

# Mathematical Modeling of Transcription Regulation by Protein Assemblies at Promoters: Regulation of E2F Dependent Genes

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## ABSTRACT

Coherent regulation patterns seem to occur frequently in systems that control cell proliferation and other cell functions. Groups of mutually interacting proteins can bind to several different promoter elements of a gene and thereby exert either stimulatory or inhibitory effects on the initiation or elongation of the transcribed RNA. Understanding of such sophisticated regulatory systems is often beyond the reach of intuition and requires rigorous mathematical modeling, capable of revealing the coherent dynamics of interconnected control signals. Here, using the E2F control network as an example, we address the question how pathway coherence affects the characteristics of the control system, particularly with respect to robustness and dynamic range of controls.

Transcription factors of the E2F family bind to promoters for various genes involved in progress through the cell cycle. Together with other factors (e.g. Sp1), E2F promotes synthesis of enzymes for DNA replication. E2F forms heterodimers with DP-1 to produce an active transcriptional complex. E2F family members are regulated by interaction with retinoblastoma (Rb) protein, whose activity is synchronized with the cell cycle machinery via the action of cyclin/cdk complexes. Since deregulation of E2F can change the fate of a cell from life to death, careful regulation of E2F-dependent genes has to be in place in order to maintain normal cell homeostasis. Recent findings demonstrate [1] that increased E2F activity can contribute to tumor development by stimulating cell cycle progression, but also overexpression of E2F1 can inhibit tumorigenesis through the induction of apoptosis. The latter effect makes the E2F1 a possible site for anti-cancer drug action. Thus

knowledge of the mechanism of E2F1 regulation may have profound implications for the treatment of cancer.

Here we present preliminary attempts to mathematically model the molecular machinery controlling E2F1-regulated genes. Kurt Kohn [2] has recently summarized, in the form of “interaction maps”, the available information about the controls of E2F-dependent genes via pRb, Sp1, acetylases, and deacetylases. He noted that regulation appears to go by way of multiple parallel (or “coherent”) paths to the same final effect, although the individual paths may differ significantly in kinetics. We use classical biochemical kinetics to describe the control system in terms of protein- and mRNA concentrations, which evolve according to a set of nonlinear ordinary differential equations. We solve these equations on a computer and analyze the dependence of the solutions on the parameter values of the model.

In the future we plan to extend the system to include the effects of cyclin-dependent kinases and their inhibitor proteins (e.g. p27kip1 and p16ink4a), as well as the next level of regulatory kinases and phosphatases (e.g. Wee1 and Cdc25A/B). Our goal is a realistic, predictive model of mammalian cell cycle control.

## REFERENCES

- [1] D.G. Johnson. The paradox of E2F1: oncogene and tumor suppressor gene. *Mol Carcinog.*, 27(3): 151-157, March 2000.
- [2] K.W. Kohn. Molecular interaction maps as information organizer and simulation guides. *Chaos*, 11(1): 84-97, March 2001.