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BIOPHYSICS AND MEDICAL PHYSICS

A Temperature-Compensation Mechanism in Biochemical Oscillation Models

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Abstract—Different mechanisms that underlie temperature compensation of the frequency (period) of biochemical self-oscillations are considered. A systemic approach to the elucidation of the molecular nature of temperature compensation of the frequency of biochemical self-oscillations has been characterized as better substantiated. The phenomenon of temperature compensation is not unique for circadian oscillations ("biochemical clocks") but is rather an inherent property of all multidimensional chemical oscillators. Stages with negative coefficients of control over frequency were shown to be the components of the structure of "presetting generators" of biochemical self-oscillations, and the balancing role of these stages can be considered more important as believed earlier. The calculation of control coefficients showed that the elementary stages make unequal contributions to the mechanism that underlies temperature compensation; therefore, different mutations have dissimilar effects on the temperature compensation of the period of circadian oscillations in the respective mutants.

Keywords: temperature compensation, frequency control analysis, biochemical self-oscillations.

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Temperature is among the most important factors that determine the rates of biochemical and biophysical processes. All molecular processes depend on temperature; therefore, one can expect a substantial dependence of the period (frequency) of biochemical self-oscillations on temperature. However, experimental studies of the temperature dependence of the period of biochemical self-oscillations showed that the period of the biochemical clock was only weakly dependent on the temperature of the reaction medium in a certain physiologically acceptable temperature range [1–8]. This phenomenon is termed temperature compensation.

A large number of studies have been dedicated to the molecular foundations of temperature compensation of the period of biochemical self-oscillations [2–9]. However, the molecular mechanisms and the biophysical principles of this phenomenon have not been elucidated as yet.

Periodic phenomena occur widely in biochemical processes [10]; therefore, a brief description of the main characteristic properties of biochemical oscillations is relevant. Analysis of the published data revealed three basic properties of biochemical oscillations.

1. Biochemical oscillations are endogenous and do not require exogenous physicochemical factors.

2. The period (frequency) and amplitude of biochemical oscillations are determined by the internal parameters of the oscillatory system; the period varies in a rather wide range.

3. The period of biochemical oscillations termed circadian oscillations or biochemical clocks is close to 24 h and shows a rather weak dependence on temperature (temperature compensation is observed).

The first two properties are determined by the self-induced character of biochemical oscillations and the emergence of these oscillations upon a specific interaction of the reagents. The characteristics of self-oscillations are determined by internal parameters and do not depend on the initial conditions. The rate constants of elementary stages are the most universal internal parameters in the kinetics of biochemical reactions; therefore, one can assume that these constants determine the period of biochemical self-oscillations.

The local approach and the systemic approach are the two alternatives that have been currently proposed for the analysis of temperature compensation of the period of the biochemical clock. The local approach implies that the compensation process occurs at each individual elementary stage in the biochemical reaction chain. Some proponents of the local approach assume that the mechanism of temperature compensation at the enzyme level consists in the formation of

a special tertiary structure of the enzyme protein that changes with temperature in order to prevent a significant variation of enzyme activity upon temperature changes [11]. However, this assumption does not appear sound, since the temperature dependences of elementary chemical processes can usually be described by the Arrhenius equation:

$$k_i = A_i e^{-\frac{E_i}{RT}}, \quad (1)$$

where E_i is the activation energy, R is the universal gas constant, T is the absolute temperature, and A_i is the preexponential factor. This formula is based on the assumption of A_i being independent of temperature. The Arrhenius equation implies that the increase in temperature leads to an exponential increase in the rate constant of the chemical reaction. The activation energy E_i of the chemical processes that take place in the cell is close to 10 kcal/mol (41.9 kJ/mol) [11]. Let us estimate the relative change of the rate constant at this E_i value. Formula (1) can be easily modified to obtain the expression:

