# Stability analysis of *Escherichia coli* chemotaxis distorted by external noise: A comparison of algorithmic and neural filters

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***Abstract*—**Under realistic conditions, the chemotaxis of *Escherichia coli*, and other bacteria, is under the influence of noise within the cells and from the environment. While the cells have their own mechanisms to filter intra-cellular noise and chemical ligand binding noise, external filters are required for environmental noise. The stability of the chemotaxis of *E. coli* to external noise has been analyzed here through the Lyapunov exponents of the concentration of CheR, a key chemosensory protein. Based on earlier studies, environmental noise was considered to have a Gaussian distribution characterized by the Fano factor, F. Four algorithmic filters and an auto-associative neural filter have been compared for their ability to filter the noise and restore stability to noise-distorted chemotaxis; this was measured by the largest Lyapunov exponent of CheR. All filters helped to remedy the distortions within limited ranges of F, with a neural filter being better than all algorithmic filters. Each filter displayed peak effectiveness at two values of F, thus corroborating and expanding the stochastic resonance reported with just intra-cellular and ligand binding noise. The effectiveness of the neural filter suggests the possibility of further improvements through other network architectures.

***Keywords*—**Escherichia coli, Chemotaxis, Stability, External noise filter, Stochastic resonance.

## I. INTRODUCTION

In the absence of any stimulus, cells of *Escherichia coli* and other bacteria move randomly in an undisturbed uniform environment. As a result, a population of cells shows no net migration in any preferred direction. However, when a chemical stimulus is present, the cells sense the stimulus and reorient their movements such that they are biased dominantly either toward or away from the chemical. This is called chemotaxis, and it has been observed in many natural as well as created situations [1-3]. Most applications of chemotaxis pertain to chemical attractants (or chemoattractants), where the cells move toward the stimulus since that serves as a source of their metabolism.

Although a chemoattractant induces the cells to move toward it, this movement is not a direct traversal. The movements consist of alternate short periods of straight-line motion (a "run") and a change of direction (a "tumble"). A typical run is of about 1s, whereas the tumbling interval is a tenth of that [4]. The tumbles provide periodic corrections to the directions of the runs so that a population of cells stays broadly on course toward the attractant.

During chemically induced motility, the cells are often under the influence of a number of sources of noise, some from within the cells and some from outside. Intra-cellular noise arises because cellular events involve molecules, such as DNA, mRA and gene-encoded proteins, that are present in low concentrations and participate in probabilistic collisions that are inter-dependent [5,6]. There are two main sources of extra-cellular noise. One is the noise associated with the binding of a ligand of a chemoattractant to a corresponding receptor cluster on the cell surface. This is the first step in a chain of events that leads to recognition of the attractant and consequent reorientation's of cell motility [7]. The second source is noise from the environment in which the cells navigate. This is manifested as fluctuations in the macroscopically observed variables [8,9].

Bacterial cells have inherent mechanisms to filter intra-cellular noise and chemical ligand binding noise. These mechanisms have been described in various studies [5,6,10]. A common noise-attenuating mechanism is through negative feedback, which is known in control theory to impart stability and thereby counteract the destabilizing effects of excessive noise. Bacterial chemotaxis uses a sophisticated form of negative feedback called integral feedback; this provides not only stability but also robustness [11]. Models for chemotaxis under the influence of intra-cellular noise have also been reviewed [12-14].

Although the effects of environmental noise have been analyzed for different bacterial cultures [9,15], these have been for production systems, where the interest was in generating more of cell mass or a particular protein and not in chemotaxis. Since all sources of noise interact and influence cell motility, it is important to filter these noises appropriately so that chemotaxis is not impaired. Since *E. coli* has its own filtering mechanisms for intra-cellular noise and ligand binding noise, which have been analyzed earlier [5,10], this communication analyzes different strategies to filter external noise in conjunction with the cell's own filtering mechanisms.

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## II. CHEMOTAXIS MODEL AND ITS ANALYSIS

Barkai and Leibler [16] present a seminal analysis of bacterial chemotaxis that has been the forerunner of many other studies, which have expanded and refined their model. The present work is based on one such model proposed by Rao et al. [17]. This was chosen because it incorporates the essential features of the chemosensory system without being too complicated. The starting entities in their model are the chemoreceptors, which detect chemical signals and transmit them into the chemosensory system. *E coli* has five chemoreceptor genes, *aer*, *tap*, *tar*, *trg* and *tsr*, each with its own receptor complex [7]. According to Barkai and Leibler [16], each such complex may exist in either an active state ($T^A$) or an inactive state ($T^I$).

