An approximate internal model principle:
Applications to nonlinear models of
biological systems

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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 has an internal model in the feedback loop. In this paper we relax the requirement that the response of the system adapts perfectly, but instead allow regulation to within a neighborhood of zero. We show, in a nonlinear setting, that systems with the ability to detect input signals and approximately adapt require an approximate model of the input. We illustrate our results by analyzing a well-studied biological system. These results generalize previous work which treats the perfectly adapting case.

1. 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 (Francis and Wonham 1975), and related regulation problems for nonlinear systems have been considered in (Hepburn and Wonham 1984*a*, Hepburn and Wonham 1984*c*, Hepburn and Wonham 1984*b*, Isidori and Byrnes 1990). 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 (Alon *et al.* 1999, Block *et al.* 1983). 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 (Yi *et al.* 2000). Other examples in biology in which the role of feedback control systems is to achieve adaptation include blood calcium regulation (El-Samad *et al.* 2002), neuronal control of the prefrontal cortex (Miller and Wang 2006), tryptophan regulation in *E. coli* (Venkatesh *et al.* 2004), and the *Dictyostelium* chemotactic response to step changes in chemoattractant (Yang and Iglesias 2006).

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 (Koshland *et al.* 1982). This "signal detection" property has been characterized and used in conjunction with adaptation to show the IMP in linear and nonlinear systems (Sontag 2003). 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 (Koshland *et al.* 1982, Lauffenburger 2000). 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 nonlinear systems that adapt approximately, rather than perfectly, to a given class of input. This study is a direct extension of a previous proof of the IMP in systems with detection and adaptation (Sontag 2003) as well as our earlier analysis of approximate internal models in linear systems (B. W. Andrews and Sontag 2006). We first provide a formal definition of signal detection and then show that nonlinear systems with signal detection and approximate adaptation must contain an "approximate" model of the input. We then illustrate our findings by considering a general receptor modification system such as the one found in *E. coli* (Barkai and Leibler 1997, Iglesias and Levchenko 2001), which adapts perfectly under typical assumptions. We show, however, that when some of these

assumptions are relaxed, the system adapts only approximately to step inputs and thus contains an approximate internal model of an integrator; see also (Alon 2007).

2. PRELIMINARIES

We consider single-input single-output systems of the form

$$\dot{x}(t) = f(x(t), \varepsilon) + u(t)g(x(t), \varepsilon) \qquad (1)$$
$$y(t) = h(x(t), \varepsilon)$$

where f, g, and h are smooth functions of x and ε over the domain of interest. The system has input $u(t)$, output $y(t)$, and initial condition $x(0) = x^0$. Owing to the explicit dependence on a parameter of interest ε, we denote (1) an ε-parameterized system, Σ_ε. Inputs are assumed to be generated by an exosystem Γ of the form

$$\Gamma = \begin{cases} \dot{w}(t) &= Q(w(t)) \\ u(t) &= \theta(w(t)), \end{cases} \qquad (2)$$

where Q and θ are smooth functions of w, so that the interconnection of Σ_ε and Γ (Figure 1) is

$$\dot{w} = Q(w) \qquad (3)$$
$$\dot{x} = f(x, \varepsilon) + \theta(w)g(x, \varepsilon)$$
$$y = h(x, \varepsilon).$$

We assume that $|\theta(w)| \leq m$. The functions Q and θ define a particular class of inputs $\mathcal{U}$ where each $u(t) \in \mathcal{U}$ is generated from a different initial condition $w(0) = w^0$. The exosystem is assumed to be Poisson-stable, meaning that for any initial condition w^0, the solution contains w^0 in its omega-limit set (Sontag 2003).
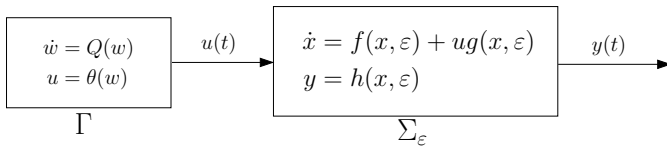

Fig. 1. Exosystem and system.

We next recall the definition of relative degree (Isidori 1995):

Definition 1. The system Σ_ε has relative degree $r \leq n$ at the point x^0 if

(1) $L_g L_f^i h(x) = 0$ for all $i = 0, \ldots r - 2$ and for all x in a neighborhood of x^0.
(2) $L_g L_f^{r-1} h(x^0) \neq 0$.

