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A feasibility analysis of bacterial chemotaxis under the influence of external noise

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Abstract

Bacteria moving in response to chemical attractants are subject to noise from the environment in addition to that within the cells. Environmental noise is observed typically through fluctuations in the concentrations of the chemoattractant. Interactions between two or more sources of noise may upset the chemotactic motility of the cells. This possibility is investigated here for *Escherichia coli* through a pair of conditions derived earlier. These conditions relate the tumbling time, the sensing time and the adaptation time of the cells. It is observed that chemotaxis is not feasible if the normalized variance of the external noise exceeds a critical value. This critical value does not depend on the expression of CheR, a key protein in the chemosensory system, and it agrees with similar values reported by others for intra-cellular noise. These observations indicate that stochastic resonance may be a prime factor enhancing chemotaxis in the presence of noise.

Keywords: *Escherichia coli*; chemotaxis; external noise; time constants; feasibility; stochastic resonance

Introduction

Many bacteria change their normal random motions in response to an attractive chemical in their vicinity. Their movements then get directed (statistically) such that a population of bacterial cells is seen to have bulk motion biased toward the chemoattractant. This phenomenon, called chemotaxis, has been observed experimentally (Armitage 1999; Berg 2000; Sourjik and Berg 2004) and analyzed mathematically (Lebiedz et al. 2004; Rao et al. 2004; Andrews et al. 2006). These studies show that bacteria do not move directly toward a chemical. Instead, their movements comprise a series of alternate 'run' and 'tumbles'. The runs are straight line movements and the tumbles are changes in direction. Since the sensory ability of bacterial cells is usually limited to distances that are small compared to the spread of a chemoattractant (Berg 2000; Wadhams and Armitage 2004), the tumbles provide timely corrections to the runs so that the cells remain on course toward the chemoattractant.

For many reasons, the unicellular organism *Escherichia coli* has been a favored work-horse to study bacterial chemotaxis under different conditions. These include its well-characterized physiology, its simple chemotaxis signaling pathway that contains all essential features, its ability to respond even to small changes in the concentration of a chemoattractant, and its utility as either a natural host or a surrogate host for plasmids coding for desired features or products (Wadhams and Armitage 2004; Andrews et al. 2006; Bray et al. 2007). Owing to their small size, cells of *E. coli* cannot directly perceive spatial variations; instead, spatial changes (for example, in the chemoattractant concentration) are sensed in terms of temporal changes as the cells move. The detection of a chemoattractant, transmission of this information through the cells and its translation to directed movements (chemotactic motility) is implemented by an elaborate chemosensory network (Baker et al. 2006). The salient features of this network that are relevant to the present analysis are described in the next section.

While navigating toward or through chemical stimulants, the cells are subject to noise from within and from the extra-cellular environment. Intra-cellular noise pervades the genetic networks and the small concentrations of mRNA, DNA and gene-encoded proteins (Rao et al. 2002; Paulsson 2004). Extra-cellular noise is a ubiquitous feature of most real environments, and it is seen as fluctuations in the macroscopically monitored variables (Newman et al. 2006; Patnaik 2006a). In chemotactic cultures the binding of the molecules of the chemical attractant to receptors on the surfaces of the cells is a prominent source of external noise.

Since both intra-cellular and extra-cellular noise interact and affect the chemosensory system, it is possible that in certain situations they may disturb the system to an extent that makes chemotactic motility unfeasible. This possibility is supported by previous studies of other microbial cultures, which have shown that noise may cause substantial changes in culture behavior, including the generation of chaos from monotonic or oscillating performance (Weiss et al. 1994; Patnaik 2005). Although the importance of determining the feasibility of chemotaxis was recognized many years ago by

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Oosawa and Nakaoka (1977), its rigorous implementation with a plausible mathematical model was done much later.

