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MODELING TEMPERATURE COMPENSATION IN CHEMICAL AND BIOLOGICAL OSCILLATORS

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ABSTRACT

All physicochemical and biological oscillators maintain a balance between destabilizing reactions (as, for example, intrinsic autocatalytic or amplifying reactions) and stabilizing processes. These two groups of processes tend to influence the period in opposite directions and may lead to temperature compensation whenever their overall influence balances. This principle of "antagonistic balance" has been tested for several chemical and biological oscillators. The Goodwin negative feedback oscillator appears of particular interest for modeling the circadian clocks in *Neurospora* and *Drosophila* and their temperature compensation. Remarkably, the Goodwin oscillator not only gives qualitative, correct phase response curves for temperature steps and temperature pulses, but also simulates the temperature behavior of *Neurospora frq* and *Drosophila per* mutants almost quantitatively. The Goodwin oscillator predicts that circadian periods are strongly dependent on the turnover of the clock mRNA or clock protein. A more rapid turnover of clock mRNA or clock protein results, in short, a slower turnover in longer period lengths. (*Chronobiology International, 14(5), 499–510, 1997*)

Key Words: Circadian—Ultradian rhythm—Temperature compensation—Goodwin model—Homeostasis.

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TEMPERATURE COMPENSATION AND GENERAL HOMEOSTASIS IN PERIOD

During the early studies of circadian oscillations, Pittendrigh discovered that the *Drosophila* emergence rhythm was sufficiently temperature compensated to serve as a useful clock (1). Temperature compensation means that the period of the rhythm remains practically unchanged at different environmental temperatures as long as the temperature remains constant. After Pittendrigh's discovery, temperature compensation was soon found in plants, unicells, and mammals. Today, temperature compensation is considered to be an essential property of circadian rhythms in order to assure a precise day length measurement uninfluenced by environmental temperature fluctuations (2–8). Temperature-compensation has also been observed in certain ultradian rhythms (9–13).

Interestingly, temperature compensation appears only to be one facet of a general homeostatic mechanism (14) that keeps the circadian period constant against general environmental fluctuations, such as, for example, nutrient supply, pH, and D_2O.

Q_{10} VALUES AND OVERALL ACTIVATION ENERGIES

To characterize the influence of temperature on an oscillatory or nonoscillatory process, one may use either the overall activation energy or Q_{10} values. The Q_{10} value is simply the ratio between reaction velocity v (or frequency f in an oscillatory process) at temperature T + 10°C divided by the velocity (frequency) at temperature T, that is,

$$Q_{10}(T) = \frac{v(T + 10°C)}{v(T)} = \frac{f(T + 10°C)}{f(T)} \tag{1}$$

It should be kept in mind that Q_{10} is a function of T. For temperature intervals T_1, T_2 not exactly separated by 10°C, Q_{10} can be calculated by

$$Q_{10} = \left(\frac{f_2}{f_1}\right)^{10/T_2 - T_1} \tag{2}$$

and is related to the activation energy by

$$E_{act} = R\frac{T_1 \cdot T_2}{10} \ln Q_{10} \tag{3}$$

where R is the gas constant. Generally, the activation energy E_i is regarded to be temperature independent. E_i is related to the rate constant k_i by the Arrhenius equation

$$k_i = A_i \exp(-E_i/RT) \tag{4}$$

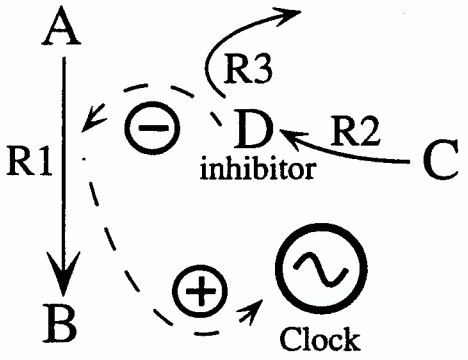
where A_i is often treated as a constant.

For complex systems like enzyme-catalyzed reactions (15,16) the overall activation energy may become dependent on the temperature.

Most circadian rhythms have Q_{10} values near 1 and keep this value often with high precision, although the underlying physiological processes have Q_{10} values of about 2 or even higher.

CONCEPT OF OPPOSING REACTIONS

In 1957, Hastings and Sweeney (17) suggested that "opposing" reactions may explain the temperature compensation of the rhythm even if the underlying processes are not temperature compensated themselves. A kinetic treatment of this approach is considered in Scheme 1:



Scheme 1.

