Signal Detection and Approximate Adaptation Implies an Approximate Internal Model

Burton W. Andrews and Pablo A. Iglesias
Electrical and Computer Engineering
The Johns Hopkins University
Baltimore, MD 21218
bwa@jhu.edu, pi@jhu.edu

Eduardo D. Sontag
Mathematics
Rutgers University
New Brunswick, NJ 08903
sontag@math.rutgers.edu

Abstract— The proper function of many biological systems requires that external perturbations be detected, allowing the system to adapt to these environmental changes. It is now well established that this dual detection and adaptation requires that the system have an internal model in the feedback loop. In this paper we relax the requirement that the response of the system adapt perfectly, but instead allow regulation to within a neighborhood of zero. We show that linear systems with the ability to detect input signals and approximately adapt require an approximate model of the input. We illustrate our results by analyzing two well-studied biological systems.

I. INTRODUCTION

Many problems in control can be framed as output regulation problems where the goal is to drive the output of a system to zero for a particular class of input signals. The internal model principle (IMP) states that such regulation can only be achieved if the system contains an "internal model" of the input being regulated. The IMP was originally derived for linear systems [5], and related regulation problems for nonlinear systems have been considered in [6]–[8], [11]. While output regulation is usually referred to in the context of engineering problems, it is crucial for the proper functioning of many biological organisms. Biological systems must be able to detect changes in their environment and adjust their internal states accordingly — a process commonly referred to as "homeostasis" or "adaptation." For example, successful chemotaxis (movement towards high concentrations of chemical attractant) of *E. coli* depends on the ability of the bacteria to adapt to step changes in chemoattractant [1], [3]. This adaptation property has been shown to require integral control, achieved in *E. coli* via receptor methylation, and hence the existence of an internal model of a step input [23]. Other examples in biology in which the role of feedback control systems is to achieve adaptation include blood calcium regulation [4], neuronal control of the prefrontal cortex [17], tryptophan regulation in *E. coli* [20], and the *Dictyostelium* chemotactic response to step changes in chemoattractant [22].

Some important distinctions between biological and engineering systems must be taken into account when studying biological systems in the context of regulation. Unlike typical regulation problems in engineering, where the goal may be to attenuate the effect of a disturbance as much as possible, in biological systems, sensing changes in the input signals may be equally important for achieving proper cell function [13]. This "signal detection" property has been characterized and used in conjunction with adaptation to show the IMP in linear and nonlinear systems [19]. Another important distinction of biological systems is that, in many cases, the study of biology is essentially an analysis problem rather than a design problem. Therefore, while an engineer should aim to design a control system with no less than perfect regulation, such a concept may not necessarily be relevant in analyzing biological systems, where the system only adapts partially [13], [14]. Although biological systems may be modeled with simplifying assumptions that lead to perfect adaptation, relaxation of these assumptions may yield an output that only adapts to within some tolerable range of the desired value.

In light of the above discussion, this paper investigates the properties of a linear system that adapts approximately, rather than perfectly, to a given class of input. We first provide a formal definition of signal detection and then extend the IMP and the work in [19] to show that a system with signal detection and approximate adaptation must contain an "approximate" model of the input. We then illustrate our findings by considering two different models of perfectly-adapting systems in biology that only approximately adapt when key assumptions are relaxed: a model of the chemoattractant-induced response of *Dictyostelium* [22], and a general receptor modification system such as the one found in *E. coli* [2], [9].

II. THEORY

We first describe a "signal detection" property, and then discuss approximate adaptation and its internal model implications.

A. Signal Detection

To define signal detection, we first recall the following notations:
1) The function $f(x) = O(g(x))$ as $x \to x_0$ if there exists a $C > 0$ such that $|f(x)| \le C|g(x)|$ as $x \to x_0$.
2) The function $f(x) = o(g(x))$ as $x \to x_0$ if $\forall \epsilon > 0$, $|f(x)| \le \epsilon|g(x)|$, as $x \to x_0$.

3) The function $f(x) = \Omega(g(x))$ as $x \to x_0$ if $\exists C > 0$ such that $|f(x)| \geq C|g(x)|$ as $x \to x_0$.

