Chapter 21
Dynamic Modeling and Parameter Identification for Biological Networks:
Application to the DNA Damage and Repair Processes

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ABSTRACT

DNA damage and repair processes are key cellular phenomena that are being intensely studied because of their implications in the onset and therapy of cancer. This chapter introduces a general dynamic model of gene expression, and proposes a genetic network modeling framework based on the interconnection of a continuous-time model and a hybrid model. This strategy is applied to a network built around the p53 gene and protein, which detects DNA damage and activates the downstream nucleotide excision repair (NER) network, which carries out the actual repair tasks.

Then, two different parameter identification techniques are presented for the proposed models. One is based on a least squares procedure, which treats the signals provided by a high gain observer; the other one is based on a Mixed Extended Kalman Filter. Prior to the estimation phase, identifiability and sensitivity analyses are used to determine which parameters can be and/or should be estimated. The procedures are tested and compared by means of data obtained by in silico experiments.

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INTRODUCTION

Systems biology is emerging as a new interdisciplinary subject, and several tools are being developed within this framework. It is largely recognized that new systems-level knowledge is required in order to achieve a better understanding of biological phenomena (Sontag, 2005), and to allow for further insights and predictions for already well understood problems (Brazma, 2006).

Among the several problems tackled by systems biology, this chapter focuses on the dynamic modeling and parameter analysis and identification. In particular, we study a dynamic model for DNA damage sensing and repair. The sensing phase is carried out by p53 action, while the repair phase is performed by nucleotide excision repair (NER). The model is based on ordinary differential equations and hybrid systems, and allows us to study the time evolution of NER, from DNA damage sensing, through NER activation, to damaged single strand DNA excision.

Based on the proposed models, sensitivity analysis and identifiability analysis are carried out and parameter estimation techniques are introduced and evaluated by means of *in silico* simulations. These problems are generally recognized as key issues in systems biology (Aldridge et al., 2006; Kitano, 2001). Some simulation results are presented and discussed. Finally, the Appendix provides some biological background.

BACKGROUND

When in 1953 James Watson and Francis Crick described the DNA double helix, its structure seemed so solid and stable that research on notions such as DNA damage and repair was initially hindered (Friedberg, 2003). Actually, DNA is continuously exposed to several types of damage. The most relevant kind of DNA damage is helix-distorting lesions throughout the genome. These lesions are generated by different causes, including the formation of DNA adducts after administration of common drugs used in cancer therapy (Fayad et al., 2009), such as cisplatin and other platinum-based compounds. Another type of damage occurs when internal or environmental factors, such as exposition to radiation, cause breakages in both strands of the DNA helix. This event, called double strand breaks (DSB) can be lethal to the whole organism if not properly treated, since they can induce cancer and hereditary diseases (Bolderson et al., 2009).

Cells react to DNA damage in three basic ways. If the damage level is very low it is *tolerated*: the cell has specific structures to operate DNA replication and transcription even in presence of lesions. If the damage is more serious, it is *repaired*: the cellular growth is arrested (cell cycle arrest) and one of the several repair mechanisms available is started. If the damage level is too high to be effectively treated, *apoptosis* is started: this is a programmed death through which the cell eliminates itself from a population that might otherwise suffer the serious pathological consequences of the transmission of disrupted genetic material (Letai et al., 2008).

Sensing DNA damages is a very complex process, which involves a large number of pathways. A genetic network built upon the p53 gene and protein plays a key role in this process. First discovered in 1979, the actual tumor suppressing function of p53 was clarified only twenty years later (Vogelstein et al., 2000). The fact that DSBs induce an increase in p53 levels which, in turn, induce apoptosis has been demonstrated for the first time by Yonish-Rouach et al. (1991), and it is now generally accepted (Meek, 2009).

Among a number of different mechanisms for DNA repair, in this chapter, we consider *nucleotide excision repair* (NER). It is a versatile DNA repair mechanism that enables cells to eliminate helix-distorting lesions throughout the genome (Cleaver et al., 2009).

DNA damage is investigated by means of dynamic mathematical modeling, in the framework