Phase Response of the Cell Cycles to Perturbations

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***Short Abstract* — The aim of our study is to understand the regulatory network that controls asymmetric cell division in *Caulobacter crescentus*. We periodically perturbed the cell cycle and quantified its responses by a phase resetting curve that related the change of phase to the phase immediately before perturbation. Stochastic simulations based on this curve reproduced the experimental observations. Comparison of the response to that predicted by an existing model indicates the need for additional elements in deriving the dynamics.**

***Keywords* — biological oscillator, cell cycle, phase resetting, phase locking.**

I. Purpose

Our study aims to discover how we can put constraints on biological systems despite an inherent lack of knowledge in their components. To achieve this goal, we perturb the system of interests in various ways and observe its responses. We specifically study the regulatory network controlling the asymmetric cell division in the bacterium *Caulobacter crescentus* due to the relative abundant knowledge on the underlying mechanism and the ease of cell cycle control at the single cell level [1].

Experimentally, we periodically changed the expression of a key protein in mutant *Caulobacter* cells and collected single cell data about the time of divisions. In this extended abstract, we will demonstrate how we quantify the response by a phase resetting curve and how the form of the curve constrains the underlying mechanism.

II. Methods and Results

In the model, the cell cycle is represented as an oscillator and the perturbation drives the oscillator away from its ordinary orbit. The relaxation to its intrinsic orbits causes a time (phase) difference between the perturbed and the unperturbed oscillators. Whether advance or delay occurs depends on not only the perturbation but also the state of the system immediately before perturbation. A phase resetting curve describes how much an oscillator changes its phase under a perturbation as a function of its current phase [3].

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A. Building the phase resetting curve

We built the phase resetting curve through two approaches: 1) by its definition and 2) by the frequencies of stable phase locking. In the first approach, we obtained the current phase and the phase change of a cell cycle from the time of the perturbation and the previous cell division. In the second approach, we solved the equation of motion for the phase under stable phase locking, in which the cell cycle was synchronized to the perturbation. The result showed that the frequency of the perturbation was related to the constant phase difference between the perturbation and the cell cycle in successful locking through the phase resetting curve. Both approaches gave a sinusoidal phase resetting curve with asymmetric preference for phase advance and delay. Stochastic simulations using the derived phase resetting curve reproduced behaviors similar to experiments.

B. Constraints on models

The phase resetting curve is asymmetric and the experiments indicated the region of stable phase locking is skewed to low frequencies relative to the intrinsic one, i.e., cell cycles are better entrained by pulses of long periods than those of short periods. We examined how this feature could improve our understanding of the regulatory mechanism of *Caulobacter* cell cycle. Simulation using an existing model [2] predicted an opposite direction of skewness. Adjustments in the model parameters failed to correct the skewness without destroying the oscillations. We believed the discrepancy might come from unknown components in the system or a different mechanism for the oscillations.

III. Conclusion

A phase resetting curve is an effective tool in studying the network functionality of biological oscillators including cell cycle. It quantifies the responses of oscillators to external perturbations and puts constraints on the underlying mechanism.

References

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