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Internal Models in Control, Bioengineering, and Neuroscience

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Abstract

Internal models are nowadays customarily used in different domains of science and engineering to describe how living organisms or artificial computational units embed their acquired knowledge about recurring events taking place in the surrounding environment. This article reviews the internal model principle in control theory, bioengineering, and neuroscience, illustrating the fundamental concepts and theoretical developments of the few last decades of research.

1. INTRODUCTION

Mark Twain, apprenticed as a teenager to a Mississippi river pilot, later reported his mentor as saying, "You only learn *the* shape of the river; and you learn it with such absolute certainty that you can always steer by the shape that's *in your head*, and never mind the one that's before your eyes" (2, p. 73). In more abstract terms, the idea that incorporating an appropriate model of the external world enables special abilities, such as adapting to external stimuli or executing smart operations in the presence of partial information, pervades many fields of science. In his classic monograph *The Nature of Explanation* (3), psychologist Kenneth Craik stated that "only [an] internal model of reality. . .enables us to predict events which have not yet occurred in the physical world, a process which saves time, expense, and even life" (p. 82); in other words, "the nervous system is viewed as a calculating machine capable of modeling or paralleling external events," and "this process of paralleling is the basic feature of thought and of explanation" (p. 121).

Many studies in neuroscience support Craik's vision. Vertebrates clearly act proactively rather than reactively, acquire new skills, and maintain mastered skills in response to changes in the external environment and the motor system. There are many reasons to believe that these abilities are enabled by the presence of internal models in the brain that compute the expected sensory consequences of a given motor command and produce sensory prediction error signals when the actual sensory input does not match expectations. Properties of this kind are also observed in some invertebrates whose nervous systems implement predictions of the sensory consequences of actions (4, 5). Investigating the neural implementation of these internal models and their computations is an active area of research. Internal models are also crucial for the proper functioning of many biological organisms that must be able to detect changes in their environment and adjust their internal states accordingly, a process commonly referred to as homeostasis or adaptation (6, 7). For example, successful chemotaxis (movement toward high concentrations of a chemical attractant) of *Escherichia coli* depends on the ability of the bacteria to adapt to step changes in the chemoattractant (8).

The mathematical framework where the notion of an internal model finds its most developed characterization is that of control and systems theory. By the 1930s, thanks to research at Bell Telephone Laboratories, the mathematical foundation of classical linear feedback control was soundly established. It had two implications: (*a*) Error feedback can reduce parameter sensitivity and final tracking error, but only at the expense of high loop gain, and (*b*) adding an internal model allows one to reduce the final tracking error to zero regardless of (reasonable) parameter perturbations and requires only moderate loop gain. A familiar example is the integrator component of the classical proportional–integral–derivative (PID) controller used to track (specifically) step reference inputs. In general, the price to be paid for perfect tracking was extra control complexity, including a stabilizing compensator, specific to the reference signals to be tracked. Later, Smith (9) incorporated an internal model in his scheme of predictive control, and in the mid-1970s, a series of seminal studies (see, e.g., 10, 11) on parameter-insensitive perfect asymptotic tracking led to the recognition of both error feedback and the internal model as necessary and sufficient structural features of robust linear multivariable systems. The necessary part, in particular, is known as the internal model principle (IMP) of control theory (10). The sufficient part, moreover, generalizes the PID control to arbitrary linear exogenous systems, as well as outputs of arbitrary dimension (11). More specifically, the IMP claims that asymptotic regulation is achieved in the presence of plant parameter variations "only if the controller utilizes feedback of the regulated variable, and incorporates in the feedback path a suitably reduplicated model of the dynamic structure of the exogenous signals which the regulator is required to process" (10, p. 193). Generalizations to nonlinear systems (with a differential geometry perspective) were initially obtained by Hepburn & Wonham (12, 13; see also 14), mainly in the case of step reference signals, and then extended to

general exosystems by Isidori & Byrnes (15) and Huang & Rugh (16). Since then, many attempts have been made to make the nonlinear framework even more general and constructive, and output regulation is still an active research area in control theory.

As presented by Sontag (6), and as is the case for many principles in mathematics, nowadays the IMP is regarded not as a single theorem, but rather as a mold for many possible frameworks and theorems formulated in different ways according to the specific scientific field. Moreover, while in control engineering the IMP is used mostly as a tool for the synthesis of control solutions, in neuroscience and biology it instead plays a role in the analysis of complex systems. Indeed, necessary conditions found in abstract mathematical settings inform scientists about what to expect and where to look when trying to understand how organisms interact with the external world. The two different approaches—that of the engineer and that of the scientist—build on the same principles and have the potential for fruitful cross-fertilization. On the one hand, the analysis of natural phenomena may guide the designer toward specific design choices. On the other hand, "designing is understanding" (17, p. 4), and the success of some engineering strategies can help scientists decode the functioning of specific phenomena. In this direction, and with the aim of bridging research skills and viewpoints from control, biology, and neuroscience, this article presents an overview of the concepts and tools that are behind the IMP. The main goal is to delineate the mold of the IMP developed in the control community and how it is interpreted in the two fields of biology and neuroscience. We begin in Section 2 with a broad overview of the development of internal models in control theory. In Sections 3 and 4, respectively, we describe how internal models enter in biology and neuroscience. Finally, Section 5 presents some closing remarks and a perspective on the future.

2. OUTPUT REGULATION IN CONTROL THEORY

2.1. Problem Formulation and Historical Background

The problem of robust output regulation is usually cast in the following terms. Consider a finite-dimensional, time-invariant, controlled plant modeled by equations of the form

$$\dot{x} = f(w, x, u), \quad e = h_e(w, x), \quad y = h(w, x), \qquad 1.$$

in which $x \in \mathbb{R}^n$ is a vector of state variables, $u \in \mathbb{R}^m$ is a vector of inputs to be used for control purposes, $w \in \mathbb{R}^{n_w}$ is a vector of inputs that cannot be controlled and include exogenous commands/disturbances and constant uncertain model parameters, $e \in \mathbb{R}^p$ is a vector of regulated outputs that include tracking errors and any other variable that needs to be steered to zero, and $y \in \mathbb{R}^q$ is a vector of outputs that are available for measurement. The problem is to design a controller, which receives $y(t)$ as input and produces $u(t)$ as output, so that, in the resulting closed-loop system, $x(t)$ remains bounded and $\lim_{t \to \infty} e(t) = 0$, regardless of what the exogenous input $w(t)$ actually is.

The exogenous input $w(t)$ is assumed to be an (undefined) member of a fixed family of functions of time, the family of all solutions of a fixed ordinary differential equation of the form (known as the exosystem)

$$\dot{w} = s(w) \qquad 2.$$

obtained when its initial condition $w(0)$ is allowed to vary on a prescribed set W. For convenience, it is assumed that the set W on which the state of Equation 2 is allowed to range is a compact set, invariant for the dynamics of Equation 2.

The control law for Equation 1 is to be provided by a system modeled by equations of the form

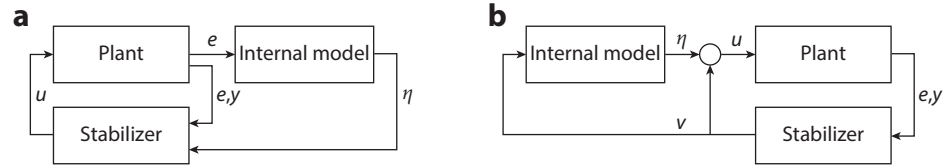$$\dot{x}_c = f_c(x_c, y), \quad u = h_c(x_c, y), \qquad 3.$$

Figure 1

Control architectures based on (*a*) postprocessing and (*b*) preprocessing internal models.

with state $x_c \in \mathbb{R}^{n_c}$. The initial conditions $x(0)$ of the plant shown in Equation 1 and $x_c(0)$ of the controller shown in Equation 3 are allowed to range over fixed compact sets $X \subset \mathbb{R}^n$ and $X_c \subset \mathbb{R}^{n_c}$, respectively. The controller shown in Equation 3 solves the problem of output regulation if, in the closed-loop system

$$\dot{w} = s(w), \quad \dot{x} = f(w, x, h_c(x_c, h(w, x))), \quad \dot{x}_c = f_c(x_c, h(w, x)), \quad e = h_e(w, x), \qquad 4.$$

regarded as an autonomous system with output e, the positive orbit of $W \times X \times X_c$ is bounded and $\lim_{t \to \infty} e(t) = 0$ uniformly in the initial condition.