Inoue and Kaneko (2006) revived the Oosawa-Nakaoka conditions and applied them to a linear version of a model of *E. coli* chemotaxis proposed by Erban and Othmer (2004). In essence, Oosawa and Nakaoka (1977) considered that the cells have an internal memory that enables them to adapt their responses to the environmental changes they sense. These changes may be spatial or temporal. They identified three time constants characterizing chemotaxis. One is the tumbling time constant, τ, which is the inverse of the tumbling frequency. The second is the time required to detect a change, including a fluctuation, in the environment; this is the sensing time constant, τ_s. The third parameter is the well-know adaptation time, τ_a. Oosawa and Nakaoka (1977) showed that for bacterial chemotaxis is feasible only if:

$$\tau_a > \tau > \tau_s \quad (1)$$

Inoue and Kaneko (2006) applied Eq. (1) to a simple two-variable linear model to test chemotactic feasibility in response to (a) a step change in a uniform chemical field and (b) a chemical gradient of a constant slope. They did not consider the presence of noise. However, as discussed above, both internal and external noise are important factors determining chemotactic behavior. Therefore, in the present work we consider the effect of noise-induced fluctuations in a uniform chemoattractant field. Inoue and Kaneko's model also did not include many important mechanistic features of the chemosensory system. To overcome these weaknesses, a more detailed, accurate and structurally informative model of chemotaxis has been employed here. The model, from Baker et al. (2006) and Rao et al. (2004), includes details of the methylation-demethylation kinetics and chemoreceptor-ligand binding kinetics, which were absorbed in a lumping procedure by Inoue and Kaneko (2006). These processes have a significant effect on chemotaxis and hence they should be considered explicitly. In addition, environmental noise, manifested as fluctuations in the chemoattractant concentration, was added to the model.

Chemosensory system of *E. coli*

E. coli swim in a liquid medium by rotating long helical flagellar filaments that are attached to rotary motors embedded in the cell wall (Berg 2000; Wadhams and Armitage 2004). Each cell has six or seven motors distributed over the cell surface, and each motor switches repeatedly between clockwise (CW) and counter-clockwise (CCW) rotations. CW rotations cause tumbles and CCW rotations create runs. As mentioned earlier, alternations between runs and tumbles determine how a swarm of bacteria moves in a chemical field. Understandably, a dominance of runs without corrective tumbles may cause the cells to move far away from the chemical stimulus; similarly, frequent tumbles without sufficiently long runs causes random motion. Thus, proper control of the durations of the CW and CCW rotations and of the switching frequency is important in propelling the cells toward a chemoattractant and preventing them from going astray.

The rotations of the flagellar motors, which directly control chemotaxis, are controlled by a complex chemosensory system whose main components are shown pictorially in Fig. 1. Chemical signals are detected by chemoreceptors projecting into the periplasmic space, from where they are transmitted across the membrane into the coiled-coil region of the CheW binding domain in the cytoplasm (Fig. 1). This detection arises out of binding between a receptor and its corresponding chemical ligand. There are five types of chemoreceptors – Aer, Tap, Tar, Trg and Tsr – intermingled into a large number of clusters along with the chemotaxis proteins CheA and CheW (Djordjevic and Stock 1998; Li and Hazelbauer 2004).

As Fig. 1 shows, other proteins too are involved in the chemosensory system. These are CheB, CheR, CheW, CheY and CheZ. Each protein is encoded by a particular gene, named *cheA, cheB, cheR, cheW, cheY* and *cheZ* (Wadhams and Armitage 2004; Baker et al. 2006). The functions of these proteins are summarized in Table 1.

The third stage is adaptation. To explain this briefly, we invoke previous reports (Sourjik and Berg 2004; Rao et al. 2004; Wadhams and Armitage 2004; Baker et al. 2006) that receptor-ligand binding causes reversible methylation of the receptor. Simultaneously, CheB promotes demethylation of the chemoreceptor, thereby forming a closed loop containing the CheR protein. Methylation and demethylation are thus intimately associated with the effectiveness of the signal transduction process and they determine the robustness of adaptation (Alon et al. 1999). CheR catalyzes the methyl-esterification of specific glutamate residues in the chemoreceptors, while CheB removes these methyl groups (Sourjik and Berg 2004; Baker et al. 2006). The effects of noise-induced fluctuations in the chemoattractant molecules may thus be expected to be transmitted to the CheB and CheR proteins and consequently to the methylation-demethylation system.

