A CROSSTALK-BASED LINEAR FILTER IN BIOCHEMICAL SIGNAL TRANSDUCTION PATHWAYS FOR THE INTERNET OF BIO-THINGS

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ABSTRACT

Novel emerging tools are allowing the manipulation and control of biological cells and their functions, e.g., sensing, actuation, and communication through biochemical stimuli. These tools have the potential to enable the implementation of man-made networks of biological computing devices, i.e., Internet of Bio-things. In this work, signal transduction pathways, i.e., cells' chemical reactions that process biochemical signals, are proposed for the design of analog linear filters to be utilized as components in the Internet of Bio-things. These filters, which exploit the crosstalk of signal transduction pathways to achieve the desired response, are here modeled and analyzed. The relations between filter properties and biochemical parameters are presented with the goal of designing a notch filter. A preliminary numerical example is also given as proof-of-concept.

Index Terms— Biochemical filter design, crosstalk, molecular communication, signal transduction pathway, internet of bio-things.

1. INTRODUCTION

Recent advances in synthetic biology and genetic code engineering are enabling an increasingly finer control and manipulation of the physical and biochemical processes in biological cells [1, 2]. These processes range from the production of specific types of molecules in response to determinate environmental conditions, to the execution of basic logic operations in the biochemical domain, similar to those realized in electronics. Biological cells have the natural ability to sense and release information from/to the environment, and communicate with each other through the reception, processing, and emission of molecules. These abilities have been studied and abstracted in telecommunication engineering with a bio-communication paradigm called Molecular Communication (MC) [3, 4, 5, 6].

Specific functionalities embedded in the cells' genetic code allow multiple cells communicating through MC to interconnect in nature into bio-networks and perform collaborative tasks, such as microbial communities in the soil or in the human gut [7]. The possibility to manipulate the biochemical processes underlying MC, and control the way cells sense and respond to biochemical information, has the potential to revolutionize the cutting edge field of the Internet of Things [8] by enabling the realization of uniquely identifiable biological computing devices, or genetically-engineered cells, and their interconnections and interactions with the environment [9, 10]. This subfield, which we define as the Internet of Bio-things, will enable a plethora of new applications in diverse areas, including medicine, such as implantable cell-based devices and systems; industry, such as bio-fuel production or food safety control systems; and agriculture, such as engineered-microbe-based soil monitoring and control.

In this work, we take a signal processing view, and propose to analyze sequences of chemical reactions embedded in biological cells for the manipulation and transformation of biochemical signals coming from the external environment. These reaction sequences, known as signal transduction pathways, can be interpreted as linear systems under some assumptions [11, 12]. Through these pathways, cells respond to multiple external stimuli simultaneously by sensing the time-varying pattern of specific molecule concentrations surrounding the cell [13]. These pathways present a variety of mechanisms to regulate signal transduction in a way that signals may be either attenuated or terminated in the cellular space, or cytoplasm, before stimulating a genetic code program in the nucleus [14]. Often, pathways regulate each other towards a common goal. This interaction among pathways is called crosstalk, and it is meant to transduce external and internal information into vital cellular decisions related to, e.g., immunity, stress responses, apoptosis, differentiation and growth [15, 16]. Examples of crosstalk-regulated path-

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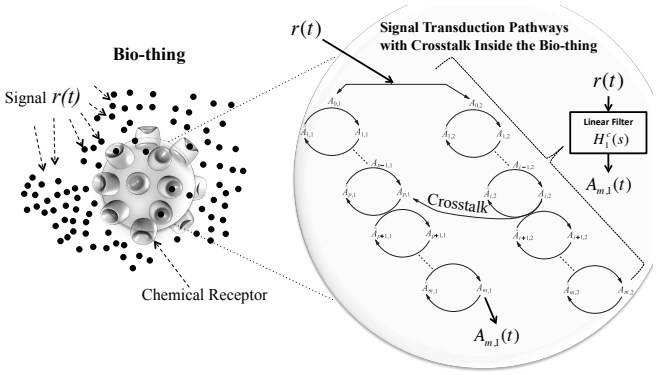