The case in which the system shown in Equation 1 and the exosystem shown in Equation 2 are linear was originally studied by Francis (18), Francis & Wonham (19), and Davison (11), which highlighted the fundamental role of the IMP in the solution of such problems. The internal model–based regulator proposed by Davison (11), shown in **Figure 1a**, is based on a suitable replica of the exosystem dynamics (the internal model) driven by the error, and a stabilizer designed to stabilize the extended system given by the plant and the internal model. This regulator is intrinsically robust—that is, it is able to steer the error asymptotically to zero even in the presence of uncertainties in the plant that do not affect the linearity of the system or the asymptotic stability of the loop. Early attempts to extend the theory to nonlinear systems for the special case where the exogenous input is constant were made in the mid-1970s by Francis & Wonham (19) and later by Desoer & Lin (20), Hepburn & Wonham (12), and Huang & Rugh (16). The research on the nonlinear output regulation problem for the general case where the exogenous input is time varying began in 1990, when Isidori & Byrnes (15) gave a general formulation of the problem and discussed the existence of local solutions. In particular, the solvability of the nonlinear output regulation problem was related to the solvability of a set of nonlinear partial differential and algebraic equations known as regulator equations (see Equation 7 below). The design method proposed by Isidori & Byrnes (15) presumed the availability of an accurate model of the controlled plant. If only the regulated output is available for measurement and the model is affected by uncertain parameters, then to solve a problem of (robust) output regulation, one must establish an appropriate nonlinear version of the IMP.

Initial progress in this direction was made by Huang & Lin (21), who, inspired by an example from Byrnes & Isidori (22), realized that the steady-state tracking error in a nonlinear system is a nonlinear function of the exogenous signals, and that a good internal model should be able to reproduce the solution of the nonlinear regulator equations. Based on this observation, the concept of a *k*th-order internal model was conceived, and a solution of the robust output regulation problem for an uncertain nonlinear system was given under the assumption that the solution of the regulator equations of the system is a polynomial in the exogenous input (23, 24). Further results in this direction were given by Byrnes et al. (25) and Khalil (26). All of these contributions were limited by the fact that the stabilization task is based on an eigenvalue assignment problem for the linear approximation of an augmented system. Indeed, a regulator designed in this way is

unable to yield global or semiglobal robust regulation. Moreover, like the regulators in References 11, 18, and 19, it cannot deal with uncertainties in the exosystem.

Since the mid-1990s, research on the output regulation problem has made further advancements in two directions. First, the solution of the local robust output regulation problem has been extended to cover the cases of semiglobal or global robust output regulation. Second, adaptive output regulation techniques have been developed for dealing with uncertain exosystems. For these purposes, the original concept of a nonlinear internal model was not adequate, and efforts have been made to give it a more general characterization. The key elements for this generalization are the concepts of immersion and steady-state generators, first proposed by Byrnes et al. (25) and then further enriched and generalized in a series of papers (e.g., 27–29), leading to a variety of internal models for different scenarios.

2.2. Steady-State Analysis

Consider the closed-loop system shown in Equation 4 and assume, as postulated in the definition of the output regulation problem given in Section 2.1, that the positive orbit of the set $W \times X \times X_c$ of initial conditions is bounded. Then, all trajectories of such a system asymptotically approach a compact invariant set, known as the steady-state locus (30), which is the graph of a (possibly set-valued) map defined on W. If such a map is single valued, then the steady-state locus can be given the expression $\mathcal{S} = \{(w, x, x_c) : w \in W, x = \mathbf{x}(w), x_c = \mathbf{x}_c(w)\}$, in which $\mathbf{x}(\cdot)$ and $\mathbf{x}_c(\cdot)$ are functions defined on W. Then, in the closed-loop system, each exogenous input $w(t)$ gives rise to a unique steady-state response, expressed as $x_{ss}(t) = \mathbf{x}(w(t))$ and $x_{c,\,ss}(t) = \mathbf{x}_c(w(t))$. A consequence of the fact that the steady-state locus is invariant under the flow of Equation 4 is that the maps $\mathbf{x}(\cdot)$ and $\mathbf{x}_c(\cdot)$, if continuously differentiable, satisfy the following pair of partial differential equations:

$$\frac{\partial \mathbf{x}}{\partial w}s(w) = f(w, \mathbf{x}(w), b_c(\mathbf{x}_c(w), b(w, \mathbf{x}(w)))), \quad \frac{\partial \mathbf{x}_c}{\partial w}s(w) = f_c(\mathbf{x}_c(w), b(w, \mathbf{x}(w))). \qquad 5.$$

A consequence of the second requirement in the definition of the output regulation problem given in Section 2.1—that $\lim_{t \to \infty} e(t) = 0$ uniformly in the initial condition—is that the steady-state response of the regulated output [i.e., $e_{ss}(t) = b(w(t), x_{ss}(t))$] is identically zero. Hence, the map $\mathbf{x}(\cdot)$ satisfies

$$b_e(w, \mathbf{x}(w)) = 0. \qquad 6.$$

The constraints thus found can be organized as follows. Set

$$\mathbf{u}(w) = b_c(\mathbf{x}_c(w), b(w, \mathbf{x}(w))).$$

Then, from the first equation in Equation 5 along with Equation 6, it is seen that the pair $(\mathbf{x}(\cdot), \mathbf{u}(\cdot))$ satisfies

$$\frac{\partial \mathbf{x}}{\partial w}s(w) = f(w, \mathbf{x}(w), \mathbf{u}(w)), \quad b_e(w, \mathbf{x}(w)) = 0, \qquad 7.$$

while from the second equation in Equation 5, it is seen that the pair $(\mathbf{x}_c(\cdot), \mathbf{u}(\cdot))$ satisfies

$$\frac{\partial \mathbf{x}_c}{\partial w}s(w) = f_c(\mathbf{x}_c(w), b(w, \mathbf{x}(w))), \quad \mathbf{u}(w) = b_c(\mathbf{x}_c(w), b(w, \mathbf{x}(w))).$$

The first pair of equations (Equation 7), known as the nonlinear regulator equations, are seen as a necessary condition that the plant must fulfill so that the problem of output regulation is solvable, and they express the fact that, in steady state, when $x(t) = \mathbf{x}(w(t))$ and $u(t) = \mathbf{u}(w(t))$, the regulated variable $e(t)$ identically vanishes. The second pair of equations are seen as a necessary condition

that the controller must fulfill, and they express the fact that, in steady state, the controller—subject to the input $y(t) = h(w(t), \mathbf{x}(w(t)))$—generates the required output $u(t) = \mathbf{u}(w(t))$ needed to force the regulated variable $e(t)$ to remain identically zero.

In the special case in which $e = y$, the second pair of equations, in view of the second condition of Equation 7, simplify to

$$\frac{\partial \mathbf{x}_c}{\partial w}s(w) = f_c(\mathbf{x}_c(w), 0), \quad \mathbf{u}(w) = h_c(\mathbf{x}_c(w), 0). \qquad 8.$$

In a nutshell, the equations in question express the fact that the controller incorporates an internal model of the feedforward input $\mathbf{u}(w(t))$ needed to secure the desired (zero) steady-state response of the regulated variable.

2.3. General Characterization of Internal Models

If we put Equation 8 in slightly more abstract terms, it can be seen that a basic ingredient in the construction of a regulator is a steady-state generator, defined as follows.

Definition 1. The autonomous system (with output u)

$$\dot{w} = s(w), \quad u = \mathbf{u}(w), \qquad 9.$$

is said to be immersed into the system

$$\dot{\xi} = \varphi(\xi), \quad u = \gamma(\xi), \qquad 10.$$

defined on a set $\Xi \subset \mathbb{R}^q$ if there exists a smooth map $\tau : W \to \Xi$ such that

$$\frac{\partial \tau(w)}{\partial w}s(w) = \varphi(\tau(w)), \quad \mathbf{u}(w) = \gamma(\tau(w)). \qquad 11.$$

If this is the case, then the triplet (τ, φ, γ) is said to be a steady-state generator.

Having introduced the concept of a steady-state generator, we are ready to give a general characterization of the concept of an internal model as follows. Consider a system

$$\dot{\eta} = \alpha(\eta, u) \qquad 12.$$

in which $\alpha : \mathbb{R}^q \times \mathbb{R}^m \mapsto \mathbb{R}^q$ is a sufficiently smooth function, vanishing at the origin.