Here, the Lie derivative $L_f h(x) = \frac{\partial h}{\partial x} f(x)$ is the derivative of $h(x)$ along the vector field $f(x)$. Note that if $x(t^0) = x^0$ for some time t^0, the derivatives of the system output are

$$y^{(i)}(t) = L_f^i h(x(t)), \text{ for all } i < r \text{ and all } t \text{ near } t^0$$

and

$$y^{(r)}(t^0) = L_f^r h(x^0) + L_g L_f^{r-1} h(x^0)u(t^0).$$

Thus, a useful characterization of the relative degree is the number of times the output of the system must be differentiated to be dependent on the input. For linear systems, the relative degree equals the difference between the degree of the denominator and numerator polynomials of the transfer function. Also, note that the Lie derivatives $L_f^i h$ and $L_g L_f^{r-1} h$ depend on ε, although this dependency is not explicitly written.

Following (Sontag 2003), we make two technical assumptions. If the relative degree is r, we define:

$$\tilde{g}(x) = \frac{1}{L_g L_f^{r-1} h(x)} g(x),$$
$$\tilde{f}(x) = f(x) - (L_f^r h(x))\tilde{g}(x),$$
$$\tau_i := \mathrm{ad}_{\tilde{f}}^{i-1} \tilde{g}, \qquad i = 1, \ldots, r$$

where $\mathrm{ad}_f g := [f, g] = \frac{\partial g}{\partial x} f - \frac{\partial f}{\partial x} g$ is the Lie bracket of the vector fields f and g.

We first assume that the τ_i are complete for $i = 1, \ldots, r$; that is, the solution of the initial value problem $\dot{x} = \tau_i(x)$, $x(0) = x^0$ is defined for all $t \in \mathbb{R}$ for any initial state x^0.

We also assume that the vector fields τ_i commute with each other; i.e. $[\tau_i, \tau_j] = 0, \forall i, j$.

These two assumptions, which are automatically satisfied for linear systems, guarantee the existence of a requisite change of variables.

Finally, we 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 $|f(x)| \leq c|g(x)|$ as $x \to x_0$.
(2) 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 $x \to x_0$.

3. RESULTS

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

3.1 Signal detection

We wish to describe a system's ability to detect input signals. Such a property should capture the notion that the system's initial response to an input is of the same order of magnitude as the input. Recall that, for a system with relative degree r at a point $x(t_0) = x^0$,

$$y^{(r)}(t_0) = L_f^r h(x^0) + L_g L_f^{r-1} h(x^0)u(t_0),$$

implying that $y^{(r)}(t_0) = \Omega(u(t_0))$ as $t \to t_0$. The magnitude of the system's initial response, determined by its rth derivative, is directly dependent on the magnitude of the input. We thus introduce the following definition as a suitable description of the signal detection property.

Definition 2. The system Σ_ε has the ability to detect an input signal $u(t)$ if a relative degree exists and is independent of ε.

3.2 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. Lemma 5 and Theorem 6 are extensions of Lemma 3.1 and Theorem 1 presented in (Sontag 2003).

Definition 3. The ε-parameterized system Σ_ε, with relative degree r, adapts approximately to a class of inputs $\mathcal{U}$, where each $u(t) \in \mathcal{U}$ is generated by Γ, if there exists

a function $K(\varepsilon) = O(\varepsilon)$ (as $\varepsilon \to 0$), such that for all $u(t) \in \mathcal{U}$, $\limsup_{t \to \infty} |y^{(i)}(t)| \leq K(\varepsilon)$ for $i = 0, \ldots, r$.

This definition requires that the output of an approximately adapting system, in addition to eventually being small, is eventually slowly varying (i.e., the derivatives are small). This constraint on the derivatives is necessary for the main theorem below and is reminiscent of similar constraints required for derivative control in the context of approximate output regulation (Sureshbabu and Rugh 1995) as well as for input-output stability of sampled systems (Iglesias 1995).

Definition 4. An ε-parameterized system Σ_ε is said to have an approximate internal model of $\mathcal{U}$ if it can be decomposed into the system shown in Figure 2, where $\Sigma_{IM,\varepsilon}$ has state representation

$$\Sigma_{IM,\varepsilon} = \begin{cases} \dot{z}_2 & = f_2(y, z_2, \varepsilon) \\ \kappa & = \varphi(z_2, \varepsilon), \end{cases}$$

and for each $u \in \mathcal{U}$, there exists a solution z_2 that satisfies $|\varphi(z_2, \varepsilon) - u| = O(\varepsilon)$ when $y = O(\varepsilon)$.

