Feedback Control of Signal Dynamics in a Mitogen-Activated Protein Kinase (MAPK) Pathway Model

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Abstract

Mitogen-activated protein kinases (MAPKs) are enzymes that convert extracellular signals into various outputs such as cell growth, differentiation and cell death. Employing a model that describes a MAPK cascade signal pathway we introduce a feedback control approach to regulate the MAPK dynamics via an external input to the MAPK cascade. Numerical simulations shows the effectivity of the feedback control laws proposed.

Keywords: MAPK; Metabolic Pathways; Pathway Model; Feedback Control; Biological Systems.

1 Introduction

Control technology has been applied in a wide variety of industrial and domestic environments, improving performance, safety and efficiency [1]. Cellular processes, a keystone in the field of biology, has been only benefited recently from such technological advances [2]. Interesting and promising developments are starting to take place both in terms of new algorithms and new applications that have led to a renewed interest in the application of systems and control theory to molecular and cell-biology [3]. The efforts in the control of metabolic processes reported at different conferences [4] and special issues in interdisciplinary journals [5] are impressive indications of this trend. The goals of feedback control in this kind of systems may be to cause excitation or suppression of oscillations, entrainment and synchronization, or transitions from chaotic to periodic oscillations and vice versa [2,3,6,7].

In the recent years, considerable effort has been directed toward the development of computer models aimed at simulating the intracellular complexity of a large number of metabolic processes [6,8]. In particular, intracellular signaling or signal transduction, namely the mechanism by which extracellular signals are converted into cellular responses, has attracted considerable attention. Molecules involved in the pathways are usually multifunctional in sense that they are generally involved in more than a single pathway. Cells are able to receive many different chemical signals from their surrounding, and have the capability to react to signal pattern in an appropriate way [6,8]. The signals are processed by the intracellular signaling network, which is mainly constructed by proteins which react with each other [2,6]. Beside bacterial chemotaxis [9], calcium oscillations [8,9], and cell-cycle control [6], the MAPK cascade [10-14], a three molecule module present in all eucaryotes, has become a model system for quantitative analysis of signaling pathways. Obviously, developmental signalling events must be precisely regulated. A signal that is produced in the wrong time or place will lead to inappropriate developmental responses [6,7], which can be dangerous and cells must be protected against this.

MAPK cascades have been implicated in a variety of intercellular processes including regulation of the cell cycle, apoptosis, cell growth and responses to stress [10-14]. These molecules are of crucial importance in the development of memory and wound healing [13]. Abnormal changes in MAPK pathway regulation often mediate various pathologies, most notably cancer [11,14]. This central role of MAPK mediated signal transduction in most reg-

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ulatory processes makes it an especially attractive metabolic pathway for feedback control studies.

In this work, exploiting a signaling MAPK pathway model we design a model-based feedback control law for the purpose of controlling cell function regulated by the MAPK dynamics. Numerical simulations on a MAPK cascade model shows the effectiveness of the control law proposed. This work is organized as follows: In Section 2, we provide the dynamical model of the MAPK cascade. In Section 3 we develop the model-based control approach to regulate the MAPK dynamics. Numerical simulations in sections 2 and 4 shows the uncontrolled and controlled behavior respectively of the MAPK signal dynamics. Finally, the paper closes with some concluding remarks in Section 5.

2 MAPK Signaling Cascade Mechanism and Model

A very powerful device for regulation of metabolic pathways is a cascade of interconvertible enzymes [17]. In a cascade a target enzyme exists in two forms: a catalytically active state e_p and an inactive (or less active) form e. These two forms can be interconverted by the action of two modifier enzymes: one that activates and another that inactivates. Recently, genetic and biochemical analyses have identified the universally conserved mitogen- activated protein (MAP) kinase cascade as one of the most ubiquitous signal transduction systems [11,12,14]. Most of the intracellular portion of the signaling pathway is a cascade of protein phosphorylations and dephosphorylations (phosphorylations and dephosphorylations are nothing but structural changes). Each step leads to activation or inhibition of further, downstream events or feeds back on upstream events. Every basic activity of the cell happens through signaling. This pathway is activated after a variety of cellular stimuli and regulates numerous physiological processes, particularly the cell division cycle [13].