Methylation and demethylation of the receptor complexes is a key factor that controls signal transduction and robust adaptation of the chemosensory system [18,19]. Let $T_i$ be the concentration of receptors with i residues methylated, and $\alpha_i(L)$ the probability that the complex $T_i$ is active when the concentration of chemoattractant is L. Then, simple mass balances lead to:

$$T^A = \sum_{i=0}^{4} \alpha_i(L) T_i \tag{1}$$

$$T^I = \sum_{i=0}^{4} (1 - \alpha_i(L)) T_i \tag{2}$$

Detection of a signal starts a chain of events that results in either clockwise (CW) or counter-clockwise (CCW) rotation of motors embedded in the cell wall. These motors are attached to long helical flagella protruding outward, whose movements propel the cells through the surrounding medium[4,7]. CW rotations cause tumbles and CCW rotations generate runs. The translation of chemical signals from the chemoreceptors to the rotations of the flagellar motors involves the phosphorylation of three essential chemosensory proteins --- CheA, CheB and CheY --- and a motor switching protein FliM. Rao et al. [17] presented the equations given below for their rates of change.

$$\frac{dA_P}{dt} = 50 T^A A - 100 A_P Y - 30 A_P B \tag{3}$$

$$\frac{dB_P}{dt} = 30 A_P B - B_P \tag{4}$$

$$\frac{dM_P}{dt} = 5 M Y_P - 19 M_P \tag{5}$$

$$\frac{dY_P}{dt} = 100 A_P Y - 0.1 Y_P - 5 M Y_P + 19 M_P - 30 Y_P \tag{6}$$

The native and phosphorylated forms of the Che proteins are related as [20]:

$A + A_P = 5$

$B + B_P = 2$

$M + M_P = 5.8$

$Y + Y_P + M_P = 17.9$

Since Eq.(3) contains $T^A$, which in turn depends on $T_i$ (i = 0, 1, 2, 3, 4), the rates of change of each $T_i$ are also required. They may be expressed as [17]:

$$\frac{dT_0}{dt} = -r_R (1 - \alpha_0(L)) T_0 + r_B \alpha_1(L) T_1 \tag{7}$$

$$\frac{dT_i}{dt} = -r_R (1 - \alpha_i(L)) T_i + r_B \alpha_{i+1}(L) T_{i+1} + r_R (1 - \alpha_{i-1}(L)) T_{i-1} - r_B \alpha_i(L) T_i ; i = 1,2,3 \tag{8}$$

$$\frac{dT_4}{dt} = r_R (1 - \alpha_3(L)) T_3 - r_B \alpha_4(L) T_4 \tag{9}$$

It may be seen that Eqs. (7) and (9) have only two terms each whereas Eq. (8) has four. This difference reflects the fact that chemoreceptors that are partially methylated (i = 1, 2, 3) can be both demethylated and methylated further, whereas unmethylated receptors ($T_0$) can only be methylated and fully methylated ones ($T_4$) can only get demethylated. Equations (7)-(9) also incorporate the mechanistic feature [7,10,17] that CheB is responsible for demethylation and CheR for methylation. Their rates follow Michaelis-Menten kinetics.

$$r_B = \frac{k_b B_p}{K_B + T^A} \tag{10}$$

$$r_R = \frac{k_r R}{K_R + T^I} \tag{11}$$

Given Eqs. (10) and (11), the rate of methylation of the receptor $T_i$ is

$$r_M = r_R (1 - \alpha_i(L)) T_i \tag{12}$$

and its rate of demethylation is

$$r_D = r_B \alpha_i(L) T_i \tag{13}$$

The probabilities $\alpha_i(L)$ also follow similar expressions.

$$\alpha_i(L) = \frac{a_i^L L}{K_L + L} + \frac{a_i K_L}{K_L + L} \tag{14}$$

This model has been analyzed earlier, both without external noise [10] and with noise but no filtering [21]. The latter work analyzed the system through its sensitivity coefficients. Here we employ the Lyapunov coefficient since previous studies [22,23] have shown this to be a reliable and informative single index of microbial culture performance in the presence of noise. The Lyapunov exponent is briefly introduced later.

