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Stability Analysis of Time Delay Model of Crosstalk between ERK and STAT5a Interaction

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Abstract: *In this paper we investigate the qualitative behavior of a time delay model of the crosstalk between ERK and STAT5. We apply linear approximation to study the time delay model. The influence of some parameters on the dynamics of the model is analyzed analytically and numerically. Our qualitative results show that the model is structurally unstable. Relating this result to the physiological nature of the studied mathematical model, we prove mathematically the appearance of a crosstalk between the signaling pathways ERK and STAT in some cancer cells. This pathology appears when the process of homeostasis is disturbed and it has a non-reverse character.*

Keywords: *Crosstalk between ERK and STAT5, Time delay model, Stability analysis.*

Introduction

Signaling pathways form intracellular networks that control proliferation, differentiation and survival. Complexity arises from the large number of molecules involved in signal processing and the various interactions between them [3, 22, 23]. The signaling pathways can interact with each other, a phenomenon often called crosstalk. Crosstalk gives us a new insight about how signaling pathways interact in a dynamical way, i.e., whether they amplify, inhibit, delay or accelerate each other [15, 21, 24, 25]. Disruptions or errors of signal transfer can have catastrophic consequences and may lead to diseases, including cancer [3, 5, 6, 26].

Signal transducers and activators of transcription (STAT) are a family of latent cytoplasmic proteins that are activated to participate in gene control when cells encounter various extracellular polypeptides. STAT can be activated by tyrosine or serine phosporilation. Ligand binding to cytokine (GH, erythropoietin) or tyrosine (epidermal growth factor) receptors leads to activation of STAT through tyrosine phosphorilation. In case of cytokine receptors tyrosine phosphorilation is mediated by receptor bound members of the Janus kinase (JAK) family from 3 to 5 [3, 4, 18, 20, 22, 23]. Another essential pathway in cell signaling besides JAK-STAT is mitogen-activated protein kinase (MAPK) pathway also synonymous in literature to ERK [7, 26]. MAPK activates STAT through serine phosporilation. Phosporilation of serine has been shown to regulate DNA binding capacity and/or transcriptional activity of these STAT proteins [3, 18-20, 28]. In this way MAPK signaling pathway affects on JAK-STAT signaling pathway. Authors of paper [16] on the basis of the biochemical diagram (Fig. 1) and discussions in the work [18] suggest a dynamical model for interaction between ERK and STAT5a in CHOA cells. As it is proved in [18], in unstimulated cells STAT5a is complexed with inactive ERK that binds to STAT5a via its C-terminal substrate recognition domain to an unknown region on STAT5a. Then via its active site it

binds to the C-terminal ERK recognition sequence in STAT5a. On the other hand, upon GH stimulation, MEK activates ERK through phosphorilation of specific threonine and tyrosine residues in ERK. The active ERK phosphorilates serine 780 in STAT5a, resulting in decreased affinity between the two proteins and dissociation of the complex. This dynamical model consists of four nonlinear ordinary differential equations. Also in the papers [16, 17] the influence of diffusion on the concentrations of ERK and STAT and the possibility for Turing bifurcation on ERK-STAT crosstalk are studied.

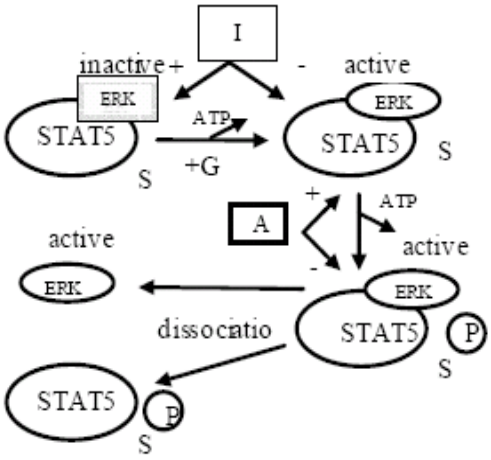

Fig. 1 PPGH – biochemical diagram for STAT5a interaction with ERK

In our previous study [10] we considered the effect of inhibition and activation on both ERK and STAT5 and the time delay of the dynamical model of ERK-STAT crosstalk. To do this we added the terms which represent inhibition and activation of both ERK and STAT5a to the dynamical model [16]. It is illustrated on Fig. 1. We also included a time delay to the model. The time delay is the time necessary for the activation of ERK and phosphorilation of STAT5a. In this way the dynamical model describing the kinetics of STAT5a/S phosphorylation and ERK activation takes form