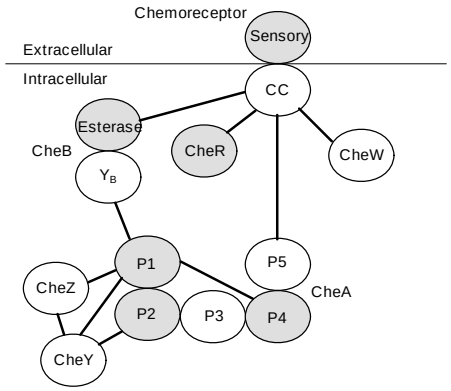

Figure 1. Schematic diagram of the chemosensory system of *E. coli*. Solid lines depict interactions. CC=coiled-coil domain; P1=histidine phosphotransfer domain; P2=response regulator binding domain; P3=dimerization domain; P4=ATP binding domain; P5=regulator domain; Y_B=CheY response regulator domain of CheB. The label CheA indicates that it comprises all of P1 to P5. Reprinted with permission from Baker MD, Wolanin PM, Stock JB, Syatems biology of bacterial chemotaxis, *Curr Opin Microbiol* **9:** 188-192, 2006. © 2005 Elsevier Ltd.

Now, the methylated receptors are multimers of CheA and CheW. As explained above, CheA plays a key role in the signaling step by contributing phosphoryl groups to CheY, which in turn controls the rotations of the flagellar motors. Since CheB and CheR regulate the methylation and demethylation processes respectively, external noise has an impact on CheY phosphorylation through these two processes, with consequent effects on motor rotations. Applying the conditions of Oosawa and Nakaoka (1977) to either CheB or CheR should therefore provide sufficient information on the feasibility of chemotaxis.

Chemotaxis model and its implementation

To obtain more realistic and reliable results than those of Inoue and Kaneko (2006), a more detailed model was used. This was taken from Rao et al. (2004), who incorporated Sourjik and Berg's

Table 1. Key proteins and their functions in the *E. coli* chemosensory system (see Fig. 1).

Protein	*Function*
CheA	Phosphorylates the response regulator, CheY, which then binds to the flagellar motors
CheB	Demethylates the chemoreceptor, thereby forming a feed-back loop with CheR
CheR	Methylates the chemoreceptor, thereby changing the kinase activity of CheA
CheW	Regulates CheA activity by forming multimeric complexes with CheA and the chemoreceptors
CheY	Response regulator that controls tumbling by changing the spin of the flagellar motors
CheZ	Mediates ATP binding and phosphorylation of CheY through the histidine phosphotransfer domain

(2004) model for the phosphorylation of CheY into the chemotaxis model of Barkai and Leibler (1997). In Barkai and Leibler's approach a receptor complex may exist in either an active (T^A) or an inactive (T^I) state. Let T_i be the concentration of receptor complexes with i residues methylated, and $\alpha_i(L)$ the probability that the complex T_i is active when the concentration of the chemoattractant is L. Then it follows that

$$T^A = \sum_{i=0}^{4} \alpha_i(L) T_i \quad (2)$$

$$T^I = \sum_{i=0}^{4} (1-\alpha_i(L)) T_i \quad (3)$$

The indices in Eqs. (2) and (3) run from 0 to 4 because there are five chemoreceptor genes; aer, tap, tar, trg and tsr.

The translation of chemical signals from the chemoreceptors to the rotation of the flagellar motor involves the phosphorylated forms of three chemosensory proteins – CheA, CheB and CheY – and the motor switching protein FliM. Their rates of change are described by the following equations (Rao et al. 2004).

