Connection between the Bacterial Chemotactic Network and Optimal Filtering

Kento Nakamura and Tetsuya J. Kobayashi

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A connection between bacterial chemotactic network and optimal filtering

Kento Nakamura and Tetsuya J. Kobayashi*
Department of Mathematical Informatics, Graduate School of Information Science and Technology, the University of Tokyo
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The chemotactic network of *Escherichia coli* has been studied extensively both biophysically and information-theoretically. Nevertheless, connection between these two aspects is still elusive. In this work, we report such a connection. We derive an optimal filtering dynamics under the assumption that *E. coli*'s sensory system optimally infers the binary information whether it is swimming up or down along an exponential ligand gradient from noisy sensory signals. Then we show that a standard biochemical model of the chemotactic network is mathematically equivalent to this information-theoretically optimal dynamics. Moreover, we demonstrate that an experimentally observed nonlinear response relation can be reproduced from the optimal dynamics. These results suggest that the biochemical network of *E. coli* chemotaxis is designed to optimally extract the binary information along an exponential gradient in a noisy condition.

Living things have developed sensory systems to behave and navigate themselves adaptively in changing and uncertain environments. One of the most-analyzed such systems is the sensory system of *Escherichia coli* for chemotaxis. In *E. coli* chemotaxis, a cell obtains information of a spatial gradient of a ligand from the temporal change in the ligand concentration that it experiences by swimming in the gradient. An *E. coli* cell can sense a positive change in the ligand concentration when it swims along the increasing direction of the gradient and vice versa. The swimming trajectory of *E. coli* consists of a series of ballistic swimming called run interrupted with random reorientations of direction called tumbling. By inhibiting the frequency of tumbling when it senses a positive change in an attractant concentration, the *E. coli* cell can elongate the run length toward the direction of the higher concentration.

The mechanism of the sensory system has been intensively studied both experimentally and theoretically. Experimental studies have revealed the response of *E. coli* to various temporal profiles of concentration by measuring behaviors of motor rotation [1, 2] and signaling molecules [3, 4]. Theoretical studies have proposed and analysed biochemical models that can reproduce the properties of experimentally observed responses such as high sensitivity to weak changes in concentration [4–7] and sensory adaptation [8]. Based on these works, Tu *et al* proposed a simplified biochemical model [9], which can explain various aspects of the responses simultaneously [10]. This standard biochemical model has been widely employed for various purposes such as analysis of sensory-motor coordination [11], fold-change detection [12, 13], and thermodynamics of sensory adaptation [14].

In the biochemical model [9], the sensory system consists of receptor complexes, each of which takes either active or inactive state. Active receptors send a signal via mediator proteins and control the rotation of flagellar motors. The ratio of active receptors, termed receptor activity a_t, is subjected to a feedback regulation through receptor modification, which is characterised by methylation level m_t. The receptor activity a_t is determined by the free energy difference f_t between active and inactive states:

$$a_t = \frac{1}{1+\exp(f_t)}. \tag{1}$$

The free energy difference f_t comprises additive effects of the methylation level m_t and of the ligand concentration $[L]_t$ as

$$f_t = N(-\alpha m_t + \log[L]_t + C), \tag{2}$$

where $N, \alpha > 0$, and C are biochemical constants. Equations (1) and (2) take the form of the Monod-Wyman-Changeux (MWC) model describing allostery [15] where N specifies the receptor cooperativity producing high sensitivity [4, 6, 7]. The methylation level m_t is modulated by the receptor activity a_t as

$$\frac{\mathrm{d}m_t}{\mathrm{d}t} = F(a_t), \tag{3}$$

where F is assumed to be a monotonically decreasing function. Since $\mathrm{d}a_t/\mathrm{d}m_t > 0$ and $F'(a_t) < 0$, the dynamics of the methylation level m_t with the function F constitutes a negative feedback regulation over the receptor activity a_t. Due to the negative feedback, this biochemical network displays the sensory adaptation [8], that is, when the concentration $[L]_t$ is stationary, the receptor activity converges to a single value $\bar{a}$ such that $F(\bar{a}) = 0$ which is independent of the stationary ligand concentration.