Fig. 1. Pictorial representation of a bio-thing provided with the linear filter realized through a crosstalk interaction between two signal transduction pathways with the input signal $r(t)$ and output signal $A_{m,1}(t)$.

ways in cells involve G-proteins [17], and cyclic adenosine monophosphate (cAMP) and the way mitogen-activated protein (MAP) kinases are regulated [18, 19]. cAMP acts by interacting with the MAP kinase pathway so as to regulate cell proliferation [20]-[21], as well as cell survival [22].

In particular, our goal is to design an analog linear filter that, in contrast to traditional electrical filters, processes signals in the biochemical domain. We propose a notch, or bandstop filter, which has important applications in sensing and communication systems, such as those envisioned for enabling the Internet of Bio-things. This filter, based on the crosstalk interactions in signal transduction pathways, is able to suppress the reception of biochemical signals that oscillate around a certain frequency, while allowing the cell to receive all the other frequency components of the signals. In [23], the filtering behavior of generic chemical reactions, and the design of a multiple input-multiple output notch filter is provided, while we propose a single input-single output filter from a specific biochemical process. In [12], linear models of simple signal transduction pathways are provided without mentioning either crosstalk or filter design.

The rest of the paper is organized as follows. Sec. 2 includes the signal-processing-based modeling of the proposed filter, while Sec. 3 contains the analysis of the filter parameters to be taken into account for the notch filter design, and a numerical example. Finally, Sec. 4 concludes the paper.

2. CROSSTALK-BASED FILTER MODEL

In this paper, we consider a model of a bio-thing, i.e., a genetically-engineered cell, which is provided with chemical receptors able to sense the concentration of molecules in the environment, as shown in Fig. 1. This concentration of molecules, which varies with time, is denoted with the signal $r(t)$, as function of the time t, and it is considered homogeneous in the space surrounding the bio-thing. Inside the bio-thing, a crosstalk interaction between two signal transduction pathways, which take $r(t)$ as input, returns the output signal $A_{m,1}(t)$. In the following, we detail the model of this interaction as a linear filter $H_1^c(s)$, where s is the complex argument in the Laplace transform domain [24], with the following expression:

$$H_1^c(s) = \frac{H_1(s)}{\prod_{d=0}^{i}(s+k_{d,2}^-)}\left[\prod_{d=0}^{i}(s+k_{d,2}^-) + \gamma\prod_{d=0}^{p-1}(s+k_{d,1}^-)\right] \tag{1}$$

where γ is defined as

$$\gamma = s_c \cdot \frac{k_c}{k_{p,1}}\frac{\prod_{d=0}^{i} k_{d,2}}{\prod_{d=0}^{p-1} k_{d,1}}\,, \tag{2}$$

and, as detailed later, $H_1(s)$ is the overall transfer function of the first pathway without crosstalk

$$H_1(s) = \prod_{d=0}^{m}\frac{k_{d,1}}{s+k_{d,1}^-}\,. \tag{3}$$

The parameters $k_{d,q}$ and $k_{d,q}^-$, where $d = 0, 1, \ldots, m$ and $q = 1, 2$, are the pseudo-first-order forward and backward reaction rates, respectively, at stage d in the pathway q, s_c and k_c and the sign and rate, respectively, of the crosstalk from the i-th stage of the second pathway to the p-th stage of the first pathway.

