Nonlinear Protein Degradation for Temperature Compensation

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***Abstract*—**Robustness of genetic circuits is very important, thus it is necessary to know which mechanisms are responsible for their robust phenotypes. We adopt cooperative stability for genetic oscillators to realize the cooperation in the process of protein degradation, where cooperative stability denotes that high-order oligomers are more stable than the monomeric components. Then linear programming method is applied to analyze the influence of protein degradation to the temperature sensitivity of the period of the oscillators. One notable property of circadian oscillators is temperature compensation, meaning its period is insensitive to the variation of temperature, but the mechanism underlying temperature compensation is still unclear. Our theoretical results show nonlinear protein degradation by cooperative stability is more beneficial for realizing the temperature compensation of circadian clocks than the linear protein degradation model.

***Keywords*—**Oscillators, temperature compensation, robustness.

I. Introduction

Biological robustness can be defined as the biological systems' ability to function reliably despite internal and external perturbations. If we understand biological mechanisms which promote robustness, we can utilize engineering principles for designing genetic circuits with robust phenotypes and promote the development of synthetic biology.

Genetic oscillators are important devices in biological systems, which can exhibit rich dynamical behaviors despite their simplicity in topologies. We employ oscillators as examples to analyze their properties in the presence of perturbations. Phase and period play important roles in the biological oscillators because they have to robustly entrain or synchronize to signals, e.g. light. Phase sensitivity analysis can be applied to measure the changes in phase and period induced by perturbation.

The organisms have many mechanisms to resist perturbations, and one of them is cooperation in their life activities. In their model Buchler *et al*. included cooperation in the step of protein degradation, and pointed out that nonlinear protein degradation is important for widening oscillation parameter space and achievable by cooperative stability [1]. This means dimers or high-order oligomers are more stable to proteolysis than monomers. They employed linear stability analysis to analyze the stability of steady state for linear and nonlinear models of Repressilator [2] with only negative feedback. We not only extend the model of cooperative stability to Atkinson oscillator [3] with both positive and negative feedback, but also analyze the influence of nonlinear protein degradation to the robustness of phase and period when perturbed externally.

Biological systems acquire the ability for robustness through evolution to maintain the phenotypic properties in the presence of extrinsic stimuli, e.g. variation of temperature. Circadian clocks are able to keep their periods almost unchanged when the temperature varies. This robustness against the temperature variation, a famous mechanism in circadian clocks, is known as temperature compensation. Although the period of the circadian clock is insensitive to the thermal variation, the rate of every kinetic reaction is highly temperature dependent. The mechanisms how the circadian rhythms realize the temperature compensation are still unknown. In our study, we analyze the periods' temperature sensitivity in linear and nonlinear protein degradation models of oscillators. Through this analysis, we find that nonlinear protein degradation induced by cooperative stability can easily achieve temperature compensation. This conclusion could provide principles for designing circadian clocks with ability of temperature compensation.

II. Mathematical Model

Ample experimental evidences suggested many proteins of organisms perform their functions in the form of dimers or even higher-order oligomers. The stability of oligomers to proteolysis is improved when compared with that of monomers because of reduced degradation rate of proteins, and this enhanced stability is referred to cooperative stability [1].

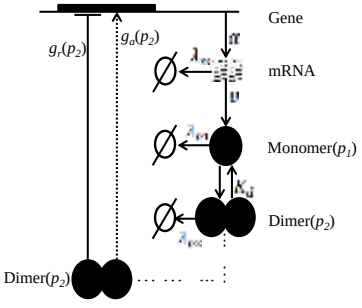

Fig.1The expression of genes with cooperative stability. α represents the transcriptional rate at full activation, the degradation rate of mRNA is λ_m. The monomers p_1 is synthesized at the rate ν and decays at λ_{p1}. The concentration of dimers (p_2) depends on the dissociation constant K_d and the decay rate λ_{p2}. The solid and dashed lines indicate repression and activation for transcription respectively.

We study the influence of nonlinear protein degradation to properties of Repressilator and Atkinson oscillator. The model of gene expression with cooperative stability is shown in Fig. 1.

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When $\lambda_{p1} = \lambda_{p2}$, it shows the degradation rate in total protein is linear, while $\lambda_{p1} > \lambda_{p2}$ corresponds to nonlinear. We employ Repressilator and Atkinson oscillator instead of circadian oscillators to analyze the temperature compensation of the linear and nonlinear protein degradation models.

The values of the parameters adopted in our research are physiologically realizable in bacteria. The detail explanation and feasible values of the parameters have been summarized in paper [1] and the references therein.