$$\frac{dk_i}{k_i} = \frac{E_i}{RT}\frac{dT}{T}. \quad (2)$$

Formula (2) can be used to demonstrate that the increase of the temperature by $dT = 1$ K, that is, by ~0.33% (at $T = 300$ K) leads to a 5.6% increase of the rate constant, and at $dT = 3$ K (1%) the increase of the rate constant amounts to 16.8%. The increase in the rate constant that accompanies a slight increase in temperature is apparently rather high. Moreover, an experimental curve of the temperature dependence of the period of circadian oscillations [10] can be used to calculate that a temperature increase by 4 K (~ 1.34%) at $T = 298$ K would evoke a decrease of the period by 2.6% and a 28.4% increase of the rate constant (according to the formula (1)). The height of the energy barrier for conformational transitions amounts to tens of kJ/mol; therefore, the above-mentioned temperature change (for instance, a $dT = 5$ K increase corresponds to a 41.5 kJ/mol increase in the average kinetic energy) would be insufficient to evoke a conformational change in an enzyme protein. Therefore, the assumption of a temperature compensation mechanism based on the existence of a specific tertiary structure of an enzyme protein that changes with temperature to provide for an insignificant change of the periodic activity of the enzyme does not appear valid.

Another hypothesis developed within the local approach was proposed in [9]. This hypothesis states that the A_i in the Arrhenius formula (1) decreases with increasing temperature, and the decrease is equal to the increase of the exponential factor in (1). Therefore, the fold change of the product $A_i \times \exp(E_i/RT)$ is close to one, that is, the rate constants remain almost unchanged.

Importantly, the applicability of the Arrhenius equation for enzymatic reactions is essentially limited in the general case due to thermal conformational changes in the structure of the enzyme. These changes are the reason for the temperature dependence of the rate of enzymatic reaction being described by a curve with a maximum. The rising part of the curve reflects a regularity typical for all chemical reactions, whereas the descending part demonstrates a decrease of enzyme activity related to conformational changes (and ultimately, denaturation) of the protein molecule and the related disruption of the molecular structure that determines the activity of the enzyme. Research on temperature compensation of the period of the biochemical clock involves the analysis of small deviations of the temperature from the "physiological" values. Therefore, it is not necessary to take thermal denaturation of the enzyme into consideration and the temperature dependence of the rate of enzymatic reactions in this temperature range can be estimated according to the Arrhenius equation.

The study in [9] stated that A_i in the Arrhenius formula characterizes the concentrations of free enzymes (enzymes not bound to the substrate) at stage i of the enzymatic reaction; therefore, A_i decreases with increasing temperature. It was further assumed that a temperature increase caused an increase in the concentration of the enzyme-substrate complex, and the concentration of free enzymes decreased, since the total amount of enzymes in the system was constant.

However, the molecular kinetic theory states that A_i is determined by the number and molecular characteristics of the effective intermolecular collisions that depend on temperature as well. In fact, the theory of active collisions states that the temperature dependence of the rate constant (in the strict approximation) is expressed by the Trautz-Lewis equation:

$$k_i = N_A \pi d^2 \left(\frac{8kT}{\mu\pi}\right)^{\frac{1}{2}} \times e^{\frac{-E_i}{RT}} = A_i e^{\frac{-E_i}{RT}}, \quad (3)$$

where N_A is Avogadro's number, d is the sum of the radii of the reacting pairs of particles, k is the Boltzmann constant, μ is the reduced mass of the interacting pairs of particles, and T is the absolute temperature. This expression shows that A_i does depend on temperature, but this dependence is rather weak in comparison with the exponential dependence; therefore, the former dependence is often neglected in the rough approximation. As evident from the above, the concept of a decrease of A_i upon an increase in temperature does not agree with the results of theoretical analysis.

Thus, the local approach to the clarification of the mechanism of temperature compensation of the period of biochemical self-oscillations encounters serious contradictions.

The concept of a systemic mechanism of temperature compensation was first proposed in [2]. The essence of the systemic mechanism consists in the existence of stages that react to temperature changes in opposite ways if a temperature-compensated multistage periodic biochemical reaction is considered. This approach can be validated if a quantitative assessment of the changes of the period of oscillations upon temperature changes is performed. Here, it is necessary to emphasize that the reasoning presented above implies the analogous character of the changes of all rate constants upon an increase/decrease in temperature. Therefore, the changes of the period can be followed by monitoring the changes in the rate constants of the elementary stages.