In many situations the environmental noise experienced by the cells may be described by a Gaussian distribution

[21,24,25]. The noise may be characterized by the ratio of its variance and its mean, referred to as the Fano factor [26], which is the ratio of the variance to the mean:

$$F = \sigma_w^2/\mu_w \tag{15}$$

Here w is the time window of observation.

## III. THE LYAPUNOV EXPONENT VIS-A-VIS CHEMOTAXIS

The Lyapunov exponent, λ, provides a convenient quantitative measure of the stability of a system after a disturbance. This is done by quantifying the rate of divergence of the disturbed trajectory of system performance from its initial path. Since chemotaxis involves frequent changes in the path of motion, a convenient basis to compare the two trajectories is the average distance traversed by a cell over a span of time since this distance is sensitive to the prevailing conditions [10,21,27].

Let $x_0$ be the average distance for noise-free chemotaxis and x(t) the distance under the effect of Gaussian noise. In general, both $x_0$ and x may vary with time but previous studies [10,21,28] indicate that $x_0$ is reasonably constant, a feature consistent with robust perfect adaptation [17,19]. Even if $x_0$ is constant, x will vary with time and so will the differential distance Δx. In fact, Δx may also depend on $x_0$; let $\Delta x(x_0, t)$ denote this value at a given time t and $\Delta x(x_0, 0)$ the initial separation. A dynamic system is then stable if the separation of the disturbance-free path and the disturbed path does not increase with time; this condition may be written as:

$$\sup\left|\Delta x(x_0, t)\right| \le C\exp(\lambda t\left|\Delta x_0\right|); C \in R \tag{16}$$

The number λ is called the Lyapunov exponent. A multi-variable system may obviously have more than one Lyapunov exponent; then the largest exponent, $\lambda_{max}$, is sufficient to characterize stability [29]:

$$\lambda_{max} = \lim_{t\to\infty,\left|\Delta x_0\right|\to 0} \frac{1}{t}\frac{\left|\Delta x(x_0, t)\right|}{\left|\Delta x_0\right|} \tag{17}$$

If $\lambda_{max} < 0$, the (chemotactic) process is stable, i.e. it will return to its initial state after the disturbance is removed. This, of course, implies robustness [5,16,17,19]. In the limit $\lambda_{max} \to -\infty$, the process is said to be superstable, i.e. it is robust to a disturbance of any magnitude. A positive $\lambda_{max}( > 0)$ signifies an unstable process, for which a disturbance can cause a permanent change of behavior. A very large $\lambda_{max}$ can result in even a small disturbance upsetting bacterial motility sufficiently severely to cause chaotic behavior.

The boundary between stable and unstable behavior, i.e. $\lambda_{max} = 0$, has intrinsic importance. Strictly, $\lambda_{max} = 0$ denotes neutral stability, i.e. the altered process is not far from its initial state and remains stable. Sometimes this may be acceptable. In a practical sense, however, $\lambda_{max}$ fluctuates around zero for a noise-affected process. If the fluctuations are small enough, depending on F, the chemotaxis remains stable, a condition described as marginal stability. Since a certain degree of fuzziness is a feature of many microbial processes in realistic situations, marginal stability is practically more relevant than neutral stability.

## IV. INTRODUCTION TO THE NOISE FILTERS

Noise in the chemoattractant concentration was filtered by each of five devices: (i) first-order low pass Butterworth filter (LPBF(1)), (ii) second-order LPBF (LPBF(2)) (iii) extended Kalman filter (EKF), (iv) cusum filter (CF), and (v) auto-associative neural filter (ANF). These filters were chosen on the basis of previous investigations [15,22,23] that revealed their effectiveness for microbial cultures. The first four are algorithmic in the sense that they operate through mathematical models of the process and the filter. The ANF does not strictly require a process model. Even though chemotaxis has been represented here by a model comprising Eqs. (1)-(12), it may well be replaced by either the performance data alone or, for instance, an artificial intelligence depiction such as another neural network. Since these filters are described in detail elsewhere [30], they are briefly introduced here.

