

Temperature Compensation for Circadian Oscillations: A Brief Theoretical Explanation

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Abstract

This chapter discusses temperature dependence of homogeneous chemical oscillations in two different systems: the Belousov–Zhabotinsky reaction in a continuously stirred tank reactor (CSTR) and a circadian oscillatory system. A theoretical framework is proposed to investigate the temperature dependence of chemical oscillations and the mechanisms responsible for temperature compensation. The theory is based on distribution of activation energies around the experimental mean and averaging of rate constants. It can conclude both cases. The finite width of the activation energy distribution associated with the corresponding rates characterizes the compensatory kinetics of circadian oscillations, whereas a vanishing width corresponds to Arrhenius-type temperature-dependent kinetics. Both scenarios are supported by experimental findings reported in the existing literature. The theoretical findings are in good agreement with the experimental observations.

Keywords: *Circadian Rhythm; Oscillatory Reactions; Stochasticity; Temperature Dependence*

Introduction

The speed of a chemical or biochemical reaction depends on temperature. When the temperature increases, the reaction speed also increases. This is a well-known principle explained by the Arrhenius rate equation, which states that the rate constant has an exponential dependence on temperature. This relationship has remained central to chemistry, biology, and physics for more than a century. However, the temperature of a reaction does not remain steady throughout the reaction time. There are different examples, such as the application of homogeneous temperature oscillatory fields, which can be achieved by varying temperature gradients spatially, as well as temperature compensation in chemical and biological systems. Temperature compensation refers to the ability of a biological clock or system to maintain a nearly constant rhythm or rate despite changes in environmental temperature (Kidd *et al.*, 2015; Xiao *et al.*, 2025).

In circadian rhythms, temperature compensation ensures that the internal biological clock continues to function with an approximately 24-hour cycle even when the surrounding temperature changes (Dunlap, 1999; Maeda & Nakamichi, 2025). Normally, most chemical and biochemical reactions speed up with increasing temperature and slow down with decreasing temperature. However, circadian oscillations remain relatively stable because of temperature compensation.

This property is important because it helps organisms maintain regular physiological and behavioral activities under varying environmental conditions (François *et al.*, 2012). Without temperature compensation, circadian rhythms would become faster in warm conditions and slower in cold conditions, disrupting normal biological functions.

All these applications have attracted wide attention. Studies have revealed extensive information regarding the temperature dependence of physiological regulatory functions and the adaptation of bio-organisms to their surrounding thermal environments (Field & Noyes, 1974). The frequencies and amplitudes of complex oscillations in the Belousov–Zhabotinskii (BZ) reaction within a stirred tank reactor are influenced by temperature variations (Zaikin & Zhabotinsky, 1970; Dutt & Müller, 1993). Furthermore, it has been reported

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that introducing a temperature gradient can initiate the propagation of traveling waves in oscillatory glycolysis within yeast extracts (Foerster *et al.*, 1990). Numerous studies demonstrate that temperature serves as an important factor in regulating feedback mechanisms in biochemical systems.

A closely related phenomenon is the temperature compensation observed in circadian oscillations of cells and living organisms (Hastings & Swinny, 1957). These oscillations help organisms synchronize physiological processes with the natural 24-hour light–dark cycle on Earth. When a particular biochemical process or reaction rate becomes insensitive to temperature changes, the effect is commonly termed “immediate temperature compensation.” Various mechanisms responsible for enzymatic temperature adaptation have been discussed in the referenced studies.

Circadian Oscillations

Circadian oscillations are natural rhythms that repeat approximately every 24 hours, influencing various biological processes in living systems. They are regulated by a circadian clock, primarily located in the suprachiasmatic nucleus (SCN) of the brain, which coordinates these rhythms with external cues like light and darkness (Mieda, 2020). These rhythms are crucial for regulating sleep–wake cycles, hormone secretion and other physiological functions. Light is the primary environmental factor that influences circadian oscillations, helping the body maintain synchronization with external day and night conditions. Circadian oscillations regulate many important body functions such as the sleep–wake cycle, hormone secretion, body temperature, metabolism, and feeding behavior. For example, melatonin secretion increases during the night to promote sleep (Jia *et al.*, 2025), while alertness and body activity are generally higher during the daytime.

Circadian oscillation is fundamentally a biochemical oscillation and an essential feature while understanding chemical oscillations in the concept of a limit cycle formed by the interacting components involved in the rate-determining steps. Most characteristic properties of such oscillatory behavior can be effectively described within the framework of a limit cycle. However, because kinetic rate constants are generally temperature dependent, the dynamics of limit-cycle oscillations, including their associated periods, would ordinarily be expected to exhibit significant variations in response to changes in temperature. In contrast, circadian systems exhibit remarkable insensitivity of oscillatory periods to temperature variation. The time period of the BZ oscillation is temperature-dependent, whereas circadian oscillations are temperature-insensitive. The search for an explanation of this type of insensitivity began several years ago. The explanation proposed by Rouf *et al.* (2003), which suggests that temperature compensation results from a delicate balance between opposing positive and negative contributions involving control coefficients and activation energies, has gained broad acceptance in the scientific community (Hong *et al.*, 2007).

This theoretical framework is applied to circadian systems, and it is observed that one of the fundamental requirements of such a mechanism is the presence of a specific set of activation energies. In many cases, these activation energies need to be considerably high, thereby reducing the likelihood of the associated reaction pathways (Ruoff *et al.*, 1999; Ruoff *et al.*, 2003). Furthermore, the combination of control coefficients responsible for maintaining the required balance is not necessarily unique.

This finding for the stringent delicate balance conditions leads to find another theoretical logic for the temperature compensation for the circadian oscillations.

Average Rate Constant, Temperature Dependence

In complex biological organisms, the number of reacting species involved in the rate-determining steps may vary significantly as they traverse potential barriers containing multiple local minima. Furthermore, during the transition from the reactant well to the product well, a species may follow multiple pathways characterized by different activation energies, depending on the nature of enzymatic complexation and the local heterogeneity of the reaction medium. This suggests that the kinetics may be more appropriately

described by an average rate constant rather than a single rate constant. To address this issue, a framework is proposed in which the averaging of rate constants is performed over a distribution of activation energies centered around the experimental mean value. The width of this distribution can be estimated based on the requirement of temperature-compensated kinetics within a cell, indicating that the distribution width reflects the self-regulating nature of the biological system.

Since BZ-type and other oscillating chemical reactions are not self-regulatory, their oscillation periods depend on temperature and follow Arrhenius kinetics. It is shown that, in such cases, the width of the activation energy distribution tends to vanish, thereby reducing the system to the conventional Arrhenius temperature dependence of the rate constant.

To obtain an overall average rate constant from a distribution of energies around an mean value of experimental data, a distribution function $P(E; \langle \Delta E^2 \rangle, \langle E \rangle)$ is introduced where (E) represents energy of activation. The normalisation property of the distribution function is maintained such that

$$\int_0^\infty dE P(E; \langle \Delta E^2 \rangle, \langle E \rangle) = 1$$

Let us further assume that the spread in activation energies is temperature dependent and is given by $\langle \Delta E^2 \rangle = \frac{B}{RT}$ where R is the Universal gas constant and B is the numerically derivable constant from the proposed theoretical framework. Averaging over over Arrhenius rate constant ($k = Ae^{\frac{-E}{RT}}$) for a reaction step is then given by

$$\langle k \rangle = \int_0^\infty dE Ae^{(-E/RT)} P(E; \langle \Delta E^2 \rangle, \langle E \rangle)$$

Where frequency factor is designated by A. Temperature compensation means the first derivative with respect to the temperature is null. Which means

$$\frac{\partial \langle k \rangle}{\partial T} = 0$$

This yields the relation

$$\frac{1}{RT^2} \langle E.k \rangle + \int_0^\infty dE k \frac{\partial P}{\partial T} = 0$$