The method of metabolic control analysis can be used for quantitative assessment of temperature-dependent changes in the period of oscillations. Temperature compensation of the period considered within the concept framework of metabolic control implies the negative values of some factors of frequency control upon positive changes in the values of the rate constants.

The modern theory of metabolic control [12] defines the metabolic control coefficients as the ratio of the relative increment of systemic or local characteristics of the metabolic process (∂Y) to the relative increment of a certain regulatory parameter that induces the abovementioned increment (∂Z). The metabolic control coefficients are calculated using the system of differential equations (mathematical model) that describes the dynamic behavior of a biochemical process:

$$C_Z^Y = \frac{\partial Y/Y}{\partial Z/Z}. \quad (4)$$

Let us represent the frequency as a complex function of temperature: $\omega(T) = \omega(k_i(T))$ in order to devise a quantitative characteristic of the response of the frequency to a temperature change, and then

$$\frac{\partial \omega}{\partial T} = \sum_{i=1}^{n} \frac{\partial \omega}{\partial k_i}\frac{\partial k_i}{\partial T}.$$

As follows from the above,

$$\frac{T}{\omega}\frac{\partial \omega}{\partial T} = \sum_{i=1}^{n} \frac{k_i}{\omega}\frac{\partial \omega}{\partial k_i}\frac{T}{k_i}\frac{\partial k_i}{\partial T}. \quad (5)$$

Let us denote $C_{k_i}^{\omega} = \frac{k_i}{\omega}\frac{\partial \omega}{\partial k_i}$ in formula (5), where $C_{k_i}^{\omega}$ are the coefficients of the rate-constant control over frequency; $C_T^{k_i} = \frac{T}{k_i}\frac{\partial k_i}{\partial T}$ is the coefficient of temperature control over the rate constant, and $C_T^{\omega} = \frac{T}{\omega}\frac{\partial \omega}{\partial T}$ is the coefficient of temperature control over frequency.

The Arrhenius equation (1) can be used to obtain the expression

$$C_T^{k_i} = \frac{E_i}{RT}. \quad (6)$$

Let us take (6) into account in (5) to obtain

$$C_T^{\omega} = \frac{1}{RT}\sum_{i=1}^{n} C_{k_i}^{\omega} E_i. \quad (7)$$

Formula (7) allows for quantitative assessment of the relative change in frequency upon a change in temperature if the coefficients of the rate-constant control over frequency and the activation energy of the corresponding stage are known. However, formula (7) leads to an important qualitative conclusion that validates the systemic mechanism of temperature compensation, since the temperature compensation considered within the concept framework of metabolic control implies that the coefficient of temperature control over frequency must be equal (or sufficiently close) to zero ($C_T^{\omega} \approx 0$). Formula (7) shows that C_T^{ω} can be only equal to zero if some coefficients of rate-constant control over the frequency have negative values, since the values of the activation energy E_i are essentially positive. This implies a decrease of the frequency (an increase of the oscillation period) of some stage of the process upon a temperature increase. That is, temperature compensation requires the existence of stages with self-oscillation frequencies that react to temperature changes in opposite ways.

Thus, it is necessary to calculate the coefficients of the rate-constant control over frequency $C_{k_i}^{\omega}$ for the elucidation of the mechanism of temperature compensation.

Calculation of the coefficients of control over frequency. A well-known postulate of the theory of oscillations states that the frequency of a stable self-oscillating process is equal to the coefficient at the imaginary part of the root of the characteristic equation, that is, the Jacobian eigenvalues of a system of differential equations that describe the kinetic behavior of the reaction system [13]. These coefficients are determined by the values of the parameters of the system. Therefore, the coefficients of control over frequency can be derived from (4), where ∂Y is the frequency increment and ∂Z is the increment of the parameter under investigation, if the explicit analytical form of the coefficient at the imaginary part of the eigenvalue as a function of the parameters is known. The coefficients of control over frequency can be found using simple calculations in the simple cases when an analytical expression for the dependence of the Jacobian eigenvalues of a system of kinetic equations on the system parameters can be obtained.