$$\begin{aligned}
\frac{de_1}{dt} &= -k_0 e_1 s_1 + k_2 e_2 - I, \\
\frac{de_2}{dt} &= k_0 e_1(t-\tau) s_1(t-\tau) - k_2 e_2 + I, \\
\frac{ds_1}{dt} &= -k_1 e_1 s_1 + k_3 s_2 + A, \\
\frac{ds_2}{dt} &= k_1 e_1(t-\tau) s_1(t-\tau) - k_3 s_2 - A.
\end{aligned} \tag{1}$$

The concentration variables e_1, e_2, s_1, s_2 are denoting concentrations of ERK-inactive, ERK-active, STAT5a-unphosphorylated and STAT5a-phosphorylated respectively. Kinetic constants k_0 and k_1 are proportional to the frequency of collisions of ERK and STAT5a protein molecules and present rate constant of reactions of associations; k_2 and k_3 are constants of exponential growths and disintegrations; $I > 0$ and $A > 0$ are inhibitor and activator sources respectively. The source $I > 0$ inhibits the inactivation of active ERK, and A activates the dephosphorylation of phosphorylated STAT5a. The terms I and A can be also considered as some effective (apparent) inhibitor and activator, under condition that they

present really some in-flux and out-flux of the active ERK and phosphorylated STAT5a respectively.

In the next section we present the analytical results concerning the qualitative behavior of the time delay model (1). The following two sections present analytical and numerical results which illustrate the influence of the different values of the bifurcation parameters on the model. In the final section we discuss and summarize our results.

Qualitative analysis

In this section we investigate the qualitative behavior of the model (1). Firstly, we consider the influence of parameters $k_0, k_1, k_2, k_3, e_1, e_2, s_1, s_2$, I, A and τ on the system behavior. To analyze (1) it can be noted that only two equations of the four ones are independent. It is easy to show that between concentrations e_1, e_2, s_1, s_2 exist the relations

$$e_1 + e_2 = \mathrm{e}_0 \ , \ s_1 + s_2 = \mathrm{s}_0 . \tag{2}$$

Further we used relations (2) to find the equilibrium states of system (1). Thus, the steady state is

$$\bar{e}_1 = \frac{k_2 e_0 - I}{k_0 \bar{s}_1 + k_2}, \quad \bar{e}_2 = \frac{k_0 \bar{e}_1 \bar{s}_1 + I}{k_2}, \quad \bar{s}_1^{(1,2)} = \frac{-b \pm \sqrt{b^2 + 4c}}{2}, \quad \bar{s}_2 = \frac{k_1 \bar{e}_1 \bar{s}_1 - A}{k_3}, \tag{3}$$

where

$a = k_0 k_3$, $b = [(k_1 e_0 + k_3)k_2 - k_1 I - (k_3 s_0 + A)k_0]/a$, $c = (k_3 s_0 + A)k_2 / a$, $d = \sqrt{b^2 + 4c}$, e_0 and s_0 are initial concentrations of ERK and STAT5a respectively.

One of the two equilibriums has positive values ($\bar{s}_1^{(1)}$) and the other – negative ones ($\bar{s}_1^{(2)}$). From a physiological point of view only the positive values are actual concentrations. Therefore it is denoted, that $\bar{E}(\bar{e}_1, \bar{e}_2, \bar{s}_1, \bar{s}_2) > 0$ is equilibrium state (fix point) of the time delay system (1). In order to investigate the character of the fix point $\bar{E}$, we first obtain the characteristic equation for the liner part of system (1). Next, we consider small perturbations about the equilibrium level, i.e.

$$e_1 = \bar{e}_1 + x \, , \ e_2 = \bar{e}_2 + y \, , \ s_1 = \bar{s}_1 + z \, , \ s_2 = \bar{s}_2 + w \, . \tag{4}$$

