Chapter III
Mathematical Description of Time Delays in Pathways Cross Talk

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ABSTRACT

In this chapter we investigate how the inclusion of time delay alters the dynamic properties of (a) delayed protein cross talk model, (b) time delay model of RNA silencing (also known as RNA interference), and (c) time delay in ERK and STAT interaction. The consequences of a time delay on the dynamics of those systems are analysed using Hopf's theorem and Lyapunov-Andronov theory. Our analytical calculations predict that time delay acts as a key bifurcation parameter. This is confirmed by numerical simulations.

INTRODUCTION

The aim of this review is to give an extended analytical consideration of the role of time delay in the behaviour associated with dynamical models: (i) delayed protein cross talk model; (ii) time delay model of RNA silencing and (iii) time delay in ERK and STAT interaction.

Some of the results presented here are obtained and published in the papers (Nikolov, Kotev, Georgiev, & Petrov, 2006; Nikolov, Kotev, & Petrov, 2006a; Nikolov, Kotev, & Petrov, 2006b; Nikolov, Vera, Wolkenhauer, Yankulova, & Petrov, 2007; Nikolov & Petrov, 2007; Nikolov, Vera, Kotev, Wolkenhauer, & Petrov, 2008), but new considerations and improvements are also made. The investigations, conducted on time-delay mathematical models, examine how the time-delay influences the processes of protein synthesis, the RNA silencing and the interaction of the ERK and STAT proteins. Using the Lyapunov-Andronov theory and the Hopf theorem, the bifurcation values of the time delay are discovered, the zones of stability and instability are determined, and from there – the zones of norm and pathology (cancer) for each process. Thus, the greatest advantage of such an approach is revealed, namely – the theoretical forecast (prediction) of various diseases, including cancer.

Dynamical Aspects of Protein Cross Talk and Time Delay

The notion *cross talk* is introduced in the intracellular kinetics to denote the mutual interaction between signalling pathways (Wolkenhauer, Ullah, Wellstead, & Cho, 2005; Wolkenhauer, Streenath, Wellstead, Ullah, & Cho, 2005). It is realized by corresponding cross talk of the pathways elements, i.e. proteins. So the study of *protein cross talk* is necessary step in investigating the nature of pathways cross talk. The last is also necessary to analyze more complex networks of pathways. In some cases authors talk just about protein interactions having in view interaction between at least two proteins (Pircher, Petersen, Gustafsson, & Haldosen, 1999). On the other hand, in terms of systems theory, the protein interaction can be defined as feedback between two proteins. That's why this type of interaction is also called *feedback loop.*

Let us consider a simple hypothetical interaction between two proteins X and Y presented by the following kinetic equations:

$$\frac{dx}{dt} = k_1 y \tag{1.1.1}$$

$$\frac{dy}{dt} = -k_2 x - k_1 y \tag{1.1.2}$$

where x and y are the concentrations of the proteins X and Y respectively. The kinetic sense of the system (1.1.1)-(2) consists in the following two processes: (i) The protein

Y spontaneously degrades in a protein X with a reaction rate constant k_1; (ii) The protein X activates the degradation of protein Y with a proportionality coefficient k_2. The system (1.1.1)-(2) can be written in the form of following linear oscillator with attenuation:

$$\frac{d^2x}{dt^2} + k_1 \frac{dx}{dt} + k_1 k_2 x = 0 \tag{1.1.3}$$

Here the rate constant k_1 plays role of a friction coefficient of the oscillator.

Let us further suppose that the protein X needs some time τ to activate the degradation of protein Y. That means the rate of degradation $\frac{dy(t)}{dt}$ of Y in the moment t, is proportional to the concentration $x(t - \tau)$ of X in a previous moment $t - \tau$. Thus instead of (1.1.1)-(2), we should write: