Global Robustness of A Three Protein Circadian Oscillator

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Short Abstract — Three protein circadian oscillations in cyanobacteria sustain for weeks [1]. To understand how cellular oscillations function robustly in stochastic fluctuating environments, we used a stochastic model to uncover two natures of circadian oscillation[1]: the potential landscape related to steady state probability distribution of protein concentrations and the corresponding flux related to speed of concentration changes which drive the oscillations. The barrier height of escaping from the oscillation attractor on the landscape provides a quantitative measure of the robustness and coherence for oscillations against intrinsic and external fluctuations. These results correlated with experiments can help to design robust oscillatory networks.

***Keywords* — Landscape, Flux, Robustness, Dissipation, Coherence, Limit Cycle, Oscillation, Cellular Network.**

I. Background

Biological rhythms widely exist in living organisms, such as membrane potential oscillations, cardiac rhythms, calcium oscillations, glycolytic oscillations, cell cycles and circadian clocks. In the cell, there are finite numbers of molecules (typical on the order of several hundreds). So the intrinsic statistical fluctuations, usually not encountered in the bulk due to the large number averaging, can be significant. On the other hand, the fluctuations from highly dynamical and inhomogeneous environments of cell interior provide the source of the external noise. Therefore it is important to investigate how the rhythms robustly function against the stochastic fluctuations.

The underlying natures of the cellular rhythmic behavior have been explored by experimental and theoretical approaches [2]. For example, oscillations have been found to be robust and sustain for weeks for circadian clock in cyanobacteria[1]. The biological clock dynamics is often described by deterministic or stochastic chemical reaction networks. Complex non-linear phenomena can emerge from these studies, such as bifurcations and chaos. With slightly different initial conditions, the system characterized by the trajectories of the protein concentrations can behave drastically differentially. The resulting dynamics can lead to periodic oscillations (limit cycle). Robustness issue is usually only analyzed locally around the fixed points or limit cycles. Global stability is still hard to see.

Here, instead of focusing on deterministic or stochastic trajectories which are local in nature, we developed a global approach to robustness of circadian oscillation in cyanobacteria by directly exploring the probabilistic distribution in the whole protein concentration space (therefore global) for oscillations with a stochastic model. The current approach enables us to borrow some fruitful analysis from landscape theory of protein folding [3] where quasi equilibrium are assumed while here we emphasize the non-equilibrium natures.

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II. Results

We uncovered two distinct natures essential for characterizing the global probabilistic dynamics for circadian oscillations in cyanobacteria [1]: the underlying potential landscape directly (logarithmically) related to the steady state probability distribution and the corresponding flux related to the speed of the protein concentration changes [4][5][6]. We found that the underlying potential landscape for the oscillation has a distinct closed ring valley shape when the fluctuations are small. This global landscape structure leads to attractions of the system to the ring valley. On the ring, we found that the non-equilibrium flux is the driving force for oscillations. Therefore, both structured landscape and flux are needed to guarantee a global robust oscillation.

The barrier height separating the oscillation ring and other areas derived from the landscape topography, is shown to be correlated with the escaping time from the limit cycle attractor, and therefore provides a quantitative measure of the robustness for the network.

The landscape becomes shallower and the closed ring valley shape structure becomes weaker (lower barrier height) with larger fluctuations. We observe that the period and the amplitude of the oscillations are more dispersed and oscillations become less coherent when the fluctuations increase.

When the fluctuations become very large, the landscape is flattened out and coherence of the oscillations is destroyed. Robustness decreases. When the fluctuations are small, changing the inherent parameters of the system such as chemical rates, equilibrium constants and concentrations can lead to different robust behaviors such as multi-stability.

By exploring the sensitivity of barrier height on the parameters of the system, we find concentrations of Kai and the associated binding constants important for robust oscillations. This provides a basis for reengineering and design.

We have used a stochastic model to uncover the underlying landscape of circadian clock oscillation. We found barrier heights as a quantitative measure for robustness. These results correlated with experiments [3] can help designing robust networks by reengineering the wirings against fluctuations.

References

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