Frequency control factors in models 1–5

Model 1	$C^{\omega}_{k_i}$	Model 2	$C^{\omega}_{k_i}$	Model 3	$C^{\omega}_{k_i}$	Model 4	$C^{\omega}_{k_i}$	Model 5	$C^{\omega}_{k_i}$
k_1	0.5	V_m	0.431	k_1	0.549	k_1	0.268	k_1	0.009
k_2	0.0	k_1	0.510	k_2	–0.098	k_2	0.286	k_2	0.004
k_3	0.5	k_2	0.056	k_3	0.095	k_3	–0.167	k_3	1.598
				υ_{0x}	0.375	k_{+4}	–0.505	k_4	–1.354
				υ_{0z}	0.078	k_{-4}	0.573	k_5	0.086
						k_{+5}	0.775	k_6	0.418
						k_{-5}	–0.229	k_7	0.228
Sum	1	Sum	0.997	Sum	0.999	Sum	1.001	Sum	0.997

The explicit analytical form of the coefficient at the imaginary part of the eigenvalue is often unknown; therefore, computer software is used to calculate the value of the coefficient. A numerical experiment can be performed in such cases. The changes in the imaginary part of the eigenvalue $\Delta\lambda$ that correspond to a small increment of the parameter ΔP are calculated and the coefficients of control over frequency are calculated after the replacement of infinitesimal increments by finite difference values in (4).

$$C^{\lambda}_{P} = \frac{\Delta\lambda/\lambda}{\Delta P/P}. \tag{8}$$

Model 1: The self-oscillatory Volterra model. The model is described by the following system of equations:

$$\begin{cases} \dfrac{dx}{dt} = k_1 x - k_2 xy, \\ \dfrac{dy}{dt} = k_2 xy - k_3 y. \end{cases} \tag{9}$$

System (9) is known to have a characteristic polynomial that can be expressed as

$$\lambda^2 + k_1 k_3 = 0. \tag{10}$$

The roots of the equation (10) (the eigenvalues of the Jacobian for the system (9)) are purely imaginary:

$$\lambda_{1,2} = \pm i\sqrt{k_1 k_3}. \tag{11}$$

As shown above, the frequency of the periodic solution of the system (9) will be expressed as

$$\omega = \sqrt{k_1 k_3}. \tag{12}$$

The coefficients of control over frequency are easy to calculate:

$$C^{\omega}_{k_1} = \frac{k_1}{\omega}\frac{\partial\omega}{\partial k_i} = \frac{1}{2}\frac{k_1}{\sqrt{k_1 k_3}}\sqrt{\frac{k_3}{k_1}} = \frac{1}{2},$$

$$C^{\omega}_{k_2} = 0,$$

$$C^{\omega}_{k_3} = \frac{k_3}{\omega}\frac{\partial\omega}{\partial k_3} = \frac{1}{2}\frac{k_3}{\sqrt{k_1 k_3}}\sqrt{\frac{k_1}{k_3}} = \frac{1}{2}.$$

Similar results can be obtained in numerical experiments. Here and below, the SBW software package (developed by H. Sauro and coauthors, http:/www.sbml.org) was used to calculate the eigenvalues of the Jacobian of a system of differential equations. A numerical solution of the system (9) can be used to find the numerical value of the coefficient at the imaginary part of the eigenvalue for a given set of parameters. As an example, $k_1 = 10$, $k_2 = 50$, and $k_3 = 10$ yield $\lambda_{1,2} = 0 \pm i10.00$.

Let us increase the increment parameters by 1% in order to determine $C^{\omega}_{k_i} = 0$. The corresponding frequency increment is 0.05. The infinitesimal increments can be replaced by finite differences according to (8) to obtain:

$$C^{\omega}_{k_1} = \frac{k_1}{\omega}\frac{\Delta\omega}{\Delta k_1} = \frac{10}{10}\times\frac{0.05}{0.1} = 0.5.$$

Similar calculations can be used to find the values of other coefficients: $C^{\omega}_{k_2} = 0$, $C^{\omega}_{k_3} = 0.5$ (table).

