Lose and gain: impacts of ERK5 and JNK cascades on each other

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Abstract Kinase cascades in ERK5 (Extracellular signal-regulated kinases) and JNK (c-Jun N-terminal kinases) signaling pathways mediate the sensing and processing of stimuli. Cross-talks between signaling cascades is a likely phenomenon that can cause apparently different biological responses from a single pathway, on its activation. Feedback loops have the potential to greatly alter the properties of a pathway and its response to stimuli. Based on enzyme kinetic reactions, mathematical models have been developed to predict and analyze the impacts of cross-talks and feedback loops in ERK5 and JNK cascades. It has been observed that, there is no significant impact on neither ERK5 activation nor JNKs' activation due to cross-talks between them. But it is due to cross-talks and feedback loops in ERK5 and JNK cascade, ERK5 gets activated in a transient manner in the absence of input signals. Planning to obtain the parameter values from the experimentalist and the result should be validated by experimental verification.

Keywords Dynamic systems · Enzyme kinetic reactions · Cross-talks · Feedback loops · ERK5 cascade · JNK cascade

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Introduction

Cells must be able to process multiple information in parallel and, they must also be able to combine this information in order to trigger the appropriate response (Berg et al. 2002). This is achieved by wiring signaling pathways such that they can interact with each other, a phenomenon often called cross-talk (Sreenath et al. 2007). There have been attempts to quantify cross-talk in signaling networks. In one study cross-talk was categorized by a classification of the input–output relations of signaling networks. Quantification consisted of counting the occurrence of each category in a pair wise comparison of pathways. Another study quantified the degree of cross-talk between two pathways, by relating the number of realized interactions between two pathways to the number of hypothetically possible interactions (Schaber et al. 2006). This definition was restricted to pathways that do not share components. Both studies considered topological and structural properties of signaling networks and did not account for temporal and dynamic aspects. In our previous work, we have predicted the impacts of cross-talks between ERK5 and JNK kinase cascades (Sundaramurthy et al. 2009).

Complicated biochemical signaling pathways regulate the function of living cells. Such regulatory networks often have downstream components that provide input to components that act earlier in a pathway, creating feedback loops (Langlois et al. 1995). These feedback loops have the potential to greatly alter the properties of a pathway and how it responds to stimuli (Aronson et al. 1994; Bliss et al. 1982; Chen and Tan 2000; Lauffenburger 2001; Wolkenhauer and Mesarovic 2005). Positive and negative feedback loops around MAPK (Mitogen-activated protein kinase) cascades have been a topic of

interest in biological literature. For example, in (Ferrell and Machleder 1998), one finds the study of positive feedback (on Mos by ERK) in the context of progesterone-induced oocyte maturation in frogs. In another example, Kholodenko (2000) and Wolkenhauer and Mesarovic (2005) looked at negative feedback, also in an ERK cascade, but affecting upstream proteins. JNK activation is an autocatalytic, in his work Bagowski and Ferrell (2001) has proposed two possible feedbacks, one from MAPK to MAPKK (Mitogen-activated protein kinase kinase) and the other from MAPKK to MAPKKK (Mitogen-activated protein kinase kinase kinase) in JNK cascade in xenopus oocytes. We have identified the only possible feedback loops in JNK cascade are from JNK's to MKK's (unpublished work). In this work, based on enzyme kinetic reactions, mathematical models have been developed to predict and analyze the impacts of cross-talks and feedback loops in the ERK5 and JNK kinase cascades (Tables 1, 2 and 3).

ERK5 and JNK cascades as a system of interacting proteins

In the processes of cellular signaling, protein-protein interactions play a central role. Protein kinases are enzymes that covalently attach phosphate to the side chain of serine, threonine, or tyrosine of specific proteins inside cells and protein phosphatases remove the phosphates that were transferred to the protein substrate by the kinase. In this manner, the action of MAPKs and protein phosphatases reciprocally and rapidly alter the behavior of cells as they respond to changes in their environment. MAPK activity is regulated through three-tiered cascades composed of a MAPK, MKK or MAPKK and MEKK or MAPKKK (Beato et al. 1995). A MAPKKK that is activated by extracellular stimuli phosphorylates a MAPKK on its serine and threonine residues. This MAPKK activates a MAPK through phosphorylation of its serine and tyrosine residues (Johnson and Lapadat 2002). The activated MAPKs, in turn,