The MAPK sequential cascade of reactions was initially speculated to serve as an amplifier of an upstream receptor-ligand binding event [12]. More recent analysis indicates that, in many cases, it acts as a switch providing an almost threshold-like input-output response to receptor activation, with a new steady-state level of MAP kinase activity that is substantially higher than the original baseline level, if the input stimulus is above of some threshold [14]. Operation as a switch in this manner could be useful for regulating gene expression events required for a cell decision to divide or differentiate, and this operation can be obtained as a module representing a proportional control scheme in which variables are modulated in response to the immediate difference between a desired output and current output [16]. Interestingly, however, in other situations, this same class of molecular network undergoes exact adaptation or integral feedback control, behavior similar to that of the bacterial chemotaxis pathway [9], with MAP kinase activity proceeding through a transient peak back to its original baseline level in response to continuous ligand-receptor occupancy [16].

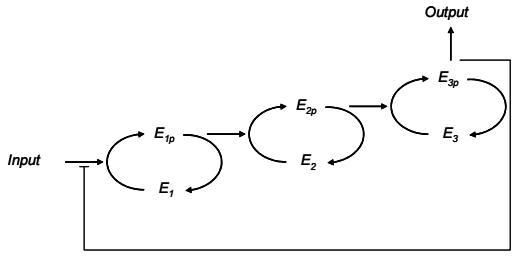

Figure 1: Reaction network in the MAPK cascade model.

Three models of MAPK can be found in the literature. Huang and Ferrell [17] developed a model to describe MAPK activation in *Xenopus oocytes*, they focused on the role of MAPK in all-or-none decisions. Within a large model of second messenger cascades in neurons, Bhalla and Iyengar [12] also consider the MAPK module. They focus rather on properties of the whole network like bistability and oscillations than on features of small modules. Another model is described by Asthagiri and Laufenburger [11], where they illustrate how the MAPK cascade shows adaptation.For our purposes, we consider the simplest possible model as considered by Shvartsman *et al.*, [18]. The model of the MAPK cascade consists of three enzymes, e_1, e_2, and e_3 (1). The three stages in the cascade model the sequential activation of Raf, MAPK kinase (MEK), and MAPK [18]. "Kinases" at each level of the cascade can be in one of the two forms, "base" and "active," which are interconverted by two distinct enzymes. Active forms of e_1 and e_2 catalyze forward reactions of the following stages. In the model, the "phosphatases" catalyzing reactions 2, 4, and 6 are constitutively active [18]. The maximal rate of reaction 1 depends on the magnitude of the input to the cascade (μ). The phosphorylated form of e_3 decreases the input to the cascade reaction; this reflects the fact that formation of the signaling complex stimulating the input to the cascade can be negatively regulated by the active form of extracellular signal regulated kinase

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Table 1: MAPK model parameter values

b_1	0.1	c_3	0.01	e_2	0.01
b_2	0.1	d_1	1.0	e_3	0.01
b_3	0.5	d_2	1.0	τ_1	1
c_1	0.1	d_3	1.0	τ_2	1
c_2	0.01	e_1	0.1	τ_3	1

(ERK) type 2 (ERK2) MAPK [11,18].

Let e_{1P}, e_{2P} and e_{3P} denote the dimensionless (scaled by the total amount of the enzyme) concentrations of the active ("phosphorylated") form of the enzymes. The MAPK cascade model is a connection of three SISO systems given by [18],

$$\begin{aligned}\frac{dx_1}{dt} &= -\frac{b_1 x_1}{c_1 + x_1} + \frac{\mu}{1 + k x_3^{\tau_3}} \frac{d_1(1 - x_1)}{e_1 + (1 - x_1)} \\ \frac{dx_2}{dt} &= -\frac{b_2 x_2}{c_2 + x_2} + x_1^{\tau_1} \frac{d_2(1 - x_2)}{e_2 + (1 - x_2)} \\ \frac{dx_3}{dt} &= -\frac{b_3 x_3}{c_3 + x_3} + x_2^{\tau_2} \frac{d_3(1 - x_3)}{e_3 + (1 - x_3)}\end{aligned} \tag{1}$$