Definition 2. Suppose the pair $(s(w), \mathbf{u}(w))$ admits a steady-state generator (τ, φ, γ). The system shown in Equation 12 is an internal model candidate if

$$\alpha(\tau(w), \gamma(\tau(w))) = \varphi(\tau(w)). \qquad 13.$$

The composition of the plant and internal model candidate characterizes what is called the augmented system:

$$\dot{\eta} = \alpha(\eta, u), \quad \dot{x} = f(w, x, u), \quad e = h_e(w, x). \qquad 14.$$

A consequence of the definition of the internal model candidate is that, in the augmented system, the manifold $\mathcal{M} = \{(w, \eta, x) : w \in W, \eta = \tau(w), x = \mathbf{x}(w)\}$ is rendered invariant by means of the control $u = \mathbf{u}(w)$, and on such a manifold the regulated output is identically zero. In fact,

$$\frac{\partial \tau(w)}{\partial w}s(w) = \alpha(\tau(w), \mathbf{u}(w)), \quad \frac{\partial \mathbf{x}(w)}{\partial w}s(w) = f(w, \mathbf{x}(w), \mathbf{u}(w)), \quad h_e(w, \mathbf{x}(w)) = 0.$$

To further illustrate the role of the internal model, define $\bar{\eta} = \eta - \tau(w)$, $\bar{x} = x - \mathbf{x}(w)$, and $\bar{u} = u - \gamma(\eta)$, which changes the system shown in Equation 14 into a system of the form

$$\dot{\bar{\eta}} = \bar{\alpha}(w, \bar{\eta}, \bar{u}), \quad \dot{\bar{x}} = \bar{f}(w, \bar{\eta}, \bar{x}, \bar{u}), \quad e = \bar{h}(w, \bar{x}), \qquad\qquad 15.$$

where $\bar{\alpha}(w, \bar{\eta}, \bar{u})$, $\bar{f}(w, \bar{\eta}, \bar{x}, \bar{u})$, and $\bar{h}(w, \bar{x})$ vanish at $(\bar{\eta}, \bar{x}, \bar{u}) = (0, 0, 0)$ for all $w \in W$.

Thus, if an output feedback control law of the form

$$\dot{\xi} = f_s(\xi, e), \quad \bar{u} = h_s(\xi, e), \qquad\qquad 16.$$

with $f_s(0, 0) = 0$ and $h_s(0, 0) = 0$, stabilizes the equilibrium $(\bar{\eta}, \bar{x}, \xi) = (0, 0, 0)$ of the resulting closed-loop system shown in Equation 15, then the controller

$$u = \gamma(\eta) + h_s(e, \xi), \quad \dot{\eta} = \alpha(\eta, u), \quad \dot{\xi} = f_s(e, \xi), \qquad\qquad 17.$$

solves the output regulation problem for the original plant shown in Equation 1. In this way, the robust output regulation problem for Equation 1 has been converted into a robust stabilization problem of the equilibrium at the origin of the augmented system shown in Equation 15.

2.4. Construction of Internal Models

From the previous discussion, it follows that the design of an internal model must fulfill two purposes: to make sure that the identity shown in Equation 13 holds and to make sure that the system shown in Equation 15 is stabilizable by means of a feedback of the form shown in Equation 16. A simple strategy to fulfill the identity shown in Equation 13 is to pick

$$\alpha(\eta, u) = \varphi(\eta) + N[u - \gamma(\eta)], \qquad\qquad 18.$$

where N is a matrix of design parameters. In this case, the controller shown in Equation 17 becomes

$$u = \gamma(\eta) + h_s(e, \xi), \quad \dot{\eta} = \varphi(\eta) + N h_s(e, \xi), \quad \dot{\xi} = f_s(e, \xi).$$

The matrix N could be chosen so as to induce, on the internal model, some good properties, such as being input-to-state stable (ISS) (31), thus making it easier to design the stabilizer shown in Equation 16. In what follows, we provide an overview of a few typical internal models widely used in practice. For simplicity, we assume $m = 1$.

2.4.1. Canonical linear internal model.
The canonical linear internal model was first proposed by Nikiforov (32) and later formalized by Serrani & Isidori (33) and Serrani et al. (34). Suppose that the system shown in Equation 9 is immersed into the linear system

$$\dot{\xi} = \Phi \xi, \quad u = \Gamma \xi,$$

and the pair (Φ, Γ) is observable. Let $(\tilde{M}, \tilde{N}) \in \mathbb{R}^{q \times q} \times \mathbb{R}^{q \times 1}$ be any controllable pair, with $\tilde{M}$ Hurwitz and such that the spectra of the matrices Φ and $\tilde{M}$ are disjoint. Then, the Sylvester equation $T\Phi - \tilde{M}T = \tilde{N}\Gamma$ has a unique nonsingular solution. Hence, α in Equation 18 can be taken as

$$\alpha(\eta, u) = M\eta + Nu,$$

in which

$$M = T^{-1}\tilde{M}T, \quad N = T^{-1}\tilde{N}. \qquad\qquad 19.$$

Note that we could also pick

$$\alpha(\eta, u) = \tilde{M}\eta + \tilde{N}u, \qquad\qquad 20.$$

which corresponds to a steady-state generator $(\tilde{\tau}, \tilde{\varphi}, \tilde{\gamma})$, with $\tilde{\tau}(\xi) = T\tau(\xi)$, $\tilde{\varphi}(\xi) = T\Phi T^{-1}\xi$, and $\tilde{\gamma}(\xi) = \Gamma T^{-1}\xi$. A particular advantage of Equation 20 is that it can handle uncertain exosystems (see, e.g., 32, 34–36; for adaptive designs for multivariable and possibly non-minimum-phase linear systems, see 37).

2.4.2. Two nonlinear internal models.   The existence of the canonical linear internal model requires the system shown in Equation 9 to be immersed into a linear system, which essentially requires the nonlinearities in the plant shown in Equation 1 to be polynomial. To weaken this restriction, two nonlinear models have been developed. The first one was given by Huang & Chen (28) under the assumption that the system shown in Equation 9 can be immersed into a nonlinear system of the form shown in Equation 10 with $\varphi(\xi) = \Phi\xi$ for some matrix Φ. The particular form of this immersed system leads to a nonlinear internal model of the form shown in Equation 18 with

$$\alpha(\eta, u) = (M + N\Gamma)\eta + N(u - \gamma(\eta)), \qquad\qquad 21.$$

where Γ is the gradient of γ at the origin, the pair (Φ, Γ) is observable, and the pair (M, N) is the same as in Equation 19. Under some assumption on γ, Equation 21 is globally ISS. Byrnes & Isidori (27) proposed another nonlinear internal model under the assumption that there exist an integer q and a sufficient smooth function $g : \mathbb{R}^q \to \mathbb{R}$ vanishing at the origin such that

$$L_{\mathbf{u}}^q s(w) + g(\mathbf{u}, L_{\mathbf{u}}^q s(w), \dots, L_{\mathbf{u}}^{q-1} s(w)) = 0.$$

In fact, in this case, the system shown in Equation 9 can be immersed into a nonlinear system of the form shown in Equation 10 with $\varphi(\xi) = \mathrm{col}(\xi_2, \dots, \xi_q, g(\xi_1, \dots, \xi_q))$ and $\gamma(\xi) = \xi_1$. If $g(\cdot)$ is bounded, then N can be chosen in such a way that the internal model is ISS. Adaptive approaches in which g is estimated online from data have been proposed by Forte et al. (38) and Bin & Marconi (39).

2.4.3. A general internal model.   All three of the above internal model candidates are constructed under various assumptions on the solution $\mathbf{u}(w)$ of the regulator equations. Marconi et al. (29) have proposed a general internal model. Specifically, it has been shown that there exist a number $\ell > 0$ and a subset $S \subset \mathbb{C}$ of zero Lebesgue measure such that, if $q \geq 2n_w + 2$ and $(M, N) \in \mathbb{R}^{q \times q} \times \mathbb{R}^{q \times 1}$ is a controllable pair with M having eigenvalues in $\{\lambda \in \mathbb{C} : \mathrm{Re}[\lambda] \leq -\ell\} \setminus S$, then there exist a continuous map $\gamma : \mathbb{R}^q \to \mathbb{R}$ and a continuously differentiable map $\tau : W \to \mathbb{R}^q$ such that Equation 11 is satisfied with $\varphi(\xi) = M\xi + N\gamma(\xi)$. As a result,

$$\dot{\eta} = M\eta + Nu \qquad\qquad 22.$$

is an ISS internal model.

The applicability of the internal model shown in Equation 22 relies on the explicit construction of the function γ. But this function is only known to exist. Methods for constructing a locally Lipschitz approximation of such a function were discussed by Marconi & Praly (40), while adaptive methods constructing it online from data have been proposed by Pyrkin & Isidori (41), Bernard et al. (42), and Bin et al. (43). Note that Marconi et al. (29) used this internal model to study the semiglobal robust output regulation problem for some non-minimum-phase nonlinear systems.

2.5. Post- and Preprocessing Internal Models, the Chicken-and-Egg Dilemma, and the Robustness Issue

The internal model–based regulator given in Equation 17 has a structure shown in **Figure 1b**, which is different from the one originally proposed by Davison (11) in the linear setting, shown in

Figure 1*a*. Following the terminology used by Isidori & Marconi (44) and Bin & Marconi (45), we refer to the two architectures as preprocessing and postprocessing.