Now to make use of some partial derivative and specialize the case for normal Gaussian distribution function, one can easily obtain the following transcendental equation

$$B = \frac{\langle k.E \rangle}{\frac{1}{2} \left[\frac{(RT)^2 \langle k(E - \langle E \rangle)^2 \rangle}{B^2} - \frac{RT \langle k \rangle}{B} \right]}$$

Now two different scenarios can easily be concluded

(i) Temperature-compensating kinetics—For a given experimental average activation energy value and temperature (T), the above algebraic equation can be solved numerically in a self-consistent manner to determine the parameter (B). The obtained value of (B), and consequently the corresponding distribution width, produces an average rate constant that exhibits clear temperature compensation. As a result, the oscillation period remains nearly unaffected by changes in temperature.

In contrast, for chemical reactions occurring in homogeneous systems such as a petri dish or continuously stirred tank reactor (CSTR), the spread in activation energies approaches zero because only a single

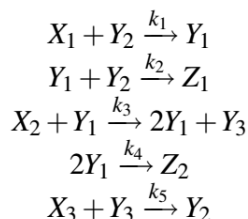
discrete activation energy is available ($\rightarrow 0$). Under these conditions, the Gaussian distribution ($P(E)$) becomes a delta function, a $\delta(E -)$. Consequently, the expression for the average k becomes Arrhenius.

$$\langle k \rangle = Ae^{(-\langle E \rangle / RT)}$$

These expressions form the basis for describing the kinetics of biochemical systems. Therefore, in biological systems, the distribution of activation energies—whether arising through mutation or other processes—must possess a self-regulating nature such that the width of the distribution adjusts automatically to satisfy the condition of temperature compensation. Since this adjustment is statistical in origin, it is inherently more robust than the condition proposed by Rouff *et al.* (1999), which requires a much stricter balance.

Belousov-Zhabotinskii Reaction and Oregonator Model

Field and Noyes originally proposed Oregonator model as a highly idealized minimal representation of the Belousov–Zhabotinskii (BZ) reaction, was developed to describe the cerium-ion-catalyzed oscillatory malonic acid. The model consists of some reacting species, namely Y_1 , Y_2 , Y_3 and X_1 , X_2 , X_3 and is characterized by the following reaction steps.



Here the X 's are the large numbers and treated as constants. The Gillespie algorithm is applied for stochastic simulation of the abovementioned reaction steps. The resultant temperature dependence is just that of the Arrhenius rate law (Figure 1).

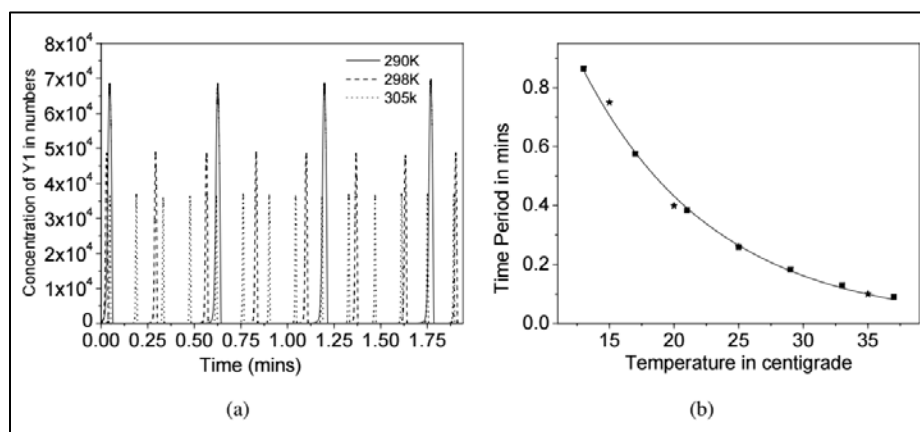


Figure 1: (a) Numerical Simulations Showing the Oscillatory Behavior in the Oregonator Model at Different Temperatures (b) Dependence of the Time Period of Oscillation on Temperature (Sen et al., 2008)

To study temperature compensation within the framework, the model of Gonze and Goldbeter (2006) is considered. The oscillatory dynamics of both models were investigated using stochastic simulation techniques based on the approach developed by Gillespie (1977). The objective is to incorporate stochastic

effects directly into dynamic reactions. Following the Gillespie algorithm, a stochastically determined reaction probability density is introduced.