where $x_1 = e_{1P}$, $x_2 = e_{2P}$ and $x_3 = e_{3P}$. b_i and d_i are equilibrium Michaelis constants and c_i and e_i maximum reaction velocities rescaled by the total amount of enzyme at a given stage of the cascade. The input to the signaling cascade is given by $\mu = \mu_0 + G_2 R_T C$, where μ_0 denotes input to the signaling network, independent of endogenous ligand, and G_2 quantifies the efficiency with which occupied receptor stimulates the input to the signaling cascade. Numerous hormones and neurotransmitters mediate their physiological actions by altering the phosphorylation of specific proteins. R_T is the total number of cell surface receptors and C is the surface density of occupied surface receptors [18].

Negative feedback coupled with kinetic time lags can give rise to oscillatory behavior, *i.e.*, periodic oscillations, even for fixed values of external conditions [11,18]. Numerical simulations with data given in Table 2.1 shown that as the parameter k increases a Hopf bifurcation occurs at around $k = 5.1$ (2). However, oscillations in MAPK cascades do not appear to occur naturally, thus, in order to assure lack of oscillations in MAPK a feedback control law is designed in next section.

3 Feedback Control of MAPK Signalling

In this section we develop a robust feedback control scheme to regulate the signal dynamics of MAPK.

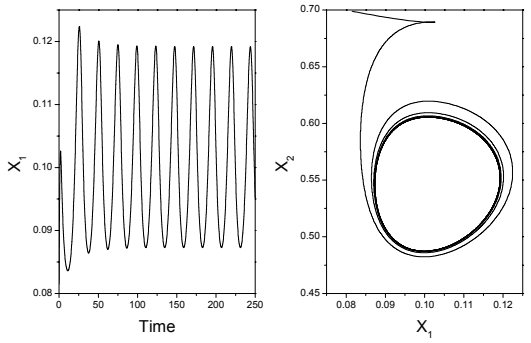

Figure 2: Uncontrolled behavior of the MAPK cascade dynamics.

The control approach is based on the mathematical model that describes MAPK cascade dynamics. The control objective is the regulation of the first enzyme in the cascade cycle x_1 about a constant reference value by manipulation of an external stimuli, $\mu = u(t)$. Inputs can be delivered to the MAPK cascade by different means, *e.g.*, by integrins, one of the numerous growth factor receptor systems, or ionizing radiation [11,18]. Thus, the dynamics of first enzyme can be written as

$$\begin{aligned}\frac{dx_1}{dt} &= -\frac{b_1 x_1}{c_1 + x_1} + \frac{1}{1 + k x_3^{\tau_3}} \\ &\quad \frac{d_1(1 - x_1)}{e_1 + (1 - x_1)} u(t)\end{aligned} \tag{2}$$

The rationale behind the selection of x_1 as the controlled variable is that the first enzyme in the cascade as a direct effect in the dynamical behavior of the next enzymes x_2 and x_3.

Let $x_{1,ref}$ denote the reference value. The problem is how to find the feedback law in order to achieve the desired dynamic behavior for the first enzyme in the MAPK cascade, x_1

$$\frac{dx_1}{dt} = -\varpi_c (x_1 - x_{1,ref}) \tag{3}$$

where $\varpi_c > 0$ is a closed-loop parameter. Notice that the dynamics (3) is asymptotically stable about the reference value $x_{1,ref}$ with ϖ_c as the inverse of a convergence time, *i.e.*, τ_c^{-1}.

Our feedback control law is based on a matching scheme. Provided that,

$$1 + k x_3^{\tau_3} \frac{e_1 + (1 - x_1)}{d_1(1 - x_1)} \neq 0 \qquad \text{for all } t > 0$$

which is evident since variables x_i takes only nonnegative values between {0-1} and $k, e_1, d_1, \tau_3 > 0$, exact model matching between (2) and (3) is achieved

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by the following feedback function

$$u(t) = (1+kx_3^{\tau_3})\frac{e_1+(1-x_1)}{d_1(1-x_1)}\begin{bmatrix} \frac{b_1x_1}{c_1+x_1} \\ -\varpi_c(x_1-x_{1,ref}) \end{bmatrix} \quad (4)$$

This control law requires perfect knowledge of the parameters. Due the uncertainty about the values of the rate constants and kinetic values in metabolic processes, the following assumptions are made for control design purposes:

1. Estimates $\{\overline{k}, \overline{e_1}, \overline{d_1}, \overline{b_1}, \overline{c_1}, \overline{\tau_3}\}$ of the parameters $\{k, e_1, d_1, b_1, c_1, \tau_3\}$ are known. This is not a serious restriction since is possible to get typical estimates of them.