As remarked in References 44–48, while postprocessing architectures are more appealing for handling general multivariable systems, they pose some structural problems in the constructive design of the regulator for nonlinear systems (in this way justifying the research drift toward preprocessing schemes observed so far and summarized in the previous sections). In fact, a chicken-and-egg dilemma arises in the design of the stabilizer and the internal model, because the former depends on the latter (since it is expected to stabilize the cascade between the plant and internal model) and the latter also depends on the former (since the cascade of the two is expected to provide the ideal steady-state input) (see 45, 49). For linear systems, a sequential design of the two units is possible since the harmonics of the ideal state inputs are known a priori (as coincident with the exosystem modes) and are independent of the stabilizer. The nonlinear case is more challenging and calls for a synergistic design of the stabilizer and internal model in which both are simultaneously designed to guarantee the invariance of the steady-state manifold associated with a zero regulation error and its attractiveness. The adoption of a mix of adaptive and identification tools is one possible approach (investigated in 39, 42, 43).

The quest for robustness is a further fundamental research topic when dealing with the design of the regulators for multivariable nonlinear systems (50, 51). As shown by Bin et al. (51), the formal requirement of robustness necessarily asks one to specify which property must be preserved under system uncertainties (with zero asymptotic regulation error being only one—often quite idealistic—possible property) and which kind of topology is used to model system uncertainties. In the case of nonlinear systems, insisting on the ideal property of zero regulation error in the presence of arbitrary plant uncertainties seems to be unrealistic, to the point that Bin et al. (51) proved that no finite-dimensional robust regulator exists if unstructured perturbations are considered. This result motivates research toward approximate but robust designs, such as the adaptive approaches mentioned above and the one given by Astolfi et al. (46), or toward infinite-dimensional internal models, such as those already used in the context of iterative learning and repetitive control (52–54), thus opening the way to broader notions of the IMP depending on the adopted achievable property and the topology in which perturbations are intended.

3. AN INTERNAL MODEL PRINCIPLE IN SYSTEMS BIOLOGY AND BIOENGINEERING

Organisms depend critically, for their adaptability and survival, on their ability to formulate appropriate responses to chemical and physical environmental cues, distinguishing background signals from informative inputs. They must maintain a narrow range of concentration levels of vital quantities (homeostasis and adaptation) while at the same time appropriately reacting to informative changes in the environment (signal detection). This is achieved by regulatory changes in metabolism and gene expression, which are in turn mediated by signal transduction and gene regulatory networks in individual cells that process sensed chemicals (such as nutrients or chemokines) or physical inputs (such as temperature, pressure, or electric potentials). Much theoretical, modeling, and analysis effort has been devoted to understanding these aspects of living systems, traditionally in the context of steady-state responses to constant or step-changing stimuli. In the field of synthetic biology, and motivated by the need to tune the dynamics and improve the robustness of designed gene circuits, biological engineers have proposed various ways to mimic natural molecular feedback control mechanisms, including mechanisms for adaptation (55). The antithetic controller design, briefly discussed in this section in the context of the IMP, is a particularly notable solution to the adaptation problem through genetic engineering or enzymatic pathways.
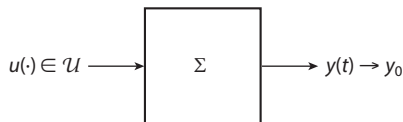
$$u(\cdot) \in \mathcal{U} \longrightarrow \boxed{\Sigma} \longrightarrow y(t) \to y_0$$

Figure 2

The system discussed in Section 3, which has a regulated output $y(t)$ when inputs are in $\mathcal{U}$.

To study the simplest formulation, in this section we will say that a system Σ regulates against all external input signals u in a given class $\mathcal{U}$ of time functions (e.g., $\mathcal{U}$ might be the class of all constant inputs or of all inputs that are periodic with a certain period) if a certain quantity $y(t)$ associated with the system (the output, in control-theory terms) has the property that $y(t) \to y_0$ as $t \to \infty$ whenever the system is subject to an input signal from the class $\mathcal{U}$ (**Figure 2**), where y_0 is a fixed value that does not depend on the particular input $u \in \mathcal{U}$. In control theory, this would be called a disturbance rejection property (or, if the output is the error signal with respect to a desired reference input, a tracking problem).

In biology, one often uses the term adaptation for this property. An example studied by Yi et al. (56) from a control-theoretic viewpoint is that of bacterial *E. coli* chemotaxis, where adaptation against constant inputs (chemoattractants) plays a central role in enabling motion in the directions of nutrient change. If the nutrients being sensed do not change much during a time interval, then they are sensed as constant, and no directed motion happens. In this example, and simplifying a little to give the intuitive idea, y_0 is the internal concentration of a kinase, a chemical signaling protein. At this special value y_0, the bacterium moves purely at random, instead of actively trying to move in a directed fashion. Adaptation against constant inputs is achieved by an integrator embedded in the system, in which the methylation state of a receptor serves as a memory (integrator), and the error is the average kinase activity relative to its basal value.

The question that the IMP asks is, If a system Σ is seen experimentally to regulate against all inputs in $\mathcal{U}$, then what can be said about its internal structure? Answers to this question may help guide experimentalists and modelers by ruling out putative mechanisms and suggesting a search for components responsible for adaptation.

A bit more formally, the IMP states, roughly, that if the system Σ adapts to $\mathcal{U}$, then it necessarily must contain a subsystem Σ_{IM} that can itself generate all inputs in the class $\mathcal{U}$. The terminology arises when thinking of Σ_{IM} as a model of a system that generates the external signals. For example, if $y(t) \to y_0$ as $t \to \infty$ whenever the system is subject to any external constant signal (i.e., the class $\mathcal{U}$ consists of all constant functions), then the system Σ must contain a subsystem Σ_{IM} that generates all constant signals (typically an integrator, since constant signals are generated by the differential equation $\dot{u} = 0$). If, instead, $y(t) \to y_0$ as $t \to \infty$ whenever the system is subject to a sinusoidal signal at frequency ω [i.e., the class $\mathcal{U}$ consists of all functions of the type $A \sin(\omega t + \phi)$, for some fixed ω but different possible amplitudes A and phases ϕ], then Σ should have a subsystem Σ_{IM} that generates these signals (such as a harmonic oscillator $\dot{x}_1 = x_2, \dot{x}_2 = -\omega^2 x_1$), and so forth. In addition, the IMP specifies that, in an appropriate sense, the subsystem Σ_{IM} must have only y as its external input, receiving no other direct information from other parts of the system or the input signal u. One intuitive interpretation is that Σ_{IM} generates its best guess of the external input u based on how far the output y is from y_0. Pictorially, if we have the situation shown in **Figure 2**, then there must be a decomposition of the system Σ into two parts, as shown in **Figure 3**, where the system Σ_{IM} (with $y \equiv y_0$) is capable of reproducing all the functions in $\mathcal{U}$. The IMP originates in the biological cybernetics literature, and like any principle, it is not a specific result, but rather is a guide for different theorems, which hold under different technical assumptions and whose
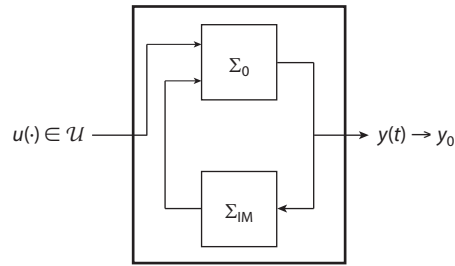
Figure 3

Decomposition of Σ into Σ_0 and Σ_{IM}, the latter driven by $y(t)$.

conclusions will depend on the precise meaning of "class of external signals," "reproducing all functions," and so on.

The theory of Francis and Wonham applies to systems Σ that are already partitioned into a plant and a controller. The robustness assumption amounts to the requirement that the given controller should perform appropriately [in the sense that the regulation objective $y(t) \to y_0$ is achieved] even when the plant subsystem—but most definitely not the controller subsystem—is arbitrarily perturbed. The conclusion is that the controller is driven by y and incorporates a model of the external signals. (It is obvious that some additional condition, such as structural stability, must be imposed, since otherwise the trivial system Σ that simply outputs $y \equiv y_0$ for every possible input signal u adapts but does not contain any subsystem generating the signals in $\mathcal{U}$.)

In biological applications, it is very difficult to think of a plant and controller as different objects—the system regulates itself, and therefore the separate robustness of a controller is arguably not a natural condition. In addition, few biological systems behave in even approximate linear regimes. Thus, it is desirable to have theorems that (*a*) apply to nonlinear systems Σ, (*b*) do not require the system Σ to be split between plant and controller subsystems, and (*c*) do not require structural stability (robustness) in the sense of the Francis and Wonham theory.

We review here a result from Sontag (6), illustrated with an example from Shoval et al. (57), that shows that, under certain Lie-algebraic conditions on the system and assuming that the inputs in $\mathcal{U}$ are not too unstable, the IMP holds when we impose instead of robustness a condition that amounts to a signal detection property: that the output must reflect sudden changes in the input (thus ruling out the trivial solution $y \equiv y_0$).