Table 1 Parameter values used in (8)

Eq. no.	Parameter values
(8a)	$k_1 = 1.5, k'_1 = 0.25, Km_1 = 15, K'm_1 = 15, c_1 = 1.05, c'_1 = 0.05, Cm_1 = 15, C'm_1 = 15, c_2 = 0.03, c'_2 = 2.05, Cm_2 = 15, C'm_2 = 15, u = 100, \bar{x}_1 = 300$
(8b)	$k_2 = 0.025, k'_2 = 0.75, Km_2 = 15, K'm_2 = 15, c_3 = 0.06, c'_3 = 2.6, Cm_3 = 15, C'm_3 = 15, c_4 = 2.5, c'_4 = 1.5, Cm_4 = 15, C'm_4 = 15, \bar{x}_2 = 300$
(8c)	$k_3 = 1.25, k'_3 = 0.5, Km_3 = 15, K'm_3 = 15, k_4 = 0.5, k'_4 = 1.5, Km_4 = 15, K'm_4 = 15, \bar{x}_3 = 300$
(8d)	$k_5 = 1.25, k'_5 = 0.015, Km_5 = 15, K'm_5 = 15, k_6 = 2.25, k'_6 = 0.019, Km_6 = 15, K'm_6 = 15, \bar{x}_4 = 300$
(8e)	$k_7 = 0.25, k'_7 = 1.15, Km_7 = 15, K'm_7 = 15, k_8 = 0.025, k'_8 = 1.05, Km_8 = 15, K'm_8 = 15, \bar{x}_5 = 300$
(8f)	$k_9 = 2.5, k'_9 = 0.05, Km_9 = 10, K'm_9 = 8, w_1 = 1, \bar{y}_1 = 100$
(8g)	$k_{10} = 0.05, k'_{10} = 1.5, Km_{10} = 10, K'm_{10} = 8, w_2 = 1, \bar{y}_2 = 100$
(8h)	$k_{11} = 2.6, k'_{11} = 0.075, Km_{11} = 15, K'm_{11} = 15, k_{12} = 0.02, k'_{12} = 2.01, Km_{12} = 15, K'm_{12} = 15, \bar{y}_3 = 300$
(8i)	$k_{13} = 1.03, k'_{13} = 0.09, Km_{13} = 15, K'm_{13} = 15, \bar{y}_4 = 300$

Table 2 Parameter values used in (9)

Eq. no.	Parameter values
(9a)	$k_1 = 0.025; rk_1 = 0.75; km_1 = 15; rkm_1 = 15; K_P = 9; p = 1; t_d = 10; h = 10; u = 100; \bar{x}_1 = 300$
(9b)	$k_2 = 0.025; rk_2 = 0.5; km_2 = 15; rkm_2 = 15; K_P = 9; p = 1; t_d = 10; h = 10; u = 100; \bar{x}_2 = 300$
(9c)	$k_3 = 1.25; rk_3 = 0.015; km_3 = 15; rkm_3 = 15; k_4 = 2.25; rk_4 = 0.019; km_4 = 15; rkm_4 = 15; \bar{x}_3 = 300;$
(9d)	$k_5 = 2.25; rk_5 = 0.15; km_5 = 15; rkm_5 = 15; k_6 = 0.025; rk_6 = 1.05; km_6 = 15; rkm_6 = 15; \bar{x}_4 = 300;$
(9e)	$k_7 = 2.5; rk_7 = 0.05; km_7 = 15; rkm_7 = 15; k_8 = 0.05; rk_8 = 1.5; km_8 = 15; rkm_8 = 15; \bar{x}_5 = 300;$

Table 3 Parameter values used in (10)