Although the biochemical model captures integral parts of the sensory system and its behaviors, there is room for discussion from the view point of noise tolerance. Because the sensory system relies on stochastic ligand-receptor interactions and receptor modifications, the sensing signal inevitably contains noise. This noise would cause a fatal influence on the chemotactic performance because it can bury the actual temporal changes

* Also at Institute of Industrial Science, the University of Tokyo; tetsuya@mail.crmind.net

in ligand concentration and could end up with misdirections of the motor control. Therefore, the sensory system of *E. coli* is expected to have a certain noise filtering property, and several works have investigated impacts of noise in information transmission and favorable traits for noise filtering [16]. However, these works focused on linear responses by ignoring the underlying biochemical network and resultant nonlinear properties of the *E. coli* sensory system. Even though some others considered a possible biochemical implementation of an ideal noise-immune system based on nonlinear filtering theory [17], the correspondence with actual biological systems, especially that of the gradient sensing in chemotaxis, is still elusive.

In this paper, we utilize nonlinear filtering theory to derive a noise-tolerant gradient sensing dynamics and consider its biochemical implementation in *E. coli* 's cell. In particular, we find that the derived optimal noise-filtering system excellently coincides with the biochemical model of the *E. coli* sensory system [9] and reproduces a nonlinear response relation measured experimentally.

As a minimal setting of the temporal gradient sensing, we consider a run-tumble motion of *E. coli* on one dimensional axis along with a monotonically increasing ligand concentration. The gradient sensing in this setting becomes the problem of determining whether the cell is swimming up or down the gradient. This assumption is mainly due to the limited capacity of the cell that may not be able to recognize the three dimensional physical space. Let $\xi_t \in \mathbb{R}$ and $X_t \in \{-1, +1\}$ be the location of the cell and the direction of swimming along the axis at time $t \in [0, \infty)$. We assume that an *E. coli* cell runs ballistically with a constant speed $v > 0$ as $\mathrm{d}\xi_t/\mathrm{d}t = vX_t$ and that each run and its direction is interrupted by a stochastic tumbling motion. By approximating the tumbling motion as an instantaneous event[18], we model the random changes in direction X_t due to tumbling with a continuous-time Markov chain:

$$\frac{\mathrm{d}\boldsymbol{p}_t}{\mathrm{d}t} = \begin{pmatrix} -r & r \\ r & -r \end{pmatrix} \boldsymbol{p}_t, \tag{4}$$

where $\boldsymbol{p}_t = (\mathbb{P}(X_t = +1), \mathbb{P}(X_t = -1))^{\mathbb{T}}$, r is the time-independent transition rate between $X_t = \pm 1$, and the initial condition is set as $\pi := \mathbb{P}(X_0 = -1)$. Note that the transition rate of direction X_t would be smaller than the rate of tumbling event because each tumbling does not always lead to the flipping of the direction.

Next, we assume that the ligand concentration depends exponentially on the location as $[L]_t \propto \exp(c\xi_t)$ where $c > 0$ is a constant. This assumption is natural because the spatial distribution of a ligand typically obeys diffusion. Then, we set an observation process, Y_t, that defines the sensing information which can be obtained by the *E. coli* 's system about concentration, $[L]_t$, at each time t. By adding a noise term to the ligand-dependent term in Eq. (2), we set

$$Y_t := -\log[L]_t - \sqrt{\sigma} W_t \tag{5}$$

where W_t is the standard Wiener process and σ is the intensity of noise. It should be noted that W_t can also be interpreted approximately as the noise from methylation [19] because the methylation level m_t additively appears in Eq. (2). See supplementary material (SM) for other possible ways of modeling ligand profile and noise property and their consequences, which includes Refs. [20].

By applying the nonlinear filtering theory under the above settings and assumptions [21], we can derive the optimal way to infer X_t in the form of the following stochastic differential equation:

$$\frac{\mathrm{d}Z_t}{\mathrm{d}t} = -R(Z_t - 1/2) + KZ_t(1 - Z_t) \circ \frac{\mathrm{d}Y_t}{\mathrm{d}t}, \tag{6}$$

where $\circ$ is the Stratonovich integral and the initial condition is $Z_0 = \pi$ (See SM for details of derivation). This equation describes the dynamics of posterior probability $Z_t = \mathbb{P}(X_t = -1 \mid Y_{0:t})$ of the descending direction given the time series of the noisy sensing $Y_{0:t} := \{Y_{t'} | t' \in [0, t]\}$ when its parameter values match those of tumbling, run, gradient, and noise as $R = R_{\mathrm{OPT}} := 2r$, $K = K_{\mathrm{OPT}} := 2vc/\sigma$. The estimate for the current direction considered here rather than future one is appropriate because *E. coli* continuously modulates run and tumble that should depend on whether it is currently swimming up or down the gradient.