A common characteristic of a signal transduction pathway is the presence, at each stage in the cascade, of an input protein species A_{i-1}, the kinase, an inactive (nonphosphorylated) protein species $\widehat{A}_i$, and an active protein species A_i, as illustrated in Fig. 1. The kinase A_{i-1} activates the phosphorylation of A_i with rate k_i^+, while A_i undergoes dephosphorylation with rate k_i^-. Phosphorylation is the chemical process through which a protein, stimulated by a protein kinase, acquires a phosphate group, therefore changing its "state" from low-energy to high-energy. Dephosphorylation is the opposite process where a phosphorylated protein loses the phosphate group. When in the high-energy state, a protein becomes the protein kinase for the next stage of the cascade

The differential equation underlying the reaction through which the molecules in the signal $r(t)$ bind on chemical receptors at the bio-thing, activating two different pathways, is described by the following differential equation:

$$\frac{dA_{0,q}(t)}{dt} = k_{0,q}^+ r(t) A_{0f}(t) - k_{0,q}^- A_{0,q}(t), \tag{4}$$

where q is the pathway index, $q \in \{1, 2\}$, $A_{0f}(t)$ and $A_{0,q}(t)$ are the concentrations of unbound and bound receptors, respectively, and $k_{0,q}^+, k_{0,q}^-$ are the receptor-ligand binding reaction rates for pathway q. The differential equation governing the activation of kinase $A_{i,q}$ at stage i in pathway q, with $i \in \{1, \ldots, m\}$, can be written as follows:

$$\frac{dA_{i,q}(t)}{dt} = k_{i,q}^+ A_{i-1,q}(t)\widehat{A}_{i,q}(t) - k_{i,q}^- A_{i,q}(t), \tag{5}$$

where $A_{i,q}(t)$ denotes the concentration of protein species $A_{i,q}$ at time t, $A_{i-1,q}(t)$ is the concentration of the kinase phosphorylating $A_{i,q}$, and $\widehat{A}_{i,q}(t)$ denotes the concentration of the inactive protein at stage i in pathway q.

Assuming a total concentration of chemical receptors $A^T_{0,q} = A_{0,q} + A_{0f}$, and a total concentration of inactive and active protein at stage i $A^T_{i,q} = A_{i,q} + \widehat{A}_{i,q}$, we define, in line with [13], $k_{i,q} = k^+_{i,q} A^T_{i,q}$ as the pseudo-first order rate constant at stage i in pathway q. Although (4) and (5) show in general a non-linear behavior of the pathway reactions, they can be approximated by linear differential equations in scenarios where saturation effects are negligible [25, 26]. This corresponds to the following assumptions: i) the total receptor concentration $A^T_{0,q}$ is constant, ii) $A^T_{0,q}$ is much higher than the bound receptors concentration $A_{0,q}$, iii) the pathways are weakly activated [13], that means $A_{i,q} \ll A^T_{i,q}$. As a consequence, we obtain

$$\frac{dA_{i,q}}{dt} = k_{i,q} A_{i-1,q} - k^-_{i,q} A_{i,q}\,, \tag{6}$$

where $A_{i-1,q}$ for $i = 0$ corresponds to the signal $r(t)$. By applying the Laplace transform [24] to (6), and considering the cascade of each stage i in each pathway q as a linear and time-invariant system with frequency response $H_{i,q}(j\omega)$, the overall transfer function of each pathway, in the case where no crosstalk is taken into account, is given by

$$H_q(s) = \prod_{i=0}^{m} H_{i,q}(s) = \prod_{i=0}^{m} \frac{A_{i,q}(s)}{A_{i-1,q}(s)} = \prod_{i=0}^{m} \frac{k_{i,q}}{s + k^-_{i,q}}. \tag{7}$$

The protein kinase from the stage m, $A_{m,q}(t)$, is then related to the input signal $r(t)$ through the Laplace relationship $A_{m,q}(s) = H_q(s)R(s)$, where $R(s)$ and $A_{m,q}(s)$ are the Laplace transforms of $r(t)$ and $A_{m,q}(t)$, respectively, and $H_q(s)$ is given by the expression in (7).

A common phenomenon arising during the binding process in cells regards the activation of different signaling cascades that may interact with each other through a phenomenon called crosstalk [13], as shown in Fig. 1. In the following, we show that crosstalk, from a system design point of view, has the effect of introducing zeros in the transfer function of the affected pathway, thus distorting the overall transfer function from the expression in (7), and consequently the frequency response of the pathway under consideration.