Definition 1. A system has the ability to "detect" an input signal $u(t)$ if

$$y^{(n)}(t) = \Omega(u(t))$$

as $t \to 0$, where $y^{(n)}(t)$ is the nth derivative of the output $y(t)$ of the system and n is the relative degree of the system. The relative degree of a system is defined as the number of times the output of the system must be differentiated to be dependent on the input (for a more precise definition of relative degree, see [10]). For linear systems, the relative degree equals the difference between the degree of the denominator and numerator polynomials of the transfer function. We assume here that the input is applied at time zero.

The signal detection property implies that the system's initial response to an input, determined by its nth derivative, is of the same order of magnitude of the input; the system "detects" the input. Note that, for linear systems, this property is trivially satisfied by a nonzero transfer function.

B. Approximate Adaptation and Signal Detection Imply an Approximate Internal Model

In this section, we define approximate adaption for a class of systems and then show that an approximately adapting system with signal detection must contain an approximate model of the input in an appropriate sense.

Definition 2. An ϵ-parameterized system, denoted Σ_ϵ, with input $u(t)$ and output $y(t)$ is one that takes the form

$$\dot{x} = f(x, u, \epsilon)$$
$$y = h(x, \epsilon)$$

with initial condition $x(0) = x_0$.

This definition simply describes a general class of linear or nonlinear systems while highlighting a particular parameter of interest (note that ϵ may be a vector). We now restrict our attention to linear systems and the requirements for approximate adaptation of a linear system.

Definition 3. The ϵ-parameterized system Σ_ϵ adapts approximately to a class of inputs $\mathcal{U}$, where each $u(t) \in \mathcal{U}$ is generated by an exosystem Γ consisting of

$$\dot{x_u} = Ax_u, \quad u = cx_u, \quad \|x_{u0}\| \leq 1, \quad \mathrm{Re}\lambda_i[A] \geq 0, \quad \forall i$$

where u is scalar, if there exists a function $K(\epsilon) = O(\epsilon)$ (as $\epsilon \to 0$) such that for all $u(t) \in \mathcal{U}$, $\limsup_{t\to\infty} |y(t)| \leq K(\epsilon)$.

Assume an ϵ-parameterized system Σ_ϵ has transfer function $Y(s)/U(s) = S_\epsilon(s) = p(s)/q(s)$ where p and q are polynomials and the degree of p is less than or equal to the degree of q. The roots of q are assumed to have strictly negative real parts. Our goal is to achieve $|y(t)| \leq K(\epsilon)$ as $t \to \infty$ for all possible initial conditions of Γ

(Fig. 1). Denote the Laplace transform of the input as $U(s) = \theta(s)/\pi(s)$ where $\theta(s) = c(\mathrm{adj}(sI - A))x_{u0}$ and $\pi(s) = \det(sI - A)$. Then $US_\epsilon = (p(s)\theta(s))/(q(s)\pi(s))$.
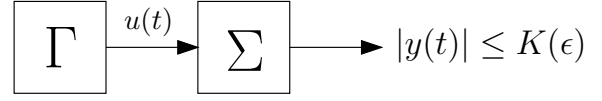

Fig. 1.   Exosystem and system

First, denote $\pi = \pi_+\pi_0$ where the roots of π_+ have strictly positive real parts, and the roots of π_0 have zero real parts. Furthermore, denote

$$\pi_0 = s^{\ell_0} \prod_{i=1}^{r}(s^2 + \omega_i^2)^{\ell_i},$$

so that there are ℓ_0 zero roots of π and r pairs of nonzero imaginary axis roots at $s = \pm j\omega_i$, $i = \{1, 2, \ldots, r\}$, each repeated ℓ_i times. We now have

$$U(s)S_\epsilon(s) = \frac{p(s)\theta(s)}{\pi_+ s^{\ell_0} \prod_{i=1}^{r}(s^2 + \omega_i^2)^{\ell_i} q(s)}. \quad (1)$$