### *(i) Low pass Butterworth filter (LPBF)*

Different orders of the LPBF are possible. The simplest, the first order LPBF, receives input signals $\bar{x}_k$ at the k-th instant of time and, based on the filtered values $\tilde{x}_{k-1}$ at the previous point of measurement, generates the current filtered signals $\tilde{x}_k$ according to the equation:

$$\tilde{x}_k = \left(\frac{T_f}{T_f + T_s}\right)\tilde{x}_{k-1} + \left(\frac{T_s}{T_f + T_s}\right)\bar{x}_k \tag{18}$$

$T_f$ is the filter time constant and $T_s$ is the data sampling interval. Filters of higher orders are created by placing two or more first order LPBFs in series; however, there are only marginal improvements beyond two orders.

### *(ii) Extended Kalman filter (EKF)*

The EKF provides efficient recursive estimates of the past, present and future states of a system even when a precise model is not available. Its performance equation is:

$$\tilde{x}_k = \hat{x}_k + A(\tilde{x}_{k-1} - \bar{x}_{k-1}) + W\bar{w}_{k-1} \tag{19}$$

Here $\hat{x}_k$ are the values from a process model and $\bar{w}_{k-1}$ is the vector of process noise. Other variables have the same meanings as in Eq.(16).

The process model may be expressed as:

$$\hat{x}_k = f(\hat{x}_{k-1}, u_k) \tag{20}$$

where $u_k$ contains the forcing functions. A is the Jacobian matrix of f with respect to $\hat{x}_{k-1}$ and W is the Jacobian with respect to $w_{k-1}$.

*(iii) Cusum filter (CF)*

Traditional filters such as those described above reduce the noise in the measurements but do not remove it; thereby some control action is still influenced by noise. The cusum (or cumulative sum) filter is statistically based with the operating equation:

$$\text{Cusum} = \sum \frac{(\tilde{x}_k - \tilde{x}_{k-1})}{\hat{\sigma}_x} \tag{21}$$

where $\hat{\sigma}_x$ is the (estimated) standard deviation of $\tilde{x}_{k-1}$.

If the process has not changed, and noise is independent at each sampling point, then Cusum will be a random walk variable with an initial value of zero. However, if the process has shifted, then the norm of Cusum will grow with each sampling. For N sampled points, if

$$|\text{Cusum}| > 3\sqrt{N} \tag{22}$$

control action is initiated. The constant 3 corresponds to 99.73% confidence level in the decision; statistically it can be shown that 95.00% confidence is represented by 2 and 99.99% by 4.

*(iv) Auto-associative neural filter (ANF)*

Under the nonideal conditions of large bioreactor operations, both process models and filtering methods have to be sufficiently simple, flexible and 'intelligent' enough to learn from usage and adapt to changing unknown conditions. Owing to their strong dependence on the process model and equation-oriented approach, algorithmic filters such as those outlined above find it difficult to accomplish this efficiently and optimally [15,22,23]. In such situations, neural networks have worked effectively in different fermentation systems. While different configurations of neural networks are possible, the auto-associative network is both germane to filtering functions and performs efficiently. A typical associative network has the configuration shown in Fig. 1. It receives a set of inputs at a particular sampling instant t and generates outputs of the same variables at the next sampling point. This predictive capability enables anticipatory control or corrective action to be taken ahead of any detrimental effect of a disturbance. This anticipatory action adds to the learning ability, robustness and model-independence of an autoassociative filter.

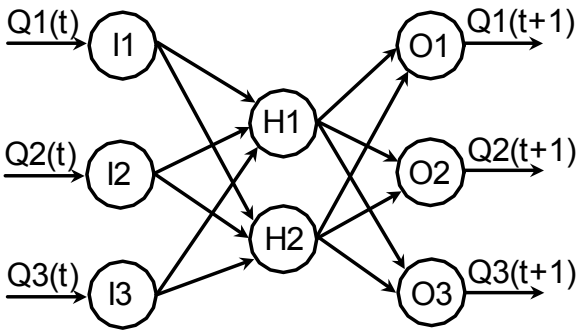


**Figure 1.** Topology of a typical autoassociative neural network. Qj(t)=value of the variable Qj at time t; Ij=j-th input neuron; Hj=j-th hidden neuron; Oj=j-th output neuron.

