



## **Dynamical Behaviour of a Time Delay Model of the ERK and STAT5 Interaction**

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**Summary:** In this paper we have done sensitive analysis of a time delay model which describes the ERK and STAT5 interaction. The results show that the type of the equilibrium point of the model can be a compound saddle-focus or a compound saddle-knot. This means that the model is structurally unstable. From the biological point of view in case of interactions between ERK and STAT the proto-oncogenes may turn into oncogenes.

**Keywords:** Sensitive Analysis, Time Delay Model, ERK – STAT5 Interactions.

### 1. INTRODUCTION

In cancer cells the signaling pathways controlling proliferation, differentiation and apoptosis are altered [3-5]. To understand key regulatory mechanisms and to predict targets for intervention at a cellular level mathematical models are used. Furthermore cross talk of signaling pathways has to be included since cells are usually stimulated by multiple factors and cell surface receptors that simultaneously activate multiple signaling pathways forming complex signaling networks [5, 6, 14, 20].

The Janus kinase / Signal transducer and activators of transcriptions (JAK/STAT) and Extracellular signal-regulated kinase (ERK) are essential intracellular signaling pathways which regulate gene expression by the phosphorylation of transcription factors. Both signaling cascades control the proliferation and differentiation of different cell types. The specific biological effects are crucially dependent on the amplitude and kinetics of STAT activity [2-4, 17-20]. In the recent decades it has been established that these pathways can interact between each other, a phenomenon called cross talk. The dynamic models allow to be obtained more clear information about the mechanisms of interaction and regulation of the signaling



pathways and networks and the response of cells respectively. The theory of non-linear dynamics allows defining behavior of the systems against perturbations or controlled reaction to stimulus.

A time delay model for interaction between ERK and STAT5a in CHO cells is proposed in the paper [9]. In the 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 phosphorylation of specific threonine and tyrosine residues in ERK. The active ERK phosphorylates serine 780 in STAT5a, resulting in decreased affinity between the two proteins and dissociation of the complex. The time delay model interactions between ERK and STAT5 has the following form

$$\begin{aligned}\frac{de_1}{dt} &= -k_0e_1s_1 + k_2e_2 - I, \\ \frac{de_2}{dt} &= k_0e_1(t - \tau)s_1(t - \tau) - k_2e_2 + I, \\ \frac{ds_1}{dt} &= -k_1e_1s_1 + k_3s_2 + A, \\ \frac{ds_2}{dt} &= k_1e_1(t - \tau)s_1(t - \tau) - k_3s_2 - A.\end{aligned}\tag{1}$$

The concentration variables  $e_1, e_2, s_1, s_2$  are denoting concentrations of ERK-inactive, ERK-active, STAT5-unphosphorylated and STAT5-phosphorylated respectively. Kinetic constants  $k_0$  and  $k_1$  are proportional to the frequency of collisions of ERK and STAT5 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. A more concrete interpretation of the inhibitor  $I$  and activator  $A$  can be given in connection with the role of the SOCS proteins in linking JAK/STAT and MEK/ERK pathways.

In the next section we present the sensitive analysis 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.

## 2. SENSITIVE ANALYSIS

In this section we investigate the dynamical behavior of the time delay model (1). The system has two steady-states. One of them 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 consider small perturbations about the equilibrium level, i.e.

$$e_1 = \bar{e}_1 + x, \quad e_2 = \bar{e}_2 + y, \quad s_1 = \bar{s}_1 + z, \quad s_2 = \bar{s}_2 + w. \quad (2)$$

The system (1) in local coordinates takes a form

$$\begin{aligned} \dot{x} &= -k_0 \bar{s}_1 x + k_2 y - k_0 \bar{e}_1 z - k_0 x z, \\ \dot{y} &= k_0 \bar{s}_1 e^{-2\tau x} x - k_2 y + k_0 \bar{e}_1 e^{-2\tau x} z + k_0 e^{-2\tau x} x y, \\ \dot{z} &= -k_1 \bar{s}_1 x - k_1 \bar{e}_1 z + k_3 w - k_1 x z, \\ \dot{w} &= k_1 \bar{s}_1 e^{-2\tau x} x + k_1 \bar{e}_1 e^{-2\tau x} z - k_3 w + k_1 e^{-2\tau x} x z. \end{aligned} \quad (3)$$

### *Linear stability analysis*

For small delay  $\tau$  ( $\tau < 1$ ), the method of linear stability analysis is much convenient to investigate the qualitative behavior of system (3). For this purpose we develop the function  $e^{-2\tau x} e^{-2\tau x}$  in Taylor's expansion and retain only linear term, then we have  $e^{-2\tau x} \approx 1 - 2\tau x$ .