In reference to Fig. 1, we assume that the ith protein kinase from pathway 2 influences the pth phosphorylation stage in pathway 1. To prove the assertions stated above, we rely on Laplace transform techniques. First, we notice that crosstalk affects the phosphorylation stages in the first cascade after stage p. The phosphorylation of kinase p is now described by the following differential equation:

$$\frac{d}{dt} A_{p,1} = k_{p,1} A_{p-1,1} - k^-_{p,1} A_{p,1} + s_c \cdot k_c \cdot A_{i,2} \tag{8}$$

where s_c is the sign of the crosstalk ($s_c = -1$ if the crosstalk has an inhibitory effect on kinase $A_{p,1}$, or $+1$ if the crosstalk promotes kinase $A_{p,1}$) and k_c is the crosstalk reaction rate.

Using Laplace analysis, kinase $A_{i,2}$ can be rewritten in terms of the signal $R(s)$ activating the two pathways

$$A_{i,2}(s) = R(s) \prod_{d=0}^{i} \frac{k_{d,2}}{s + k^-_{d,2}}, \tag{9}$$

while (8), solved for $A_{p,1}$, yields

$$A_{p,1}(s) = \frac{k_{p,1}}{\left(s + k^-_{p,1}\right)} A_{p-1,1}(s) + \frac{s_c \cdot k_c}{\left(s + k^-_{p,1}\right)} A_{i,2}(s). \tag{10}$$

Next line of pursuit consists in finding the output kinase $A_{m,1}$ from pathway 1. Toward this goal, we first notice that $A_{i,2}(s)$ is related to the input signal $R(s)$ through (9), while $A_{p-1,1}(s)$ can be found by noting that the previous kinases are not affected by crosstalk. Thus, we can write

$$A_{p-1,1}(s) = R(s) \prod_{d=0}^{p-1} \frac{k_{d,1}}{s + k^-_{d,1}} = R(s) H^b_1(s)\,. \tag{11}$$

Along the same line of thoughts, the transfer function of the phosphorylation stages from $p+1$ to m in the first signaling cascade can be written as

$$H^f_1(s) = \prod_{d=p+1}^{m} \frac{k_{d,1}}{s + k^-_{d,1}}\,. \tag{12}$$

Using the setup above, the output kinase $A_{m,1}$ of pathway 1 can be found by

$$A_{m,1} = H^f_1(s) A_{p,1} \tag{13}$$

Upon replacing (9) and (11) in (10), we find

$$A_{m,1} = \frac{H^f_1(s) R(s)}{\left(s + k^-_{p,1}\right)} \left[k_{p,1} H^b_1(s) + s_c \cdot k_c \cdot \prod_{d=0}^{i} \frac{k_{d,2}}{s + k^-_{d,2}} \right] \tag{14}$$

As a consequence, the transfer function of the first pathway in case of crosstalk from the second pathway has the following expression:

$$H^c_1(s) = \frac{k_{p,1} H^f_1(s)}{\left(s + k^-_{p,1}\right)} \left[\prod_{d=0}^{p-1} \frac{k_{d,1}}{s + k^-_{d,1}} + s_c \cdot \frac{k_c}{k_{p,1}} \cdot \prod_{d=0}^{i} \frac{k_{d,2}}{s + k^-_{d,2}} \right] \tag{15}$$

After some algebra, (15) can be rewritten as (1), where we can clearly see the presence of zeros in the transfer function.

3. NOTCH FILTER ANALYSIS

In the following, we provide an analysis of the linear filter resulting from the signal transduction pathways and their crosstalk, as expressed in (1) in terms of transfer function in the Laplace domain.

