

Mathematical Modeling of Genetic Regulatory Networks with Sequential Drug Intake for Cancer Treatment*

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Abstract

The growth of cancer usually involves interactions among multiple genes and pathways, thus combination therapy is seen as a promising treatment approach in cancer therapy. However, when a patient takes multiple drugs simultaneously, toxicity becomes a concern. A possible solution is to take the drugs sequentially. This study explores the feasibility of such a treatment strategy. Specifically, we study the response of gene regulatory networks to sequential drug inputs using switched system control. The switching logic is based on a combined time-driven and state-dependent switching function that ensures the repression of the target genes. Simulation of sequential drug inputs regulating mTOR pathway shows effectiveness of the proposed method.

1 Introduction

Many cancer treatments use combination therapy in which two or more drugs are administered synergistically to disrupt specific phases of the cancer cell reproduction cycles. However, toxicity is a major concern when multiple drugs are taken simultaneously. The vital question is: could the patient take the drugs in a sequential manner, rather than simultaneously, such that the undesired signals in the genetic regulatory networks (GRN) are blocked and yet the toxicity is tolerable? This study seeks to answer this question from a mathematical modeling perspective using hybrid systems control and stability analysis [Duan and Wu2014].

2 The Main Results

We use a switched hybrid system to model the effect of sequential drug intake on GRNs. For instance, given a GRN with two diseased genes (x_i, x_j)

$$\text{drug 1 taken : } \begin{cases} \dot{x}_i = f_i(x) - \gamma_i x_i - \gamma_1^u x_i \\ \dot{x}_j = f_j(x) - \gamma_j x_j \end{cases} \quad (1)$$

$$\text{drug 2 taken : } \begin{cases} \dot{x}_i = f_i(x) - \gamma_i x_i \\ \dot{x}_j = f_j(x) - \gamma_j x_j - \gamma_2^u x_j \end{cases} \quad (2)$$

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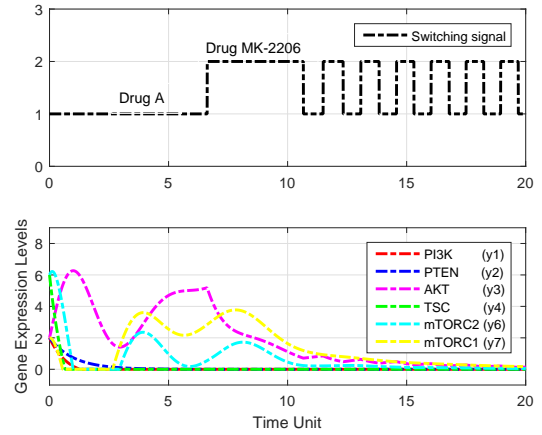


Figure 1: Switching signal and mTOR pathway dynamics.

$x_i \geq 0$ is i^{th} gene expression. $f_i(\cdot)$ is synthesis rate. $\gamma_i x_i$ is degradation rate. γ_i^u is drug effect factor. Sequential drug intake is thus modeled as switched hybrid system. Switched system stability and dwell time min-switching is then designed to drive the genes to desired state.

For mTOR pathway simulations, the drug MK-2206 (AKT blocker) is used sequentially with synthetic drug A (as PI3K inhibitor) based on the derived switching rule. Fig. 1 shows that the expression levels are stabilized translating to regulation of mTOR pathway and cell survival and proliferation.

3 Conclusion

We revisit combination therapy for cancer when toxicity is a concern. The potential effect of sequential intake of drugs is examined. *We believe this is the first attempt to mathematically model such a approach to combination therapy.*

References

[Duan and Wu, 2014] Chang Duan and Fen Wu. Analysis and control of switched linear systems via dwell-time min-switching. *Systems Control Letters*, 70:8 – 16, 2014.