Eq. no.	Parameter values
(10a)	$k_1 = 1.5, k'_1 = 0.25, Km_1 = 15, K'm_1 = 15, c_1 = 1.05, c'_1 = 0.05, Cm_1 = 15, C'm_1 = 15, c_2 = 0.03, c'_2 = 2.05, Cm_2 = 15, C'm_2 = 15, K_P = 9, p = 1, t_d = 10, h = 10, u = 100, \bar{x}_1 = 300$
(10b)	$k_2 = 0.025, k'_2 = 0.75, Km_2 = 15, K'm_2 = 15, c_3 = 0.06, c'_3 = 2.6, Cm_3 = 15, C'm_3 = 15, c_4 = 2.5, c'_4 = 1.5, Cm_4 = 15, C'm_4 = 15, K_P = 9, p = 1, t_d = 10, h = 10, \bar{x}_2 = 300$
(10c)	$k_3 = 1.25, k'_3 = 0.5, Km_3 = 15, K'm_3 = 15, k_4 = 0.5, k'_4 = 1.5, Km_4 = 15, K'm_4 = 15, \bar{x}_3 = 300$
(10d)	$k_5 = 1.25, k'_5 = 0.015, Km_5 = 15, K'm_5 = 15, k_6 = 2.25, k'_6 = 0.019, Km_6 = 15, K'm_6 = 15, \bar{x}_4 = 300$
(10e)	$k_7 = 0.25, k'_7 = 1.15, Km_7 = 15, K'm_7 = 15, k_8 = 0.025, k'_8 = 1.05, Km_8 = 15, K'm_8 = 15, \bar{x}_5 = 300$
(10f)	$k_9 = 2.5, k'_9 = 0.05, Km_9 = 10, K'm_9 = 8, w_1 = 1, \bar{y}_1 = 100$
(10g)	$k_{10} = 0.05, k'_{10} = 1.5, Km_{10} = 10, K'm_{10} = 8, w_2 = 1, \bar{y}_2 = 100$
(10h)	$k_{11} = 2.6, k'_{11} = 0.075, Km_{11} = 15, K'm_{11} = 15, k_{12} = 0.02, k'_{12} = 2.01, Km_{12} = 15, K'm_{12} = 15, \bar{y}_3 = 300$
(10i)	$k_{13} = 1.03, k'_{13} = 0.09, Km_{13} = 15, K'm_{13} = 15, \bar{y}_4 = 300$

Fig. 1 ERK5 cascade **Fig. 2** JNK cascade

phosphorylate specific serines and threonines of target protein substrates and regulate cellular activities ranging from gene expression, mitosis, movement, metabolism, and programmed death (Yang et al. 1997).

ERK5 is a MAP Kinase regulated by a wide range of mitogens and cellular stresses (Fig. 1). The potentially crucial role of ERK5 in cancers and heart diseases make this cascade highly attractive for the development of new therapeutic strategies to treat pathological conditions that

are resistant to current therapies (English and Cobb 2002). The JNKs consist of three isoforms: JNK1 and JNK2 are the products of alternative splicing of a single gene and are expressed in many tissues, but JNK3 is specifically expressed in neuronal tissue brain (Fig. 2). Members of the JNK family play crucial roles in regulating responses to environmental stress, radiation, and growth factors, and in neural development, inflammation, and apoptosis (Davis 2000).

Materials and methods

To understand cell behavior, we must understand cell signaling. To understand cell signaling, we need to understand the spatial and temporal dynamics of the components of signaling pathways. The combined effects of these interactions are difficult to predict from intuition alone. When intuition is insufficient, a mathematical model is often useful for acquiring a quantitative and predictive understanding of this complex dynamical system (Wolkenhauer et al. 2005). Differential equation models are well defined encodings of molecular interactions contributing towards the synthesis and degradation of a protein in the context of cell signaling (Kholodenko 2000). A basic assumption of this approach is that the cell presents a well-stirred biochemical reactor. The corresponding terms of production and consumption in the kinetic equations can be: (a) constant, presenting reaction of synthesis; (b) linear, presenting degradation; (b) nonlinear, presenting multi-component (often two-component) reactions or enzyme reactions of Michaelis–Menten kinetics (Wolkenhauer et al. 2005).

In signaling, activation/inactivation of proteins correspond to phosphorylation/dephosphorylation (Kholodenko 2000). In the biochemical reaction shown in Fig. 3, denoting the kinase as U , the phosphatase as P and the protein as X , and assuming a constant phosphatase, a simple biochemical model of a signaling step is given by

$$\dot{x} = v_1(u, \tilde{x}) - v_2(x) \quad (1)$$

where $v_1(\cdot)$ and $v_2(\cdot)$ are mappings, describing the reaction rates for phosphorylation and dephosphorylation, respectively, $\tilde{x}$ for the non-phosphorylated form of the protein X , u for the kinase U , and x corresponds to the activated protein X^* .