After some transformations and algebraic operations the characteristic equation of (3) takes its final form

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

where

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

In order to investigate the stability of equilibrium point  $\bar{E}$  we use Routh-Hurwitz conditions [1,7,8,13]. Here these conditions are

$$p_1 = (p + 2a_1\tau) = k_0\bar{s}_1 + k_2 + k_1\bar{e}_1 + k_3 + 2(k_0k_2\bar{s}_1 + k_1k_3\bar{e}_1)\tau > 0 \quad (5)$$

$$q_1 = (b_1 - a_1 + 2c_1\tau) = k_1k_2\bar{e}_1 + k_0k_3\bar{s}_1 + k_2k_3 + 2k_1k_2k_3\bar{e}_1\tau > 0, \quad (6)$$

$$r_1 = (d_1 - c_2) = k_0k_2k_3\bar{s}_1 > 0, \quad (7)$$

$$s = 0, \quad (8)$$

$$R = [k_1\bar{e}_1 + k_0\bar{s}_1 + k_2 + k_3 + 2(k_0k_2\bar{s}_1 + k_1k_3\bar{e}_1)\tau]. \quad (9)$$

$$.(k_1k_2\bar{e}_1 + k_0k_3\bar{s}_1 + k_2k_3 + 2k_1k_2k_3\bar{e}_1\tau).k_0k_2k_3\bar{s} - (k_0k_2k_3\bar{s}_1)^2 > 0.$$

It is seen that in our case conditions (5) - (7) and (9) are always valid, but (8) 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 [10, 13]. Whether we will have the first or the second type depends on the roots of the characteristic equation (4). 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 (4) has one root equal to zero, and the type of the other roots is determined by the expression:

$$\Omega = 27r_1^2 - 18p_1q_1r_1 + 4q_1^3 + 4p_1^3r_1 - p_1^2q_1^2. \quad (10)$$



From (10) 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 (4) 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 (4) besides one zero root also has a negative real root and two complex conjugate roots with negative real parts.

The theory of dynamics systems considers various aspects of stability in critical cases, as well as the bifurcation phenomena accompanying the loss of stability at equilibrium states [1, 7, 8, 13]. Here, we mention only the two most common and simple cases [11, 13] where the characteristic equation (4) (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

$$s = 0 \text{ and } \Delta_k > 0, k = 1, 2, 3, \quad (11)$$

where  $\Delta_k$  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. 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. 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 [12, 20]. However, in case of crosstalk between ERK and STAT5 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 [3, 5, 17, 18].



### 3. 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 cross talk between ERK and STAT5 pathways we assign the intervals within which the parameters change on the basis of data about the JAK-STAT and MAPK pathways [2, 6, 19, 20] in accordance with biochemical kinetics. For the numerical simulations we assume the following intervals of the parameters

$$\begin{aligned} k_0 \in [0.5, 4] \text{ min}^{-1}, k_1 \in [0.7, 4] \text{ min}^{-1}, k_2 \in [0.1, 4] \text{ min}^{-1}, \\ k_3 \in [0.2, 0.6] \text{ min}^{-1}, \tau \in [0.1, 1] \text{ sec}, e_0 \in [1.10^{-3}, 1.10^{-2}] \\ e_0 \in [1.10^{-3}, 1.10^{-2}] \text{ mM}, s_0 \in [1.10^{-2}, 1.10^{-1}] \text{ mM}, \\ I \in [1.10^{-4}, 1.10^{-3}] \text{ mM}, A \in [1.10^{-5}, 1.10^{-4}] \text{ mM}. \end{aligned} \quad (12)$$

We examine the influence of all parameters (12) 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 kinetic constant  $k_0$  is chosen. In the Fig. 1 it is shown the type of the roots of (4) beside of zeros root as function of the  $k_0$ . It is seen that the  $\Omega$  can be negative and positive. In this case the type of steady state changes from compound-knot to saddle-focus by bifurcation. The system has the same type of equilibrium state when  $e_0$  and  $\tau$  vary in their intervals.