For approximate adaptation, the output must at least be bounded. Thus, p must contain the unstable roots π_+ of π. In addition, repeated imaginary axis roots in the denominator of (1) cause unbounded outputs; therefore, p must cancel enough of these roots so that, at most, single copies of the imaginary axis roots exist. Thus, we denote $p = \pi_+\hat{\pi}_0 p_1$, where

$$\hat{\pi}_0 = s^{k_0} \prod_{i=1}^{r}(s^2 + \omega_i^2)^{k_i}$$

and $k_i \geq \ell_i - 1$, $i = \{0, \ldots, r\}$, is the total number of pairs of imaginary axis roots of $p(s)$ that correspond to imaginary axis roots of $\pi(s)$. This yields

$$U(s)S_\epsilon(s) = \frac{p_1(s)\theta(s)}{s^{\ell_0 - k_0} \prod_{i=1}^{r}(s^2 + \omega_i^2)^{\ell_i - k_i} q(s)}. \quad (2)$$

If $k_i \geq \ell_i$ for all $i \geq 0$, the FVT applies and we have perfect adaptation. If $\ell_i - k_i = 1$ for some i, then

$$U(s)S_\epsilon(s) = \frac{p_1(s)\theta(s) \prod_{i:k_i \geq \ell_i}(s^2 + \omega_i^2)^{k_i - \ell_i}}{s \prod_{i:\ell_i - k_i = 1}(s^2 + \omega_i^2) q(s)},$$

where we have assumed without loss of generality that $\ell_0 - k_0 = 1$ (otherwise B simply equals 0 in (3) below) and it is understood that the products are over indices corresponding to nonzero imaginary axis roots. By partial fraction expansion,

$$U(s)S_\epsilon(s) = \sum_{i:\ell_i - k_i = 1}\left\{\frac{A_i}{s - j\omega_i} + \frac{A_i^*}{s + j\omega_i}\right\} + \frac{B}{s} + \frac{C}{q(s)}, \quad (3)$$

where

$$A_i = \frac{\prod_{n:k_n \geq \ell_n}(-\omega_i^2 + \omega_n^2)^{k_n - \ell_n} p_1(j\omega_i)\theta(j\omega_i)}{(j\omega_i)^{\ell_0 - k_0}(2j\omega_i) \prod_{n:\ell_n - k_n = 1, n \neq i}(-\omega_i^2 + \omega_n^2)q(j\omega_i)}$$

and

$$B = \frac{\prod_{i:k_i \geq \ell_i}(\omega_i^2)^{k_i-\ell_i} p_1(0)\theta(0)}{\prod_{i:\ell_i-k_i=1}(\omega_i^2)q(0)}.$$

Because q is assumed to have stable roots, the contribution of $C/q(s)$ to the output eventually dies out. Thus,

$$y(t) \approx B + \sum_{i:\ell_i-k_i=1} 2\mathrm{Re}(A_i)\cos(\omega_i t) + 2\mathrm{Im}(A_i)\sin(\omega_i t)$$

as $t \to \infty$ and

$$|y(t)| \leq |B| + 2\sum_{i:\ell_i-k_i=1} |\mathrm{Re}(A_i)| + |\mathrm{Im}(A_i)|$$

$$\leq |B| + 4\sum_{i:\ell_i-k_i=1} |A_i|.$$

Note that $|A_i|$ and $|B|$ scale linearly with θ and hence with $\|x_{u0}\| \leq 1$. Defining $K_0(p_1(0)) := \sup_{\|x_{u0}\|\leq 1} |B|$ where $\omega_0 = 0$, and $K_i(p_1(j\omega_i)) := 4\sup_{\|x_{u0}\|\leq 1} |A_i|$ for $i \neq 0$, we have

$$|y(t)| \leq \sum_{i:\ell_i-k_i=1} K_i(p_1(j\omega_i))$$

for all admissible initial conditions of Γ. Although not explicitly stated, $p_1(j\omega_i)$ is a function of ϵ. Thus, if $p_1(j\omega_i) = O(\epsilon)$, for all i, then defining $K(\epsilon) := \sum K_i(p_1(j\omega_i))$, implies that $|y(t)| \leq K(\epsilon) = O(\epsilon)$ and therefore the system adapts approximately. Thus, we have proved the following lemma.