Model 2: The glycolysis model (Bier et al. [14]. Let us consider the self-oscillatory model of glycolysis proposed in [14] as another example (symbols as proposed by the author [14]):

$$\begin{cases} \dfrac{dG}{dt} = V_m - k_1 GT, \\ \dfrac{dT}{dt} = 2k_1 GT - k_2\dfrac{T}{K_m + T}, \end{cases} \tag{13}$$

where G are the glucose and ATP concentrations, respectively, V_m is the constant rate of glucose supply, and T is the activity (or concentration) of the enzyme phosphofructokinase. The model assumes that the kinetics of ATP consumption obeys the Michaelis-Menten equation.

As stated in [14], system (13) has a periodic solution at the following parameter values: $V_m = 0.36$, $k_1 = 0.02$, $k_2 = 6$, and $K_m = 13$.

A numerical solution of the system of equations (13) yields $\lambda_{1,2} = 0.00664 \pm 0.112374i$ as the eigenvalue of the Jacobian of the system (13). Therefore, the frequency of the periodic solution of the system (13) is $\omega = 0.112374$.

The control coefficients listed in the table are subsequently calculated as described for the previous model.

As evident from the table, none of the control coefficient values is negative in models 1 and 2 considered above; this implies that absence of temperature compensation in the processes described by these models.

Let us consider models that include negative control coefficients.

Model 3: Three-dimensional oscillator (Sh.K. Bayramov [15]). A three-component system of reactions that exhibits oscillatory behavior is described as follows:

$$y + z \xrightarrow{k_1} 2y,$$
$$x + y \xrightarrow{k_2}, \qquad (14)$$
$$x \xrightarrow{k_3}.$$

This scheme can be described by a system of differential equations:

$$\frac{dx}{dt} = \upsilon_{ox} - k_2xy - k_3x,$$
$$\frac{dy}{dt} = k_1zy - k_2xy,$$
$$\frac{dz}{dt} = -k_1zy + \upsilon_{oz},$$

where υ_{ox} and υ_{oz} are the constant rates of the influx of reagents X and Z, respectively. As shown in [15], the only stationary state becomes unstable at $k_1 < k_2$, and non-decaying oscillations of reagent concentrations emerge in the system.

The oscillations of reagent concentrations were observed at the rate constant values $k_1 = 200$, $k_1 = 5500$, $k_3 = 5$, $\upsilon_{ox} = 5.0 \times 10^{-4}$, and $\upsilon_{oz} = 1.0 \times 10^{-4}$ and the concentration values $[x] = 8.0 \times 10^{-5}$, $[y] = 2.3 \times 10^{-4}$, and $[z] = 2.2 \times 10^{-3}$.

The coefficients of control over frequency calculated as described above are listed in the Table.

Model 4: A four-dimensional non-autocatalytic model of self-oscillations of Kai proteins (Sh.K. Bayramov [16]) (the rank of the matrix of stoichiometric coefficients is 4). A mathematical model of circadian oscillations of cyanobacterial Kai proteins (KaiA, KaiB, and KaiC) was proposed in [16], and phosphorylation and dephosphorylation of KaiC that involved KaiA and KaiB proteins was shown to be the source of circadian auto-oscillations of Kai proteins in vitro. The symbols used in the formulas below are the following: k_i is the rate constant of the stage i of the reaction and [KaiX] denotes the concentration variable for the reagent KaiX. KaiXY denotes the interaction between the KaiX and KaiY proteins and KaiCp denotes the phosphorylated KaiC protein. The putative stages R1–R6 of the circadian oscillations of Kai proteins are the following:

R1: KaiA1 + KaiCp → KaiA2 + KaiCp;

R2: KaiA2 + KaiC + ATP → KaiA1 + KaiCp + ADP;

R3: KaiCp + KaiB → KaiC + KaiB + P;

R4: KaiB + KaiA2 ↔ KaiA2B;

R5: KaiB + KaiA1 ↔ KaiA1B.