Process R1 ($A \rightarrow B$) is assumed to control the period of the oscillator, while R2 ($C \rightarrow D$) produces an inhibitor of reaction R1 (species D; due to its turnover, process R3, D may be assumed to be in a steady state). In kinetic terms, the period of the rhythm may increase (let us say) proportional to the rate of process R1 and inversely proportional to the steady-state concentration of D. In such a case, using the Arrhenius equation shows that temperature compensation is expected to occur when the activation energy E_2 (relating to the temperature dependence of reaction R2) is equal to the sum of activation energies E_1 and E_3, that is,

$$E_2 = E_1 + E_3 \tag{5}$$

Dunlap and Feldman (18) have used this concept to explain the temperature behavior of the *frq* mutants in *Neurospora crassa*.

RATE CONSTANT RATIOS AND DIFFUSION-CONTROLLED REACTIONS

Pavlidis and Kauzman (19) proposed a biochemical oscillator model for circadian rhythms including activation and inactivation of an enzyme. To obtain temperature compensation, three requirements were necessary: (i) rate constant ratios were assumed to be temperature independent, (ii) certain rate constant values had to be assumed to be diffusion controlled to become practically independent of temperature, (iii) the product between a rate constant k_j and the steady-state concentration of an enzyme species e_l, $k_j e_l$, had to be temperature independent.

Although these assumptions appear to be rather special, there is experimental evidence that certain enzyme-catalyzed reactions (R4) in

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} P + E \qquad \text{(R4)}$$

poikilothermic organisms show an "instantaneous" (20) temperature compensation. In these systems, it was found that, for nonsaturating substrate (S) concentrations, K_M values were increasing with temperature and thus compensating for the corresponding increase in V_{max}. The overall rate given by $v = V_{max}[S]/K_M$ and the rate constant ratio $k_1k_2)/(k_{-1} + k_2$ become independent of temperature. The mechanism that may lead to such a compensation lies apparently in the temperature-induced conformational change of proteins (21–23).

MEMBRANES AND TEMPERATURE COMPENSATION

Several biological membranes have been shown to adapt to different temperatures (24), that is, maintain an unchanged fluidity by varying the ratio between saturated and unsaturated lipids on changes in temperatures. The possibility that temperature compensation of circadian clocks is related to membrane properties was proposed by Sweeney (25) and Njus et al. (26,27). Different aspects of the role of membranes in circadian rhythms can be found in reviews by Engelmann and Schrempf (28) and Vanden Driesche (29). Lakin-Thomas, Brody, and Coté (30) give a review on temperature compensation in *Neurospora crassa* and membrane composition.

CONCEPT OF ANTAGONISTIC BALANCE

When analyzing chemical oscillatory models, Ruoff found that any reaction kinetic oscillator can, in principle, be temperature compensated (31). The reason for this is that any chemical oscillator in general has two types of component processes (32), that is, period-increasing and period-decreasing reactions. For each component process i, a rate constant k_i and a corresponding activation energy E_i can be assigned. The temperature dependence of the period P is a function of the temperature dependence of the rate constants k_i

$$P = f(k_1, k_2, \ldots, \ldots, k_N) \qquad (6)$$

where N is the total number of component processes, m is the number of period-increasing processes, and n is the number of period-decreasing processes with $N = m + n$. The temperature dependence of P can then be written as

$$\frac{\partial P}{\partial T} = \sum_{i=1}^{n+m} \left(\frac{\partial f}{\partial k_i}\right)\left(\frac{\partial k_i}{\partial T}\right) \qquad (7)$$

$$= \frac{f}{RT^2} \sum_{i=1}^{n+m} \left[\frac{1}{f}\left(\frac{\partial f}{\partial k_i}\right)k_i\right] \times E_i \qquad (8)$$

$$= \frac{f}{RT^2} \sum_{i=1}^{n+m} \left(\frac{\partial \ln(f)}{\partial \ln(k_i)}\right) \times E_i = \frac{f}{RT^2} \sum_{i=1}^{n+m} b_i E_i \qquad (9)$$

In case of temperature-compensation, $\partial P/\partial T = 0$, and we can split the sum in period-increasing and period-decreasing contributions and get the condition for antagonistic (32) balance in temperature dependence:

$$\sum_{i(\text{P-decreasing})}^{n} b_i E_i = - \sum_{j(\text{P-increasing})}^{m} b_j E_j \qquad (10)$$

In other words, in any (reaction) kinetic oscillator temperature compensation is expected to occur whenever the E_i weighted sum of $\partial \ln(f)/\partial \ln(k_i)$ of period-increasing reactions balances the corresponding sum of period-decreasing reactions.