Lemma 1. *A linear ϵ-parameterized system adapts approximately to inputs in class $\mathcal{U}$ if (i) the poles of inputs in class $\mathcal{U}$ with strictly positive real parts are contained as zeros of the system, (ii) all but at most one copy of each imaginary-axis pole of the input is cancelled by the system, and (iii) $p_1(j\omega_i) = O(\epsilon)$ as $\epsilon \to 0$ for all imaginary axis poles $j\omega_i$ of the input that are not fully cancelled by zeros of the system.*

The first two conditions guarantee boundedness of the output, and the third condition guarantees that the output satisfies the requirement for approximate adaptation. Also note that if (i) holds and all imaginary-axis poles of the input are contained as zeros of the system, then the system adapts perfectly.

Definition 4. An ϵ-parameterized system Σ_ϵ is said to have an "approximate" internal model of $\mathcal{U}$, where $\|u_0\| \leq 1$ for all $u \in \mathcal{U}$, if it can be decomposed into the system shown in Fig. 2, and $\lim_{\epsilon\to 0}\Sigma_{IM,\epsilon} =: \Sigma_{IM}$ can generate all inputs $u(t) \in \mathcal{U}$ when $y(t) = 0$.

Theorem 1. *A linear ϵ-parameterized system that is able to detect and adapt approximately to inputs in class $\mathcal{U}$ contains an approximate model of $\mathcal{U}$.*

Proof. Assume the linear system Σ_ϵ adapts approximately to input class $\mathcal{U}$, where ϵ will be defined below. By Lemma 1 and by writing $q/p = a + b/p$ as in [19], we can decompose Σ_ϵ into the feedback loop of Fig. 3. Though π is written
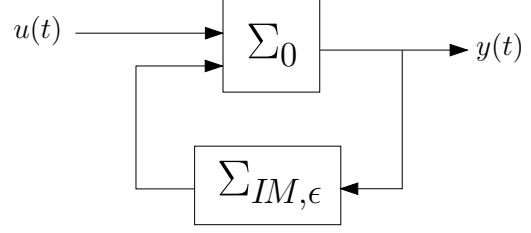

Fig. 2. Internal model decomposition of Σ_ϵ

explicitly in the denominator of the system in the feedback loop, an exact model of the input does not exist due to the cancellation of some roots of π by the roots of the numerator corresponding to the indices $i \geq 0$ for which $\ell_i - k_i = 1$. However, as $p_1(j\omega_i) \to 0$ for these i, $j\omega_i$ become roots of $p_1(s)$ and cancel the numerator roots in the limit. When this happens, the roots of π are no longer cancelled, and the system contains a model of all inputs $u(t) \in \mathcal{U}$. Thus, by taking $\epsilon := p_1(j\boldsymbol{\omega})$ and

$$\Sigma_{IM,\epsilon} := \frac{b\prod_{i:\ell_i-k_i=1}(s^2+\omega_i^2)s^{\ell_0-k_0}}{\pi p_1 \prod_{i:k_i\geq\ell_i}(s^2+\omega_i^2)^{k_i-\ell_i}}, \quad \text{and}$$

$$\Sigma_{IM} := \frac{b}{\pi p_2 \prod_{i:k_i\geq\ell_i}(s^2+\omega_i^2)^{k_i-\ell_i}s^{k_0-\ell_0}},$$

where

$$p_2 = \frac{p_1}{\prod_{i:\ell_i-k_i=1}(s^2+\omega_i^2)},$$

we have $\lim_{\epsilon\to 0}\Sigma_{IM,\epsilon} = \Sigma_{IM}$ with Σ_{IM} being capable of generating all inputs in $\mathcal{U}$. $\square$
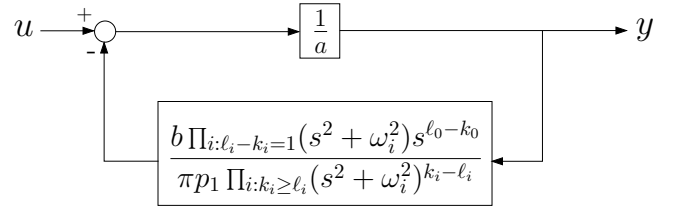

Fig. 3. Internal model decomposition of a linear, approximately adapting system.