After some transformations time delay system (1) in local coordinates has the form

$$\begin{aligned}
\dot{x} &= -k_0 \bar{s}_1 x + k_2 y - k_0 \bar{e}_1 z - k_0 xz \, , \\
\dot{y} &= k_0 \bar{s}_1 e^{-2\tau\chi} x - k_2 y + k_0 \bar{e}_1 e^{-2\tau\chi} z + k_0 e^{-2\tau\chi} xy \, , \\
\dot{z} &= -k_1 \bar{s}_1 x - k_1 \bar{e}_1 z + k_3 w - k_1 xz \, , \\
\dot{w} &= k_1 \bar{s}_1 e^{-2\tau\chi} x + k_1 \bar{e}_1 e^{-2\tau\chi} z - k_3 w + k_1 e^{-2\tau\chi} xz \, .
\end{aligned} \tag{5}$$

Further, we neglect the terms of second and third order in small quantities, and thus the stability matrix obtains the form

$$\begin{pmatrix} -k_0\bar{s}_1-\chi & k_2 & -k_0\bar{e}_1 & 0 \\ k_0\bar{s}_1 e^{-2\tau\chi} & -k_2-\chi & k_0\bar{e}_1 e^{-2\tau\chi} & 0 \\ -k_1\bar{s}_1 & 0 & -k_1\bar{e}_1-\chi & k_3 \\ k_1\bar{s}_1 e^{-2\tau\chi} & 0 & k_1\bar{e}_1 e^{-2\tau\chi} & -k_3-\chi \end{pmatrix}. \quad (6)$$

After resolving the matrix and performing transformations we get characteristic equation of the linearized part of system

$$\chi^4 + p\chi^3 + b_1\chi^2 + d_1\chi = (a_1\chi^2 + c_1\chi)e^{-2\tau\chi}, \quad (7)$$

where

$p = k_0\bar{s}_1 + k_2 + k_1\bar{e}_1 + k_3$, $a_1 = (k_0k_2\bar{s}_1 + k_1k_3\bar{e}_1)$; $c_1 = k_1k_2k_3\bar{e}_1$,

$b_1 = (k_2 + k_3)k_1\bar{e}_1 + (k_2 + k_3)k_0\bar{s}_1 + k_2k_3$, $d_1 = k_1k_2k_3\bar{e}_1 + k_0k_2k_3\bar{s}_1$.

Linear stability analysis

For small delay τ ($\tau < 1$), the method of linear stability analysis is much convenient to investigate the qualitative behavior of equation (7). For this purpose we develop the function $e^{-2\tau\chi}$ in Taylor's expansion and retain only linear term, then we have $e^{-2\tau\chi} \approx 1 - 2\chi\tau$. After some transformations and algebraic operations the characteristic equation (7) takes its final form

$$\chi^4 + p_1\chi^3 + q_1\chi^2 + r_1\chi + s = 0, \quad (8)$$

where

$p_1 = (p + 2a_1\tau)$, $q_1 = (b_1 - a_1 + 2c_1\tau)$, $r_1 = (d_1 - c_1)$, $s=0$.

In order to investigate the stability of equilibrium point (3) we use Routh-Hurwitz conditions. Here these conditions are

$$p_1 = (p + 2a_1\tau) = k_0\bar{s}_1 + k_2 + k_1\bar{e}_1 + k_3 + 2(k_0k_2\bar{s}_1 + k_1k_3\bar{e}_1)\tau > 0, \quad (9)$$

$$q_1 = (b_1 - a_1 + 2c_1\tau) = k_1k_2\bar{e}_1 + k_0k_3\bar{s}_1 + k_2k_3 + 2k_1k_2k_3\bar{e}_1\tau > 0, \quad (10)$$

$$r_1 = (d_1 - c_2) = k_0k_2k_3\bar{s}_1 > 0, \quad (11)$$

$$s = 0, \quad (12)$$

$$R = [k_1\bar{e}_1 + k_0\bar{s}_1 + k_2 + k_3 + 2(k_0k_2\bar{s}_1 + k_1k_3\bar{e}_1)\tau] \times (k_1k_2\bar{e}_1 + k_0k_3s_1 + k_2k_3 + 2k_1k_2k_3\bar{e}_1\tau).k_0k_2k_3\bar{s} - (k_0k_2k_3\bar{s}_1)^2 > 0. \quad (13)$$

Generally, the stability of a steady state depends on the real part of the roots of the characteristic equation – χ. If all roots are negative then the equilibrium state is stable. If with at least one root $\chi > 0$, then the solution is unstable. Therefore, the condition for the change of stability will be at $\chi = 0$.

