Chapter 8
Predictive Dynamical Modelling MicroRNAs Role in Complex Networks[1]

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ABSTRACT

The aim of this chapter is to give an extended analytical consideration of mathematical modelling of the microRNA role in cancer networks. For this purpose, ordinary and partial differential equations are used for synthesizing and analyzing the models of gene, microRNAs and mRNAs concentration alterations as time-dependent variables related by functional and differential relations. The architecture of the models and the definitions of their components are inspired by the qualitative theory of differential equations. This chapter's analysis shows that it is able to ensure the authenticity and validity of the following qualitative conclusions: (a) the rates of protein production decrease with the increasing constant production rate of microRNA at microRNA-mediated target regulation on mRNAs; (b) time delay has a stabilizing role in the interaction between the miRNA-17-92 cluster and the transcription factors E2F and Myc.

INTRODUCTION TO THE SPECIFIED SCOPE

Dynamical modelling is an efficient *predictive* tool in the theory of microRNAs (cited as miRNAs to the end of this chapter) regulation of cancer networks. In this analytical review we widely use ordinary and partial differential equations for synthesis and analysis of gene, miRNAs and mRNA concentrations as time-dependent variables related by functional and differential relations between

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them. When we write differential equations, the main assumption is that concentrations of different substances are spatially homogeneous and vary continuously, which is not rigorously true for gene regulatory networks in principle and especially for cancer ones. Moreover, the deterministic behaviour of dynamical systems of differential equations is also not always exactly valid for the cases considered here. However, we often restrict our modelling to *qualitative* synthesis and analysis in terms of such named qualitative theory of dynamical systems, which notions and terms are very similar to those of molecular biology, so the *predictive* power of the models conserve their validity. In addition the method of differential equations allows very detailed description of the dynamical regulatory behaviour directly from the corresponding experimental biochemical diagrams containing full information about the network (or its module), which is difficult to obtain by another methods.

A principal problem toward complete understanding of miRNAs functions is to identify the target genes regulated by individual miRNAs. Most of them do not pair with perfect complementarity to their targets such that bioinformatical prediction is difficult and experimental validation is required. As a first movement toward target identification, global miRNA expression patterns are necessary to be reviewed, what is a main subject of our work in this specified scope.

Our goals are: (i) Considering the present insights into the miRNAs regulated functional modules of human cancers; (ii) Determining some computational approaches for modelling miRNAs role in cancerogenesis; (iii) Analysing the analogy (possibly inverse) between miRNAs roles in cancerogenesis and somitogenesis.

It is well-known that miRNA regulation is involved in many important biological processes such as cell proliferation, apoptosis and metabolism, the dysfunction of which state important hallmarks for human cancers. By considering connections of the miRNAs to target networks on different layers such as signalling, protein-protein interaction, metabolism and gene regulatory networks, we will be able to have some understanding how to identify and model the link between miRNA expression and cancer relevant read-outs on the molecular and cellular level.

At present, it is well established that gene expression in the human organism is post-transcriptionally regulated by miRNAs. MiRNAs are a class of small noncoding RNAs, typically ≈22nt size, that function is to modulate the activity of specific mRNA targets (Aguda et al., 2008). They are estimated to comprise 1-5% of animal genes (Khanin & Vinciotti, 2008), making them one of the most abundant classes of regulators. Their widespread and important role in animals is highlighted by recent estimates that up to approximately one-third of an organism's protein-coding genes are subject to miRNA-mediated control (Krek et al., 2005; Lewis et al., 2005; Stark et al., 2005). Current target-prediction computer programs (Watanabe et al., 2007; Maziere & Enright, 2007) predict that miRNAs play a central role in many biological (cellular) processes, including developmental timing, cell proliferation, apoptosis, metabolism, cell differentiation, somitogenesis and tumorgenesis (Alvarez-Garcia & Miska, 2006; Ambros, 2004; Gusev, 2008). In addition, miRNAs are a related class of short RNA molecules with an analogous functional role in Ribo Nucleic Acid interference (RNAi) (Bartel, 2004; Piriyapongsa & King Jordan, 2008). RNAi was elucidated for *Caenorhabditis elegans* (Fire et al., 1998) and according to (Plasterk, 2002; Waterhouse et al., 2001) each cell has a miniature "immune system" able to generate and amplify specific responses to a variety of gene transcripts. In other words, by RNAi, we can stop or significantly reduce the production of the specific protein encoded by the target gene.

It is seen from the literature, data sets are processed, normalised and statistically evaluated in order to identify defined, manually and preprocessed expression patterns for each available