would enable us to determine whether the tumbling rate is really anomalously large compared to the optimal. The natural explanation, should the conflict prove genuine, is that the actual tumbling rate represents something more like the optimal tumbling rate in the intermediate signal to noise (SNR) ratio regime, where we have no solution, and that the bacteria are more or less permanently adapted to this regime because the cost of adapting to low signal to noise ratio outweighs the potential gains. However, note that the optimal tumbling rate in the high SNR limit is roughly $2D_{rot} \sim 0.3\ s^{-1}$, similar to what we have found for the low SNR limit, so it is by no means obvious that tumbling rates at some intermediate SNR ratio should be as large as $\sim 1\ s^{-1}$.

In addition to determining the distribution of run times in the absence of chemoattractant, Ref. [6] also measured some of the effects of small gradients on this distribution. One of the interesting things found was an indication of a peculiar asymmetry in the response of the bacteria to small gradients. *E. coli* tumbled less often when swimming up the gradient of the chemoattractant, but not more often when swimming down the gradient of the chemoattractant. We have seen that, at a high signal to noise ratio, bacteria following the optimal strategy will be surprisingly reluctant to tumble because of the finite amount of time required to tumble, and the fact that there is some chance that rotational diffusion will improve their prospects. This may explain some of the observed reluctance to tumble if the bacteria are in a medium signal to noise ratio regime. In fact, the asymmetry is only clearly observed for runs that are longer than 1.5 s, so perhaps a minimum integration time, and the accompanying boost in signal to noise ratio, is required for the asymmetry. Any detailed attempt to explain the asymmetry would require more detailed measurements of the responses of *E. coli* than are currently available for free swimming bacteria, and this is another area where the collection of more data on free swimming bacteria would be of great value.

At a low signal to noise ratio, there is a possibility for asymmetry in responses other than the cost of tumbles: we expect an exponential, not linear, dependence of the tumbling rate on the sensory input. In fact, Ref. [30] observed the response of free swimming *E. coli* to temporal gradients of glutamate, and found that their results were best fit by an exponential dependence on the rate of change of receptor occupancies, which in the concentration region treated implied an exponential sensitivity to gradients in concentration. They did not, however, claim to have ruled out a linear dependence, and further measurements of the response of the tumbling rate in bacteria adapted to a low signal to noise ratio environment would be of great value. It would also be of great value if bacteria could be placed in a range of spatial gradients of the chemoattractant, and then stimulated with an additional temporal gradient to see if the response crossed over from one appropriate for the low signal to noise ratio case to one appropriate for the high signal to noise ratio case, i.e., tumbling at a fixed value of the estimated angle from the concentration gradient.

The predictions we have made for the optimal filter to be used in the low signal to noise ratio limit can be compared to the results of Refs. [11,16,31], where tethered [23] bacteria were exposed to impulselike bursts of chemoattractant. If the strategy the bacteria employ involves linearly filtering some function of sensory inputs, then the response a time t later under these conditions is related to $\dot{F}(t)$, and so the temporal properties of the derivative of the filter can be determined from these experiments. Evidence for the very long tail in the derivative of the filter expected of the optimal strategy for a low signal to noise ratio was not found in these experiments. However, the filter found there does extend about 4 s into the past, which is significantly longer than the time scale for the bacterium to disorient. The improvement in chemotactic performance that would result from a longer integration time is very small, while the difficulty of building a faithful, long term memory is clearly substantial, so the result is not surprising. The long time behavior of the filter may still be adaptive, but the limit of a truly small signal to noise ratio appears to be beyond the range (if any) of that adaptation.

At intermediate times the derivative of the optimal filter contains a term with an exponential decay rate given by $2D_{rot} + z\bar{r} \sim 1\ s^{-1}$ (for the realistic assumptions of short tumble times and finite disorientation during tumbles). A feature of almost exactly those characteristics is seen in the filter found in Ref. [11], and it appears that the optimal filtering strategy may in fact be rather close to the filtering strategy inferred from the response observed in those experiments. However, one should be cautious, since the agreement is the result of using the experimental value for $\bar{r}$ which is not in agreement with theoretical expectations (unless our value of D_{rot} or z is badly off), and there are worries about the adap-

tive state of tethered bacteria [32]. Also, the tethered experiments were interpreted in terms of a linear, but thresholded, response in the rate of transitions from running to tumbling, and vice versa; this is not readily reconciled with the proposed deterministic strategy and the resulting exponential dependence of the effective rate of such transitions on the filtered signal.

It is probably not sensible to compare the behavior of the filter at short times (100 ms or shorter) with theoretical expectations, since responses on this time scale are not particularly important for chemotactic performance, while constraints due to the actual physical signal processing mechanisms of the bacteria are severe on this time scale.

In summary, the filter observed has a behavior very similar to what is expected for the optimal filter at time scales on the order of a second. On longer time scales it decays faster than the optimal rate for a low signal to noise ratio, but at a rate that is clearly slower than the natural time scale for the bacterium to disorient, in qualitative agreement with that characteristic of the optimal filter. There is some question as to the adaptation state of the tethered bacteria, but since they spend most of their time in the complete absence of chemoattractant signals, the most reasonable proposal is that they are adapted to a low signal to noise ratio. The tethered experiments do not make any attempt to identify an adaptation to the signal to noise ratio or diffusion constant in the characteristics of the filter. In fact, they are ill suited to such a test, since the tethered bacterium experiences such unnatural conditions that its adaptive state is difficult to determine.