2. The phosphorylated ("active") form of the enzyme x_1 is available for measurement. This is a reasonable assumption, since current experimental test measure the active forms of enzymes.

We can write the enzyme x_1 dynamics as,

$$\begin{aligned} \frac{dx_1}{dt} &= -\frac{\overline{b_1}x_1}{\overline{c_1}+x_1} + \eta(x_1,x_2,u) + \frac{1}{1+\overline{k}x_3^{\overline{\tau_3}}} \quad (5) \\ &\quad \frac{\overline{d_1}(1-x_1)}{\overline{e_1}+(1-x_1)}u(t) \end{aligned}$$

where

$$\begin{aligned} \eta(x_1,x_2,u) &= -\left[\frac{b_1x_1}{c_1+x_1} - \frac{\overline{b_1}x_1}{\overline{c_1}+x_1}\right] - \\ &\quad \begin{bmatrix} \frac{1}{1+\overline{k}x_3^{\overline{\tau_3}}}\frac{\overline{d_1}(1-x_1)}{\overline{e_1}+(1-x_1)} - \\ \frac{1}{1+kx_3^{\tau_3}}\frac{d_1(1-x_1)}{e_1+(1-x_1)} \end{bmatrix} u(t) \quad (6) \end{aligned}$$

is the model error function. Since the uncertain term η, requires the perfect knowledge of parameters $\{k, e_1, d_1, b_1, c_1, \tau_3\}$ in order to get an estimated signal $(\overline{\eta})$ of η we introduce the following observer [19,20],

$$\frac{d\overline{\eta}}{dt} = \varpi_e(\eta - \overline{\eta}) \quad (7)$$

where ϖ_e is an estimation design parameter. From (5), we know that,

$$\eta = \frac{dx_1}{dt} + \frac{\overline{b_1}x_1}{\overline{c_1}+x_1} - \frac{1}{1+\overline{k}x_3^{\overline{\tau_3}}}\frac{\overline{d_1}(1-x_1)}{\overline{e_1}+(1-x_1)}u(t)$$

Therefore,

$$\begin{aligned} \frac{d\overline{\eta}}{dt} &= \varpi_e\Big(\frac{dx_1}{dt} + \frac{\overline{b_1}x_1}{\overline{c_1}+x_1} - \frac{1}{1+\overline{k}x_3^{\overline{\tau_3}}}\frac{\overline{d_1}(1-x_1)}{\overline{e_1}+(1-x_1)} \\ &\quad u(t) - \overline{\eta}\Big) \end{aligned}$$

introduce the variable $w \stackrel{def}{=} \varpi_e^{-1}\overline{\eta} - x_1$. Then, the estimator (7) can be realized as follows:

$$\begin{aligned} \frac{dw}{dt} &= \frac{\overline{b_1}x_1}{\overline{c_1}+x_1} - \frac{1}{1+\overline{k}x_3^{\overline{\tau_3}}}\frac{\overline{d_1}(1-x_1)}{\overline{e_1}+(1-x_1)}u(t) - \overline{\eta} \\ \overline{\eta} &= \varpi_e(w+x_1) \quad (8) \end{aligned}$$

By using the above estimation of the uncertain term, an inverse-dynamics feedback function that leads to the desired controlled dynamics of the active form of enzyme x_1 is given by

$$u(t) = -(1+\overline{k}x_3^{\overline{\tau_3}})\frac{\overline{e_1}+(1-x_1)}{\overline{d_1}(1-x_1)}\begin{bmatrix} \overline{\eta} - \frac{\overline{b_1}x_1}{\overline{c_1}+x_1} + \\ \varpi_c(x_1-x_{1,ref}) \end{bmatrix} \quad (9)$$

Thus, the feedback function is composed by the feedback function (9) and the modeling error estimator (8).