Definition 4 states that a system Σ_ε contains an approximate internal model of an input class $\mathcal{U}$ if it contains a subsystem that is capable of generating inputs that are close to those in $\mathcal{U}$ when the output y is small. Note that in the limit as $\varepsilon \to 0$, $\varphi(z_2, \varepsilon) \to u$, and $\Sigma_{IM,\varepsilon}$ approaches a perfect internal model Σ_{IM} which can generate all $u \in \mathcal{U}$ exactly when $y = 0$.
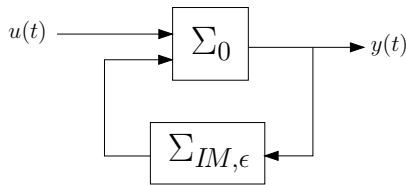

Fig. 2. Internal model decomposition of Σ_ε

Before proceeding to the main theorem, we provide the following Lemma which extends previous results on exact adaptation (Sontag 2003).

Lemma 5. Suppose that Σ_ε adapts approximately to input class $\mathcal{U}$. For all w^0, there exists a solution $\sigma = (w(\cdot), x(\cdot))$ of the composite system such that $w(0) = w^0$ and $|y^{(i)}(t)| \leq K(\varepsilon)$, $i = 0, \ldots, r$ for all $t \geq 0$.

Proof. We will show that there exists a solution σ such that $(w(t), x(t)) \in \mathcal{L}_\varepsilon$, $\forall t \geq 0$ where $\mathcal{L}_\varepsilon$ is defined as the set of all pairs (w, x) such that:

$$\left| L_f^i h(x) \right| \leq K(\varepsilon), \quad i = 0, \ldots, r-1$$

and

$$\left| L_f^r h(x) + L_g L_f^{r-1} h(x) \theta(w) \right| \leq K(\varepsilon).$$

First, choose an arbitrary solution $\sigma_0 = (w(\cdot), x(\cdot))$ of the composite system such that $w(0) = w^0$, and let $\Omega = \Omega^+[\sigma_0]$ be the omega-limit set of σ_0.

Claim (i): if $(\omega, \xi) \in \Omega$ then $(\omega, \xi) \in \mathcal{L}_\varepsilon$. This can be seen as follows. By definition, there exists a sequence $t_k \to \infty$ such that $x(t_k) \to \xi$ and $w(t_k) \to \omega$. Owing to the approximate adaptation assumption, and because h (and thus any Lie derivative of h) is smooth, it follows that

$$\left| L_f^i h(\xi) \right| = \lim_{k \to \infty} \left| L_f^i h(x(t_k)) \right|$$
$$= \lim_{k \to \infty} \left| y^{(i)}(t_k) \right|$$
$$\leq \limsup_{t \to \infty} \left| y^{(i)}(t) \right|$$
$$\leq K(\varepsilon)$$

for $i = 0, \ldots, r-1$. Moreover,

$$\left| L_f^r h(\xi) + L_g L_f^{r-1} h(\xi) \theta(\omega) \right|$$
$$= \left| \lim_{k \to \infty} L_f^r h(x(t_k)) + \lim_{k \to \infty} L_g L_f^{r-1} h(x(t_k)) \theta(w_k) \right|$$
$$= \lim_{k \to \infty} \left| L_f^r h(x(t_k)) + L_g L_f^{r-1} h(x(t_k)) \theta(w_k) \right|$$
$$= \lim_{k \to \infty} \left| y^{(r)}(t_k) \right|$$
$$\leq \limsup_{t \to \infty} \left| y^{(r)}(t) \right| \leq K(\varepsilon).$$

Thus, $(\omega, \xi) \in \mathcal{L}_\varepsilon$ as claimed.

Claim (ii): There exists an x^0 such that $(w^0, x^0) \in \Omega$. To show this, we choose a sequence $t_i \to \infty$ such that $w(t_i) \to w^0$ — this is possible because of the Poisson stability of the exosystem. The sequence $x(t_i)$ is bounded, so there exists a convergent subsequence t_{i_j} such that $x(t_{i_j}) \to x^0$ for some x^0. This implies that $(w^0, x^0) \in \Omega$.

To complete the proof, let $\sigma = (w, x)$ be a solution of the composite system for $w(0) = w^0$ and $x(0) = x^0$ where x^0 is chosen such that $(w^0, x^0) \in \Omega$ (Claim (ii)). Ω is invariant so $\sigma(t) \in \Omega$, $\forall t \geq 0$ and this implies that $(w(t), x(t)) \in \mathcal{L}_\varepsilon$ $\forall t$ (Claim (i)) as required.