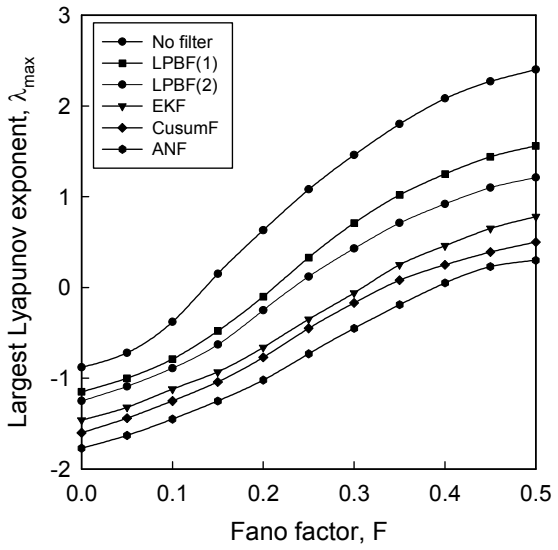


**Figure 2.** Variation of the largest Lyapunov exponent with the Fano factor without any filter and with different noise filters. LPBF(1)=low pass Butterworth filter (LPBF) of the first kind; LPBF(2)=LPBF of the second kind; EKF=external Kalman filter; CusumF=cusum filter; ANF=auto-associative neural filter.

## V. APPLICATION AND DISCUSSION

A previous analysis [20] has revealed that the sensitivities of phosphorylated CheA, CheB, CheY and the FliM-CheY complex, which control the chemical signal transduction processes [7,10,17], increase monotonically with the concentration, L, of the chemoattractant. Since no aberrations in the monotonicity were observed, a representative value of L = 2 was chosen for the present study. With this value, Eqs. (1)-(12) were solved for different values of the Fano factor, F, signifying different distributions of the external Gaussian noise; the values of the parameters and initial conditions are listed in Table 1. From the time-domain plots thus obtained, the largest Lyapunov exponents, $\lambda_{max}$, were calculated according to Eq.(17) for each of the variables.

The objective of this communication being to obtain preliminary insight into the performances of different noise filtering devices, as a prelude to the selection of one or two for detailed applications, attention was focused on one critical variable. Briefly, in the chemosensory mechanism of *E. coli*, changes in the frequency of CheY phosphorylation govern the frequency of switching of the flagellar motors between CW and CCW rotations. These changes occur in response to changes in the signals provided by the chemoreceptors; in the present case, the changes are triggered by noise-induced fluctuations in the chemoattractant concentration. The fluctuations cause corresponding variations in the methylation of glutamate residues in the chemoreceptors, a process that is regulated by CheR [7,31]. Thus, CheR is a critical intermediate that determines the efficiency of *E. coli* chemotaxis.

Figure 2 portrays the variation of the largest Lyapunov exponent, $\lambda_{max}$, with the Fano factor, F, without any filter and with the filters studied. With no filter, chemotaxis is distorted very soon (for F > 0.14) while an ANF is able to maintain stable performance over a much wider noise spectrum (up to F = 0.4). All algorithmic filters are inferior to the ANF, an observation supported by studies of other microbial cultures too [15,22,23]. The order of merit of the filters also agrees with these studies, including the observation that the CF and the EKF are only marginally different. These similarities are not unexpected because, even though refs. [15,22,23] did not address chemotaxis directly, they pertain to bioreactors where access to the substrates and nutrients depends on chemotaxis.

To gain more insight in filtering efficiencies, two measures of the performances may be defined. One is the performance of the process for each type of filter relative to that without a filter; this may be defined as:

$$\beta = 100\left(\frac{\lambda^{f}_{max} - \lambda^{0}_{max}}{\lambda^{0}_{max}}\right) \tag{23}$$

The other index, γ, evaluates the j-th filter with reference to that immediately inferior to it i.e. the (j-1)-th filter:

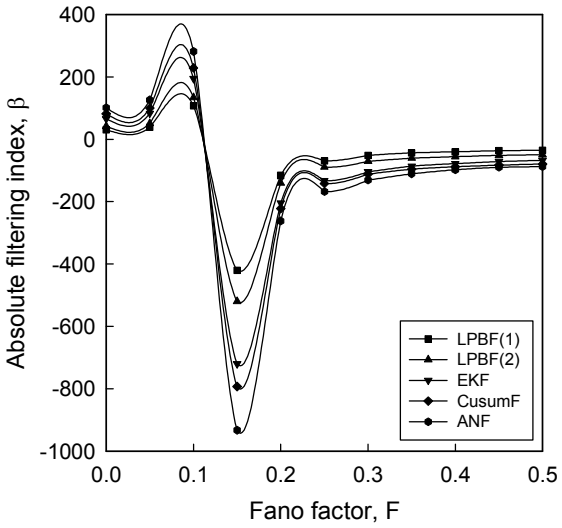


**Figure 3.** Variation of the absolute filtering index β with the Fano factor without any filter and with different noise filters. See Eq. (16) for the definition of β, and the title of Fig. 1 for the abbreviations.