C. Example: Step-input ϵ-adaptation

For a single step input, $U(s) = 1/s$, so $\ell_0 = 1$ and $\pi_0(s) = 1$. Let us first consider perfect adaptation which requires $k_0 \geq 1$ by Lemma 1. Assume for this example that $q(s) = s + \alpha$, where $\alpha > 0$ is constant. Because the degree of p must be less than or equal to the degree of q and $k_0 \geq 1$, we must have $k_0 = \ell_0 = 1$ and $p_1(s)$ must be a constant β yielding $p(s) = \beta s$. Thus

$$S(s) = \beta s/(s+\alpha). \tag{4}$$

In terms of Figure 2, $\Sigma_0 = \beta$ and $\Sigma_{IM} = \alpha/(\beta s)$ which is capable of generating step inputs. An example response is shown in Figure 4A.
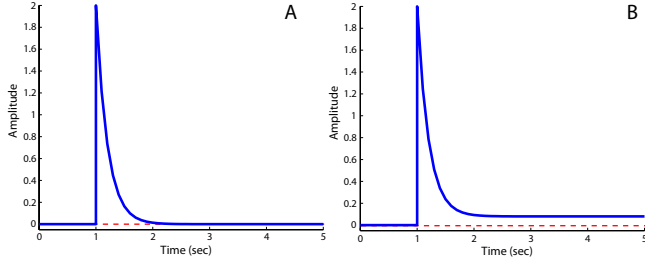
Fig. 4. Adaptation examples for a step input with $\beta = 2$ and $\alpha = 5$. Panel A shows the perfect adaptation case when $\epsilon = 0$, and panel B shows approximate adaptation with $p_1(0) = 0.25$. The dashed line indicates the pre-stimulus steady-state level.

For approximate adaptation, we need $k_0 = \ell_0 - 1$, so k_0 must be zero and $p(s) = p_1(s)$. Because the degree of p must be less than or equal to the degree of q, we have $p(s) = \beta s + p_1(0)$, where β is a constant. Thus,

$$S(s) = \frac{\beta s + p_1(0)}{s + \alpha}. \tag{5}$$

For the feedback decomposition of Figure 2, $\epsilon = p_1(0)$ so that condition (iii) of Lemma 1 is satisfied, $\Sigma_0 = \beta$,

$$\Sigma_{IM,\epsilon} = \frac{(1/\beta)(\alpha - p_1(0)/\beta)}{s + p_1(0)/\beta},$$

and $\Sigma_{IM} = \alpha/(\beta s)$. An example response is shown in Figure 4B.

III. BIOLOGICAL EXAMPLES

A. Excitation-Inhibition Model

In *Dictyostelium* cells, the activation of key signaling molecules involved in chemoattractant sensing can be modeled by the system shown in Figure 5 [15], [16], [22]. This system is described by the following set of differential equations:

$$\frac{dE}{dt} = -k_{-e}E + k_e(E_T - E)C$$
$$\frac{dI}{dt} = -k_{-i}I + k_i(I_T - I)C$$
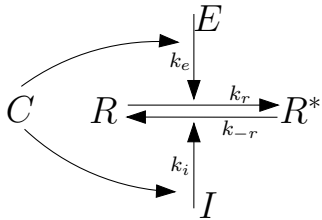$$\frac{dR^*}{dt} = -k_{-r}R^*I + k_r(R_T - R^*)E$$

Fig. 5. Model of the activation of a response regulator R via chemoattractant-driven excitation and inhibition enzymes as found in the chemotactic system of *Dictyostelium* [16], [22].

If we assume $C \ll k_{-e}/k_e$, $C \ll k_{-i}/k_i$, and $R_T \gg R$,

then the system simplifies to

$$\dot{E} = -k_{-e}E + k_eC$$
$$\dot{I} = -k_{-i}I + k_iC$$
$$\dot{R}^* = -k_{-r}IR^* + k_r R_T E,$$

where E_T and I_T have been incorporated into the constants k_e and k_i. After a change of variables [22], we have

$$\dot{e} = -e + c$$
$$\dot{i} = -\alpha i + \alpha c$$
$$\dot{r} = -\beta ir + e$$