Referring to a power-law representation, one would have:

$$v_1(u, \tilde{x}) = k_1 u^a \tilde{x}^b, v_2(x) = k_2 x^c.$$

Choosing $a = b = c = 1$, the Eq. (1) is written as

$$\dot{x} = k_1 u(t) \tilde{x}(t) - k_2 x(t). \quad (2)$$

Fig. 3 Biochemical reaction

If we assume that the total $\bar{x} = \tilde{x}(t) + x(t)$ is constant for all time t , the following differential equation models a signaling step (Hlavacek et al. 2006)

$$\dot{x} = k_1 u(t) (\bar{x}(t) - x(t)) - k_2 x(t). \quad (3)$$

If Michaelis–Menten kinetics is assumed then the model (Kholodenko 2000; Wolkenhauer et al. 2005) is obtained as:

$$\dot{x} = \underbrace{\frac{k_1 u(t) (\bar{x}(t) - x(t))}{K_{m_1} + (\bar{x}(t) - x(t))}}_{\text{phosphorylation}} - \underbrace{\frac{k_2 x(t)}{K_{m_2} + x(t)}}_{\text{dephosphorylation}}. \quad (4)$$

The constants K_{m_1} and K_{m_2} are Michaelis–Menten constants.

As the signal transfer between the cell surface and the nucleus occurs in a stepwise manner, a systems biologist will also think of a step by step biochemical reaction of the whole pathway with network systems of interacting signaling substances receiving inputs and engendering outputs. Feedback loops are one among the interactions in signaling cascades, in which the information from the downstream components is sent back to the upstream components of the system.

When feedback loops from a protein x_j further down the pathway, up to x_i are introduced then the model is modified to the following form:

$$\dot{x} = k_1 u(t) F(x_j) (\bar{x}_i(t) - x_i(t)) - k_2 x_i(t) \quad (5)$$

where for the function $F(x_j)$, a commonly used choice is $F(x_j) = 1 / (1 + (x_j/K)^n)$, the constant $n \geq 1$ defines the steepness of the feedback function, K is a constant that defines the strength of the feedback (Fig. 4) (Wolkenhauer et al. 2005). The main requirement for the choice of a

Fig. 4 Graph of the feedback function

function $F(x_j)$ is that at $x_j = 0$, we should have $F(x_j) = 1$. Mechanistic interpretations and experimental evidence for this function is discussed in the literature (Ferrell 1996; Goldbeter 1996; Huang and Ferrell 1996; Li and Qian 2003) and the other types of feedback functions can be found in the literature (Onn Brandman et al. 2008; Quincey et al. 2009; Tsai et al. 2008).

Fig. 5 ERK5 and JNK cascades with cross-talks

Fig. 6 JNK cascade with feedback loops from JNKs' to MKKs'

When transport delay t_d is introduced in the feedback loop, then the model is written as:

$$\dot{x}_i = k_1 u(t) \left[\frac{1}{1 + (x_j(t - t_d)/K)^n} \right] (\bar{x}_i(t) - x_i(t)) - k_2 x_i(t) \quad (6)$$

With the Michaelis–Menten kinetics and transport delay t_d in the feedback loop, the model is written as:

Fig. 7 ERK5 and JNK cascades with cross-talks and feedback loops

Fig. 8 Reaction schemes involved in activation (phosphorylation) and inactivation (de-phosphorylation) of the proteins in ERK5 and JNK cascades with cross-talks

Fig. 9 Reaction schemes of activation (phosphorylation) and inactivation (de-phosphorylation) of the proteins in JNK cascade with feedbacks loop from JNKs' to MKKs'

Fig. 10 Reaction schemes of activation (phosphorylation) and inactivation (de-phosphorylation) of the proteins in ERK5 and JNK cascades with cross-talks and feedback loops

$$\dot{x}_i = \frac{k_1 u(t) \left[1 / \left(1 + (x_j(t - t_d) / K)^n \right) \right] (\bar{x}_i(t) - x_i(t))}{\underbrace{K m_1 + (\bar{x}_i(t) - x_i(t))}_{\text{phosphorylation}}} - \frac{k_2 x_i(t)}{\underbrace{K m_2 + x_i(t)}_{\text{dephosphorylation}}} \quad (7)$$

Results and discussion

In this work, the MATLAB function ode113, an ODE (ordinary differential equation) solver based on a variable order Adams–Bashforth–Moulton PECE(predict-evaluate-correct-evaluate) method (Shampine et al. 2003) has been used to solve the system of ODEs, and the MATLAB function dde23, a DDE (Delay Differential Equation) solver based on the explicit Runge–Kutta (2,3) method

(Shampine and Thompson 2001) has been used to solve the system of DDEs, and considered the plots, which represents the concentration of activated MAPKs' only for the sake of analysis. Availability of quantitative values for molar concentrations and reaction rate constants has been a bottleneck for the researchers who are interested to study the dynamic behaviors of the signaling pathways for which pathway diagram alone deposited in the databases. Since the molar concentrations and reaction rate constants are not same in the cell types and organisms, we have assumed reasonable values for the parameters representing them, in concurrence with the values used in the other MAPK pathway modeling works published in the journals (Kholodenko 2000; Wolkenhauer et al. 2005). Also, the molar concentrations for MAPKs, MAPKKs and MAPKKKs has been taken such that molar concentration of MAPKs are lesser than that of MAPKKs and MAPKKKs, and the molar concentration of MAPKKs and MAPKKKs are equal as it has been observed and used in practice.

The plot in (Fig. 11) has been obtained by simulating the system of Eq. (8f–i), which represents the dynamical model of ERK5 cascade, responses to unit-step input signals (Fig. 1). The plots in (Fig. 12) have been obtained by simulating the system of Eq. (8a–e) without cross-talk terms i.e. $c_i = c'_i = 0; i = 1$ to 4. This represents the dynamical model of JNK cascade (Fig. 2). The plots in (Fig. 13) have been obtained by simulating the system of Eq. (8a–i), which represents the dynamical model of ERK5 and JNK cascades with cross-talks and unit-step input signals (Fig. 5). From the Figs. 11 and 12, it has been observed that ERK5 and JNK1 are getting activated in a sustained manner, and JNK2 and JNK3 are getting activated in an ultrasensitive manner. Also, from the Fig. 13, it has been observed that, there is no significant impact on ERK5 activation or JNKs' activation due to cross-talks between them (Figs. 6, 7, 8, 9 and 10).

Fig. 11 Simulation of ERK5 cascade with unit-step input signal

Fig. 12 Simulation of JNK cascade

Fig. 13 Simulation of ERK5 and JNK cascades with cross-talks, and unit-step input signal

The plots in Fig. 14 has been obtained by simulating the system of delay differential Eq. (9a–e), which represents the dynamical model of JNK cascade with feedback loops from JNKs' to MKKs'. From Figs. 12 and 14, it has been observed that, the positive feedback from JNKs' to MKKs' enhances the ultrasensitive activation of JNK2 and JNK3, and the sustained activation of JNK1. Thus, JNK's gains its ultrasensitive and sustained way of getting activated due to the feedback loops. The plots in Figs. 15 and 16 have been obtained by simulating the system of Eq. (10a–i), which represents the dynamical model of ERK5 and JNK cascades with cross-talks and feedback loops responses to unit-step input signals and zero input, respectively. From Figs. 15 and 16, it has been observed that due to cross-talks and feedback loops in ERK5 and JNK cascade, ERK5 gets activated in a transient manner in the absence of input

Fig. 15 Simulation of ERK5 and JNK cascades with cross-talks, feedback loops, and unit-step input signal

Fig. 14 Simulation of JNK cascade with feedback loops from JNKs' to MKKs'

Fig. 16 Simulation of ERK5 and JNK cascades with cross-talks, feedback loops, and zero input

signals. Thus, ERK5 lost its sustained way of getting activated due to the cross-talks and feedback loops in JNK cascade.

It has been observed that, the qualitative behavior of the stimulus/response curves such as ultra sensitive/sustained/transient manner of activation of ERK5, JNKs' does not vary for a range of input signals (1–5 nM), reaction rate constants (0.001–3 nM/s), molar concentrations of kinases (100–300 nM). Michaelis–Menten's constants (10–20 nM), time delay t_d = (10–40 min), for the values of n , P = 1, 2, and for the feedback of more than one type of JNK at a time from JNKs to MKKs. Only the time taken by the activated ERK5, JNKs' to reach the saturation has been varying. It might be due to the robust nature of the kinase cascades. In general, the transient activation of ERK5 triggers cell proliferation, whereas sustained activation brings about differentiation (English and Cobb 2002), and the sustained JNK1 activation might associate with survival (Johnson and Lapadat 2002). In future, there are plans to obtain the parameter values from the experimentalist who has been working on the same pathways, and to validate the results by experimental verification.

Acknowledgments Conflict of interest None.

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