$$\frac{dA_P}{dt} = 50T^A A - 100A_P Y - 30A_P B \quad (4)$$

$$\frac{dB_P}{dt} = 30A_P B - B_P \quad (5)$$

$$\frac{dM_P}{dt} = 5MY_P - 19M_P \quad (6)$$

$$\frac{dY_P}{dt} = 100A_P Y - 0.1Y_P - 5MY_P + 19M_P - 30Y_P \quad (7)$$

The native and phosphorylated forms of the Che proteins are related as (Sourjik and Berg 2002), where the numbers are in nM:

$$A + A_p = 5$$
$$B + B_p = 2$$
$$M + M_p = 5.8$$
$$Y + Y_p + M_p = 17.9$$

Since T^A is present in Eq. (4) and this variable depends on T_i (i = 0, 1, 2, 3, 4) according to Eq. (2), it is necessary to formulate the rates of change of T_i. Using mass balances, Rao et al. (2004) derived the equations given below for each dT_i/dt.

$$\frac{dT_o}{dt} = -r_R(1-\alpha_0(L))T_0 + r_B\alpha_1(L)T_1 \quad (8)$$

$$\frac{dT_i}{dt} = -r_R(1-\alpha_i(L))T_i + r_B\alpha_{i+1}(L)T_{i+1} + r_R(1-\alpha_{i-1}(L))T_{i-1} - r_B\alpha_i(L)T_i;\ i = 1,2,3 \quad (9)$$

$$\frac{dT_4}{dt} = r_R(1-\alpha_3(L))T_3 - r_B\alpha_4(L)T_4 \quad (10)$$

It may be noted that Eqs. (8) and (10) have only two terms on the right side whereas Eq. (9) has four. This difference arises because receptors with 1, 2 and 3 methylated residues can be both methylated and demethylated, while unmethylated receptors (T_0) can only be methylated and fully methylated ones (T_4) can only get demethylated.

In Eqs. (8)-(10), r_B is the rate of reaction of CheB in demethylation and r_R the corresponding rate for CheR in methylation. These rates follow Michaelis-Menten equations of the form (Rao et al. 2004; Emonet and Cluzel 2008):

$$r_B = \frac{k_b B_P}{K_B + T^A} \quad (11)$$

$$r_R = \frac{k_r R}{K_R + T^I} \quad (12)$$

and so do the probabilities $\alpha_i(L)$ in Eqs. (2) and (3):

$$\alpha_i(L) = \frac{a_i^L L}{K_L + L} + \frac{a_i K_L}{K_L + L} \quad (13)$$

The requirement that the sum of the probabilities be unity,

i.e. $\sum_{i=1}^{4} \alpha_i(L)$,

for any value of L places constraints on the choice of the parameters a_i and a_i^L. Such a constraint cannot be imposed on K_L since it is an equilibrium property of the chemosensory system. Earlier studies (Levin 2003; Paulsson 2004; Andrews et al. 2006; Emonet and Cluzel 2008) of stochastic gene expression suggest that the environmental noise may be characterized as a Gaussian distribution with zero mean and an adjustable variance. With this noise considered to be present in L, Eqs. (4)-(13) were solved numerically, using the parameters values shown in Table 2. From the time-domain plots thus obtained, the values of τ, τ_s and τ_a were calculated as explained by Inoue and Kaneko (2006) and described briefly in the Introduction. The sensing time constant τ_s is the time required for the response following a perturbation in the chemoattractant concentration L to reach a peak, and the adaptation (or relaxation) time τ_a is the time required for the response to return to its pre-perturbed value. Experimental results (Alon et al. 1999; Levin 2003; Rao et al. 2004) of the tumbling frequency, $1/\tau$, show that it satisfies two conditions: (i) $1/\tau$ becomes sufficiently smaller than $1/\tau^*$ for a large value of L and (ii) it is sufficiently larger than $1/\tau^*$ for small L. Here τ^* is the value of τ corresponding to the fixed point. To determine the effect of τ, Inoue and Kaneko proposed the analytic function specified below, where δ_1, δ_2 and λ are empirical parameters that define the distribution.

Table 2. Values of the parameters and initial conditions (Barkai and Leibler 1997; Sourjik and Berg 2002).