Let us first clarify the concept of stochasticity. Stochasticity refers to the property of being adequately described by a probability distribution and is therefore associated with a probabilistic modeling framework. Although the terms stochasticity and randomness are often used interchangeably, they are technically distinct. Stochasticity pertains to the mathematical description of a system, whereas randomness refers to the inherent unpredictability of the underlying phenomenon. One of the simplest continuous-time stochastic processes is Brownian motion, which was first observed by the botanist Robert Brown while examining pollen grains suspended in water under a microscope. There should always be some other ways by which the reaction may take place. Among them the minimum energy path is the experimental one. The averaging method is discussed above. For the circadian oscillation model the rate constants are investigated by averaging the Gaussian distribution width around the mean experimental activation energy. It is observed that the time periods are not sensitive towards temperature here. As it is self-regulatory it can adjust its width to get it compensated. In contrast, chemical oscillations such as those observed in a BZ reaction within a CSTR or in glycolysis in a cell-free yeast extract are non-endogenous, with their dynamics being determined primarily by external reaction conditions, such as the stirring rate and other experimental parameters. In such cases, the width of the activation energy distribution is expected to approach zero.

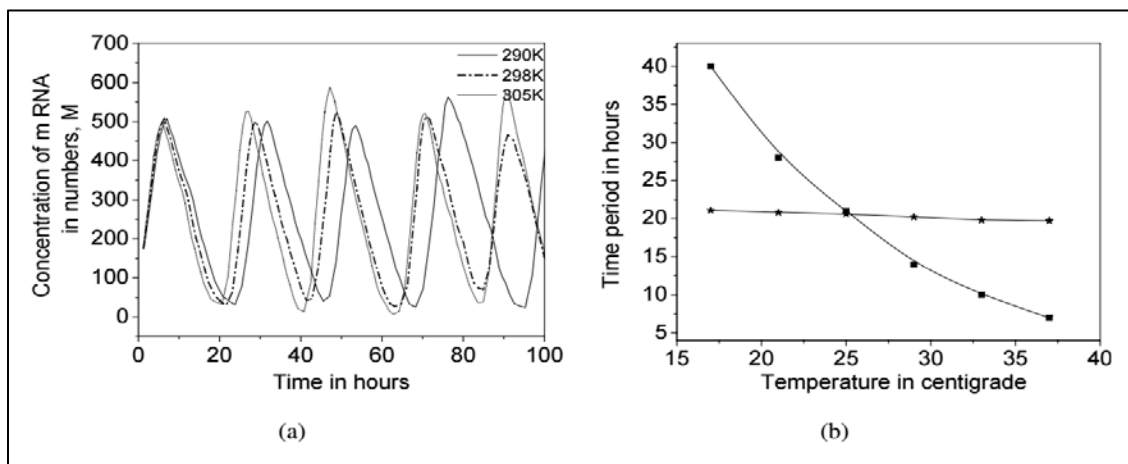


Figure 2: (a): Oscillations of m-RNA Obtained by Stochastic Simulation of the Model for Circadian Rhythm by Gonze-Goldbeter with Temperature Compensated Rate Constants (b): Temperature Dependence (Dark square) and Temperature Compensation (Dark stars) of the Time Period (Sen et al., 2008)

Conclusion

A simple theory is developed to explain the temperature compensation of circadian oscillation. The BZ reaction model and Gonze Goldbeter model for mRNA oscillation in *Drosophila* are used. The Gillespie algorithm is used for numerical simulation. The analysis demonstrates temperature dependence by the Arrhenius theory, and the same compensated behavior exhibits two far-away cases of the activation energies. Additional experimental studies on the temperature dependence of chemical oscillations may reveal intermediate regimes of the distribution width where partially compensated behavior and deviations from Arrhenius-type oscillatory kinetics can arise.

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