Feedback Control Theory Reveals Tradeoff between Robustness and Stability in the p53-MDM2 Network

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Short Abstract — **Protein levels within cells are regulated in a robust way by gene networks when facing disturbances from the environment. Gene networks often include feedback mechanisms to maintain steady protein levels and to tolerate disturbances. However, feedback can also cause a system to oscillate transiently, hence gene networks somehow have to balance the trade-off between disturbance rejection and the unwanted transient behavior. We analyze this tradeoff in the p53-MDM2 feedback mechanism. Cells have to carefully maintain the level of p53 because p53 is needed for DNA damage repair, though too much p53 can trigger apoptosis (programmed cell death). Using feedback control theory, we demonstrate that the gene network specifically adopts post-translational regulation over transcriptional regulation in order to achieve a better tradeoff between disturbance rejection and transient oscillatory behavior.**

I. Introduction

MANY natural systems, including biological systems, are robust to failure in an environment of uncertainty [1].

One common feature of robust systems is their resilience towards adverse disturbances. In control theory, it has been long known that feedback, a situation in which two (or more) sub-systems are connected in a way that their dynamics are coupled, can make a system resilient toward disturbances [2,3]. A well-known example of feedback in the context of gene networks is negative autoregulation, in which a transcription factor represses the transcription of its own gene and reduces the effect of noise exerted on the transcription process [4]. However, excessive feedback can make a system unstable and oscillate transiently [3], which can adversely affect the system as disturbances do. Therefore, there is a subtle trade-off between robustness against disturbance and stability and it is unclear how gene networks balance this trade-off. In this article, using feedback control theory, we explain how the optimal tradeoff can be achieved by the p53-MDM2 feedback mechanism in mammalian cells.

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II. Results

One way of evaluating the robustness of the p53-MDM2 feedback loop is to determine the steady-state error due to disturbances. Using the Laplace domain analysis, we show feedback can reduce the steady-state error and improve robustness against disturbances. In addition to steady-state error, the system also has to minimize the transient response (such as overshoot) to disturbances. To quantitatively analyze the transient behavior of the p53-MDM2 feedback, we estimate its parameter ranges from the experimental data and used the estimated values for analysis.

Our results demonstrate that post-translational and transcriptional feedback (suppression of p53 by MDM2) has the same effect on reducing the steady-state error of p53. However, post-translational feedback more effectively minimizes overshoots generated by disturbance rejection. This insight explains the experimental observation that MDM2 suppresses p53 post-translationally via ubiquitination [5,6] rather than through a transcriptional mechanism [7].

III. Conclusion

Using feedback control theory, we demonstrate that the p53-MDM2 feedback network specifically adopts post-translational regulation over transcriptional regulation in order to achieve a better tradeoff between disturbance rejection (robustness) and overshoot generated by the feedback (stability).

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