We are now ready for our main result.

Theorem 6. A system Σ_ε that detects inputs and adapts approximately to input class $\mathcal{U}$ contains an approximate internal model of $\mathcal{U}$.

Proof. We assume, without loss of generality, that the system Σ_ε has relative degree r.

We first define

$$\tilde{x} := \begin{bmatrix} x \\ \varepsilon \end{bmatrix}, \quad \tilde{f}(\tilde{x}) := \begin{bmatrix} f(x, \varepsilon) \\ 0 \end{bmatrix}, \quad \tilde{g}(\tilde{x}) := \begin{bmatrix} g(x, \varepsilon) \\ 0 \end{bmatrix},$$

and $\tilde{h}(\tilde{x}) := h(x, \varepsilon)$ and rewrite Σ_ε as

$$\tilde{\Sigma} = \begin{cases} \dot{\tilde{x}}(t) & = \tilde{f}(\tilde{x}(t)) + u(t)\tilde{g}(\tilde{x}(t)) \\ y(t) & = \tilde{h}(\tilde{x}(t)) \end{cases} \tag{4}$$

Note that $\tilde{x}^0 = \begin{bmatrix} x^0 \\ 0 \end{bmatrix}$. Because Σ_ε detects inputs, $L_{\tilde{g}} L_{\tilde{f}}^{r-1} \tilde{h}(\tilde{x}^0) \neq 0$, and it is easy to show that the relative degree of $\tilde{\Sigma}$ is also r.

It is possible to show (Isidori 1995) the existence of a change of variables, $z = \Phi(x)$, for $\tilde{\Sigma}$ such that the system in the new coordinates is

$$\dot{\zeta}_1 = \zeta_2$$
$$\vdots$$
$$\dot{\zeta}_{r-1} = \zeta_r$$
$$\dot{\zeta}_r = b(z_1, z_2, \varepsilon) + a(z_1, z_2, \varepsilon)u$$
$$\dot{z}_2 = f_2(y, z_2, \varepsilon)$$
$$\dot{\varepsilon} = 0$$

where $z = [z_1, z_2]^\top$, $z_1 := [\zeta_1, \ldots, \zeta_r]^\top$, and the output is $y = \zeta_1$. The functions $a(z, \varepsilon) = L_f^r h(x, \varepsilon)$ and $b(z, \varepsilon) = L_g L_f^{r-1} h(x, \varepsilon)$ are evaluated at $x = \Phi^{-1}(z)$.

If we let the function f_2 (the zero dynamics) describe the dynamics of the internal model, then we seek a function $\varphi(z_2)$ such that, for each $u \in \mathcal{U}$, the solution of $\dot{z}_2 = f_2(O(\varepsilon), z_2)$ satisfies $|\varphi(z_2(t)) - u(t)| = O(\varepsilon)$ for some initial condition (z_1^0, z_2^0). To show this, first pick w^0 such that $u(t) = \theta(w(t))$ and $w(0) = w^0$. From the lemma, we know that there exists a solution $\sigma = (w(\cdot), z_1(\cdot), z_2(\cdot))$ such that $|y(t)|, |\dot{y}(t)|, \ldots, |y^{(r)}(t)| \le K(\varepsilon)$, for all t. This implies that $|\zeta_1|, \ldots, |\zeta_r| = O(\varepsilon)$ and $\left|\dot{\zeta}_r(t)\right| = O(\varepsilon)$. Also, note that a function $f(\varepsilon) = O(\varepsilon)$ (as $\varepsilon \to 0$) implies that $\lim_{\varepsilon \to 0} f(\varepsilon) = 0$. Thus, $\lim_{\varepsilon \to 0} z_1 = \mathbf{0}$, and we have

$$\lim_{\varepsilon \to 0} a(z_1, z_2, \varepsilon) = a(\mathbf{0}, \lim_{\varepsilon \to 0} z_2, 0)$$
$$\lim_{\varepsilon \to 0} b(z_1, z_2, \varepsilon) = b(\mathbf{0}, \lim_{\varepsilon \to 0} z_2, 0)$$

and

$$|a(z_1, z_2, \varepsilon) - a(\mathbf{0}, z_2, 0)| = O(\varepsilon)$$
$$|b(z_1, z_2, \varepsilon) - b(\mathbf{0}, z_2, 0)| = O(\varepsilon).$$