The respective individual rate equations (υ_1–υ_5) were selected according to the law of acting masses:

R1: $\upsilon_1 = k_1 \times [\text{KaiA1}] \times [\text{KaiCp}]$;

R2: $\upsilon_2 = k_2 \times [\text{KaiA2}] \times [\text{KaiC}]$;

R3: $\upsilon_3 = k_3 \times [\text{KaiCp}] \times [\text{KaiB}]$;

R4: $\upsilon_4 = k_{+4} \times [\text{KaiB}] \times [\text{KaiA2}] - k_{-4} \times [\text{KaiA2B}]$;

R5: $\upsilon_5 = k_{+5} \times [\text{KaiB}] \times [\text{KaiA1}] - k_{-5} \times [\text{KaiA1B}]$.

The ATP concentration in the solution is assumed incommensurably larger than the concentrations of the KaI proteins in the equation for the reaction rate R2; therefore, ATP is regarded as a reservoir component.

The kinetic behavior of the components is described by a system of differential equations:

$$\begin{cases} \frac{d[\text{KaiA1}]}{dt} = \upsilon_2 - \upsilon_1 - \upsilon_5, \\ \frac{d[\text{KaiA2}]}{dt} = \upsilon_1 - \upsilon_2 - \upsilon_4, \\ \frac{d[\text{KaiB}]}{dt} = -\upsilon_4 - \upsilon_5, \\ \frac{d[\text{KaiC}]}{dt} = \upsilon_3 - \upsilon_2, \\ \frac{d[\text{KaiCp}]}{dt} = \upsilon_2 - \upsilon_3, \\ \frac{d[\text{KaiA1B}]}{dt} = \upsilon_5, \\ \frac{d[\text{KaiA2B}]}{dt} = \upsilon_4. \end{cases}$$

The analysis performed in [16] showed that non-decaying self-oscillations emerged in the system if the sufficient conditions for the existence of self-oscillations were fulfilled:

$$\begin{cases} \upsilon_{+4} = \upsilon_{-4} \gg \upsilon_{+5} = \upsilon_{-5}, \\ \upsilon_1 = \upsilon_2 = \upsilon_3 \gg \upsilon_{+5} = \upsilon_{-5}, \\ \dfrac{[\mathrm{KaiA1}]}{[\mathrm{KaiA2}]} > 1 + \dfrac{[\mathrm{KaiB}]}{[\mathrm{KaiA2}]} + \dfrac{[\mathrm{KaiB}]}{[\mathrm{KaiA1B}]}, \\ \dfrac{k_{+5}}{k_{-5}} > 0.5\dfrac{k_{+4}}{k_{-4}}. \end{cases}$$

The frequency control coefficients calculated according to the procedure described above at the rate constant values $k_1 = 3.1\ \mu M^{-1}\ h^{-1}$, $k_2 = 6.17\ \mu M^{-1}\ h^{-1}$, $k_3 = 1120\ \mu M^{-1}\ h^{-1}$, $k_{+4} = 10\ \mu M^{-1}\ h^{-1}$, $k_{-4} = 1.5\ h^{-1}$, $k_{+5} = 0.5\ \mu M^{-1}\ h^{-1}$, and $k_{-5} = 0.03\ \mu M^{-1}\ h^{-1}$ and the initial reagent concentrations [KaiA1] = 1.8 μM, [KaiA2] = 1.15 μM, [KaiB] = 0.0047 μM, [KaiC] = 0.082 μM, [KaiCp] = 0.12 μM, [KaiA1B] = 0.27 μM, and [KaiA1B] = 0.034 μM are shown in the table.

Model 5: A five-dimensional autocatalytic model of auto-oscillations of Kai proteins (A. Mehra et al. [17]) (the rank of the matrix of stoichiometric coefficients is 5). A mathematical model of circadian oscillations of cyanobacterial Kai proteins (KaiA, KaiB, and KaiC) that described autocatalytic phosphorylation and dephosphorylation of KaiC upon the interaction of KaiA and KaiB proteins was proposed in [17]. This model had periodic solutions for the concentrations of Kai proteins in vitro.