Even for simple oscillator models, the function f is rarely described analytically, and approximative functions f_{appr} or numerical solutions to f must be sought. A useful "Ansatz" is the following:

$$f_{appr} = \tau_o \prod_i k_i^{\beta_i} \qquad (11)$$

because $\partial \ln(f_{appr})/\partial \ln(k_i) = \beta_i$. In this approach, β_i is assumed to be temperature independent.

Model Oscillators Based on Autocatalysis

To test the validity of the antagonistic balance (Eq. 10), the Brusselator (31,33,34), the Kauffman–Wille model (34,35), and the Oregonator (36,37) were explicitly investigated. In these three oscillators, the driving force (32) of the oscillations is due to an intrinsic autocatalysis, and temperature compensation can be obtained over an extended temperature range. Figure 1 shows the limit cycle behavior for the temperature-compensated Brusselator during a temperature step. It is seen that, although the period is practically identical for the two temperatures, there are different limit cycles for different temperatures.

Also, phase shifts are observed in the temperature-compensated Brusselator after exposure to external temperature steps and temperature pulses. However, calculated phase response curves (PRCs) show no agreement with experimental PRCs from circadian rhythms. Also, for the Kauffman–Wille model little resemblance to experimental phase response curves has been found (34).

The Goodwin Model

In 1965, Goodwin described a biological oscillator based on a negative feedback loop (38) (Fig. 2A). Now, about 30 years later, experimental evidence begins to emerge that the core mechanism of the circadian rhythms in *Drosophila* (39,40) and *Neurospora* (41) represent such a negative feedback as considered originally by Goodwin. The importance of feedback control in circadian oscillators has also been emphasized by Johnsson and Karlsson (42,43).

We have studied the temperature-compensated Goodwin oscillator in which variables X, Y, and Z represent clock mRNA, clock protein, and a transcriptional inhibitor, respectively. Not only does the Goodwin oscillator show a principally correct phasing between clock mRNA and clock protein (39; Fig. 2B), but phase response curves for temperature steps and temperature pulses are now similar to what is experimentally observed (Figs. 2C, 2D).

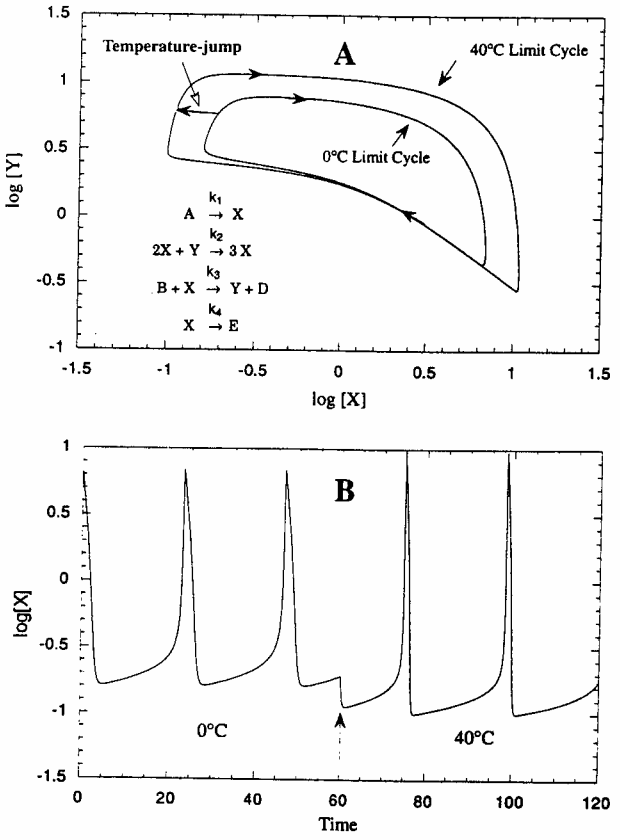


FIGURE 1. A. Limit cycles of the temperature-compensated Brusselator at 0°C and 40°C. The antagonistic balance in temperature is $1.87E_1 + 0.954E_2 = 1.175E_3 + 0.984E_4$. $E_1 = 6.57$ kJ/mol, $E_2 = E_3 = E_4 = 14$ kJ/mol. "Temperature jump" indicates an instantaneous 0°C → 40°C change. B. The corresponding 0°C → 40°C jump shown in a log [X] time plot. All rate constants are 1.0 at 283 K.