Remark 1 *The model-based control approach has only two control design parameters, i.e., ϖ_c and ϖ_e. The closed-loop parameter ϖ_c can be chosen as the inverse of the mean time of the open-loop dynamics. On the other hand, the estimation parameter $\varpi_e > 0$, which determines the smoothness of the modeling error and the inverse of the time-derivative estimation, can be chosen as $\varpi_e < \frac{1}{2}\varpi_c$ [19,20].*

Remark 2 *To the best of our knowledge, only Sontag [21] has been considered feedback control studies for the MAPK cascade model. In Sontag´s paper were derived small gain theorems with application in MAPK cascade model.*

Remark 3 *The stability analysis of the closed-loop systems is beyond of the scope of this paper. However, this can be borrowed with stability arguments from singular perturbation theory [20].*

4 Numerical Simulations

We have taken the following cases in order to illustrate the control performance: (i) regulation of the oscillatory behavior to a constant reference value, and (ii) enforcing of the oscillatory dynamics to a desired controlled periodic behavior. Two motivations for considering constant and controlled periodic references: (i) as in Sontag´s paper [21] we were motivated by the problem of guaranteeing the nonexistence of oscillations in the MAPK signaling pathway, and (ii) despite periodic oscillations are a suitable means for switching on different processes, the physiological relevance of sustained oscillations in the MAPK-cascade is not clear and experimentally only

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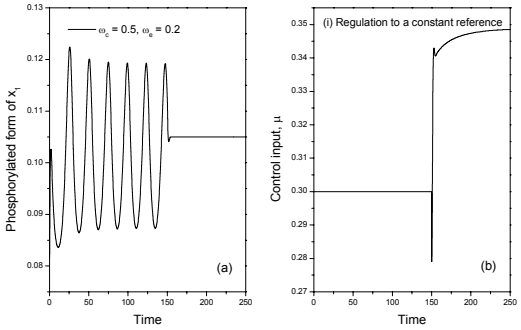

Figure 3: Regulation of the oscillatory behavior.

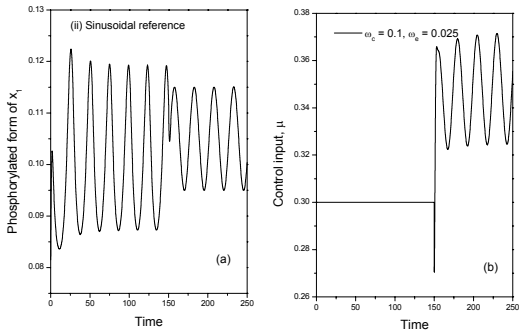

Figure 4: Enforcing of a new periodic behavior.

damped oscillations were shown [15]. If the damped oscillations induced by the negative feedback loop show only few periods and the steady-state is at a very low activation level of MAPK , the dynamics can be interpreted as adaptation [15]. Adaptation, sometimes also referred as desensitization, seems to be an important property of biological systems, because it allows organisms to have a similar functionality for a wide range of different environments [6].

In Figure 3-a we shown the time evolution of the active form of enzyme x_1 for case (i). It can be seen that we can successfully perform the regulation of the oscillatory behavior via the control law (8) and (9). The control law is turn on at $t = 150$ units and ϖ_c and ϖ_e are set at 0.5 and 0.2 respectively. Figure 3-b shows the temporal evolution of the control input. It can be seen from Figure 3 that in order to regulate the oscillatory behavior to a constant reference value, the required control control input is a step external input.

Figure 4-a shows the tracking of a sinusoidal reference, *i.e.*, case (ii). We can successfully perform full tracking of a sinusoidal signal. In this case, ϖ_c and ϖ_e are set at 0.1 and 0.025 respectively. It can be seen from Figure 4-b that the control input has a periodic behavior. This can be related to the observation made in numerous experimental and theoretical studies that forcing an oscillatory system by a periodic input can readily produce a new periodic behavior [2,6]. behavior. The above simulation results indicate good regulation and tracking performance of the closed-loop system.