Upon observing that the constant reaction rates $k^-_{d,2},\ \forall d = 0,\dots,i$, and $k^-_{d,1},\ \forall d = 0,\dots,m$, are real and positively valued, a close look at the transfer function $H^c_1(s)$ in (1) reveals the presence of only real poles located on the negative real axis of the complex plane, i.e., $s = -k^-_{d,2},\ \forall d = 0,\dots,i$, and $s = -k^-_{d,1},\ \forall d = 0,\dots,m$. Moreover, $H^c_1(s)$ presents a number of zeros given by $N_z = \max\{i, p-1\}$. The particular shape of the frequency response is then influenced by the locations of the zeros on the complex plane [24].

We wish to design a notch filter where the notch (zero) is placed on an undesired frequency component of the signal $r(t)$ in input to the signal transduction pathways. To be specific, let us consider pathways characterized by a cascade of three stages of phosphorylation including the chemical receptor binding process indexed by $d = 0$. Moreover, let us assume that the first kinase $A_{1,2}$ on the second pathway interacts with the first kinase $A_{1,1}$ in the first pathway. With this assumptions, $m = 2$, $i = 1$ and $p = 1$, and the transfer function $H^c_1(s)$ in (1) becomes:

$$H^c_1(s) = \frac{\prod_{d=0}^{2} \frac{k_{d,1}}{s+k^-_{d,1}}}{\prod_{d=0}^{1}(s+k^-_{d,2})} \left[\prod_{d=0}^{1}(s+k^-_{d,2}) + \gamma(s+k^-_{0,1})\right] \tag{16}$$

After some algebra, (16) can be rewritten as

$$H^c_1(s) = \eta \frac{\left[s^2+\alpha s+\beta\right]}{\prod_{d=0}^{2}(s+k^-_{d,1})\prod_{d=0}^{1}(s+k^-_{d,2})}, \tag{17}$$

where:

$$\begin{aligned} \gamma &= s_c k_c \frac{k_{0,2}k_{1,2}}{k_{0,1}k_{1,1}}, \\ \eta &= k_{0,1}k_{1,1}k_{2,1}\,, \\ \alpha &= k^-_{0,2}+k^-_{1,2}+\gamma\,, \\ \beta &= \gamma k^-_{0,1} + k^-_{0,2}k^-_{1,2}\,. \end{aligned}$$

By applying the quadratic formula, the two zeros of (17) are located in

$$s = -\frac{\alpha}{2} \pm \sqrt{\left(\frac{\alpha}{2}\right)^2 - \beta}\,. \tag{18}$$

Assuming complex-conjugate zeros, i.e., $\left(\frac{\alpha}{2}\right)^2 - \beta < 0$, (18) becomes

$$s = -\frac{\alpha}{2} \pm j\sqrt{\beta - \left(\frac{\alpha}{2}\right)^2}\,. \tag{19}$$

For the zeros to fall on the imaginary axis of the complex plane, we set $\alpha = 0$ and find a relationship among the constant rates for this condition to hold. Using the expressions of α and γ in (17), we find the following relationship:

$$\alpha = 0 \quad \Rightarrow \quad \gamma = -(k^-_{0,2} + k^-_{1,2}). \tag{20}$$

By substituting the second side of (20) in (17), and by solving for k_c, we find

$$k_c = \frac{k_{0,1}k_{1,1}}{k_{1,2}k_{0,2}} \frac{\gamma}{s_c}\,, \tag{21}$$

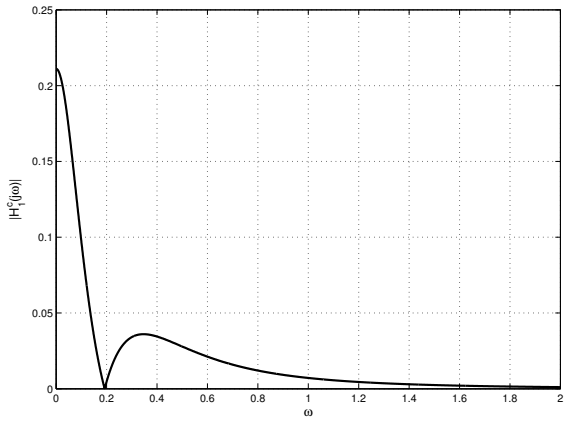

Fig. 2. Magnitude of the frequency response of the filter expressed in (17) for a set of typical values for the biochemical parameters [13].

where we set $s_c = -1$ to obtain a positive value for k_c.