Choosing

$$\varphi(z_2) = -\frac{b(\mathbf{0}, z_2, 0)}{a(\mathbf{0}, z_2, 0)},$$

we have, noting that $a \ne 0$ (from the definition of relative degree), and dropping explicit dependence of a and b on ε for convenience of notation,

$$|\varphi(z_2(t)) - u(t)|$$
$$= \left| -\frac{b(\mathbf{0}, z_2)}{a(\mathbf{0}, z_2)} - \frac{\dot{\zeta}_r - b(z_1, z_2)}{a(z_1, z_2)} \right|$$
$$= \left| \frac{-b(\mathbf{0}, z_2)a(z_1, z_2) - \dot{\zeta}_r a(\mathbf{0}, z_2) + a(\mathbf{0}, z_2)b(z_1, z_2)}{a(\mathbf{0}, z_2)a(z_1, z_2)} \right|$$
$$= \left| \big(-b(\mathbf{0}, z_2)a(z_1, z_2) + a(z_1, z_2)b(z_1, z_2) \right.$$
$$\left. - a(z_1, z_2)b(z_1, z_2) + a(\mathbf{0}, z_2)b(z_1, z_2) - \dot{\zeta}_r a(\mathbf{0}, z_2)\big) \right.$$
$$\left. \times 1/\big(a(\mathbf{0}, z_2)a(z_1, z_2)\big) \right|$$
$$= \left| \big(a(z_1, z_2)\big(b(z_1, z_2) - b(\mathbf{0}, z_2)\big) - \dot{\zeta}_r a(\mathbf{0}, z_2) \right.$$
$$\left. + b(z_1, z_2)\big(a(\mathbf{0}, z_2) - a(z_1, z_2)\big)\big)/\big(a(\mathbf{0}, z_2)a(z_1, z_2)\big) \right|$$
$$= \left| \frac{a(z_1, z_2)O(\varepsilon) + b(z_1, z_2)O(\varepsilon) - O(\varepsilon)a(\mathbf{0}, z_2)}{a(\mathbf{0}, z_2)a(z_1, z_2)} \right|$$
$$= O(\varepsilon).$$

Thus we have shown that an approximately adapting system with the signal detection property must contain an approximate internal model of the input class.

4. BIOLOGICAL EXAMPLE: 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 3 (Iglesias and Levchenko 2001, Barkai and Leibler 1997). A receptor on the membrane of the cell can exist in one of four states: unmodified, unbound to ligand (R); unmodified, bound to ligand (RL); modified, unbound to ligand (D); or modified, bound to ligand (DL). The modification and demodification reactions are catalyzed by inhibition and excitation enzymes, respectively. Typically, excitation is assumed to operate at saturation ($k_{M_E} \ll D$ and $k_{M_E} \ll DL$, where k_{M_E} is the Michaelis-Menten constant) and inhibition is assumed in the linear regime ($k_{M_I} \gg R$ and $k_{M_I} \gg RL$). Only fractions of the unmodified receptors, $\alpha_1 R$ and $\alpha_2 RL$, are assumed to be in an "active" state. The total activity $A = \alpha_1 R + \alpha_2 RL$ directly affects the state of the flagellar motor and thus drives the movement of the bacteria. We assume that the inhibition enzyme acts only on active receptors. Under the above assumptions, the dynamics describing R and RL become decoupled from D and DL:

$$\frac{dR}{dt} = k_{-1}E_T - k_1 I_T \cdot \alpha_1 R - k_r R \cdot L + k_{-r} RL$$
$$\frac{dRL}{dt} = k_{-2}E_T - k_2 I_T \cdot \alpha_2 RL + k_r R \cdot L - k_{-r} RL$$
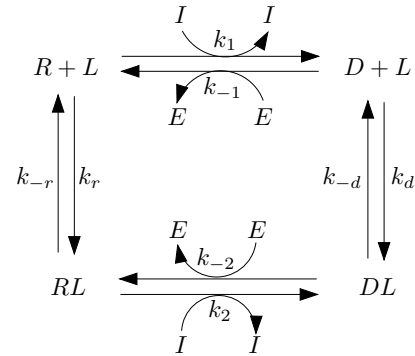

Fig. 3. General model of adaptation via receptor modification. Both the modified and unmodified form of the receptor can bind ligand. Such a scheme is found in the signal transduction pathway of E. coli.