The model was described by the following system of kinetic equations:

$$\begin{cases} \dfrac{d[\mathrm{KaiA}]}{dt} = k_5[\mathrm{KaiABCp}] - k_1[\mathrm{KaiA}][\mathrm{KaiC}] - k_3[\mathrm{KaiACp}][\mathrm{KaiA}][\mathrm{KaiC}], \\ \dfrac{d[\mathrm{KaiB}]}{dt} = k_6[\mathrm{KaiABCp}] - k_4[\mathrm{KaiACp}][\mathrm{KaiB}], \\ \dfrac{d[\mathrm{KaiC}]}{dt} = k_7[\mathrm{KaiCp}] - k_1[\mathrm{KaiA}][\mathrm{KaiC}] - k_3[\mathrm{KaiACp}][\mathrm{KaiA}][\mathrm{KaiC}], \\ \dfrac{d[\mathrm{KaiCp}]}{dt} = k_6[\mathrm{KaiBCp}] - k_7[\mathrm{KaiCp}], \\ \dfrac{d[\mathrm{KaiAC}]}{dt} = k_1[\mathrm{KaiA}][\mathrm{KaiC}] - k_2[\mathrm{KaiAC}], \\ \dfrac{d[\mathrm{KaiCp}]}{dt} = k_2[\mathrm{KaiAC}] - k_4[\mathrm{KaiACp}][\mathrm{KaiB}] + k_3[\mathrm{KaiACp}][\mathrm{KaiA}][\mathrm{KaiC}], \\ \dfrac{d[\mathrm{KaiBCp}]}{dt} = k_5[\mathrm{KaiABCp}] - k_6[\mathrm{KaiBCp}], \\ \dfrac{d[\mathrm{KaiABCp}]}{dt} = k_4[\mathrm{KaiACp}][\mathrm{KaiB}] - k_5[\mathrm{KaiABCp}], \end{cases} \quad (15)$$

where KaiXY denotes interactions between KaiX and KaiY proteins and KaiCp denotes a fully phosphorylated KaiC protein.

System (15) has a periodic solution for the following values of the parameters (rate constants) [17]: $k_1 = 0.0001\ \mu M^{-1}\ h^{-1}$, $k_2 = 0.4\ h^{-1}$, $k_3 = 0.45\ \mu M^{-2}\ h^{-1}$, $k_4 = 3.65\ \mu M^{-1}\ h^{-1}$, $k_5 = 4.0\ h^{-1}$, $k_6 = 0.09\ h^{-1}$, and $k_1 = 0.18\ h^{-1}$.

The frequency control coefficients for the model [17] calculated as described above are listed in the table.

CONCLUSIONS

Several conclusions can be drawn from the above. Firstly, it should be emphasized that the systemic approach to the clarification of the molecular nature of temperature compensation of the frequency of biochemical self-oscillations (termed the "distributed" approach in [5]) is better justified than the local approach. Secondly, the phenomenon of temperature compensation is not unique for circadian oscillations ("biochemical clocks"), but rather is inherent for all multidimensional (with more than two independent variables) chemical oscillators, as mentioned in a number of studies [2–9]. In fact, the table shows that stages with negative control coefficients occur in three-dimensional oscillators and systems with a higher number of dimensions. Thirdly, the stages with negative coefficients of control over frequency are the components of a "critical fragment," that is, a fragment of the reaction system that destabilizes the stationary state of the system and thus acts as a "presetting generator" of biochemical self-oscillations [18]. One can assume that the balancing effect of these stages is more significant than believed earlier. Fourthly, the table shows that the elementary stages make unequal contributions to the mechanism of temperature compensation. These contributions are not defined exclusively by the values of the control coefficients, but rather depend on the respective values of

activation energy (the heights of the energy barriers, as evident from the formula (7)) as well. The results we obtained contribute to the understanding of the causes of dissimilar effects of different mutations on the temperature compensation of the period of circadian oscillations in different mutant animals, as described in [8].

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