Under this set of the optimal parameter values, the first term represents a model-based prediction, which works as active forgetting because the current belief should becomes non-informative gradually due to the stochastic change in direction X_t (Eq. (4)). Thereby, without the second term (sensing signal), Z_t converges to the stationary probability of the direction, $1/2$, as $t \to \infty$. The second term corresponds to the update of the posterior by new observation (Eq. (5)). Its form and coefficient are determined depending on the settings of Y_t (see SM for detail). The optimal gain of this term, K_{OPT}, describes the signal-to-noise ratio (SNR) because σ and $2vc$ specify the noise intensity and the steepness of the temporal change in the ligand concentration during a run, respectively. When SNR is high, using sensing signal with large K is beneficial, whereas when SNR is low, bet-hedging according to the model prediction, $Z_t \approx 1/2$, with small K becomes beneficial. We call the dynamics of Z_t described by Eq. (6) the filtering dynamics hereafter.

Next, we reveal the relation between the filtering dynamics and the biochemical network of *E. coli* chemotaxis by demonstrating that Eq. (6) can be equivalent to Eqs. (1),(2), and (3) if noise is neglected.

To this end, we introduce a coordinate transformation from the posterior probability Z_t to the log-posterior ratio $\theta_t := \log(1 - Z_t)/Z_t$. From the chain rule for derivatives, $\mathrm{d}\theta_t/\mathrm{d}t = (\mathrm{d}\theta_t/\mathrm{d}Z_t)(\mathrm{d}Z_t/\mathrm{d}t)$, we obtain the following equivalent representation of the filtering dynamics:

$$\frac{\mathrm{d}\theta_t}{\mathrm{d}t} = R\frac{Z_t - 1/2}{Z_t(1 - Z_t)} - K \circ \frac{\mathrm{d}Y_t}{\mathrm{d}t}. \tag{7}$$

By defining a new variable μ_t for the prediction dynamics as

$$\frac{\mathrm{d}\mu_t}{\mathrm{d}t} := -\frac{R}{\kappa}\frac{Z_t - 1/2}{Z_t(1-Z_t)}, \tag{8}$$

then we can formally integrate Eq. (7) as

$$\theta_t = -\kappa\mu_t + K\left[\log[L]_t + \sqrt{\sigma}W_t\right] + \phi. \tag{9}$$

where we use Eq. (5), $\phi := \log\{(1-\pi)/\pi\} - K\log[L]_0 + \kappa\mu_0$ is a constant of integration, and $\kappa > 0$ is an arbitrary constant. Finally, Z_t in Eq. (8) can be obtained by the inverse transformation from θ_t to Z_t:

$$Z_t = \frac{1}{1+\exp(\theta_t)}. \tag{10}$$

These transformations unveil that Eqs. (10),(9), and (8) for the filtering dynamics are equivalent to Eqs. (1),(2), and (3) for the biochemical model of *E. coli* chemotaxis, respectively (see also table S1 in SM for comparison). Without violating this correspondence, a degree of freedom can be introduced by a constant shift of θ_t as $\tilde{\theta}_t := \theta_t + \bar{\theta}$ where $\bar{\theta} \in \mathbb{R}$ is the constant. We obtain the following:

$$\begin{aligned}
\tilde{Z}_t :=& \frac{1}{1+\exp(\tilde{\theta}_t)}, \\
\tilde{\theta}_t =& \bar{\theta} - \kappa\mu_t + K(\log[L]_t + \sqrt{\sigma}W_t) + \phi, \\
\frac{\mathrm{d}\mu_t}{\mathrm{d}t} =& -\frac{R}{\kappa}\left\{\frac{\tilde{Z}_t - 1/2}{\tilde{Z}_t(1-\tilde{Z}_t)}\mathrm{e}^{-\bar{\theta}} + \frac{\tilde{Z}_t}{1-\tilde{Z}_t}\sinh(\bar{\theta})\right\},
\end{aligned} \tag{11}$$