where α and β are constants. We define Σ to be the linearization of this system about the steady-state values $e_0 = i_0 = c_0$ and $r_0 = 1/\beta$, where the ϵ subscript on Σ is dropped to emphasize that Σ is perfectly adapting, as will be seen below. The transfer function from c to r is

$$S(s) = (1 - \alpha)\frac{s}{(s + \alpha)(s + 1)(s + \gamma)},$$

where $\gamma = c_0\beta$. The system has the signal detection property provided that $\alpha \neq 1$. Also, Σ can be described in terms of the feedback of Fig. 2 with

$$\Sigma_0 = \frac{1 - \alpha}{s^2 + (1 + \alpha + \gamma)s + (\alpha + \gamma + \alpha\gamma)} \quad \text{and}$$
$$\Sigma_{IM} = \frac{\alpha\gamma}{(1 - \alpha)s}.$$

Considering $\mathcal{U}$ to be the class of step inputs, Σ adapts perfectly to $\mathcal{U}$ due to the differentiator in the numerator of $S(s)$, and an internal model of $\mathcal{U}$ is evident from the integrator in Σ_{IM}.

Now, we relax the initial assumptions on the excitation and inhibition rates to $Ck_e/k_{-e} = C\epsilon_1$ and $Ck_i/k_{-i} = C\epsilon_2$. Following the same analysis as above, the system after the change of variables becomes

$$\dot{e} = -e + c - \epsilon_1 \rho ec \tag{6}$$
$$\dot{i} = -\alpha i + \alpha c - \epsilon_2 \rho \alpha ic \tag{7}$$
$$\dot{r} = -\beta ir + e \tag{8}$$

where $\rho = k_{-e}^2/(k_e k_r)$. Denote the linearization of this system about a chemoattractant concentration $c = c_0$ and the corresponding steady-state values of e, i, and r by Σ_ϵ (we use the subscript ϵ to indicate dependence on both parameters ϵ_1 and ϵ_2). The transfer function from c to r is

$$S_\epsilon(s) = \frac{s\left(\frac{1 - \alpha}{1 + \epsilon_1 \rho c_0}\right) + \alpha\rho c_0(\epsilon_2 - \epsilon_1)}{(s + 1 + \epsilon_1 \rho c_0)(s + \alpha(1 + \epsilon_2 \rho c_0))(s + \gamma)}$$

The system Σ_ϵ has the signal detection property, and application of the FVT reveals that Σ_ϵ only adapts approximately to step inputs. Decomposition into the feedback loop of

Figure 2 results in

$$\Sigma_0 = \frac{\left(\frac{1-\alpha}{1+o(1)}\right)}{s^2 + (1+\alpha+\gamma+o(1))s + (\alpha+\gamma+\alpha\gamma+o(1))}$$

and

$$\Sigma_{IM,\epsilon} = \frac{\alpha\gamma + o(1)}{\left(\frac{1-\alpha}{1+o(1)}\right)s + o(1)}$$

where the $o(1)$ terms are as $\epsilon_1, \epsilon_2 \to 0$. Because $\lim_{\epsilon_1,\epsilon_2 \to 0} \Sigma_{IM,\epsilon} = \Sigma_{IM}$ where Σ_{IM} can generate all inputs in $\mathcal{U}$ (defined as the class of step inputs), Σ_ϵ contains an approximate model of $\mathcal{U}$. We can say that Σ_ϵ "almost" has an integrator.

The response of the excitation-inhibition system to a step input in C is shown in Figure 6. Figure 6A is under the original assumptions, and Figure 6B is under the relaxed assumptions. When the assumptions are relaxed, the system only adapts approximately.
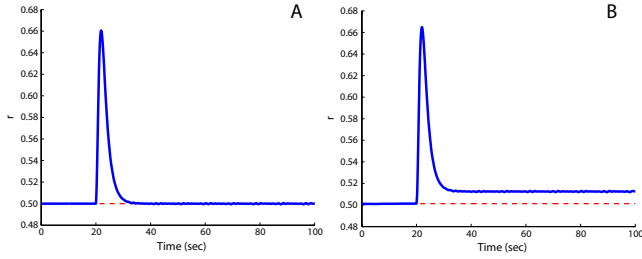

Fig. 6. Step response of the excitation-inhibition system under the original assumptions of [22] (panel A) and after relaxing these assumptions (panel B). The dashed line indicates the pre-stimulus steady-state level of r. Parameters used are $\alpha = 0.5$, $\beta = 2$, $\rho\epsilon_1 = 0$, $\rho\epsilon_2 = 0.025$, and a step from $c = 0.1$ to $c = 1$.