In previous models, the inhibition rate constants k_1 and k_2 are assumed equal, resulting in robust, perfect adaptation to step changes in ligand levels (Iglesias and Levchenko 2001). Here we show that relaxing this assumption so that $k_1 = k_2 + \varepsilon$ results in approximate rather than perfect adaptation. Moreover, the zero dynamics of the system exhibit the form of an approximate integrator as expected from Theorem 6.

Following the notation of Sontag (Sontag 2003), we define $x_1 = R$, $x_2 = RL$, $a_1 = k_{-1}E_T$, $a_2 = k_1 I_T \alpha_1$, $a_3 = k_{-r}$, $a_4 = k_r$, $a_5 = k_{-2}E_T$, and $a_6 = k_{-r} + k_1 I_T \alpha_2$. In terms of Equation (1),

$$f(x, \varepsilon) = \begin{pmatrix} a_1 - a_2 x_1 + a_3 x_2 \\ a_5 - (a_6 + \varepsilon I_T \alpha_2) x_2 \end{pmatrix}, \quad g(x) = \begin{pmatrix} -a_4 x_1 \\ a_4 x_1 \end{pmatrix}.$$

The output is the difference between the activity and steady-state activity when $\varepsilon = 0$, scaled by $k_1 I_T$:

$$y = h(x) = (a_1 + a_5) - (a_2 x_1 + (a_6 - a_3)x_2).$$

4.1 Approximate adaptation

We first show that this system adapts approximately to step (constant) inputs. Solving $\dot{x}_1 = \dot{x}_2 = 0$ gives steady states x_1^* and x_2^*:

$$x_2^* = \frac{a_2 a_5 + a_4 u a_5 + a_1 a_4 u}{-a_3 a_4 u + a_6 a_2 + a_6 a_4 u + \varepsilon I_T \alpha_2 a_2 + \varepsilon I_T \alpha_2 a_4 u}$$

$$x_1^* = \frac{a_3 a_5 + \varepsilon I_T \alpha_2 a_1 + a_6 a_1}{-a_3 a_4 u + a_6 a_2 + a_6 a_4 u + \varepsilon I_T \alpha_2 a_2 + \varepsilon I_T \alpha_2 a_4 u}$$

Note $a_3 - a_6 < 0$, so that this steady-state solution exists and uniquely provides positive states, for any u and ε.

The trace of the linearized matrix (at any point) is $-a_2 - a_4 u - a_6 - \varepsilon I_T \alpha_2 < 0$, and the determinant

$$(-a_2 - a_4 u)(-a_6 - \varepsilon i_T \alpha_2) - a_3 a_4 u$$

is positive because $a_3 < a_6$. Because the system, for constant u, has the form $\dot{x} = c + Ax$, (where A depends on u and ε), A is Hurwitz and thus the system is globally asymptotically stable (GAS).

Computing $h(x^*)$ gives the steady-state output:

$$y^* = -\frac{\varepsilon I_T \alpha_2 (a_2 a_5 + a_4 u a_5 + a_1 a_4 u)}{a_3 a_4 u - a_6 a_2 - a_6 a_4 u - \varepsilon I_T \alpha_2 a_2 - \varepsilon I_T \alpha_2 a_4 u}$$

Note that this vanishes at $\varepsilon = 0$, and is continuous in ε, which proves, together with GAS, that the system approximately adapts.

4.2 Approximate internal model

We first note that

$$L_g h = \frac{\partial h}{\partial x} \cdot g(x)$$
$$= a_2 a_4 x_1 - (a_6 - a_3) a_4 x_1,$$

which is nonzero for all x if $\alpha_1 \neq \alpha_2$. Thus, the system has a relative degree $r = 1$. To put the system into normal form, we find a change of coordinates $z = \Phi(x)$ such that Φ is smooth and $\partial \Phi / \partial x$ is nonsingular. This can be accomplished by choosing $\phi_1(x) = h(x)$ and $\phi_2(x)$ such that $L_g \phi_2(x) = 0$ and $\phi_2(x)$ is linearly independent of $\phi_1(x)$ (Isidori 1995). An obvious choice is $\phi_2(x) = x_1 + x_2$ so that

$$\frac{\partial \Phi}{\partial x} = \begin{bmatrix} -a_2 & a_3 - a_6 \\ 1 & 1 \end{bmatrix},$$

which is nonsingular for all x if $\alpha_1 \neq \alpha_2$. The inverse system is

$$\Phi^{-1}(z) = \begin{bmatrix} \dfrac{z_2(a_3 - a_6) - z_1 + (a_1 + a_5)}{a_2 - a_6 + a_3} \\ \dfrac{z_1 + a_2 z_2 - (a_1 + a_5)}{a_2 - a_6 + a_3} \end{bmatrix}.$$

