Predicting the Stability of an Epigenetic State

Chenghang Zong[1], Lok-hang So[1] and Ido Golding[1,2]

Short Abstract — **Epigenetic stability is a fundamental property of living cells, and key to cellular differentiation. Bacterial lysogeny serves as a simple paradigm for a stable epigenetic state. Here we present a combined experimental/theoretical mapping between the observed degree of epigenetic stability and parameters of the underlying regulatory circuit. We show that epigenetic stability obeys a simple exponential dependence on the number of gene-activity events during the life of the cell.**

Keywords — **Epigenetic stability, transcription bursts, lambda lysogeny, single-molecule FISH, spontaneous lysis**

I. PURPOSE

Epigenetic stability, the phenomenon in which a living cell maintains an inheritable memory of its gene-expression state independent of its genetic material [1], is a fundamental property of cells, and key to cellular differentiation. Towards forming a quantitative picture of living systems, one needs the ability to predict how stable an epigenetic state is given the specific physiological details, and to point to key parameters determining this stability.

The stable lysogenic state of a bacterial cell harboring a dormant bacteriophage (prophage) serves as one of the simplest examples for an epigenetically stable state [2,3].

II. PROCEDURES

In bacteriophage lambda, stability is maintained by the activity of one single type of protein: lambda repressor (CI), which acts as a transcription factor to repress all lytic functions from the prophage in the *E. coli* cell, as well as to regulate its own production. To analyze the stability of an epigenetic state, we need to characterize various aspects of system dynamics, including the processes of transcription, translation and gene regulation. Among these processes, the dynamics of transcription is particularly important in the sense that it connects gene regulation to protein production. Recently observed bursts at transcriptions [4] make the quantification of the transcription dynamics crucial for quantitative understanding of the overall dynamics of gene circuits.

A. Single-molecule FISH and mRNA statistics

Each mRNA molecule from the gene-of-interest in fixed cells is hybridized with ~50 probes labeled with fluorescent dye [5]. In this study, cI and cro mRNA are labeled with different colors for simultaneous detection. The statistics of mRNA numbers per cell are collected and the non-Possionian feature of the distribution indicates pulsatile behavior of transcription.

B. Transcription burst

A two-state model is introduced to describe the transcription process. The predicted negative binomial distribution is found to match experimental data very well. Both burst size and burst frequency are extracted from mRNA statistics.

C. Stochastic simulation

Transcription parameters estimated from FISH data, combined with known parameters of protein translation, allow us to construct a fully calibrated stochastic model. The model reproduces the experimentally observed mRNA distribution and predicts the switching rate from the CI-dominant (lysogenic) state to the Cro-dominant state.

D. Switching rate measurement

The switching rate is also measured experimentally. It agrees very well with theoretical prediction. A simple exponential relation is found and explained by survival probability analysis.

III. CONCLUSION

We show that burst dynamics exists in cI and cro transcription processes. The burst parameters are extracted and incorporated into the theoretical model, with which we predict the stability of lysogens, the essential phenotypic feature of the system. Our prediction shows excellent agreement with the experimentally measured stability.

REFERENCES

[1] Ptashne, M., On the use of the word 'epigenetic'. Curr Biol, 2007. 17(7): p. R233-6.
[2] Little, J.W., D.P. Shepley, and D.W. Wert, *Robustness of a gene regulatory circuit.* EMBO J, 1999. **18**(15): p. 4299-307.
[3] Svenningsen, S.L., et al., *On the role of Cro in lambda prophage induction.* Proc Natl Acad Sci U S A, 2005. **102**(12): p. 4465-9.
[4] Golding, I., et al., *Real-time kinetics of gene activity in individual bacteria.* Cell, 2005. **123**(6): p. 1025-36.
[5] Raj, A., et al., *Imaging individual mRNA molecules using multiple singly labeled probes.* Nat Methods, 2008.

[1]Department of Physics, [2]Center of the Physics of Living Cells, University of Illinois at Urbana-Champaign.