Interestingly, by decreasing one of the rate constants of the degradation reactions (k_5), temperature compensation is lost and the response is similar to that observed in the *Neurospora crassa frq7* mutant (see Ref. 44, Table 1, Row 5). In fact, the temperature behavior of *frq Neurospora* (45) and *per Drosophila* long- and short-period mutants (46) can be understood in terms of degradation of the clock protein or the corresponding clock mRNA.

In order to understand why in the Goodwin oscillator the degradation reactions play a more dominant role than synthesis reactions, we have to consider the Goodwin model as a set of amplification reactions in which intermediates X, Y, and Z are approaching (during the oscillations) alternatingly high and low steady-state values.

As Scheme 2 shows, for each intermediate I (X, Y, or Z), we have a synthesis rate (dependent on rate constant k_{synth}, i.e., k_1, k_2, or k_3) and a degradation rate (dependent on rate constant k_{degr}, i.e., k_4, k_5, or k_6):

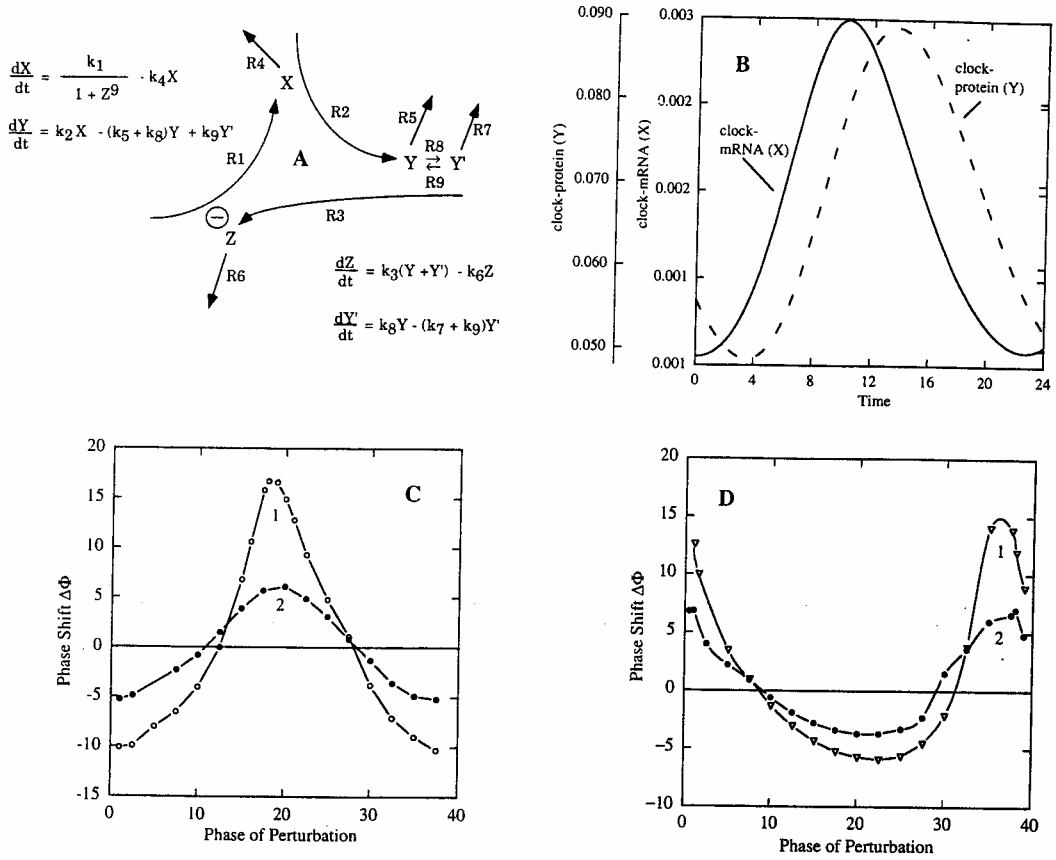
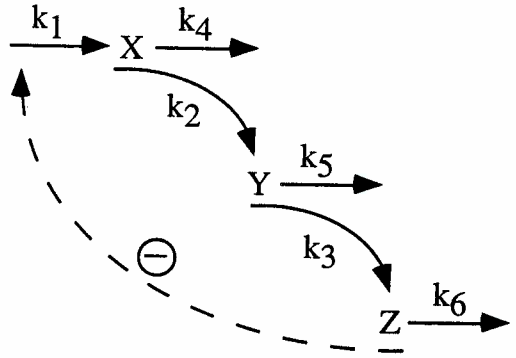