The zero dynamics are given by the differential equation

$$\dot{z}_2 = L_f \phi_2(x)|_{x=\Phi^{-1}(z)}$$

$$= [1 \; 1] \begin{bmatrix} a_1 - a_2 x_1 + a_3 x_2 \\ a_5 - (a_6 + \varepsilon I_T \alpha_2)x_2 \end{bmatrix} \Bigg|_{x=\Phi^{-1}(z)}$$

$$= z_1 - \varepsilon I_T \alpha_2 \frac{z_1 - a_2 z_2 - (a_1 + a_5)}{a_2 - a_6 + a_3}.$$

The system is approximately adapting, so $z_1 = y = O(\varepsilon)$, and the zero dynamics give rise to an internal model representative of an approximate integrator:

$$\dot{z}_2 = O(\varepsilon)$$
$$\varphi(z_2) = -\frac{b(0, z_2)}{a(0, z_2)},$$

where

$$a(z) = L_f h(x)|_{x=\Phi^{-1}(z)} \quad \text{and} \quad b(z) = L_g h(x)|_{x=\Phi^{-1}(z)}.$$

Biologically, integration is achieved via a protein CheB, which demethylates active receptor complexes. For perfect integration, the demethylation rates for ligand bound and unbound active receptors must be identical ($k_1 = k_2$); relaxation of this results in an approximate integrator.

The response of the receptor-modification system to a step input in ligand is shown in Figure 4. Figure 4A depicts the response of the system when k_1 and k_2 are assumed equal, and the response when this assumption is relaxed is shown in Figure 4B. It is clear that when $k_2 = k_1$, perfect adaptation is achieved. However, when $k_2 = k_1 + \varepsilon$, adaptation is only achieved within an order of ε.
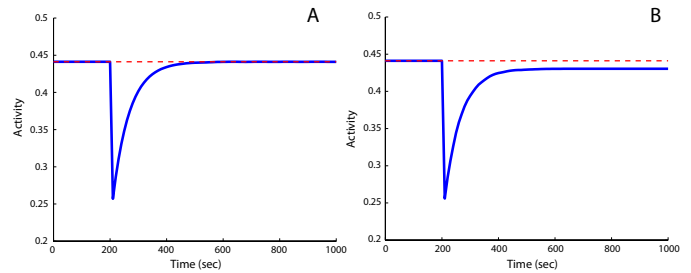

Fig. 4. Step response of the four-state receptor modification model when $k_1 = k_2$ (panel A) and when this assumption is relaxed to $k_2 = k_1 + \varepsilon$ (panel B). The dashed line indicates the pre-stimulus activity level, and $\varepsilon = 10$ (chosen large for figure visibility).

While we have demonstrated approximate adaptation in the four-state receptor modification model by relaxing the assumption that $k_1 = k_2$, similar results may be obtained by relaxing other assumptions such as saturation of the excitation reactions. For instance, the component of dR/dt due to the excitation enzyme is

$$\frac{k_{-1} E_T D}{k_{M_E} + D} = k_{-1} E_T \left(\frac{1}{k_{M_E}/D + 1} \right)$$

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

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 $K_{M_E}/D \approx -D\varepsilon$, where $\varepsilon = k_{M_E}/D_0^2$. Note that this approximation retains the dependence on D. Analysis of

an approximate internal model for the nonlinear system in this case is more tedious than that presented for $k_1 \neq k_2$ due to the inability to decouple the modified and unmodified states; however, approximate adaptation has been studied for a linearization under this scenario (B. W. Andrews and Sontag 2006).

5. 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 (Koshland *et al.* 1982, Lauffenburger 2000). 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 a published model of a perfectly adapting biological systems: the four-state receptor modification model used to model adaptation in *E. coli* (Iglesias and Levchenko 2001). We show that perfect adaptation is achieved through simplifying assumptions. When relaxed, these assumptions yield a system that does *not* adapt perfectly, but only partially, and a change of coordinates reveals the presence of an approximate internal model.

Observe that the approximate adaptation condition is formally similar to an input to output stability (Sontag 2006) 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 (Weiland and Willems 1989, Isidori *et al.* 1999); 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 (Francis and Wonham 1975).