(see SM about the class of transformations of θ with which the correspondence is preserved). Note that there is a one-to-one correspondence between a skewed posterior probability $\tilde{Z}_t$ and Z_t. Then, $\tilde{Z}_t$ corresponds to the receptor activity a_t, and they are described by the sigmoidal function of $\tilde{\theta}_t$ and f_t, respectively. The translated log-posterior ratio $\tilde{\theta}_t$ is determined by the logarithm of the ligand concentration $[L]_t$ and the prediction term μ_t, which corresponds to the dependence of the free energy difference f_t on the ligand concentration $[L]_t$ and the methylation level m_t in Eq. (2). Finally, the dynamics of prediction term μ_t corresponds to that of the methylation level m_t. Note that such a detailed correspondence with the biophysical quantities have not been derived in previous works based on the filtering theory [16, 22] where *E. coli* was assumed to estimate a continuous variable such as the direction of gradient, the ligand concentration, or its temporal change rather than the binary variable X_t in our work. This fact may suggest that the *E. coli* 's system is adapted to sensing the binary or discrete information rather than a continuous one.

Because the right-hand-side of Eq. (11) is a decreasing function of $\tilde{Z}_t$ in the same way as the feedback function $F(a_t)$ of m_t, μ_t works as a negative feedback component to $\tilde{Z}_t$. Even though $F(a_t)$ in the biochemical model cannot be determined theoretically but inferred only experimentally, the filtering dynamics provide a concrete functional form of the feedback function, $F_{\mathrm{OPT}}(\tilde{Z}) := -(R/\kappa)\{(\tilde{Z}_t - 1/2)/\{\tilde{Z}_t(1-\tilde{Z}_t)\}\mathrm{e}^{-\bar{\theta}} + \tilde{Z}_t/(1-\tilde{Z}_t)\sinh(\bar{\theta})\}$. Thus, if *E. coli* has developed the sensory system being tolerant to sensing noise near optimally, the feedback function F describing the methylation dynamics can have a similar form as F_{OPT}. To test this expectation, we compare the feedback function F_{EXP} inferred experimentally by a FRET measurement [23] with the theoretically predicted F_{OPT} by adjusting two free parameters R/κ and $\bar{\theta}$. Figure 1 shows a notable agreement between the experimental data and theoretical prediction. Both F_{EXP} and F_{OPT} share a characteristic nonlinearity; a gentle slope around $a = 0.5$ and a sharp decline near $a = 1$. From the view point of biochemical mechanism, the nonlinearity of F_{EXP} cannot be reproduced by simple linear or Michaelis-Menten models [8, 11] but by additionally assuming a nonlinear regulation possibly due to phosphorylation of the demethylation enzyme, CheB [23]. This result implies that the nonlinear *E. coli* chemotactic network is designed structurally to be robust to the sensory noise.

We further investigate whether the biochemical parameters observed experimentally in laboratory environments can satisfy the optimality in terms of filtering.

From the fitting of F_{OPT} to F_{EXP}, we have $R/\kappa \approx 2.2 \times 10^{-3}$. κ can be estimated as $\kappa = \alpha N \approx 12$ by comparing Eq. (2) and Eq. (9) and by employing a previous estimate of α and N [23]. Thus, R is calculated as $R \approx 2.6 \times 10^{-2}$. In contrast, the optimal R_{OPT} can be estimated as $10^{-0.5} \leq R_{\mathrm{OPT}} \leq 10^{0} s^{-1}$ by using $R_{\mathrm{OPT}} = 2r$ and measurements of tumbling rate [2, 24]. Thus, the obtained biochemical parameter R looks much smaller than the estimate R_{OPT} from tumbling measurements.

This discrepancy may be attributed to three possibilities: First, experimental conditions for the measurements of tumbling rate might not capture a wild condition where *E. coli* cells are supposed to perform chemotaxis. Recent studies suggest that swimming behaviors in polymeric solutions or soft agar are different from that under a liquid condition used in most experiments [25]. In particular, the tumbling frequency is shown to decrease with addition of polymeric molecules due to remodeling of signaling pathway downstream of sensory system or possibly due to motor load. In such a case, R_{OPT} may take smaller value. Second, the values of R might be underestimated because of the difficulty in estimating the biochemical parameter N. Although we used an estimate $N = 6$ in previous studies [7, 9, 23], other estimates of N are larger, $N = 15 \sim 20$ [7, 26]. Actually, R can be estimated in another way without using an estimate of N, and recent measurements estimate higher values, $R = 0.079 \sim 0.11$ [27], which is only a several-fold difference from R_{OPT}. Moreover, the adaptation rate is shown to increase several-fold with 10 °C increase of temperature ([23, 28]).