III. Ability of Temperature Compensation

Temperature compensation of circadian clocks makes the period of the oscillators insensitive to the variation of temperature T. The period's temperature sensitivity depends on two terms; the period sensitivity of parameters and temperature sensitivity of parameters. The temperature sensitivity of the period can be expressed as [4]

$$d\ln\tau/dT = \sum_i \partial\ln\tau/\partial\ln p_i \,(d\ln p_i/dT) = \frac{1}{\tau}\sum_i e_i s_i. \quad (1)$$

where $p_i (i = 1,2,\dots n)$ denotes the dynamic parameter in the oscillating system, T is the temperature, τ means the period, $e_i = \partial\tau/\partial p_i$ and $s_i = dp_i/dT$ represent the period sensitivity and the temperature sensitivity of the dynamic parameters respectively. The temperature compensation can be achieved when Eq.(1) is equal to 0 [4]. e_i, the period sensitivity of the parameters, can be calculated according to the theory of phase sensitivity analysis (Refer to [5] for details).

The temperature coefficient Q_{10} is defined as the rate of change in reaction constants when temperature rises by 10°C which can be written as $Q_{10} = \{p_i(T+\Delta T)/p_i(T)\}^{(10/\Delta T)}$. The relationship between temperature coefficient and temperature sensitivity of the parameters can be expressed as $s_i = \ln Q_{10}/10$. The experimental data of temperature coefficient were recently provided in [6]. By data fitting we find that Q_{10} is mostly distributed within a range 2~5, thus 2~5 is selected as the possible temperature coefficient region for parameters of oscillators.

As better temperature compensation is achieved when $|d\ln\tau/dT|$ is close to 0, its realizability is turned into finding the minimum for Eq.(1) in the feasible region of temperature sensitivity of the parameters s_i.

$$\min |d\ln\tau/dT| = 1/\tau|\textstyle\sum_i e_i s_i| \qquad (2)$$
$$s.t. \quad s_i = ln\, Q_{10}/10;\ 2 \le Q_{10} \le 5$$

The minimum for temperature sensitivity of the period can be obtained by solving Eq.(2) with linear programming. High values indicate the period of the oscillator is sensitive to temperature variation, whereas low values mean the period of the model is robust to the changes of the temperature. We compare the ability of temperature compensation for linear and nonlinear protein degradation models of two oscillators when protein synthesis rate at full activation ($\gamma = \alpha\nu/\lambda_m$) varies.

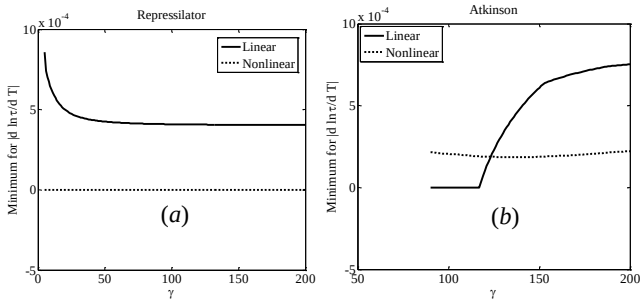

Fig. 2 Minimal $|d\ln\tau/dT|$ for (*a*) Repressilator and (*b*) Atkinson oscillator, where solid and dashed lines represent the minimum of linear and nonlinear protein degradation cases, respectively.

Realizable *in vivo* data are applied for Repressilator and Atkinson oscillator to analyze how the nonlinear protein degradation affects the temperature compensation. The calculation results show that, for Repressilator the mechanism of nonlinear protein degradation makes the temperature sensitivity of the period much closer to zero, and for Atkinson oscillator the period of nonlinear protein degradation model is more robust to thermal variation in most feasible region of parameters.

IV. Conclusions

We consider cooperative stability in Repressilator and Atkinson oscillator to check whether the mechanism of the nonlinear protein degradation can improve the robustness of the period against thermal variation. The period's temperature sensitivity depends on period sensitivity and temperature sensitivity of the parameters. We calculated the period sensitivity of the parameters by phase sensitivity analysis and determined the feasible range of temperature coefficient according to the biological experiment. Given the values and constraints, we then calculated the attainable minimal temperature sensitivity of the period by a linear programming method. The theoretical results show the nonlinear protein degradation indeed improves the ability of temperature compensation for oscillators in most situations. If it is necessary to design engineered genetic oscillators with low period sensitivity to temperature, it is one possible way to consider nonlinear protein degradation for the circuits.

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