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Temperature compensation via cooperative stability in protein degradation

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HIGHLIGHTS

- Cooperation in the process of protein degradation is proposed as the mechanism of temperature compensation in circadian clocks.
- We model the Repressilator and the Atkinson oscillator with the proposed mechanism to investigate their temperature sensitivities of the period.
- Linear programming method is used for the first time in the context of biochemical oscillators to evaluate the ability of temperature compensation.

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ABSTRACT

Temperature compensation is a notable property of circadian oscillators that indicates the insensitivity of the oscillator system's period to temperature changes; the underlying mechanism, however, is still unclear. We investigated the influence of protein dimerization and cooperative stability in protein degradation on the temperature compensation ability of two oscillators. Here, cooperative stability means that high-order oligomers are more stable than their monomeric counterparts. The period of an oscillator is affected by the parameters of the dynamic system, which in turn are influenced by temperature. We adopted the Repressilator and the Atkinson oscillator to analyze the temperature sensitivity of their periods. Phase sensitivity analysis was employed to evaluate the period variations of different models induced by perturbations to the parameters. Furthermore, we used experimental data provided by other studies to determine the reasonable range of parameter temperature sensitivity. We then applied the linear programming method to the oscillatory systems to analyze the effects of protein dimerization and cooperative stability on the temperature sensitivity of their periods, which reflects the ability of temperature compensation in circadian rhythms. Our study explains the temperature compensation mechanism for circadian clocks. Compared with the no-dimer mathematical model and linear model for protein degradation, our theoretical results show that the nonlinear protein degradation caused by cooperative stability is more beneficial for realizing temperature compensation of the circadian clock.

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1. Introduction

Circadian clocks keep their periods almost unchanged when the temperature varies. This robustness against temperature variation, a famous mechanism in circadian clocks, is known as temperature compensation [1–9]. Although the period of the circadian clock is insensitive to thermal variations, the rates of reactions such as synthesis and degradation of mRNA and proteins are highly temperature dependent [1,10]. However, the mechanisms by which the circadian rhythms compromise several reaction steps to realize temperature compensation are still unknown. Thermal variation results in differences in the reaction parameters of the dynamical systems, which in turn should change the period of the oscillators. The prevalence of the cooperative processes in nature inspired us to investigate the relationship between various levels of cooperation and the temperature sensitivity of the oscillators' period. Most previous research has been focused on cooperation at the stage of transcription [10–13], which is quite limited, and it was often difficult for the circuits to perform oscillation in the range of physiological parameter values because of insufficient cooperation. Hence, it is necessary to harness cooperativity during other processes of gene expression, such as translation and protein degradation [14].

Buchler et al. studied cooperation in protein degradation, and pointed out that nonlinear protein degradation achieved by cooperative stability can widen the oscillation parameter space [15]. Here, cooperative stability means that dimers or high-order oligomers are more stable to proteolysis than monomers. Hong and Tyson proposed a molecular mechanism for temperature compensation based on the opposing effects of temperature on the rate of nuclear import of period (PER) protein and the association rate of PER monomers [16]. But they did not consider the physiological range of the temperature sensitivity of the parameters and the effects of temperature on the other reaction parameters, such as the synthesis and degradation rates of mRNA, monomers, and dimers. We analyzed the influence of protein dimerization and cooperative stability on the temperature compensation ability of circadian clocks taking these problems into account. Biological oscillators can be classified into two types: (1) smooth oscillators containing only negative feedback loops; and (2) relaxation oscillators including both positive and negative feedback loops [17]. Circadian clocks, as special biological oscillators, belong to one of these two types, and have the basic characteristics of these oscillators. Thus, we can analyze the temperature compensation ability of the circadian rhythms by considering smooth and relaxation oscillators instead of circadian clocks. We used the Repressilator and the Atkinson oscillator [18] to analyze period robustness against temperature changes. The Repressilator is a smooth oscillator, while the Atkinson oscillator is a relaxation oscillator. Despite their simplicity in topologies, these oscillators can exhibit rich dynamical behaviors and have many properties in common with genetic oscillators [11,18–22]. Therefore, when the environmental temperature varies, the changes in the periods of the two oscillators with different mechanisms can uncover the influence on the temperature compensation ability. We analyzed the temperature sensitivity of the period for three cases using the linear programming method. Specifically, we used the mathematical models without protein dimerization, and linear and nonlinear protein degradation models for both the Repressilator and the Atkinson oscillator. The period's temperature sensitivity was adopted to classify whether the temperature compensation ability was strong or weak [1,23].

The temperature sensitivity of the period depends on two factors: the period sensitivity and the temperature sensitivity of the parameters. Phase sensitivity analysis can measure the deviations in period induced by perturbations to the reaction parameters of the systems [24–26], which are the parameters' period sensitivity needed for the calculation of the temperature sensitivity of the period. The values of the parametric temperature sensitivities have a special range according to recently provided experimental data [27]. Thus, we can obtain the best result for the minimum temperature sensitivity of the period of the oscillators by using linear programming. Our main findings are that protein dimerization and cooperative stability can improve the temperature compensation ability of the oscillators. When the temperature sensitivity of the period is higher in the oscillators, temperature compensation ability is weaker; conversely, a lower value implies a stronger temperature compensation ability. To our knowledge, this is the first report of using linear programming to evaluate the temperature compensation ability of biochemical oscillators.

2. Mathematical models of genetic oscillators

2.1. Protein dimerization and cooperative stability for the oscillators

Protein degradation substantially affects the functional properties of genetic circuits, and ample experimental evidence suggests that many proteins are functional in the form of dimers or even higher order oligomers [28,29]. The stability of oligomers to proteolysis is higher than that of monomers [30,31], and this enhanced stability is referred to as cooperative stability [15]. We studied the influence of protein dimerization and cooperative stability on the properties of two kinds of genetic oscillators: the Repressilator and the Atkinson oscillator. Although these two oscillators have been experimentally implemented in *Escherichia coli*, they exhibit oscillatory dynamics via different mechanisms. The three repressors of the Repressilator are connected in a ring topology, and the expression of each gene is inhibited by its downstream partner, forming a negative feedback loop. The Atkinson oscillator organizes repression and activation in the gene network to regulate the oscillation function. According to experimental results, the oscillation of the Repressilator disappears after a short time [19], whereas the Atkinson oscillator can maintain damped oscillation for a relatively long time [18]. The Repressilator and the Atkinson oscillator represent the smooth oscillator and relaxation oscillator according to their topologies, respectively. We considered the generic effects of protein dimerization and cooperative stability on the characteristics of these two types of oscillators.