Emergence of Qualitative States in Synthetic Circuit Driven by Growth Feedback

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***Short Abstract* — The mutual interactions between the synthetic gene circuits and the host growth could cause unexpected outcomes in the dynamic behaviors of the circuit. However, how the steady states and the stabilities of the gene circuits are affected by host cell growth is not fully understood. We developed a mathematical model for nonlinear growth feedback based on published experimental data. The model analysis predicts that growth feedback could significantly change the qualitative states of the system. Bistability could emerge in a circuit without positive feedback, and multistability emerges in the self-activation and toggle switch circuits.**

***Keywords* — growth feedback, metabolic burden, synthetic gene circuit.**

I. Introduction

The functions of synthetic gene circuits depend on the desired dynamics of the synthesis and degradation of involved exogenous genes. However, the expression of gene circuits inevitably changes the physiological state of the host cell. While the host cell growth also changes the circuit dynamics. These interactions between the host cell physiology and gene circuits form growth feedback, which could alter the expected outcome of the gene circuit design [1-5]. For example, Tan et al. showed that a monostable circuit design was found to be bistable experimentally, which is driven by growth feedback [3]. Zhangs et al. reported that the effects of the growth feedback on two bistable circuits depend on their topologies [4]. The qualitative state of the self-activation circuit could be lost due to the fast dilution of the gene expression by host cell growth, while the toggle switch is more robust. These studies demonstrate how the host growth and circuit interaction can lead to unexpected outcomes depending on the cell condition and the gene circuit topologies. However, the influence of growth feedback on gene circuits is not fully understood. Here, we focused on studying the mechanism of the steady states and the stability changes by nonlinear growth feedback.

II. Result

Ordinary differential equation models were developed for the dynamics of an exogenous expression under the dilution effect caused by growth feedback**.** A Hill function was used to describe the metabolic burden caused by the exogenous gene expression on growth rate.

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A. Data Analysis reveals a high order growth feedback

Parameter estimation for the mathematical model based on published experimental data reveals a value of Hill coefficient greater than one, indicating highly nonlinear growth feedback with a high-order metabolic burden sensitivity caused by the exogenous gene.

B. The emergence of bistability in a simple circuit with a constitutive promoter

Analysis of the model for a simple circuit with the constitutive promoter with high-order growth feedback revealed the emergence of bistability. In one state, the cell could express the gene at a high level with a slow growth rate, while in the other state, the gene is expressed at a low level with a high growth rate.

C. The emergence of multistability in self-activation and toggle switch by high order growth feedback

Further modeling analysis shows that more than two stable steady states can be seen in bistable systems. Tristabiltiy was found in the self-activation circuit with strong promoter strength. Tristabiltiy and quadrastability could be seen in the toggle switch circuit with high-order growth feedback.

D. The metabolic burden sensitivity determines the loss or emergence of the qualitative state.

The mathematical model analysis suggests that the bistable system could lose one steady state under growth feedback with low burden sensitivity. Therefore, the system can gain or lose qualitative states depending on the metabolic burden sensitivity.

III. Conclusion

Our result suggests that the growth feedback could alter the number of states in a host-circuit system. The metabolic burden sensitivity determines the loss or gain of states. While new states emerge in the system with high-order growth feedback, expected states disappear with low-order growth feedback.

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