Parameter	Units	Value	Variable	Units	Initial value
a_0	--	0	A_p	nM	0
a_1	--	0.1	B_p	nM	0
a_2	--	0.5	M_p	nM	0
a_3	--	0.75	Y_p	nM	0
a_4	--	1	L_0	nM	1
a_o^L	--	0	T_0	nM	5
a_1^L	--	0	T_1	nM	0
a_2^L	--	0.1	T_2	nM	0
a_3^L	--	0.5	T_3	nM	0
a_4^L	--	1	T_4	nM	0
k_b	sec^{-1}	5.5			
K_B	nM	10			
K_L	nM	0.255			
k_r	sec^{-1}	0.251			
K_R	--	0.3			
R	--	0.1			
δ_1	--	1			
δ_2	--	0.1			
λ	--	0.1			

$$\frac{1}{\tau(\mathrm{L})} = \frac{\delta_1 - \delta_2 \tanh[\lambda(\mathrm{L} - \mathrm{L}_0)]}{\tau^*} \qquad (14)$$

However, as they explain, interpretations of the effects of τ remain valid for any other function that meets the two conditions mentioned above. For consistency, this functional form was retained in the present analysis. For a given value of the chemoattractant concentration, L, the value of τ may be calculated if the values of the parameters δ_1, δ_2 and λ are known. Table 2 presents a feasible set of values (Inoue and Kaneko 2006) that generate values of τ which satisfy the two conditions prescribed above.

Application and discussion

The description given above of the chemosensory system of *E. coli* indicates that changes in the frequency of CheY phosphorylation govern the frequency of switching of the flagellar motors between CW and CCW rotations. It may be recalled that CW rotations generate tumbles and CCW rotations cause runs (Berg 2000; Andrews et al. 2006). Thus CheY phosphorylation directly controls the efficiency of chemotaxis.

The changes in the rate of phosphorylation occur in response to signals provided by the chemoreceptors; in the present study these signals are triggered by noise-induced fluctuations in the chemoattractant concentration. Variations in the sensory signals cause corresponding changes in the methylation of glutamate residues in the chemoreceptors, and this process is catalyzed by CheR (Djordjevic and Stock 1998). Moreover, *in vivo* fluorescence energy transfer measurements (Sourjik and Berg 2004) reveal that the levels of phosphorylated CheY adapt precisely to transient perturbations and this is controlled by the equilibrium between methylation (by CheR) and demethylation (by CheB) of the chemoreceptors. Noise may shift this equilibrium and thus upset the feasibility of chemotaxis. This likelihood is supported by the experimental results of Alon et al. (1999) and Levin (2003), based on which Andrews et al. (2006) have argued that a (noise-induced) increase/decrease in the activity of CheR causes the breaking point of the cell's integral noise filtering system (Chen et al. 2005) to shift to larger/smaller frequencies and, consequently, shorter/longer adaptation times. CheR thus plays a critical role in the chemotactic responses of the cells, particularly in their adaptation to variations in chemoattractant signal transduction. This has been confirmed by the observation that strains deleted for the *cheR* gene cannot tumble and therefore cannot adapt (Alon 1999; Emonet and Cluzel 2008).

Oosawa and Nakaoka's (1977) conditions, Eq. (1), to determine the feasibility of chemotaxis under the influence of noise were therefore applied to CheR. Conformity to or violation of these conditions by CheR provide a sufficient basis for feasibility or otherwise. Earlier investigations (Alon et al. 1999; Levin 2003; Rao et al. 2004) have shown that the adaptation time as well as the tumbling frequency (i.e. $1/\tau$) vary with the concentration of CheR. The investigators controlled the concentration of CheR by controlling the level of induction by IPTG in strains deleted for the *cheR* gene. To enable comparisons with a wild type strain, the concentration of the CheR protein was expressed relative to that in the wild type. This method was followed here too and the profiles of τ , τ_s and τ_a for two representative values of CheR are displayed in Figs. 2 and 3. Previous studies (Levin 2003; Newman et al. 2006; Xu et al. 2006) have shown that the fluctuations in the chemoattractant concentrations may be described by a Gaussian noise distribution. Levin (2003) and Chen et al. (2005) have also pointed out that the ratio of the variance to the mean is adequate to characterize this noise for chemotaxis purposes. Hence the abcissae in these Fig. 2 and 3 show different values of this ratio, called the normalized variance σ.