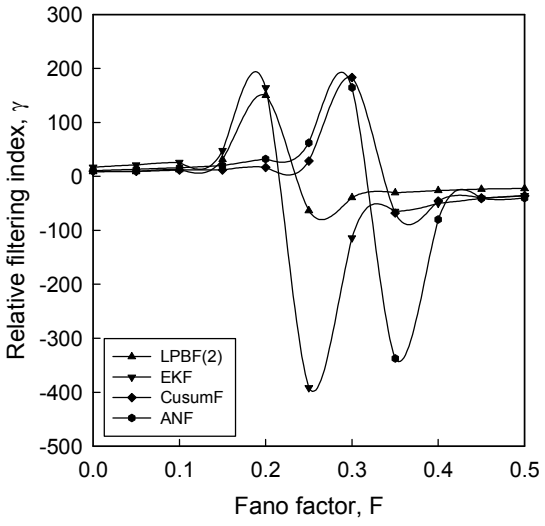


**Figure 4.** Variation of the relative filtering index γ with the Fano factor without any filter and with different noise filters. See Eq. (17) for the definition of γ, and the title of Fig. 2 for the abbreviations.

$$\gamma = 100\left(\frac{\lambda^{f}_{j,max} - \lambda^{f}_{j-1,max}}{\lambda^{f}_{j-1,max}}\right) \tag{24}$$

Figure 3 presents the variation of β with changes in F. A conspicuous feature is that each filter has a positive peak and a negative trough. The differences in the signs arise because in

certain regions of F both values of $\lambda_{max}$ have the same sign whereas in other regions they are different. Regardless of the sign, an important implication of the presence of the optima is that filtering performance is most effective for these two values of F. The bimodal distributions persist even for the relative filtering index $\gamma$ (Fig. 4), suggesting that it is not an artifact.

Although a bimodal distribution of the effect of noise is uncommon, it is not unknown. Xu and Tao [25] recently reported a similar observation for an auto-regulatory genetic network with external Gaussian noise. By contrast, many analysts [32-34] have observed single peak distributions with only intra-cellular noise. The bimodality observed here and by Xu and Tao [25] may be explained by extending their argument. The single peaks were attributed to stochastic resonance, a possibility strengthened by examples of resonance between two sources of noise entirely within the cells [9,35]. As illustrated in Fig. 5, two sources may resonate at one particular frequency, whereas resonance between three sources may be expected to occur at up to three frequencies and thus generate a maximum of three optimum points. The presence of two optima in place of three in Figs. 3 and 4 indicates that two of the resonance points are practically coincident. This may be expected because genetic noise and ligand binding noise have similar Gaussian distributions [5,10,24], which differ from that of environmental noise [9,15,25].

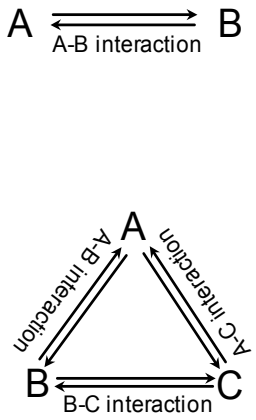


**Figure 5.** Schematic representations of interactions between two (above) and three (below) noise sources, generating one and two points of resonance respectively.

The likelihood of extra-cellular and intra-cellular noise resonating at different Fano factors is strengthened by the observation that the optima in Figs. 3 and 4 occur at F-values that are one to two orders of magnitude smaller than for intra-cellular noise only [32-34]. For promoting controlled stochastic resonance, therefore, the external filter(s) employed and the cell's internal noise filters have to be tuned differently but compatibly. This is a nascent area of research but there are indications [27,36] that neural networks may be effective in such situations, thus supporting the choice of the ANF in this and previous studies [15,22,23].