On the other hand, some experiments suitable for testing the form of the filter on free swimming bacteria was recently performed using photoreleased chemoattractant and repellant [33]. In those experiments, bacteria swimming freely in the absence of spatial gradients were exposed to steplike changes in concentration by photoreleasing caged chemoattractants and repellants at the location of the bacteria. This form of stimulation provides a δ function in the derivative of the concentration, so that the response a time t later is a measure of the filter $F(t)$ used in the low signal to noise ratio environment. These experiments find a memory time for the system slightly longer than that of the tethered experiments, around 5 s. This is marginally closer to the long time tail that is expected for the optimal filter. On the other hand, there is no indication of the intermediate time ($\sim$1 s) feature found in the data of Ref. [31], although the data in the case of Ref. [33] are somewhat noisy and the applied stimulus is so large, inducing a tumble in 100 ms with nearly unit probability, that a feature with the expected rise time of $\sim$1 s is probably not excluded.

It would be very useful to have more photorelease-based studies of the response of free swimming bacteria aimed specifically at measuring the properties of the filter on time scales of a fraction of a second to several seconds. One would like to know the filter properties as a function of the spatial gradients to which the bacteria are preadapted, and, if possible, one would also like to look for correlations between the time constants of the filter used, the rotational diffusion constant of the free swimming bacteria, and their distribution of run times. Experiments of this type could answer the important open questions of the adaptability of the form of the filter and the tumbling criterion directly. This would be a very important step in determining the extent to which *E. coli* achieves the optimal chemotactic strategy. We believe that this would provide interesting and important information about the limits of the sophistication of sensory processing in single celled organisms.

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APPENDIX

The correlation time for the chemoreceptors is expected to be on the order of 10^{-3} s or shorter. This time scale results from several considerations. First, the typical binding time for a chemoreceptor is about 10^{-4} s [15]. This will set the correlation time for the chemoreceptor inputs if (1) it is a much larger time than the time for attractant to diffuse away from a receptor, and (2) there is relatively little correlation between receptors. To see that (1) is satisfied we approximate the time to diffuse away from the receptor (that is the time to diffuse far enough away to have small chance of recapture) as (the size of the receptor)^2/(diffusion constant of attractant) which is typically 10^{-14} cm^2/10^{-5} cm s^{-1}$\sim$$10^{-9}$ s, vastly smaller than the rotational diffusion time, even if we have underestimated the distance out to which recapture is important by a sizable factor. Individual receptors therefore decorrelate on a time scale given by the binding time. What about the ensemble of receptors?

To see that the ensemble of receptors decorrelates on a time scale comparable to the binding time, recall the arguments of Ref. [15] regarding the rate of capture of diffusing molecules by a large number of small perfectly absorbing sites on the surface of an impermeable sphere. The inbound current for N patches of linear size s on a sphere of size a is given by

$$J = 4\pi D c_\infty a \, \frac{Ns}{Ns + \pi a}, \tag{A1}$$

where c_∞ is the concentration of signaling chemical per cubic centimeter at infinity. In Ref. [15], it was emphasized that this differs from the current to a perfectly absorbing sphere of radius a only by a factor of $Ns/(Ns+\pi a)$, which can approach one for reasonable choices of N, s, and a. Here, we note that this occurs because the current $4\pi D c_\infty a[Ns/(Ns+\pi a)]$ differs from that for N independent disks only by a factor of $\pi a/(Ns+\pi a)$, which is about one-half for the parameters of Ref. [15]. Clearly, the reason for the reduction from the value for N independent receptors is that some of the molecules absorbed by a given receptor would have contacted others in its absence. In fact, the average molecule that contacts an absorbing site would make contact with another binding site with probability $Ns/(Ns+\pi a)$. For receptors which bind and release

the attractant, this implies that the average molecule which binds to one receptor will bind to $1/(1-[Ns/(Ns+\pi a)])=(Ns+\pi a)/\pi a \sim 2$ others, so that, defining the number of receptors with attractor bound at time t to be $x(t)$, and assuming Poisson statistics

$$\int_0^T dt\langle x(t)x(0)\rangle - T\langle x\rangle^2 = \left(\frac{Ns+\pi a}{\pi a}\right)\tau_{\rm bind}\langle x\rangle \quad \text{(A2)}$$

$$\sim 2\,\tau_{\rm bind}\langle x\rangle. \quad \text{(A3)}$$

If the receptors decorrelated on a time scale, $\tau_{\rm decorr}$, which was much longer than $\tau_{\rm bind}$, then

$$\int_0^T dt\langle x(t)x(0)\rangle - T\langle x\rangle^2 \sim e\int_0^T dt\ \exp(-t/\tau_{\rm decorr}) \times\langle x(\tau_{\rm bind})x(0)\rangle \quad \text{(A4)}$$

$$\sim e\,\tau_{\rm decorr}\langle x(\tau_{\rm bind})x(0)\rangle, \quad \text{(A5)}$$

implying

$$\langle x(\tau_{\rm bind})x(0)\rangle \sim \frac{2\,\tau_{\rm bind}}{e\,\tau_{\rm decorr}} \quad \text{(A6)}$$

$$\ll 1, \quad \text{(A7)}$$

and the correlations among the receptors must be weak, as their correlation time is much larger than the binding time. Conversely, if $\tau_{\rm decorr}\sim\tau_{\rm bind}$, then the correlations need not be weak, but the two time scales are comparable so that $\tau_{\rm bind}$ is still the appropriate time scale.

In practice, the time to diffuse far enough away from *all* receptors should be roughly (the size of the bacterium)^2/(diffusion constant of attractant) which is typically 10^{-8} cm^2/10^{-5} cm s$^{-1}\sim 10^{-3}$ s or ten times as long as the receptor binding time. In this case, most of the correlations among chemoreceptor inputs have decayed by 0.1 ms, but some weak correlation persists out to 1 ms. Both times are still very short compared to the relevant rotational diffusion time scale, and we can approximate the noise in the binding of the chemoreceptors to be white on the other time scales of interest.

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