We study dynamical systems with inputs and outputs in the standard sense of control systems theory (58):

$$\dot{\mathbf{x}} = F(\mathbf{x}, u), \quad y = h(\mathbf{x}), \qquad\qquad 23.$$

where F and h are functions that describe the dynamics and the readout map, respectively. Here, $u = u(t)$ is a generally time-dependent input (in biology, an input is typically called a stimulus or excitation) function, $\mathbf{x}(t)$ is an n-dimensional vector of state variables, and $y(t)$ is the output (in biology, response or reporter variables). These notations are slightly different from those in the previous section. Here, u is the input received from the exosystem (see below), called w previously, and y is the regulated output. In addition, the state $\mathbf{x}$ encompasses both the state x and the controller state x_c, because we do not wish to impose an a priori decomposition between plant and controller. To describe the positivity of variables as well as other constraints, we introduce the following additional notations. States, inputs, and outputs are constrained to lie in open subsets, which we call $\mathbb{X}$, $\mathbb{U}$, and $\mathbb{Y}$, respectively, of Euclidean spaces $\mathbb{R}^n$, $\mathbb{R}^m$, and $\mathbb{R}^q$. For example, $\mathbb{U} = \mathbb{R}_{>0}$ means that the input values must be scalar ($m = 1$, $\mathbb{U} \subset \mathbb{R}^1$) and positive. The functions F and h

are differentiable. We will assume that for each piecewise-continuous input $u : [0, \infty) \to \mathbb{U}$ and each initial state $\xi \in \mathbb{X}$, there is a (unique) solution $\mathbf{x} : [0, \infty) \to \mathbb{X}$ of Equation 23 with initial condition $\mathbf{x}(0) = \xi$, and the corresponding output $y : [0, \infty) \to \mathbb{Y}$ is $y(t) = b(\mathbf{x}(t))$. For simplicity, we will restrict the discussion to scalar-input, scalar-output n-dimensional systems for which the input appears as a first-order term:

$$\dot{\mathbf{x}} = f(\mathbf{x}) + ug(\mathbf{x}), \quad y = b(\mathbf{x}). \qquad 24.$$

The vector fields f and g are smooth, and b is a smooth function.

We will illustrate the main result by means of the incoherent feedforward loop (IFFL) model that is often studied in the systems biology literature:

$$\dot{x} = \alpha u - \delta x, \quad \dot{y} = \beta \frac{u}{x} - \gamma y, \qquad 25.$$

with $b(x, y) = y$, where u, x, and y are assumed to evolve in the set of positive real numbers. In vector form, this is $\dot{\mathbf{x}} = f(\mathbf{x}) + ug(\mathbf{x})$, where the vector fields are

$$f(x, y) = \begin{pmatrix} -\delta x \\ -\gamma y \end{pmatrix} \quad \text{and} \quad g(x, y) = \begin{pmatrix} \alpha \\ \beta/x \end{pmatrix}. \qquad 26.$$

In an IFFL, the input u directly helps promote the formation of the reporter y and also acts as a delayed inhibitor, through an intermediate variable x. This incoherent counterbalance between a positive and a negative effect gives rise, under appropriate conditions, to adaptation. There are many models of IFFLs, but this is one of the simplest. IFFLs are ubiquitous in systems biology. Kim et al. (59) provided a large number of incoherent feedforward input-to-response circuits, which participate in converting EGF to ERK activation (60, 61), glucose to insulin release (62, 63), ATP to intracellular calcium release (64, 65), and nitric oxide to NF-κB activation (66); carrying out microRNA regulation (67); and many other processes. A variation of the model studied by Shoval et al. (57) was given by Tyson et al. (68) and Sontag (69) and appears in slightly modified forms in models of *Dictyostelium* chemotaxis and neutrophils (70, 71), microRNA-mediated loops (72), and *E. coli* carbohydrate uptake via the carbohydrate phosphotransferase system (73) and other metabolic systems (74). Bleris et al. (75) showed experimentally and analytically that IFFLs are especially well suited to controlling protein expression under DNA copy variability.

We will say that the system shown in Equation 24 adapts to inputs in a class $\mathcal{U}$ if for each $u \in \mathcal{U}$ and each initial state $x^0 \in \mathbb{X}$, the solution of Equation 24 with initial condition $x(0) = x^0$ exists for all $t \geq 0$ and is bounded, and the corresponding output $y(t) = b(x(t))$ converges to a fixed value $y_0 \in \mathbb{Y}$ (which does not depend on the particular input $u \in \mathcal{U}$) as $t \to \infty$. As usual in control theory, we describe the class of inputs $\mathcal{U}$ with respect to which adaptation holds through the specification of an exosystem that produces these inputs. An exosystem is simply any autonomous system Γ described by the equations

$$\dot{w} = Q(w), \quad u = \theta(w),$$

and such that the input class $\mathcal{U}$ consists exactly of the functions $u(t) = \theta(w(t))$, $t \geq 0$, for each possible initial condition $w(0)$. For example, if we are interested in step responses, we pick $\dot{w} = 0$, $u = w$. This means that the possible signals are the solutions of $\dot{w} = 0$, i.e., the constant functions of time; in other words, $\mathcal{U}$ is the set of functions $u(t)$ for which $u(t) = \bar{u}$ for all t for some $\bar{u} \in \mathbb{U}$. (In biology, the term perfect adaptation is used, or, in the context of biochemical networks and y being one of the state variables, absolute concentration robustness.) On the other hand, if we are interested in sinusoids with frequency ω, then we would use $\dot{x}_1 = x_2, \dot{x}_2 = -\omega^2 x_1, u = x_1$.

We also impose the condition that the signals in $\mathcal{U}$ do not grow without bound. Specifically, the exosystem is assumed to be Poisson stable, meaning that for every state w^0, the solution

$w(\cdot)$ of $\dot{w} = Q(w)$, $w(0) = w^0$, is defined for all $t > 0$, is bounded, and satisfies that w^0 is in the omega-limit set of w. In other words, the exosystem is almost periodic in the sense that trajectories keep returning to neighborhoods of the initial state. Both the constant and sinusoidal examples mentioned above are generated by Poisson-stable systems. By contrast, ramps (linearly growing signals) are not generated by Poisson-stable systems, since they require an unstable second-order system $\dot{w}_2 = 0$, $\dot{w}_1 = w_2$, $u = w_1$, to generate them. Thus, adaptation to ramps is not included in the scope of the theorem to be stated. The exosystem is assumed to have states that evolve on some differentiable manifold, Q is a smooth vector field, and θ is a real-valued smooth function.

The IMP claims that a copy of this exosystem must be embedded in the system shown in Equation 24. More precisely, one says that the system contains an output-driven internal model of $\mathcal{U}$ if there is a change of coordinates that brings Equation 24 into the following block form:

$$\begin{aligned}
\dot{z}_1 &= f_1(z_1, z_2) + u g_1(z_1, z_2), \\
\dot{z}_2 &= f_2(y, z_2), \\
y &= \kappa(z_1),
\end{aligned}$$

so that the subsystem with state variables z_2 is capable of generating all of the possible functions in $\mathcal{U}$. That is, for some function $\varphi(z_2)$ and for each possible $u \in \mathcal{U}$, there is some solution of

$$\dot{z}_2 = f_2(y_0, z_2)$$

that satisfies $\varphi(z_2(t)) \equiv u(t)$. A change of coordinates means that there is some integer $r \le n$ and two differentiable manifolds Z_1 and Z_2 of dimensions r and $n - r$, respectively; a smooth function $\kappa : Z_1 \to \mathbb{R}$; two vector fields F and G on $Z_1 \times Z_2$ that take the partitioned form

$$F = \begin{pmatrix} f_1(z_1, z_2) \\ f_2(\kappa(z_1), z_2) \end{pmatrix}, \quad G = \begin{pmatrix} g_1(z_1, z_2) \\ 0 \end{pmatrix};$$

and a diffeomorphism $\Phi : \mathbb{R}^n \to Z_1 \times Z_2$, such that $\Phi'(x)f(x) = F(\Phi(x))$, $\Phi'(x)g(x) = G(\Phi(x))$, and $\kappa(\Phi_1(x)) = b(x)$ for all $x \in \mathbb{U}$, where Φ_1 is the Z_1 component of Φ and a prime indicates a Jacobian. Intuitively, the signal z_2 computes an integral of a function of the output $y(t)$, and when $y(t) \equiv y_0$, z_2 is (up to the mapping φ, which may be interpreted as a sort of rescaling) a signal in $\mathcal{U}$. For example, if $\mathcal{U}$ consists of constant functions (adaptation to steps), then for $y \equiv y_0$, one obtains (for different initial conditions) the possible constant signals.