It is seen that in our case conditions (9) - (11) and (13) are always valid, but (12) is equal to zero, i.e. is not bigger than zero. In this case the type of equilibrium state is a compound saddle-focus or a compound saddle-knot [11, 14]. Whether we will have the first or the second type depends on the roots of the characteristic equation (8). If the case is of a

compound saddle-focus we have a zero root and a negative real root and two complex conjugate roots with negative real parts. If the case is of a compound saddle-knot then we have one root equal to zero and three negative real roots. In order to determine the type of the roots we should examine them on the border of the area of stability. According to [1] the border of the area of stability are $R = 0$ and $s = 0$. In our case, it is examined the type of equilibrium state of the system on the border $s = 0$**.** On this border the characteristic equation (8) has one root equal to zero, and the type of the other roots is determined by the expression:

$$\Omega = 27r_1^2 - 18p_1q_1r_1 + 4q_1^3 + 4p_1^3r_1 - p_1^2q_1^2 . \qquad (14)$$

From (14) follows that

a) if the conditions $\Omega < 0$, $p_1 > 0$, $q_1 > 0$, $r_1 > 0$, $s = 0, R > 0$ are satisfied, then the equation (8) has one root equal to zero and three negative real roots.

b) when $\Omega > 0$, $p_1 > 0$, $q_1 > 0$, $r_1 > 0$, $s = 0$, $R > 0$, then the equation (8) besides one zero root also has a negative real root and two complex conjugate roots with negative real parts.

The stability theory for systems with structurally unstable equilibrium states [1, 8, 9, 12, 14] considers various aspects of stability in critical cases, as well as the bifurcation phenomena accompanying the loss of stability at equilibrium states. Here, we mention only the two most common and simple cases [12], where the characteristic equation (8) (i) has one zero root and (ii) has a pair of complex-conjugated roots on the imaginary axis.

The first case is determined by the condition

$$s = 0 \text{ and } \Delta_k > 0 , k = 1, 2, 3, \qquad (15)$$

where Δ_k is the Routh-Hurwitz determinant. Recall that $s = (-1)^4 \det A$, where A is the matrix of the linearized system at the equilibrium state. In view of this condition, the equilibrium states associated with the first critical case are also called degenerate. Since the implicit function theorem may not longer be applied here, the persistence of such equilibrium state in a neighboring system is not necessarily guaranteed. Thus, a transition through the stability boundary in the first critical case may result in the disappearance of the equilibrium state. In this case the system is structurally unstable and through bifurcation it will lose its stability non-reversely. Generally the stability of cell signaling pathways could, from a biological point of view, be connected to homeostasis, i.e., the process of keeping an internal environment stable by making adjustments to changes in the external environment. This is achieved by a system of feedback control loops. In other words, for the stability of cell signaling processes it is essential that the cell maintains a stable condition where in fact a constant flux of molecules occurs. However, in case of crosstalk between ERK and STAT5a pathways, the homeostasis is disturbed. Studies have shown that such interaction has been observed in cancer disease which classifies this type of crosstalk as disruptive and causing disease.

The second critical case corresponds to

$$s > 0, \ \Delta_{n-1} > 0 \text{ and } \Delta_k > 0 , n = 4, k = 1, 2. \qquad (16)$$

In this case on the contrary of the first critical case, the equilibrium state is preserved in all nearby systems and can only lose its stability. Again from a biological point of view, this

means that the homeostasis can be disturbed but after a certain period of time it will restore. If cancer disease appears, it can be healed with medical assistance [12, 13].