While describing the Lyapunov exponent, it was stated that a negative $\lambda_{max}$ signified stability, and that this implied robustness in the case of chemotaxis [16,17,19]. The present results however show that not always is the process robust. This might seem to be at variance with the accepted view that *E. coli* chemotaxis exhibits robust adaptation [5,10,18,19]. To explain this apparent contradiction, it may be mentioned that certain other properties of the chemosensory network, such as the steady state concentrations of phosphorylated CheY and the adaptation time, are not robust [17,18,28]. Thus, the $\lambda_{max}$ values are compatible with the known behavior of *E. coli*. They are also compatible with the observation that robust complex systems also tend to be fragile [37]. Fragility implies that a system that is robust may be sensitive to perturbations far away from those it has experienced. Noise that is far outside the Fano window of marginal stability is of this kind, and Fig. 2 illustrates how chemotaxis can then get destabilized in spite of noise filters.

## VI. CONCLUSIONS

Noise is a ubiquitous feature of bacterial chemotaxis. It is present inside the cells (genetic noise), in the binding of chemical ligands to corresponding cell surface receptors, and in the concentration of the chemoattractant. Bacteria have internal mechanisms to filter genetic and ligand binding noise but not for external (or environmental) noise. Hence different types of filters were employed to study their effectiveness in filtering environmental noise.

Four of the filters were algorithmic and one was a neural network. Each was applied under two sets of conditions: one where external noise altered but did not destabilize the chemotaxis and the other where it did. The stability was measured by the largest Lyapunov exponent, $\lambda_{max}$, of the chemosensory protein CheR for a range of Fano factors, F, characterizing the noise. For both sets of conditions, the neural filter maintained stable chemotaxis over a wider range of values of F than the algorithmic filters. The cusum and external Kalman filters were somewhat inferior and the low pass Butterworth filters were the least effective. These results and the lack of dependence of a neural filter on a process model favor its use for noise-distorted chemotaxis. An interesting feature of all filters was the existence of two optima, indicative of two points of stochastic resonance.

## NOMENCLATURE

| | |
|---|---|
| $a_i, a_i^L$ | Parameters in the equation for $\alpha_i(L)$ |
| A | Concentration of CheA |
| $A_P$ | Concentration of phosphorylated CheA |

| | |
|---|---|
| $B$ | Concentration of CheB |
| $B_P$ | Concentration of phosphorylated CheB |
| $k_b$ | Reaction rate constant for $r_B$ |
| $K_B$ | Michaelis-Menten constant for $r_B$ |
| $K_L$ | Equilibrium constant in the equation for $\alpha_i(L)$ |
| $k_r$ | Reaction rate constant for $r_R$ |
| $K_R$ | Michaelis-Menten constant for $r_R$ |
| $L$ | Concentration of chemoattractant |
| $M$ | Concentration of FliM |
| $M_P$ | Concentration of FliM complex with phosphorylated CheY |
| $r_B$ | Rate of reaction of CheB in demethylation |
| $r_R$ | Rate of reaction of CheR in methylation |
| $R$ | Concentration of CheR |
| $T_i$ | Concentration of receptor complexes with i methylated residues |
| $T^A$ | Total concentration of active receptors |
| $T^I$ | Total concentration of inactive receptors |
| $Y$ | Concentration of CheY |
| $Y_P$ | Concentration of phosphorylated CheY |
| $\alpha_i(L)$ | Probability that $T_i$ is active at a chemoattractant concentration of L |
| $\beta, \gamma$ | Filtering indexes as defined by Eqs. (16) and (17) |
| $\lambda^0_{max}$ | Largest Lyapunov exponent without a noise filter |
| $\lambda^f_{max}$ | Largest Lyapunov exponent with a noise filter |
| $\lambda^f_{j,max}$ | Largest Lyapunov exponent with the j-th noise filter |

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**Table 1:** Values of the parameters and initial conditions [17,20].

| 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 | $T_0$ | nM | 5 |
| $a_0^L$ | -- | 0 | $T_1$ | nM | 0 |
| | | | $T_2$ | nM | 0 |
| $a_1^L$ | -- | 0 | $T_3$ | nM | 0 |
| $a_2^L$ | -- | 0.1 | $T_4$ | nM | 0 |
| $a_3^L$ | -- | 0.5 | | | |
| $a_4^L$ | -- | 1 | | | |
| $k_b$ | $sec^{-1}$ | 0.5 | | | |
| $K_B$ | nM | 5.5 | | | |
| $K_L$ | nM | 10 | | | |
| $k_r$ | $sec^{-1}$ | 0.255 | | | |
| $K_R$ | nM | 0.251 | | | |
| R | NM | 0.3 | | | |

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