Chapter 4
Bifurcation Analysis of a Model Accounting for the 14–3–3σ Signalling Compartmentalisation

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ABSTRACT

Bifurcation theory studies the qualitative changes in the phase portrait when we vary the parameters of the system. In this book chapter we adapt and extend a mathematical model accounting for the subcellular localisation of 14-3-3σ, a protein involved in cell cycle arrest and the regulation of apoptosis. The model is analysed with analytical tools coming from Lyapunov-Andronov theory, and our analytical calculations predict that soft (reversible) loss of stability takes place.

INTRODUCTION

14-3-3 proteins have crucial roles in a variety of cellular responses including signal transduction, cell cycle progression, metabolic regulation and apoptosis (Yang, Wen, Chen, Lozano, & Lee, 2003; Wilker, van Vugt, Artim, et al., 2007). Firstly identified through their high level of expression in the mammalian brain, it is currently well-known that mammals have eight different protein forms of 14-3-3 that are encoded by seven distinct genes (β, ε, γ, η, τ, ξ, σ). One particular 14-3-3 isoform, σ, is a p53-responsive gene and was characterized as a human mammary epithelium-specific marker (that is the reason why 14-3-3σ is also called stratifin). 14-3-3σ has a variety of cell functions. Regarding cancer and tumour progression, 14-3-3σ plays a role like regulator of the cell cycle, probably via cytosolic sequestration of critical cell cycle proteins like cyclin B1 and

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cdc2 in response to DNA damage and other stress signals (Hermeking, 2006). Interesting enough, 14-3-3σ can delay the initiation of apoptosis by sequestering mitochondrial p53 in the cytosol and preventing activation of Bax and other initiators of the apoptotic cascade. This assigns to 14-3-3σ a dual role in the regulation of the cell fate after DNA damage (Samuel, Weber, Rauch, Verdoodt, Eppel, McShea, Hermeking & Funk, 2001). The function of 14-3-3σ is frequently lost in human tumours including melanoma, breast and prostate cancers, which suggests that the protein may act as a tumour suppressor. However, the molecular basis for the tumour suppressor function of 14-3-3σ remains unknown (Wilker, van Vugt, Artim, et al., 2007). Moreover, 14-3-3σ is silenced in many cancers via gene methylation (Ferguson, Evron, Umbrich, & et al., 2000; Iwada, Yamamoto, Sasaki, & et al., 2000; Lodygin, Diebold, & Hermeking, 2004, Schultz et al. 2009). Remarkably, 14-3-3σ is involved in a positive feedback loop with its own activator p53 via stabilization and inhibition of ubiquitination (Yang, Wen, Chen, Lozano & Lee, 2003).

With respect to dynamic systems theory (Glass & Mackey, 1988; Shilnikov, Shilnikov, Turaev, & Chua, 2001; Nikolov, 2004), the first Lyapunov value is one of the basic analytical tools to investigate the transition between different dynamical states in biochemical systems. The (un) stability of these transitions may have important consequences on the dynamics of the system, pointing towards changes where parameters are critical for the emergence of pathological configurations. In addition, qualitative knowledge emerging from this analysis could be used in the development of diagnostic methods and in drug discovery (Nikolov, Vera, Kotev, Wolkenhauer, & Petrov, 2008; Nikolov, Vera, Rath, Kolch, & Wolkenhauer, 2009).

The present chapter extends our previous results in the mathematical modelling of 14-3-3σ (Vera, Schultz, Ibrahim, Wolkenhauer, & Kunz, 2009). We here adapt and extend the model to consider the subcellular localisation of the protein (cytosol, nucleus and mitochondria). The model is analysed with analytical tools coming from Lyapunov-Andronov theory to investigate the system and perform analytical (qualitative) predictions, which are complemented by numerical simulation.

MATHEMATICAL MODEL

Qualitative Analysis

For our investigation, we modified and expanded our previously published model (Vera, Schultz, Ibrahim, Wolkenhauer, & Kunz, 2009). The version of the model discussed here considers the synthesis, dimerisation, degradation and translocation of 14-3-3σ, but also the compartmentalisation of the signaling molecule in the cytosol, nucleus and mitochondria. The model is depicted in Figure 1. As we previously indicated, 14-3-3σ expression is mediated by p53 in response to DNA damage signalling and is able to block the progression of the cell cycle in both G1/S and G2/M transitions, but it also may delay/block the activation of apoptosis (Figure 1, left-hand side). In our model we consider the following critical events in the dynamics of 14-3-3σ: i) p53 mediated synthesis; ii) 14-3-3σ homodimerisation/activation in the cytosol; iii) translocation between cytosol and nucleus; iv) translocation between cytosol and mitochondria; and v) cytosolic degradation of 14-3-3σ (Figure 1, right-hand side).

Based on these hypotheses, we derived a model in ordinary differential Equations (ODE), which describes the dynamics of 14-3-3σ. The model considers the following variables accounting for the subcellular distribution of the protein: monomeric cytosolic (σ_c), dimeric cytosolic (σ_c^D),