The last possibility is that the system is not or can-

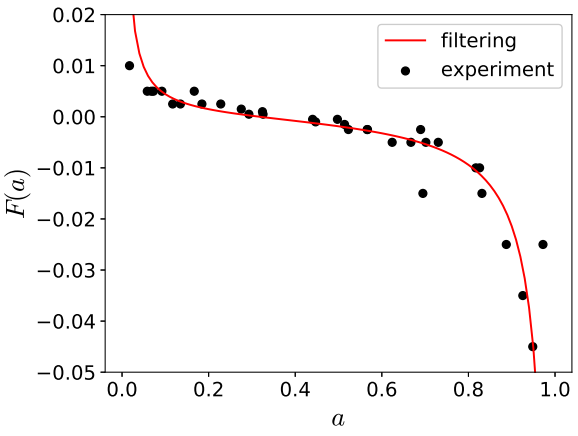

FIG. 1. Theoretically derived F_{OPT} (red curve) fitted to the experimentally obtained F_{EXP} (black points) [23]. F_{OPT} in the figure is obtained by modulating two parameters, R and $\bar{\theta}$, as $R/\kappa \approx 2.2 \times 10^{-3}$ and $1/\{1+\exp(\bar{\theta})\} \approx 0.32$ (see also SM for the fitting procedure).

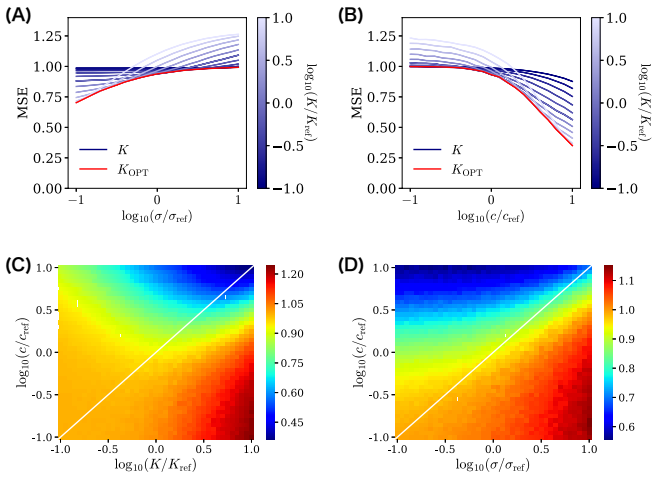

FIG. 2. MSEs of the filtering dynamics as a function of σ with fixed $c = c_{\mathrm{ref}}$ (A), as a function of c with fixed $\sigma = \sigma_{\mathrm{ref}}$ (B), as a function of K and c with fixed $\sigma = \sigma_{\mathrm{ref}}$ (C), and as a function of σ and c with fixed $K = K_{\mathrm{ref}}$ (D). Curves in (A) and (B) represent MSEs with fixed parameter $K = K_{\mathrm{ref}}$ (blue) and with the optimal parameter $K = K_{\mathrm{OPT}} = 2vc/\sigma$ (red). White lines in (C) and (D) represent the parameter region on which the parameter K is set optimal i.e. $2vc/\sigma_{\mathrm{ref}} = K$ (C) and $2vc/\sigma = K_{\mathrm{ref}}$ (D).

not be always optimized at the level of parameter values, though it is so at the level of network structure. Besides the discrepancy between R and R_{OPT}, such possibility should also be noted between N and K_{OPT}. By considering the correspondence of N with the gain K_{OPT}, which is determined by the speed of swimming, the steepness of gradient, and the intensity of sensing noise, optimal N should be variable depending on environmental conditions. Several studies suggested that N as well as other parameters are diversified in a population of cells for hedging environmental uncertainties [29].

To perform chemotaxis under the limitation in parameter adjustment, the robustness against the mismatch of parameters could be beneficial. We investigate whether such robustness is endowed or not by examining the filtering dynamics with misspecified parameter values of K. We measure the performance of the dynamics using mean square error (MSE) defined as $\left[\frac{1}{T}\int_{t=0}^{T}\{X_t-(1-2Z_t)\}^2\mathrm{d}t\right]^{1/2}$ in which $1-2Z_t = 1-2\mathbb{P}(X_t<0 \mid Y_{0:t}) = \mathbb{E}[X_t \mid Y_{0:t}]$ holds for the optimal parameter set. We define a reference value of K as $K_{\mathrm{ref}} := N = 6$ according to the correspondence between K and N. We set the swimming speed to a physiologically relevant value: $v = 20\mu\mathrm{m}\cdot\mathrm{s}^{-1}$. We define the rate of directional changes as $r = 0.1\mathrm{s}^{-1}$ and the reference of the steepness of gradient as $c_{\mathrm{ref}} := 10^{-3}\mu\mathrm{m}^{-1}$ by taking into account the conditions in previous simulation studies [11]. We set R to the optimal value, $R_{\mathrm{OPT}} = 2r = 0.2\mathrm{s}^{-1}$. As appropriate data are not available for estimating the intensity of noise, σ, we define the reference of σ as $\sigma_{\mathrm{ref}} := 2c_{\mathrm{ref}}v/K_{\mathrm{ref}}$ such that the reference parameter K_{ref} becomes optimal under $c = c_{\mathrm{ref}}$ and $\sigma = \sigma_{\mathrm{ref}}$ [30]. Note that K_{ref} is also optimal on the half-line, $(\sigma, c) = \eta(\sigma_{\mathrm{ref}}, c_{\mathrm{ref}}), \eta > 0$, because $2vc/\sigma = 2vc_{\mathrm{ref}}/\sigma_{\mathrm{ref}} = K_{\mathrm{ref}}$ holds on it.

Figure 2 shows MSEs of Eq. (6) for different K as functions of σ with fixed $c = c_{\mathrm{ref}}$ (A) and as functions of c with fixed $\sigma = \sigma_{\mathrm{ref}}$ (B). The error with fixed K is always greater than or equal to that with K adjusted to K_{OPT}. For each fixed gain K, MSE monotonously increases as SNR decreases either by the increase in the noise intensity σ (Fig. 2(A)) or by the decrease in the gradient steepness c (Fig. 2(B)), indicating that a greater SNR than the optimal one never impair the performance of the dynamics for any K. We can see a similar trend in Fig. 2 (C) and (D). These results indicate that even under the misspecification of K associated with parameters σ and c, the filtering dynamics still reliably and robustly estimate temporal gradient if a change in σ or c is one such that it increases SNR (See also SM for the robustness against the discrepancy between R and R_{OPT}).

The results of simulation also suggest how K can be chosen when the value of K_{OPT} is uncertain. With the small value of K, variation of MSE between low and high SNRs is small (Fig. 2). In contrast, large K shows a significant variation in MSE between low and high SNR cases. This means that low K can work moderately well for most of conditions whereas large K can work much better if the environmental SNR is large enough at the cost of lower performance under low SNR situations. Thus, when there is uncertainty about K_{OPT}, K also modulates the balance of risk-averting and -taking strategies of sensing.

The growth-dependent variability of K can coordinate such risks at the level of population [32]. Moreover, N, which biochemically corresponds to K, is suggested to

vary temporally at the single-cell-level [26, 33] via a receptor cluster rearrangement. The integration of biochemical modeling and optimal filtering theory may play a pivotal role in further analysis of such a gain adaptation and learning at both single-cell and population levels.

Besides deriving the desirable properties for filtering, our approach provides a prediction about what type of environments the *E. coli* 's sensory system may adapt to. In SM, we additionally show that the filtering dynamics optimized to an exponential profile can explain an experimental data of chemotactic trajectories better than that optimized to a linear gradient. This result may suggest that the *E. coli* 's biochemical system is adapted to the exponential gradient profile. Such prediction may be validated more definitely by comparing the behavior of the optimal filtering model with the swimming direction and the receptor activity measured simultaneously under different environmental conditions.

This approach may also be applied to other sensory systems; allosteric receptors with a negative feedback, e.g., G protein-coupled receptors for vision and EGF receptor in animal cells; spatial and temporal sensing by ameboid cells and worms. By considering the array of such sensory systems, we may be able to further validate the power of optimal filtering approach [22].

Finally, we should mention that our model has not yet incorporated the potential dependence of the directional dynamics $\mathrm{d}\boldsymbol{p}_t/\mathrm{d}t$ on sensing history $Y_{0:t}$ via the signal-dependent motor regulation. While the dependency can be ignored when the gradient is weak enough, it can affect the optimal behaviors, otherwise. Thus, a next crucial challenge is extending our approach so as to directly incorporate the closed cycle between sensing and control. Such extension might fill the remaining gaps between the current theory and experimental observations.

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