Numerical analysis

In this section we shall illustrate numerically some analytical results which were obtained in the previous section for system (1). In view of the lack of quantities data for parameters of crosstalk between ERK and STAT5a pathways we assign the intervals within which the parameters change on the basis of data about the JAK-STAT and MAPK pathways [2, 22, 27] in accordance with biochemical kinetics. For the numerical simulations we assume the following intervals of the parameters

$$\begin{aligned} &k_0 \in [0.5,\ 4]\,\text{min}^{-1},\ k_1 \in [0.7,\ 4]\ \text{min}^{-1},\ k_2 \in [0.1,\ 4]\,\text{min}^{-1}, \\ &k_3 \in [0.2,\ 0.6]\,\text{min}^{-1},\ \tau \in [0.1,\ 1]\,\text{sec},\ e_0 \in [1.10^{-3}, 1.10^{-2}]\,\text{mM}, \\ &s_0 \in [1.10^{-2}, 1.10^{-1}]\,\text{mM},\ I \in [1.10^{-4}, 1.10^{-3}]\,\text{mM},\ A \in [1.10^{-5}, 1.10^{-4}]\,\text{mM}. \end{aligned} \tag{17}$$

We examine the influence of all parameters (17) on the dynamic behavior of the system (1). To do this we vary one parameter at a time while the other parameters are fixed. Based on the qualitative theory of the differential equations, the parameter that varies is bifurcation one. Firstly, as bifurcation parameter the concentration of ERK – e_0 is chosen. In the Fig. 2 it is shown the type of the roots of (8) beside of zeros root as function of the e_0. It is seen that in the interval $e_0 \in [0.001,\ 0.013]$, Ω is positive and the roots are one real negative and two complex conjugated ones with a negative real part. In this case the type of steady state (3) is a compound saddle-focus. When e_0 increases in the interval $e_0 \in [0.013,\ 0.04]$ the sign of Ω becomes negative and there are 3 real negative roots. Now, the type of steady state (3) is a compound-knot. When the parameters k_0 and τ varies in its intervals, the equation (8) has the same type of roots like e_0. When parameters k_0 and τ varies in its intervals, initially Ω is negative and equation (8) has 3 real negative roots in intervals $k_0 \in [0.5, 2.6]$ and $\tau \in [0.1, 2.6]$ respectively. When Ω becomes positive for $k_0 \in [2.6, 4]$ and $\tau \in [2.6, 1]$ the characteristic equation has one real negative and two complexes conjugated ones with a negative real part.

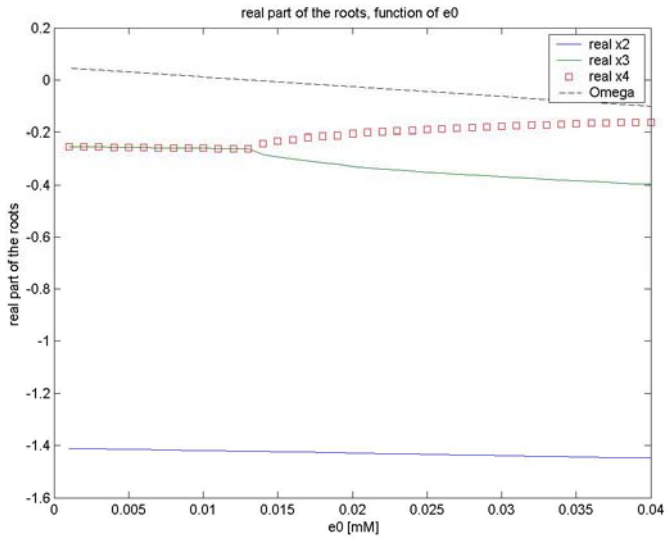

Fig. 2 Type of the roots of the characteristic equation,
for $e_0 \in [0.001,\ 0.013]$, $\Omega > 0$ and $e_0 \in [0.013,\ 0.04]$, $\Omega < 0$

From a mathematical point of view, when the assigned bifurcation parameters e_0, k_0, τ, are varied and reach a certain bifurcation value – $e_0 = 0.013$, $k_0 = 2.6$, $\tau = 2.6$ at which Ω changes its sign then a bifurcation occurs. As a result the type of equilibrium state changes from compound saddle-focus to compound saddle-knot or reversely. For example it is seen in Fig. 2 when bifurcation parameter is e_0.

Here we note that when we vary parameters s_0, k_2, k_3 in its whole intervals $s_0 \in [0.01,\ 0.05]$, $k_2 \in [0.1,\ 4]$, $k_3 \in [0.2,\ 0.6]$, Ω is always positive and the roots of Eq. (8) are: one real negative and two complex conjugated ones with a negative real part in the whole interval, respectively. Therefore, according to [11] the equilibrium points are from compound saddle-focus type. In this case subsiding oscillations will arise around this unstable equilibrium state.