For the zeros to be complex conjugate, we require that β be greater than zero. Using the expression of γ in (20), we find the following relationship:

$$\beta > 0 \quad \Rightarrow \quad k^-_{0,1} < \frac{k^-_{0,2}\cdot k^-_{1,2}}{k^-_{0,2}+k^-_{1,2}}\,. \tag{22}$$

The notch frequency of the filter given by the transfer function in (16) is then defined as

$$\omega_n = \sqrt{\beta} = \sqrt{-(k^-_{0,2}+k^-_{1,2})k^-_{0,1} + k^-_{0,2}\cdot k^-_{1,2}} \tag{23}$$

For brevity, we present a numerical proof-of-concept example of the analyzed filter with the following set of typical values for the biochemical parameters [13]: $k_{0,1} = 0.1$, $k_{0,2} = 0.5$, $k_{1,1} = 0.95$, $k_{1,2} = 0.5$, $k_{2,1} = 0.1$, $k^-_{0,2} = k^-_{1,2} = 1/3$, $k^-_{1,1} = 0.45$. By using (20), we find $\gamma = -2/3$, while from (21) we get $k_c = 0.2533$. The magnitude of the frequency response of the biochemical filter is shown in Fig. 2, where the notch is located at the frequency $\omega_n = \sqrt{\beta} = 0.1925$.

4. CONCLUSION

In this paper, a contribution is presented towards the design of components for enabling the Internet of Bio-things, intended as the communication, sensing, and actuation of biological computing devices, or genetically-engineered biological cells, through molecule exchange in biological environments. In particular, we presented the study of a filter around the biochemical processes underlying signal transduction in biological cells, and their properties in terms of crosstalk. In this direction, we modeled the signal transduction pathways and their crosstalk from a signal processing perspective, and we analytically evaluated the properties of a resulting notch, or bandstop, filter as functions of the biochemical parameters. Future work will include the design of more complex responses by exploring additional properties within signal transduction pathways.

5. REFERENCES

[1] L. J. Kahl and D. Endy, "A survey of enabling technologies in synthetic biology," *Journal of Biological Engineering*, vol. 7, no. 1, p. 13, May 2013.

[2] A. Slusarczyk, A. Lin, and R. Weiss, "Foundations for the design and implementation of synthetic genetic circuits," *Nat Rev Genet.*, vol. 13, no. 6, pp. 406–420, May 2012.

[3] M. Pierobon and I. F. Akyildiz, "A physical end-to-end model for molecular communication in nanonetworks," *IEEE Journal on Selected Areas in Communications (JSAC)*, vol. 28, no. 4, pp. 602–611, May 2010.

[4] ——, "Diffusion-based noise analysis for molecular communication in nanonetworks," *IEEE Transactions on Signal Processing*, vol. 59, no. 6, pp. 2532–2547, June 2011.

[5] ——, "Information capacity of diffusion-based molecular communication in nanonetworks," in *in Proc. of IEEE International Conference on Computer Communication, INFOCOM 2011, Miniconference*, April 2011.

[6] ——, "Noise analysis in ligand-binding reception for molecular communication in nanonetworks," *IEEE Transactions on Signal Processing*, vol. 59, no. 9, pp. 4168–4182, September 2011.

[7] C. M. Agapakis, P. M. Boyle, and P. A. Silver, "Natural strategies for the spatial optimization of metabolism in synthetic biology," *Nat Chem Biol*, vol. 8, no. 6, pp. 527–535, May 2012.