Data from Alon et al. (1999) and Levin (2003) show that, over a range of CheR expressions, the adaptation time, τ_a, is in minutes whereas the tumbling time, τ, is in seconds. Although these data are in the absence of environmental noise, the differences in magnitude are so large that the first inequality in Eq. (1) may be expected to be satisfied even under the influence of noise. This conjecture is confirmed in Figs. 2 and 3 for CheR = 1 and CheR = 3 respectively. In both cases, however, the plots for τ and the sensing time, τ_s, intersect at a particular value of the normalized variance σ. Let (σ_{cr}, τ_{cr}) denote this critical point. Then, for $\sigma < \sigma_{cr}$, $\tau > \tau_s$ and chemotaxis can occur.

If the intensity of the noise exceeds σ_{cr}, $\tau < \tau_s$, thus violating Eq. (1) and rendering chemotaxis unfeasible. From a practical perspective, this is plausible since excessive noise would "corrupt" the chemoattractant concentration to such an extent that the

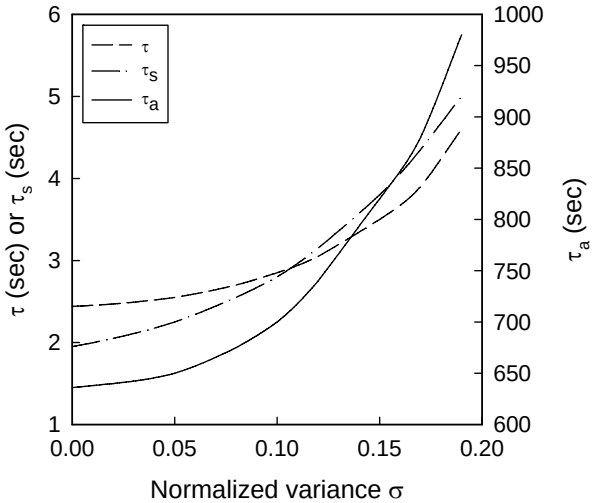

Figure 2. Variations of the tumbling (τ), sensing (τ_s) and adaptation (τ_a) times with the normalized variance (σ) for CheR expresion level of 1.

chemoreceptors would not be able to decipher the true values of the concentration.

The inability of the chemosensory system to cope with excessive noise is in consonance with the functioning of the cell's own filtering system. Cells of *E. coli* and other bacteria have a built-in filtering system that may be represented as an integral feed-back loop that is necessary and sufficient to maintain robustness of perfect adaptation (Yi et al. 2000). Incorporating such a filter into a simulation model of the *E. coli* chemosensory system, Andrews et al. (2006) have shown that the chemotactic performance deteriorates beyond a critical cut-off frequency of the filter. Although Yi et al. (2000) considered only intra-cellular noise and Andrews et al. (2006) added the noise associated with the binding of the chemical ligands to their chemoreceptors, their observations are remarkably similar to the inference drawn from the cross-over plots in Figs. 2 and 3. This similarity has two implications. One is the validation of the Oosawa-Nakaoka conditions for noise-affected chemotaxis. The other implication is the possibility of stochastic resonance between different sources of noise.

The latter inference is supported by reports of stochastic resonance being a prime contributing factor in the evolution of phenotypes resistant to hostile environments (Balaban et al. 2004), the emergence of coherent dynamics from noisy individual cells in a multi-cell system (Chen et al. 2005), and enhancement of the synthesis of certain gene-encoded proteins (Patnaik 2006).

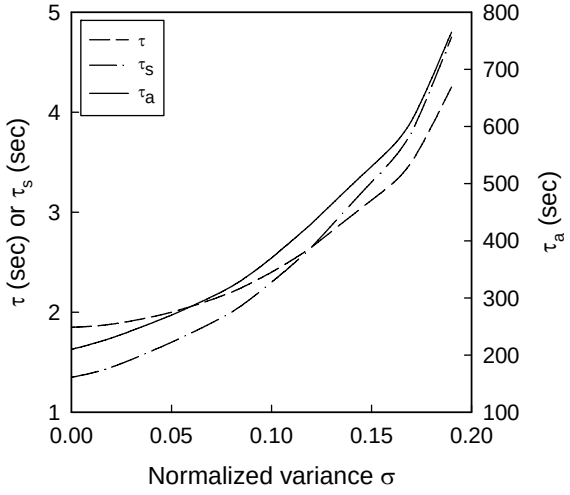

Figure 3. Variations of the tumbling (τ), sensing (τ_s) and adaptation (τ_a) times with the normalized variance (σ) for CheR expresion level of 3.