5 Conclusions

In this work, we have presented a model-based feedback control approach to regulate the MAPK dynamics. The significance of MAPK signaling dynamics stems from the crucial importance of this pathway in the control of many functions in signal transduction, such as stress-response, cell-cycle control, cell-wall-construction, osmo-sensing, growth and differentiation. The feedback control law proposed in this work could be implemented experimentally in the MAPK cascade via the introduction of plausible external actions, such as ionizing radiation. In spite that our results have been obtained for a MAPK pathway model, we expect that the control approach presented here could be used in similar models of metabolic pathways.

References

[1] Morari, M., Zafiriou, E. *Robust Process Control*, Prentice-Hall, Englewood Cliffs, New Jersey (1989).

[2] Walleczek, J. (2000). The frontiers and challenges of biodynamics research, in *Self-Organized biological dynamics and nonlinear control*. Cambridge University Press, Cambridge, UK.

[3] Wolkenhauer, O., Kitano, H., and Cho, K-H. (2003). Systems biology. *IEEE Control Sys. Mag.*, August, 38.

[4] International Conference on Systems Biology; Northwest Symposium for Systems Biology; European Control Conference 03.

[5] Focus Issue: molecular, metabolic and genetic control, *Chaos* 11, Issue 1 (2001); Special Section on Systems Biology, *IEEE Control Syst. Mag.* 24, August (2004).

[6] Tyson, J.J., Chen, K.C., Novak, B. (2003). Sniffers, buzzers, toggles and blinkers: dynamics of

ISBN: 970-32-2137-8

regulatory and signaling pathways in the cell. *Curr. Op. Cell Bio.* 15, 221.

[7] Freeman, M. (2000). Feedback control of intracellular signalling in development. *Nature*, 408, 313.

[8] Goldbeter, A. *Biochemical Oscillations and Cellular Rhythms.* Cambridge University Press, Cambridge, UK (1996).

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

[10] Puebla, H. (2004). Feedback control of intracellular calcium nonlinear dynamics. in *Conference on Computational and Mathematical Population Dynamics*, CMPD, Trent, Italy.

[11] Asthagiri, R., Lauffenburger, D.A. (2001). A computational study of feedback effects on signal dynamics in a mitogen-activated protein kinase (MAPK) pathway model. *Biotechnol. Prog.* 17, 227.

[12] Bhalla, U., Iyengar, R. (1999). Emergent properties of networks of biological signaling pathways. *Science* 283, 339.

[13] Kholodenko, B.N. (2000). Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. *Eur. J. Biochem.* 267, 1583.

[14] Wilkinson, M.G., Millar, J.B.A. (2000). Control of the eukaryotic cell cycle by MAP kinase signaling pathways. *FASEB Journal* 14, 2147.

[15] Bluthgen, N., Herzel, H. (2001). MAP-kinase-cascade: switch, amplifier or feedback controller?. in *2ndWorkshop on Computation of Biochemical Pathways and Genetic Networks*, Berlin, 55.

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

[17] Huang, C.-Y. F., Ferrell, J. E. (1996). Ultrasensitivity in the mitogen-activated protein kinase cascade. *Proc. Natl. Acad. Sci.* USA 93, 10078.

[18] Shvartsman, S.Y., Hagan, M.P., Yacoub, A., Dent, P., Wiley, H.S., Lauffenburger, D.A. (2002). Autocrine loops with positive feedback enable context-dependent cell signaling. *Am. J. Physiol. Cell Physiol.* 282, C545.

[19] Puebla, H., Alvarez-Ramirez, J., Cervantes, I. (2003). A simple tracking control for chua´s circuit. *IEEE Trans. Circ. Sys.* 50, 280.

[20] Alvarez-Ramirez, J., Suarez, R. (2000). Stabilization of a class of linear time-varying systems via modeling error compensation. *IEEE Trans. Automatic Control* 45, 738.

[21] Sontag, E.D. (2002). Asymptotic amplitudes and cauchy gains: a small-gain principle and an application to inhibitory biological feedback. *Syst. Cont. Lett.* 47, 167-179.

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