FIGURE 2. A. The Goodwin model with rate equations. Rate constants k_i refer to reactions Ri. The negative sign in the loop indicates the repression of X (mRNA) by a transcriptional inhibitor Z. Y is the clock protein. Y′ is a conformational state of the clock protein used in the *Drosophila* calculations. B. Concentration-time plots of clock-mRNA (X) and clock-protein (Y) representing *Neurospora* wild-type behavior. Rate constants (25°C): $k_1 = k_2 = k_3 = 1.0$; $k_4 = k_5 = 0.2$; $k_6 = 0.1$; $k_7 = k_8 = k_9 = 0$. Activation energies: $E_1 = 2.36 \times 10^4$ J/mol, $E_2 = 9.26 \times 10^4$ J/mol, $E_3 = 6.25 \times 10^4$ J/mol, $E_4 = 7.63 \times 10^2$ J/mol, $E_5 = 1.92 \times 10^2$ J/mol, $E_6 = 2.02 \times 10^2$ J/mol. Start concentrations: $X = 1.051 \times 10^{-3}$, $Y = 5.583 \times 10^{-2}$, $Z = 2.713$, T = 25°C. C. Phase response curve for temperature step ups. 1: 273.0 K → 274.0 K; 2: 273.0 K → 273.5 K. $k_1 = k_2 = k_3 = 1.0$, $k_4 = k_5 = k_6 = 0.1$ (283 K). $E1_1 = 1.832 \times 10^4$ J/mol, $E_2 = 2.245 \times 10^5$ J/mol, $E_3 = 1.748 \times 10^4$ J/mol, $E_4 = 296.434$ J/mol, $E_5 = 201.092$ J/mol, $E_6 = 328.277$ J/mol. Zero phase of perturbation corresponds to X maximum of 273 K limit cycle. D. Phase response curve for temperature step downs. 1: 274.0 K → 273.0 K; 2: 274.5 K → 273.0 K. Same parameters as in C, but zero phase shift in 1 corresponds to X maximum of 274 K limit cycle and in 2 to X maximum of 274.5 K.



Scheme 2.

$$\xrightarrow{k_{synth}} I \xrightarrow{k_{degr}} \quad \text{(R5)}$$

The steady-state value of I, I_{SS}, depends on both the synthesis and degradation rate constants, that is, $I_{SS} = k_{synth}/k_{degr}$. However, the time scale of approach to the steady state is only dependent on the degradation rate constant k_{degr}, as the time development of I(t) shows:

$$I(t) = I_0\, e^{-k_{degr}\cdot t} + \frac{k_{synth}}{k_{degr}}\left(1 - e^{-k_{degr}\cdot t}\right) \quad (12)$$

which is the reason why, in the Goodwin model, the synthesis rate constants k_1, k_2, and k_3 (Fig. 2A) have practically no influence on the period length (for numerical values, see also Table 1 in Ref. 47).

The temperature behavior of the short-period mutants (*frq1*, *perS*) can be understood by an increased degradation of the clock protein, while in the long-period mutants the clock protein (or clock mRNA) is degraded more slowly than in the wild-type forms (Fig. 3). For *perL*, an additional temperature-dependent equilibrium between two forms of the clock protein (Y′, Y) has to be considered (Fig. 2A) in order to simulate the temperature behavior (Fig. 3CD) (47). In fact, recent studies have shown that a PAS-C domain interaction within PER (48,49) or an interaction between PER and TIMELESS proteins (50–53) are important for the regulation of PER and for understanding temperature compensation in *per* mutants.