To prove a theorem justifying the IMP, Sontag (6) imposed several technical conditions. The first (which we will refer to here as A1) is a signal detection or sensitivity property: For some positive integer r, called in control theory a finite uniform relative degree, $L_g L_f^k b \equiv 0$, $k = 0, \ldots$, $r - 2$, and $L_g L_f^{r-1} b(x) \ne 0 \; \forall x \in \mathbb{X}$. Generally, $L_X H$ denotes the directional or Lie derivative of a function H along the direction of a vector field X: $(L_X H)(x) = \nabla H(x) \cdot X(x)$, and one understands $L_Y L_X H$ as the iteration $L_Y(L_x H)$. [In the special case that $L_g b(x) \ne 0$ for all x, the relative degree is $r = 1$, since the condition for $k < r - 1$ is vacuous.] Given that the relative degree is r, one may consider the following vector fields:

$$\widetilde{g}(x) = \frac{1}{L_g L_f^{r-1} b(x)} g(x), \quad \widetilde{f}(x) = f(x) - \left(L_f^r b(x) \right) \widetilde{g}(x), \quad \tau_i := \mathrm{ad}_{\widetilde{f}}^{i-1} \widetilde{g}, \; i = 1, \ldots r,$$

where ad_X is the operator $\mathrm{ad}_X Y = [X, Y] = $ Lie bracket of the vector fields X and Y, and $\mathrm{ad}_{\widetilde{f}}^{i-1}$ is the iteration of this operator $i - 1$ times (when $i = 1$, $\tau_i = \widetilde{g}$). One says that a vector field X is complete if the solution of the initial value problem $\dot{x} = X(x)$, $x(0) = x^0$, is defined for all t and for any initial state x^0. Two vector fields X and Y are said to commute if $[X, Y] = 0$. The two final assumptions, then, are that τ_i is complete, for $i = 1, \ldots, r$ (A2), and that the vector fields τ_i commute with each other (A3). (In the special case $r = 1$, condition A3 is automatic, since every vector field commutes

with itself.) These assumptions are satisfied for linear systems. The assumptions are also satisfied, for example, for the IFFL system in Equation 25. Indeed, since $L_g h = (0, 1) \cdot (\alpha, \beta/x)^\mathrm{T} = \beta/x$ is everywhere nonzero, we have that $r = 1$. Thus, we need only check that

$$\tau_1 = \widetilde{g} = \frac{1}{L_g h(x)} g(x) = \frac{x}{\beta} g(x) = \begin{pmatrix} \frac{\alpha}{\beta} x \\ 1 \end{pmatrix}$$

is complete, which is true because $\widetilde{g}$ is a linear vector field.

The main theorem in Reference 6 says the following: Suppose that assumptions A1–A3 hold for the system in Equation 24. If this system adapts to inputs in a class $\mathcal{U}$ generated by a Poisson-stable exosystem, then it contains an output-driven internal model of $\mathcal{U}$.

The proof of this theorem consists of showing that there is, under the stated conditions, a change of variables as claimed. The map producing the change of variables is obtained by solving a first-order partial differential equation. Conditions A1–A3, as well as the assumption that inputs appear linearly, are sufficient but not necessary for the IMP to hold. In addition, instead of a change of coordinates into the block form with states (z_1, z_2), one may state weaker versions of the IMP, which assert only the existence of a function $z_2 = \pi(x)$ so that $\dot{z}_2 = f_2(y, z_2)$ and a function φ so that $\varphi(z_2(t))$ reproduces all inputs; this can be formalized in the language of immersions, as in the previous section.

Let us now illustrate this change of variables with the system in Equation 25, or Equation 26 in vector form. This system adapts to steps (constant inputs): It is easy to see, for any constant (positive) input $u(t) \equiv u$, that there is global asymptotic stability of the steady state $x_0 = \alpha u/\delta$ and $y_0 = \frac{\beta\delta}{\alpha\gamma}$, and that y_0 is independent of u. We already checked properties A1–A3 and the system, so the theorem says that it should be possible to recast the system in integral feedback form. The proof in Reference 6 asserts the existence of a mapping $\varphi(x, y)$ whose Lie derivative along g solves the following first-order linear partial differential equation:

$$L_g \varphi = \nabla\varphi \cdot g = \alpha\varphi_x(x, y) + \frac{\beta}{x}\varphi_y(x, y) = 0.$$

Generally, such an equation may be solved using the method of characteristics. However, in our example, the solution is immediate: $\varphi(x, y) = \alpha y - \beta \log x$. The map

$$(x, y) \mapsto (z_1, z_2) = (y, \varphi(x, y)) = (y, \alpha y - \beta \log x)$$

is a diffeomorphism whose inverse is $y = z_1$ and $x = e^{(\alpha z_1 - z_2)/\beta}$. We obtain the following equations in the new coordinates (z_1, z_2):

$$\dot{z}_1 = \beta u e^{(z_2 - \alpha z_1)/\beta} - \gamma z_1,$$

$$\dot{z}_2 = \beta\delta - \alpha\gamma z_1,$$

with output $y = z_1$. This has the desired internal model form $\dot{z}_1 = f_1(z_1, z_2) + u g_1(z_1, z_2)$, $\dot{z}_2 = f_2(y, z_2)$, and $y = \kappa(z_1)$ if we define $f_1(z_1, z_2) = -\gamma z_1$, $g_1(z_1, z_2) = \beta e^{(z_2 - \alpha z_1)/\beta}$, $f_2(y, z_2) = f_2(y) = \beta\delta - \alpha\gamma y$, and $\kappa = \text{identity}$. Thus, z_2 is the variable that integrates the error: When $y = y_0 = \frac{\beta\delta}{\alpha\gamma}$, the equation for z_2 becomes $\dot{z}_2 = 0$, whose solutions are all the possible constant signals. We can also write this system in terms of the coordinates $x = e^{z_2/\beta}$, $y = z_1$, as follows:

$$\dot{x} = cx(y_0 - y), \quad \dot{y} = \beta u x e^{-\frac{\alpha}{\beta}y} - \gamma y,$$

with $c := \alpha\gamma/\beta$. More details are given in Reference 57. This system has the generic form $\dot{x} = xF(y_0 - y)$, $\dot{y} = G(x, y, u)$, of nonlinear integral feedback systems in Reference 76. Bacterial chemotaxis models often can be shown to have this form.

The antithetic controller proposed by Briat et al. (77), and subsequently implemented experimentally in *E. coli* bacteria (78) and in in vitro cell-free bacterial extracts and other systems (79–81), is based on the following underlying structure:

$$\dot{x}_1 = y_0 - \eta x_1 x_2,$$

$$\dot{x}_2 = y - \eta x_1 x_2,$$

$$\dot{x}_3 = k(x_1, x_3, u), \quad y = h(x),$$

in which the scalar x_1 and x_2 variables (actuator and sensor species, respectively) correspond to a genetically engineered controller and x_3 corresponds to the system being controlled. The input u might represent environmental parameters such as acidity or temperature or might quantify the number of copies of a particular gene inserted in cells. The interaction term $x_1 x_2$ represents an irreversible molecular binding or sequestration process in which the two controller species annihilate each other, such as an anti-σ factor binding and inactivating a σ factor (a protein needed for the initiation of transcription in bacteria). If the system converges to steady state for constant inputs u, then it is clear that $y(t) \to y_0$, the value that represents adaptation. Thus, we expect an integral controller to be present in the system (IMP with exosystem $\dot{u} = 0$). Indeed, let us simply change variables, letting z_1 consist of x_1 and x_3 and $z_2 := x_1 - x_2$. Clearly, $\dot{z}_2 = y_0 - y$, so this change of variables displays the form predicted by the IMP, with $f_2(y, z_2) = f_2(y) = y_0 - y$. Note that in the new coordinates, $\dot{x}_1 = y_0 - \eta(x_1 - z_2)x_1$, and the equations for x_3 remain unchanged. [If the original system is not affine on inputs u, then the IMP form will simply have a more general dynamics $\dot{z}_1 = f(z_1, z_2, u)$.]

4. INTERNAL MODELS IN NEUROSCIENCE

Sensorimotor integration, the transformation of sensory information into motor actions, is one of the most studied functions of the nervous system. Producing context-appropriate movement for foraging, escaping from predators, or mating is critical to animal survival. Moreover, since the output of this computation (movement) and many of its inputs (sensory stimuli) can be measured from behavior alone, sensorimotor integration can be studied in humans as well as a variety of animal species.

Many of the early studies focused on reflexive movements, in which sensory stimuli directly drive stereotypical motor actions in response. However, it has been clear for a long time (82) that many sensorimotor transformations in nature do not fall in this category but display predictive and adaptive features. The framework of control theory has been very influential in developing insight into the computations underlying these features and guiding experimental investigations of their neural implementation.

Whenever it is observed that a control system is capable of perfect (asymptotic) tracking of the reference signals produced by an exogenous system, the IMP implies that the controller must include an internal model of this exosystem (in addition to feedback control). Similarly, a control system capable of closing a sensorimotor loop with no apparent delay (or a delay that is significantly shorter than the sensory and actuation lags) must include an internal model of relevant parts of the sensorimotor plant within a feedforward or predictive control scheme. Theoretical considerations such as these can be translated into experiments that probe the use of internal models in the nervous system.