The critical role of CheR in the chemotactic response of a population of cells in a noisy environment has been underlined in two recent studies (Emonet and Cluzel 2008; Vladimirov et al. 2008). From the power spectra of the spontaneous fluctuations in the output of the *E. coli* chemosensory system (Fig. 1), they inferred that the ratio of the methylation and demethylation velocities is an experimentally compatible (Korobkova et al. 2004) index of variability in chemotactic response. This variability is maximum when CheR is expressed at wild-type level, implying that wild-type cells navigate farther up a chemoattractant gradient than mutant cells do (Andrews and Iglesias 2007). In this context, different authors (Rao et al. 2002; Levin 2003; Emonet and Cluzel 2008) have suggested that the adaptation time τ_a may be interpreted as relative measure of the sensitivity of chemotaxis to small external perturbations (or noise).

This interpretation has a molecular basis related to the chemosensory network. First, the *cheR* and *cheB* genes are located contiguously, thus reducing independent variations between the expression of the two genes. Secondly, a negative feedback loop on CheB helps to maintain the ratio of CheR to CheB, thereby moderating the chemotactic motility of an ensemble of cells even while individual members show variations caused by noise (Kollmann et al. 2005). There is in fact an optimum range of the CheR/CheB ratio that is most favorable to chemotaxis. This ratio has a correspondence with a similar optimum range for phosphorylated CheY; the latter in turn determines an optimum range for the flagellar motors (Vladimirov et al. 2008), whose direction of rotation and switching between clockwise and counter-clockwise rotations governs the runs and tumbles of the cells (Wadhams and Armitage 2004; Baker et al. 2006). While a detailed description of the sequence of events is available elsewhere (Emonet and Cluzel 2008; Vladimirov et al. 2008), the observations provide further evidence of the likelihood of noise from outside the cells destabilizing the intra-cellular chemosensory processes.

Similar to Figs. 2 and 3, the variations in τ, τ_s and τ_a were computed for CheR expression levels of 1, 2, 3, 4, 5 and 6, as in Alon et al. (1999) and Levin (2003). The corresponding values of σ_{cr} and τ_{cr} are depicted in Fig. 4. Although τ_{cr} is seen to decrease as σ_{cr} increases, it is important to observe that the ranges of both critical values are small compared to those in Figs. 2 and 3. Considering that the microbial system is affected by both intra-cellular and extra-cellular noise, these results indicate that the critical variance and the critical time constants for sensing and tumbling are practically invariant. In other words, the normalized variance of external noise above which chemotaxis is vitiated is independent of the concentration of CheR. A similar invariance has been reported by Swain et al. (2002) and Levin (2003) for intra-cellular noise, and their ranges of σ_{cr} agree with those in Fig. 4 for environmental noise. An important implication of this agreement is the possibility of tuning the internal and external noise filters to promote the stochastic resonance discussed above.

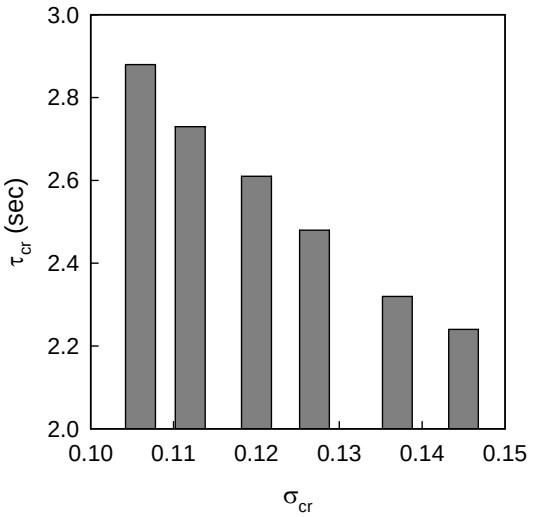

Figure 4. Dependence of the critical time constant (τ_{cr}) and the critical normalized variance (σ_{cr}) on the expression level of CheR. Values of CheR are (from the left) 1, 2, 3, 4, 5 and 6.