B. Adaptation by Receptor Modification

A general model of adaptation via the modification of receptors, such as that found in the signal transduction pathway of *E. coli*, is shown in Figure 7 [2], [9]. Typically,
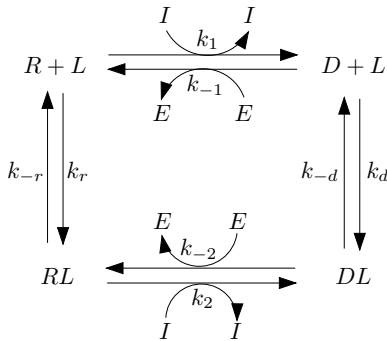

Fig. 7. General model of adaptation via receptor modification taken from [9]. Both the modified and unmodified form of the receptor can bind ligand. Such a scheme is found in the signal transduction pathway of *E. coli*.

the excitation reaction is assumed to operate at saturation

($k_{M_E} \ll D$ and $k_{M_E} \ll DL$). For example, the component of dR/dt due to the excitation enzyme is

$$\frac{k_{-1}E_T D}{k_{M_E} + D} = k_{-1}E_T \left(\frac{1}{k_{M_E}/D + 1}\right)$$
$$= k_{-1}E_T(1 - \frac{K_{M_E}}{D} + o\left(\frac{K_{M_E}}{D}\right)^2).$$

Under saturation, $K_{M_E}/D \approx 0$, and the right-hand side becomes $k_{-1}E_T$. However, if we relax this assumption by linearizing K_{M_E}/D about $D = D_0$ large, we obtain $K_{M_E}/D \approx -D\epsilon$, where $\epsilon = k_{M_E}/D_0^2$. Note that this approximation retains the dependence on D. Similar calculations for the reactions involving DL results in the system defined by the following set of differential equations:

$$\frac{dR}{dt} = k_{-1}E_T(1 + D\epsilon) - k_1 I_T \cdot \alpha_1 R - k_r R \cdot L + k_{-r}RL$$
$$\frac{dRL}{dt} = k_{-2}E_T(1 + DL\epsilon) - k_2 I_T \cdot \alpha_2 RL + k_r R \cdot L - k_{-r}RL$$
$$\frac{dD}{dt} = -k_{-1}E_T(1 + D\epsilon) + k_1 I_T \cdot \alpha_1 R - k_d D \cdot L + k_{-d}DL$$
$$\frac{dDL}{dt} = -k_{-2}E_T(1 + DL\epsilon) + k_2 I_T \cdot \alpha_2 RL + k_d D \cdot L - k_{-d}DL$$

Using the constraint $DL = R_T - R - RL - D$ and the change of variables $A = \alpha_1 R + \alpha_2 RT$ and $B = (R + RL)/(k_1 I_T)$ as in [9], the system becomes

$$\frac{dA}{dt} = -a_1(L)A + (a_0(L) - \epsilon\alpha_2 k_1 k_{-2}E_T I_T)B$$
$$+ \epsilon E_T(\alpha_1 k_{-1} - \alpha_2 k_{-2})D + b_1 A_0 + \epsilon\alpha_2 k_{-2}E_T R_T$$
$$\frac{dB}{dt} = -A - \epsilon k_{-2}E_T B + \epsilon E_T(k_{-1} - k_{-2})D$$
$$+ A_0 + \epsilon k_{-2}R_T E_T/(k_1 I_T)$$
$$\frac{dD}{dt} = a_2 A + a_3 B + (a_4(L) - \epsilon k_{-1}E_T)D + a_5$$

where A_0, $a_0(L)$, $a_1(L)$, and b_1 are defined in [9] and

$$a_2 = k_1 I_T \alpha_1/(\alpha_1 - \alpha_2)$$
$$a_3 = \frac{\alpha_1\alpha_2(k_1 I_T)^2}{\alpha_2 - \alpha_1} - k_{-d}k_1 I_T$$
$$a_4(L) = -k_d L - k_{-d}$$
$$a_5 = k_{-d}R_T - k_{-1}E_T.$$