GENERAL HOMEOSTASIS IN PERIOD

The rate constants in Eq. 1 may not only depend on temperature, but on a variety of other environmental parameters ξ, such as, for example, pH, ionic strength, and D_2O. In this case, the variation of P against ξ becomes

$$\frac{\partial P}{\partial \xi} = \sum_{i=1}^{n+m} \left(\frac{\partial f}{\partial k_i}\right)\left(\frac{\partial k_i}{\partial \xi}\right) \quad (13)$$

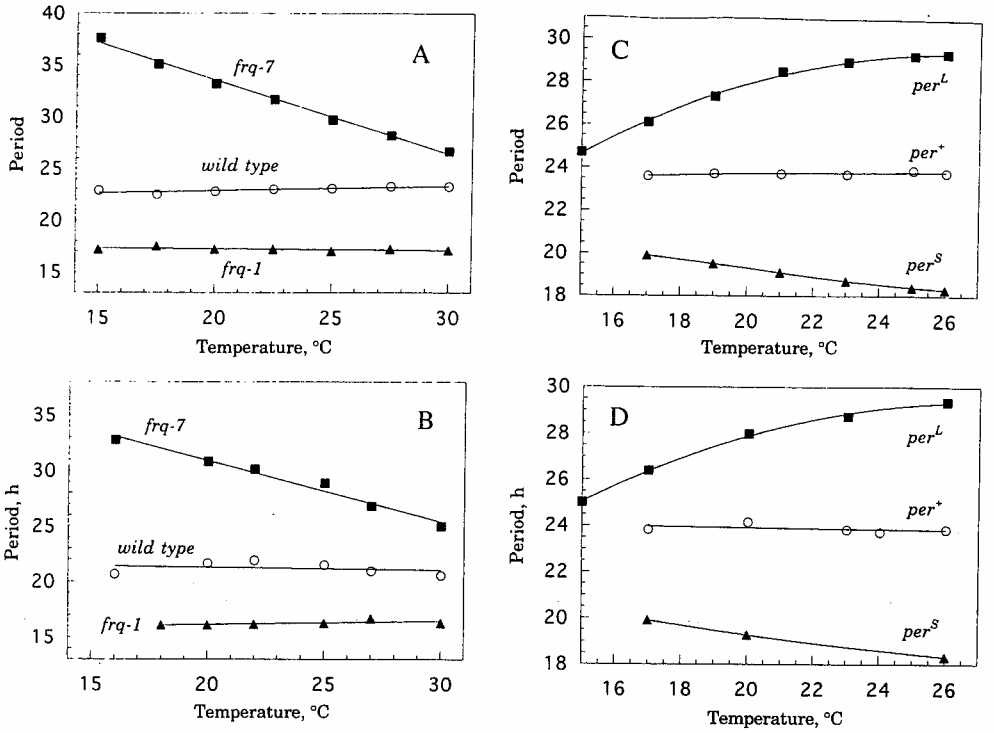


FIGURE 3. A. Calculated temperature behavior of *Neurospora frq* mutants. E_i is the activation energy of rate constant Ri. The numerical parameters are wild-type, see legend of Fig. 2B; *frq-7*: $k_5 = 0.1$ (25°C), $E_5 = 5.0 \times 10^4$ J/mol. The other parameters are as for the wild-type. B. Experimental results replotted from the work by Gardner and Feldman (45). C. Calculated temperature behavior of *Drosophila melanogaster per* mutants. The numerical parameters are: *per*$^+$: $E_1 = 2.36 \times 10^4$ J/mol, $E_2 = 9.26 \times 10^4$ J/mol, E3 $= 6.25 \times 10^4$ J/mol, $E_4 = 7.63 \times 10^2$ J/mol, $E_5 = 1.92 \times 10^2$ J/mol, $E_6 = 2.02 \times 10^2$ J/mol, $E_7 = E_8 = E_9 = 1.0 \times 10^2$ J/mol. Rate constants (25°C): $k_1 = k_2 = k_3 = 1.0$, $k_4 = 0.15$, $k_5 = 0.25$, $k_6 = 0.1$, $k_7 = 0.25$, $k_8 = k_9 = 1.0$. *per*^{S}: $k_5 = k_7 = 0.4$ (25°C), $E_5 = 5 \times 10^4$ J/mol; other parameters as for *per*$^+$. *per*^{L}: $k_5 = 0.3$, $k_7 = 0.15$ (25°C); $E_5 = 2.5 \times 10^4$ J/mol, $E_8 = 1.0 \times 10^5$ J/mol; other parameters as for *per*$^+$. D. Experimental results replotted from the work by Konopka, Pittendrigh, and Orr (46).

Because the $\partial f/\partial k_i$ term will still be positive or negative, additional antagonistic balances in ξ can be formulated when $\partial P/\partial \xi = 0$. General homeostasis of the period may be understood due to antagonistic balances in all physicochemical or physiological parameters that influence the component processes of the clock mechanism (54).

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