Here, we review some of the experimental evidence that the sensorimotor transformations performed by humans and many animal species are in fact consistent with the use of internal models

of the plant and the environment, and discuss what is known about their neural implementation. A variety of techniques and experimental preparations have been effectively employed to functionally probe these models, but revealing the neural mechanisms underlying these computations has proved challenging, with progress limited to a few special preparations and focused mostly on internal models of the plant. Therefore, while they are outside the IMP discussed in the previous sections—since they are driven by copies of the control signal u—we start by discussing evidence for forward (direct) models of the plant (for an extended discussion, including inverse models of the plant, see 1). Internal models of the environment—which directly relate to the IMP—are discussed afterward, focusing on the context of modeling the feasible trajectories of a moving target. Finally, we indulge in a bit of speculation on the relation between the two types of models and the possible utility of the IMP for future experimental investigations. Some of the fascinating questions that remain open for investigation include (*a*) to what extent internal models are explicitly represented in the nervous system, as opposed to implicitly computed; (*b*) whether there are separate neural substrates for different types of internal models and for feedback control; and (*c*) to what extent neural mechanisms implementing internal models have been conserved across species.

4.1. Internal Models of the Plant

Humans and animals can perform motor gestures that require exquisite temporal and spatial precision, such as hitting a baseball or catching evading prey. While this is theoretically achievable via pure feedback control (with the right sequence of fast reflexive corrections), the sensorimotor delay is usually large relative to the task. For example, visual processing alone takes a minimum of 20 ms in insects such as dragonflies and 100 ms or more in humans. Significant delays are also introduced in the loop by neural computations and muscle contractions to generate forces. It is hard to imagine how a purely feedback-based controller with these lags could enable a hunting dragonfly to catch its prey within 150 ms or enable a professional baseball player to hit a ball within 500 ms. Moreover, any sensory apparatus has limited resolution, and the sensory information driving the feedback loop (e.g., the prey or ball position) must be isolated from a variety of noise sources. In particular, the nervous system must distinguish useful sensory information about the external world from self-motion artifacts, which every motor gesture produces. Finally, it is unclear how context-dependent movements could be implemented in a purely reflexive system. For example, insects have an innate optomotor reflex that keeps their body orientation aligned with the horizon, but this reflex would prevent a dragonfly from performing banked turns while pursuing prey.

It is thus posited that the nervous system combines some form of model-based predictive control with sensory-driven feedback loops. As the nervous system plans and executes a motor action, a copy of the motor command [efference copy (82)] is thought to be processed through a forward model of the plant and combined with incoming delayed sensory input (afferent input). Such a control architecture (**Figure 4**) resolves the limitations of pure feedback control. The nervous system can avoid the large sensorimotor lag by closing the loop with predicted sensory input or with some predicted internal state, computed using the forward model within a state observer (e.g., by using a Kalman filter–type architecture). Moreover, the sensory consequences of self-motion can be predicted and canceled from the incoming sensory stream to improve the ability to extract sensory information about the external world. This cancellation can occur by adding to the sensory input a signal equal and opposite to the predicted contribution of self-motion ("software cancellation") or by moving the sensory apparatus (e.g., the eyes) in a way that counteracts the effect of self-motion ("hardware cancellation"). Similar mechanisms can be used to guarantee that reflexive responses are activated only by unexpected sensory inputs and
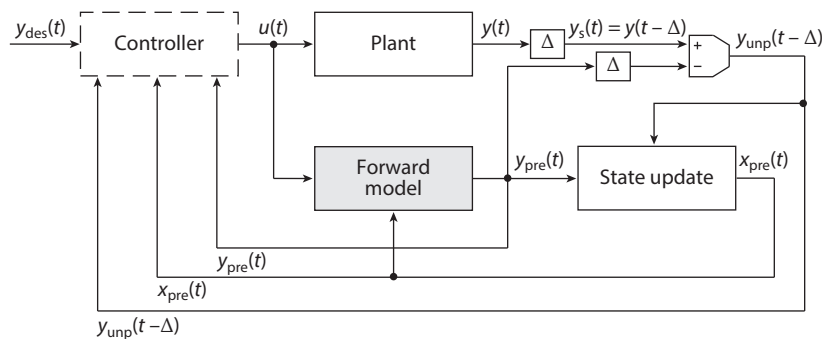
Figure 4

Example of a control architecture with a forward model of the plant, as it may be used in the nervous system to predict upcoming sensory inputs [$y_{pre}(t)$], identify the unpredicted information [$y_{unp}(t - \Delta)$] within the raw sensory signals [$y_s(t)$], or estimate internal states [$x_{pre}(t)$]. The controller may use $y_{pre}(t)$ or $x_{pre}(t)$ to close the loop without being subject to the sensorimotor lag Δ.

not by self-motion artifacts. For challenging goal-oriented tasks, such as catching prey or hitting a baseball, the nervous system may also exploit internal models of the external world to predict the future position of the goal. We discuss these models in the next subsection.

Significant insight into sensorimotor integration, at least at the computational level, can be obtained even without neural recordings, by tracking the sensory inputs and motor behavior in well-designed experimental conditions. Wolpert et al. (83) used this approach to show that humans are able to optimally combine internal model predictions and sensory feedback to estimate the current state of their arms. They asked human subjects to use one arm to move a computer-controlled manipulandum in the dark and then to report the estimated state of that arm at the end of the movement. Assistive or resistive forces were applied to the manipulandum in some of the trials. The bias and variance of the estimates in the different conditions were inconsistent with pure feedback (in this case proprioception, the sense of relative position between body parts) but were well described by an optimal linear estimator employing a forward model (Kalman filter). Mehta & Schaal (84) found similar results when they asked subjects to control a virtual inverted pendulum via a manipulandum with and without visual feedback. Controlling an inverted pendulum requires real-time control (the control sequence cannot be memorized), but subjects were able to successfully perform this task even during 500-ms periods of visual blackout, suggesting that a forward model was used to provide a persistent estimate of the pendulum state. There is also behavioral evidence for the use of forward models to predict the consequences of self-motion. For example, the latency of eye movements in tracking a moving target, which is usually 130 ms, disappears when the target is manually controlled by the subject (85)—a hardware cancellation of self-motion effects.

While behavioral evidence for forward models in the human brain is relatively rich, the investigation of their neural implementation is limited by the lack of available neural recordings. Indirect evidence, however, points to the cerebellum as a possible locus for these computations. Perturbation of the cerebellum via transcranial magnetic stimulation during a reaching task produces performance deficits consistent with the use of a delayed estimate of the arm position instead of the real-time estimated position (86). Similar motor deficits are observed in patients with cerebellar damage (87).

Direct neural evidence for forward models has been found in the cerebellum of nonhuman primates, in the context of vestibular sensing of head movement. Brooks et al. (88) recorded the

neural activity of the deep cerebellar nuclei, which send the output of the cerebellum to the rest of the brain, when the head of a monkey rotated actively toward a target and when it was rotated passively by a torque motor. They found neurons that responded only to passive rotations of the head and not to active (voluntary) rotations, reflecting a software cancellation of the sensory consequences of self-motion. When a passive rotation was added during active head rotations, the activity of the neurons was proportional to the passive component alone—the unexpected sensory input. Even more interestingly, if the same passive rotation was added to every voluntary movement, the neurons gradually reduced their activity to zero, consistent with adaptation of the forward model responsible for computing the expected consequences of self-motion, which now included the added passive term. The output of the cerebellum may thus represent the difference between predictions, made by a rapidly adaptive forward model, and actual sensory inputs. This output may be used as an innovation term (as in a Kalman filter) by other brain regions that are thought to hold the current estimate of the body state, such as the posterior parietal cortex (89, 90).

But is the forward model itself—which transforms motor signals and current state signals into predicted sensory signals—fully implemented within the cerebellum? After all, the forward model–related signals in the cerebellum reported by Brooks et al. (88) may be inherited from upstream regions or may reflect a distributed computation involving not only the cerebellum but also other regions [including the posterior parietal cortex, as argued by Mulliken & Andersen (91)]. While this question has not been definitely answered, there are anatomical, computational, and experimental considerations (92) suggesting that the forward model may be implemented within the cerebellar cortex itself (not to be confused with the cerebral cortex, of which the posterior parietal cortex is one part). The main neurons in this region (Purkinje cells) receive thousands of sensory inputs and efference copies of motor commands, organized in a strikingly regular fashion that could favor learning complex associations between these inputs. The regular high-frequency spiking patterns of these neurons (simple spikes) encode the expected sensory inputs better than the true ones (93). Purkinje cells also produce special complex spikes when a mismatch occurs between expected and actual sensory inputs—for example, when there is an unexpected sensory input after movement. Complex spikes are thought of as teaching signals, and there is evidence [at least in specific domains, e.g., eye movements (94)] that they may induce changes in the pattern of activity of simple spikes—perhaps reflecting an adaptation of the forward model.