Finally when we vary the parameters k_1, I, A in its interval $k_1 \in [0.1, 4]$, $I \in [1,10].10^{-4}$, $A \in [1,10].10^{-3}$ respectively, Ω is negative and the characteristic equation (8) has three negative real roots. Here the character of the equilibrium point (3) is a compound saddle-knot. It is depicted in Fig. 3, where parameter A is chosen for a variable parameter.

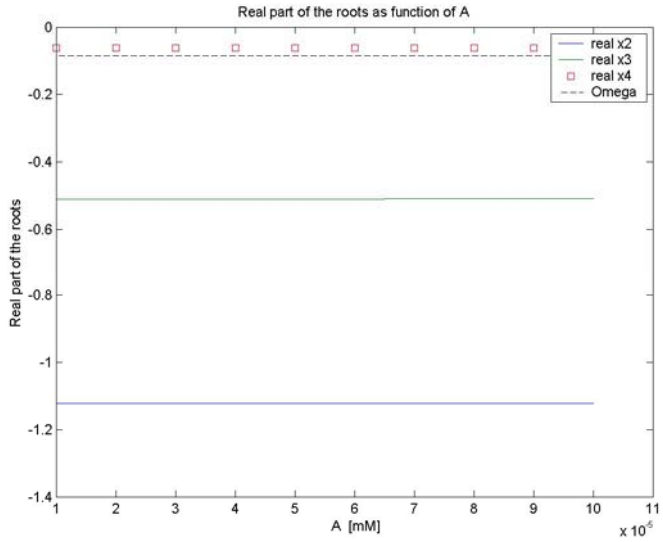

Fig. 3 The type of the roots of the characteristic equation for $A \in [1,10].10^{-3}$ when $\Omega < 0$

In this section we investigated numerically the influence of the parameters on the qualitative behavior of the linearized system (5). It follows from the numerical results that when the (bifurcation) parameters e_0, k_0, τ are taken as variables and when they reach the respective bifurcation value, bifurcation occurs in the system (5). As a result, the phase portrait of the system changes in the vicinity of its equilibrium state – from saddle-knot into saddle-focus or vice versa. When parameters s_0, k_2, k_3 are varied, the type of the equilibrium state is compound saddle-focus. And when parameters k_1, I, A are varied, the character of the equilibrium point (3) is compound saddle-knot.

With the unstable equilibrium state from the type compound saddle-knot, the oncogenesis will develop faster than the compound saddle-focus equilibrium state.

Conclusion

In this paper we have investigated the qualitative behavior of a time delay model of crosstalk between ERK and STAT5a. Also the influence of parameters on dynamics of a time delay model is analyzed. The results of qualitative analysis shows that when the characteristic equation has one zero root, this case corresponds to the first critical case of the structurally unstable systems. This first critical case is associated with disappearance of the equilibrium state which means that the system is structurally unstable. The types of unstable equilibrium are compound saddle-knot and compound saddle-focus, depending on the type of roots of the characteristic equation. Relating these results to the physiological nature of the studied mathematical model, we can make the conclusion that in reality, if there is a crosstalk between the signaling pathways ERK and STAT5a, this leads to the appearance of cancer disease. This pathology appears when the process of homeostasis is disturbed and it has a non-reverse character. The results from the numerical analysis illustrate the effect of the parameters of the time delay model on its behavior. It follows that when the parameters e_0, k_0, τ, are taken as variables and when they reach the respective bifurcation value, bifurcation occurs in the model. As a result, the phase portrait of the system changes in the vicinity of its equilibrium state – from saddle-knot into saddle-focus or vice versa. When parameters s_0, k_2, k_3 are varied, the type of the equilibrium state is compound saddle-focus. And when parameters k_1, I, A are varied, the character of the equilibrium point is compound saddle-knot. With the unstable equilibrium state from the type compound saddle-knot, the oncogenesis will develop faster than the compound saddle-focus equilibrium state.

If we have the second abovementioned critical case, and cancer disease appears, it can be healed with medical assistance.

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