REFERENCES

Alon, U. (2007). *An Introduction to Systems Biology: Design Principles of Biological Circuits.* Chapman and Hall. Boca Raton, FL.

Alon, U., M. G. Surette, N. Barkai and S. Leibler (1999). Robustness in bacterial chemotaxis. *Nature* **397**, 168–171.

B. W. Andrews, P. A. Iglesias and E. D. Sontag (2006). Signal detection and approximate adaptation implies an approximate internal model. In: *Conf. Dec. Control.* pp. 2364–2369. San Diego, CA.

Barkai, N. and S. Leibler (1997). Robustness in simple biochemical networks. *Nature* **387**, 913–917.

Block, S. M., J. E. Segall and H. C. Berg (1983). Adaptation kinetics in bacterial chemotaxis. *J. Bacteriology* **154**(1), 312–323.

El-Samad, H., J. P. Goff and M. Khammash (2002). Calcium homeostasis and parturient hypocalcemia: An integral feedback perspective. *J. Theor. Biol.* **214**, 17–29.

Francis, B.A. and W.M. Wonham (1975). The internal model principle for linear multivariable regulators. *Appl. Math. Optim.* **2**, 170–194.

Hepburn, J. S. A. and W. M. Wonham (1984a). Error feedback and internal models on differentiable manifolds. *IEEE Trans. Automatic Control* **29**, 397–403.

Hepburn, J. S. A. and W. M. Wonham (1984b). The semistable-center-unstable manifold near a critical element. *J. Math. Anal. Appl.* **103**, 321–331.

Hepburn, J. S. A. and W. M. Wonham (1984c). Structurally stable nonlinear regulation with step inputs. *Mathematical Systems Theory* **17**, 319–333.

Iglesias, P. A. (1995). Input-Output Stability of sampled-data linear time-varying systems. *IEEE Trans. Automatic Control* **40**(9), 1646–1650.

Iglesias, P. A. and A. Levchenko (2001). A general framework for achieving integral control in chemotactic biological signaling mechanisms. In: *Conf. Dec. Control.* pp. 843–848. Orlando, FL.

Isidori, A. (1995). *Nonlinear Control Systems.* 3rd ed.. Springer. London.

Isidori, A. and C. I. Byrnes (1990). Output regulation of nonlinear systems. *IEEE Trans. Automatatic Control* **35**, 131–140.

Isidori, A., B. Schwartz and T. J. Tarn (1999). Semiglobal L_2 performance bounds for disturbance attenuation in nonlinear systems. *IEEE Trans. Automatic Control* **44**(8), 1535–1545.

Koshland, D. E., A. Goldbeter and J. B. Stock (1982). Amplification and adaptation in regulatory and sensory systems. *Science* **217**(4556), 220–225.

Lauffenburger, D. A. (2000). Cell signaling pathways as control modules: complexity for simplicity?. *Proc. Natl. Acad. Sci.* **97**, 5031–5033.

Miller, P. and X. J. Wang (2006). Inhibitory control by an integral feedback signal in prefrontal cortex: A model of discrimination between sequential stimuli. *Proc. Natl. Acad. Sci.* **103**, 201–206.

Sontag, E. (2006). Input to state stability: Basic concepts and results. In: *Nonlinear and Optimal Control Theory* (P. Nistri and G. Stefani, Eds.). pp. 163–220. Springer-Verlag. Berlin.

Sontag, E. D. (2003). Adaptation and regulation with signal detection implies internal model. *Systems and Control Letters* **50**(2), 119–126.

Sureshbabu, N. and W. J. Rugh (1995). Output Regulation with Derivative Information. *IEEE Trans. Automatic Control* **40**(10), 1755–1766.

Venkatesh, K. V., S. Bhartiya and A. Ruhela (2004). Mulitple feedback loops are key to a robust dynamic performance of tryptophan regulation in *Escherichia coli*. *FEBS Letters* **563**, 234–240.

Weiland, S. and J.C. Willems (1989). Almost disturbance decoupling with internal stability. *IEEE Trans. Automatic Control* **34**, 277–286.

Yang, L. and P. A. Iglesias (2006). Positive feedback may cause the biphasic response observed in the chemoattractant-induced response of *Dictyostelium* cells. *Systems & Control Letters* **55**, 329–337.

Yi, T.-M., Y. Huang, M. I. Simon and J. C. Doyle (2000). Robust perfect adaptation in bacterial chemotaxis through integral feedback control. *Proc. Natl. Acad. Sci. USA* **97**(9), 4649–4653.