Although resonance between noise sources has been proposed as a performance enhancing factor in diverse cellular processes (Balaban et al. 2004; Chen et al. 2005; Patnaik 2006), the exact reasons for this are not yet clear (Rao et al. 2002, 2004). One plausible reason (Patnaik 2006b; Emonet and Cluzel 2008) is the possibility of energy transfer as in the cases of photochemical and sonochemical reactions. Up to a threshold level, the increased inflow of vibrational energy selectively enhances intra-cellular processes. Cells seem to possess inherent "intelligence" that enables them to decide how their metabolic processes should respond to changing conditions (Ramkrishna 2003; Clark and Grant 2005). Noise exceeding the threshold can disrupt the cells or cause runaway reactions. Rao et al. (2002) point to another explanation advanced by some investigators. They suggest that phase variations in pathogenic bacteria, where cells alternate randomly between expressing certain genes and silencing others, are promoted by suitably "cultivated" (implying filtered) noise, thereby conferring robustness to these bacteria. Although the two perspectives may seem biologically different, there is one important similarity. The underlying logic in both explanations is that mutually compatible filtering of interacting noise sources regulates competing intra-cellular processes so as to favor some of them at the cost of others.

Conclusions

Noise from the extra-cellular environment is often as significant as intra-cellular noise in the chemotactic behavior of bacterial cells. Together, these sources of noise determine whether chemotaxis can occur or will be disrupted. While intra-cellular noise has been analyzed and modeled by many investigators, the effects of environmental noise have received much less attention. The present analysis therefore addresses this lacuna.

Using *E. coli* as representative system and a chemotaxis model that contains sufficient mechanistic and biochemical detail, the effects of extra-cellular noise were investigated through a pair of feasibility conditions derived earlier. These conditions specify relationships between the tumbling time, τ, the sensing time τ_s, and the adaptation time, τ_a, of the cells. Conformity to or violation of the conditions was studied over practically relevant ranges of the normalized variance of the noise and the expression level of a key chemosensory protein, CheR.

For the entire ranges of both variables, τ_a was always larger than τ. However, beyond a critical variance, σ_{cr}, of the noise, τ_s exceeded τ, thus violating the second feasibility condition. Interestingly, the value of σ_{cr} was practically constant for all values of CheR expression and it agreed with a similarly invariant noise intensity reported by others for intra-cellular noise. These results reinforce the indication from other microbial applications that stochastic resonance may be exploited here also to improve chemotactic performance.

Nomenclature

a_i, a_i^L	parameters in the equation for $\alpha_i(L)$
A	concentration of native CheA, nM
A_p	concentration of phosphorylated CheA, nM
B	concentration of native CheB, nM
B_p	concentration of phosphorylated CheB, nM
k_b	reaction rate constant for r_B, sec^{-1}
K_B	Michaelis-Menten constant for r_B, nM
K_L	Equilibrium constant for $\alpha_i(L)$, nM
k_r	reaction rate constant for r_R, sec^{-1}
K_R	Michaelis-Menten constant for r_R, nM
L	perturbed concentration of chemoattractant, nM
L_0	unperturbed concentration of chemoattractant, nM
M	concentration of Flim, nM
M_p	concentration of the complex of Flim and phosphorylated CheY, nM
T_i	concentration of active receptors with i residues methylated, nM
T^A	concentration of active receptors, nM
T^I	concentration of inactive receptors, nM
Y	Concentration of native CheY, nM
Y_p	Concentration of phosphorylated CheY, nM
α_i	probability that T_i is active at a chemoattractant concentration of L
δ_1,δ_2,λ	parameters in the equation for τ
τ	tumbling time constant, sec
τ_a	adaptation time constant, sec
τ_s	sensing time constant, sec

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