When parameters  $s_0$ ,  $k_2$ ,  $k_3$  are varied, the type of the equilibrium state is compound saddle-focus (Fig. 2).  $\Omega$  is always positive and the roots of Eq. (4) are: one real negative and two complex conjugated ones with a negative real part in the whole interval, respectively. Therefore, according to [1, 10] 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 their intervals,  $\Omega$  is negative and the characteristic Eq. (4) has three negative real roots. Here the character



of the equilibrium point is a compound saddle-knot. It is depicted in Fig. 3, where parameter  $I$  is chosen for a variable parameter.

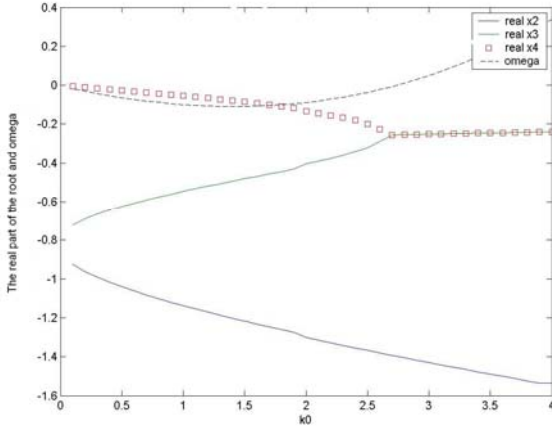


Fig. 1. The real parts of the roots as function of  $k_0$ .

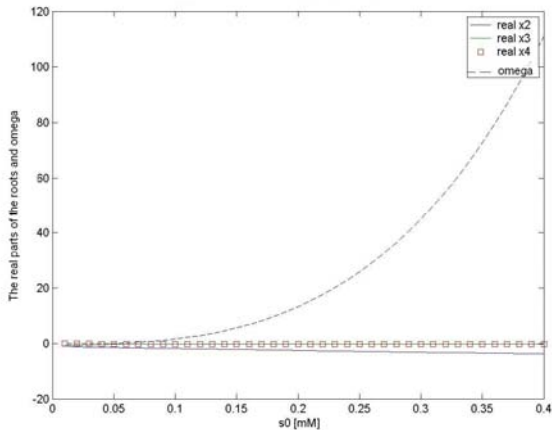


Fig. 2. The real parts of the roots as function of  $s_0$ .

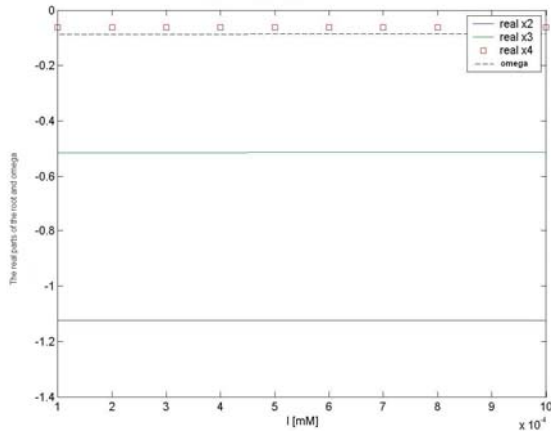


Fig. 3. The real parts of the roots as function of I.

#### 4. CONCLUSION

The sensitive analysis of the time delay model of interaction between ERK and STAT shows that the model has one unstable equilibrium point whose type can be either compound-knot or saddle-focus. The type of the equilibrium state depends on the parameters of the model. Moreover the system can change its phase portrait by bifurcation when definite parameters are varied. This means that the system is structurally unstable. From the biological point of view in case of interactions between ERK and STAT the proto-oncogenes may turn into oncogenes in the cells.

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