The closest thing to a mechanistic explanation for how a forward model may be implemented comes from a cerebellum-like region in a very different family of organisms, the mormyrid electric fishes (95). These animals sense the presence of other fishes (conspecifics, prey, etc.) by creating weakly electric fields around their bodies and monitoring changes in these fields. However, the activity of the fishes themselves affects the electric fields they use to sense the environment: Their movements in the water affect these fields, and so do the active electric pulses they emit for electrolocation and communication. These animals therefore must be able to cancel the sensory consequences of their own actions to be able to sense the environment, and in fact they do. Through a combination of complex experimental perturbations and measurements, Sawtell and colleagues (as reviewed in 95) could observe the emergence of software cancellation signals in the output of Purkinje-like cells after repeated stimulation of the inputs of these cells during specific bouts of activity. This suggests that the strengths of the synaptic (input) connections to these cells are highly adaptive and that the forward model implementation may be in these synapses, along with the biophysical properties of the cells themselves and their downstream connections.

As illustrated by the electric fish case, some animal species may be more experimentally advantageous than primates for studies of the implementation of forward models of the plant (or any other internal model). Mice are becoming increasingly popular in the sensorimotor field, as it is now possible to combine genetic techniques for measuring and perturbing neural activity

in the brain with complex behavioral paradigms (e.g., 96). Insects are also particularly appealing for their smaller nervous systems, individually identifiable neurons, and available genetic tools in some species (the fruit fly *Drosophila melanogaster*). It has long been known, for example, that during singing, crickets use efference copies of motor commands to modulate sensory inputs (97), but this could be done through a much simpler mechanism than a forward model (4). Recent behavioral and neural data, however, appear to be consistent with the hypothesis that internal models may also be implemented in the nervous systems of insects. A behavioral study of dragonfly hunting flights showed that dragonflies predictively steer their head while maneuvering to keep the image of the prey in a fixed region of the eyes (5). In experimental conditions with the prey (a computer-controlled bead) moving at a constant speed, the head rotation almost perfectly canceled in hardware the effect of self-motion as well as the predictable movement of the prey. This suggests that the head control circuitry includes a forward model and a model of prey motion, perhaps very simple ones (for a possible neural substrate, see 98). Moreover, a neurophysiological study of the fruit fly revealed that during fast, voluntary flight maneuvers, visual neurons receive motor-related inputs that are consistent in magnitude, sign, and latency with what would be needed to cancel in software the sensory consequences of the maneuver (99).

4.2. Internal Models of the Environment

The survival and success of an animal are tied to the environment in which it operates and are particularly dependent on the interactions with external actors such as prey, predators, and mates. It is thus not surprising that the nervous systems of most animals are also capable of internalizing regularities in the environment to improve perception and action selection. Having an internal model for how passive objects are physically bound to move (e.g., due to gravity) or how active external actors are likely to move (e.g., how a prey trajectory is likely to evolve in the near future) gives the nervous system similar advantages to having an internal model of its own plant. It enables an animal to properly weigh noisy sensory information against prior expectations (as in a Kalman filter) and to perform real-time control based on predicted sensory inputs or the estimated state of the environment. This avoids the large sensorimotor lag that would render pure feedback-based control ineffective and makes goal-oriented motor actions possible even when sensory inputs are unavailable or unreliable (e.g., when prey that are being pursued are visually occluded).

Here, we focus on the internal models of a moving object in the context of interception or visual tracking. This is only a subclass of all the internal models of the environment that are likely present in the nervous system, but one that is tractable experimentally since predictions and measurements can be easily compared.

To track and intercept a falling inanimate object, the human brain uses an internal model of physical properties of the world, including gravity and momentum. In a study by Lacquaniti & Maioli (100), when a person prepared to intercept a free-falling ball dropped from different heights, muscle activity at the elbow and wrist joints (measured via electromyography recordings) preceded contact by a fixed amount of time (approximately 100 ms), suggesting a correct time-to-contact estimate in the brain. Moreover, when balls of different masses were dropped, the amplitude of preparatory activity was proportional to the expected momentum of the balls at impact. Internal models of gravity may be innate rather than learned, and somewhat hard coded in the nervous system. In fact, astronauts in space are still biased toward expecting objects to fall according to gravity, which leads to incorrect interception behaviors (101), despite prolonged exposure to a 0-G environment. Similar results have been observed in simulated visual 0-G experiments on Earth. Zago et al. (102) asked subjects to intercept a ball falling behind a projector screen (when it reached the bottom edge of the screen) based on the visual cues provided by a constant-speed

(hence 0-G) target projected on the screen. The speed of the projected target and the timing of ball release were coordinated so that the positions of the physical and virtual target would match at the interception point below the screen. The performance of the subjects in this task remained well below baseline (assessed with 1-G virtual targets) even after many repetitions, and were consistent with the subjects not fully abandoning the assumption of gravity when computing the expected time to contact.

The brain can, however, switch between different internal models of a moving object depending on the context. In another experiment presented by Zago et al. (102), subjects were able to correctly intercept the 0-G virtual target if the task was changed so that the physical ball was removed and the interception was performed with the click of a mouse. Interestingly, in this task the subjects performed better when trained on 0-G rather than 1-G virtual targets. These results may be accounted for by the existence of separate internal models for passive and active targets— the gravity model may have been engaged in the task with the physical ball but not in the virtual interception task.

There is strong behavioral evidence that the nervous system can predictively track the movement of a self-propelled (e.g., prey) or externally controlled target, provided it is sufficiently smooth and regular. For example, human subjects engaged in a manual interceptive task can track without delay targets moving along sinusoidal trajectories at up to 2 Hz (103). These results are well accounted for by a computational model that augments optimal state feedback (enabled by a state predictor and a Kalman filter, as discussed for forward models of the plant) with a disturbance observer that plays the role of the internal model of an exosystem producing the sinusoidal trajectories. Similarly, monkeys can visually track complex trajectories (circles or Lissajous curves in 2D) with a delay of only a few milliseconds (2–20 ms), much shorter than the full visuomotor lag observed in response to unpredictable shifts of the target (80–100 ms) (104).

There are very few physiological studies of internal models of the environment, but the available results are similar to those described for forward models of the plant. Cerminara et al. (105) recorded neural activity from the cerebellum of cats during a visually guided reaching task, with the target moving at constant speed and disappearing for 200–300 ms in the middle of the task. They found that the simple spike activity of certain Purkinje cells was significantly modulated by the onset of target motion, and this activity remained modulated (higher or lower firing rates compared with the baseline) until the target stopped moving. Crucially, the modulation of simple spikes during target motion persisted even when the target was not visible. Since the activity of those cells did not appear to encode limb or eye movements, these results suggest that Purkinje cells may have been encoding the predicted (rather than the sensed) target motion produced by an internal model. As in the case of forward models of the plant, computational models have suggested that the cerebellar cortex may be the locus of the internal model computation (104).

While the experimental evidence is much too scarce to draw conclusions, it is tempting to speculate that the similarities between neural data recorded in the context of forward models of the plant and those recorded in the context of models of target motion (e.g., simple spike activity encoding predictions in both cases) may result from a common mechanism for learning and executing internal models. Studying the neural implementation of internal models of the environment could be a tractable alternative to studying forward models of the plant, since the complexity of the environment can be controlled experimentally. The IMP provides a useful theoretical framework for this kind of investigation, as recent work has started to recognize (106). In the context of target tracking, one approach could be to systematically increase the complexity of the exosystem producing the trajectories to be tracked, and search for neural activity that adapts to match the increased complexity of the exosystem. If the nervous system can predictively track the given

trajectories, the IMP proves that an internal copy of the exosystem must in fact be embedded in the neural controller.

5. CONCLUSIONS

In this article, we have presented some fundamental concepts about the IMP and reviewed its development in the different scientific areas of control theory, bioengineering, and neuroscience. In control theory, the IMP has a clear normative role, as it constitutes a design principle guiding the synthesis of efficient control systems. In bioengineering and neuroscience, by contrast, the relevance of the IMP lies more in necessary conditions, as they inform scientists about where to look or what to expect when studying the complex behaviors of living organisms. In view of these different interpretations and usages of the IMP, seeking a common unifying perspective seems unnatural and simplistic. We therefore made no effort in this direction, and we instead limited ourselves to reviewing the different ways in which the IMP develops in the three different areas. Nevertheless, a common theme arises: the idea that the succession of recurrent events in the environment leaves its footprint in the systems that engage with it in the form of internal models, and that these models may be encoded as physical constituents in the system. This is the essence of the IMP, and calling attention to this strikingly similar vision shared by rather different scientific domains was ultimately the main goal of this article. All of the described IMP-based theories are still subjects of active research, and establishing links between different areas aimed at unveiling common underlying structures is an increasingly important research challenge.

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