[8] J. Höller, V. Tsiatsis, C. Mulligan, S. Karnouskos, S. Avesand, and D. Boyle, *From Machine-to-Machine to the Internet of Things: Introduction to a New Age of Intelligence*. Elsevier, 2014.

[9] M. E. Ortiz and D. Endy, "Engineered cell-cell communication via dna messaging," *Journal of Biological Engineering*, vol. 6, no. 16, pp. 1–11, September 2012.

[10] M. Pierobon, "A systems-theoretic model of a biological circuit for molecular communication in nanonetworks," *Nano Communication Networks (Elsevier)*, vol. 5, no. 1-2, pp. 25–34, March-June 2014.

[11] M. Chaves, E. Sontag, , and R. Dinerstein, "Optimal length and signal amplification in weakly activated signal transduction cascades," *J. Phys. Chem. B*, vol. 108, no. 39, pp. 15 311–15 320, September 2004.

[12] J. Locasale, "Signal duration and the time scale dependence of signal integration in biochemical pathways," *BMC Systems Biology*, vol. 2, no. 108, December 2008.

[13] R. Heinrich, B. Neel, and T. Rapoport, "Mathematical models of protein kinase signal transduction," *Mol Cell.*, vol. 9, no. 5, pp. 957–970, May 2002.

[14] T. Hunter, "The age of crosstalk: Phosphorylation, ubiquitination, and beyond," *Molecular Cell*, vol. 28, pp. 730–738, December 2007.

[15] A. Oeckinghaus, M. Hayden, and S. Ghosh, "Crosstalk in nf-κB signaling pathways," *Nature Immunology*, vol. 12, no. 8, pp. 695–708, August 2011.

[16] M. Rowland, W. Fontana, and E. Deedsn, "Crosstalk and competition in signaling networks," *Biophysical Journal*, vol. 103, no. 11, pp. 2389–2398, December 2012.

[17] T. Matozaki, H. Nakanishi, and Y. Takai, "Small g-protein networks. their crosstalk and signal cascades," *Cellular Signalling*, vol. 12, no. 8, pp. 515–524, August 2000.

[18] M. Conn and E. Goldsmith, "How map kinases are regulated," *Journal of Biological Chemistry*, vol. 270, no. 25, pp. 14 843–14 846, 1995.

[19] M. Schwartz and M. Ginsberg, "Networks and crosstalk: Integrin signalling spreads," *Nature Cell Biology*, vol. 4, pp. 65–68, April 2002.

[20] M. Saxena, S. Williams, K. Tasken, and T. Mustelin, "Crosstalk in nf-κB signaling pathways," *Nature Cell Biology*, vol. 1, pp. 305–311, September 1999.

[21] M. McClean, A. Mody, J. Broach, and S. Ramanathan, "Crosstalk and decision making in map kinase pathways," *Genetics*, vol. 39, no. 3, pp. 409–414, March 2007.

[22] M. Junttila, S.-P. Li, and J. Westermarck, "Phosphatase-mediated crosstalk between mapk signaling pathways in the regulation of cell survival," *FASEB Journal*, vol. 22, pp. 954–965, April 2008.

[23] M. Samoilov, A. Arkin, and J. Ross, "Signal processing by simple chemical systems," *J. Phys. Chem. A*, vol. 106, no. 43, pp. 10 205–10 221, October 2002.

[24] B. Davies, *Integral transforms and their applications*. Springer, New York, 2002.

[25] J. Hornberg, B. Binder, F. Bruggeman, B. Schoeberl, R. Heinrich, and H. Westerhoff, "Control of mapk signalling: from complexity to what really matters," *Oncogene*, vol. 24, no. 36, pp. 5533–5542, August 2005.

[26] S. Ghaemmaghami, W. Huh, K. Bower, R. Howson, A. Belle, N. Dephoure, E. O'Shea, and J. Weissman, "Global analysis of protein expression in yeast," *Nature*, vol. 425, no. 6959, pp. 737–741, October 2003.