Defining Σ_ϵ to be the linearization of this system about $L = L_0$ and steady-state concentrations of A, B, and D, the transfer function of Σ_ϵ is

$$S_\epsilon(s) = \frac{A(s)}{L(s)} = \frac{s(b_3 + o(1)) + o(1)}{s^2 + s(a_1 + o(1)) + a_0 + o(1)}$$

where b_3 is defined in [9] and the $o(1)$ terms are as $\epsilon \to 0$. This system has the signal detection property, and decomposing $S_\epsilon(s)$ into the feedback loop of Fig. 2 gives

$$\Sigma_0 = \frac{b_3 + o(1)}{s + a_1 + o(1)}$$
$$\Sigma_{IM,\epsilon} = \frac{a_0 + o(1)}{s(b_3 + o(1)) + o(1)}$$
$$\Sigma_{IM} = \frac{a_0}{b_3 s}$$

with $\lim_{\epsilon \to 0} \Sigma_{IM,\epsilon} = \Sigma_{IM}$. Because Σ_{IM} is capable of

generating step inputs, Σ_ϵ has an approximate model of the input class consisting of step inputs. Also note that $S_\epsilon(s)$ approaches the perfectly adapting system in [9] as $\epsilon \to 0$.

The response of the receptor-modification system to a step input in ligand is shown in Figure 8. Figure 8A depicts the response of the system when the excitation reactions are assumed at saturation, and the response when this assumption is relaxed is shown in Figure 8B. It is clear that under saturation, perfect adaptation is achieved. However, when the excitation reactions do no operate under complete saturation, adaptation is only achieved within an order of ϵ.
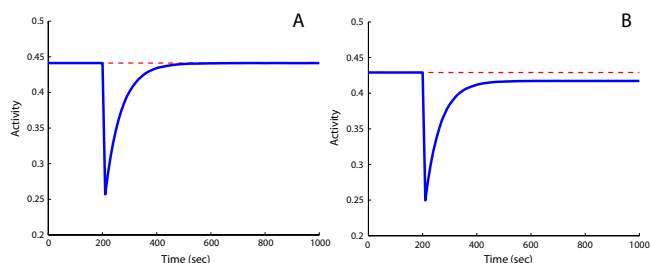

Fig. 8. Step response of the four-state receptor modification model when the excitation reactions are assumed under saturation (panel A) and when this assumption is slightly relaxed (panel B). The dashed line indicates the pre-stimulus steady-state activity level.

IV. CONCLUSIONS

Adaptation to environmental changes is a key property of many biological systems, and assumptions are usually made when modeling these systems to highlight perfect adaptation. It is plausible that real cells, however, do not adapt perfectly but rather to within some tolerable range of the steady-state adaptation level [13], [14]. We have shown that a system with such an approximate adaptation property as well as a signal detection property must contain an approximate model of the input being adapted to within the same order of precision. This is an extension of the internal model principle under the assumption that perfect regulation is not required. We have illustrated this concept by considering two published models of perfectly adapting biological systems: the excitation-inhibition model used to describe chemoattractant-induced signaling in *Dictyostelium* [22], and the four-state receptor modification model which can be used to model adaptation in *E. coli* [9]. In both cases, perfect adaptation is achieved through simplifying assumptions. When relaxed, these assumptions yield systems that do *not* adapt perfectly, but only partially. In both cases, rearrangement of the system shows the presence of an approximate internal model.

Observe that the approximate adaptation condition is formally similar to an input to output stability [18] condition, uniform on the initial states of the system and exosystem, when ϵ is seen as an input (and admits, when seen in that light, an obvious generalization to time-varying ϵ). There is also a close relation to almost disturbance decoupling with internal stability [12], [21]; however, the focus of such work is on controller design rather than the effect of system parameters on regulation as studied here. The IMP has been shown for the related regulator problem with internal stability [5], and an obvious extension of this work is the study of approximate adaptation and its internal model implications in nonlinear systems.

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