

Simple model for temperature control of glycolytic oscillations

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We introduce the temperature-dependent autocatalytic coefficient into the Merkin-Needham-Scott version of the Selkov system and consider the resulting equations as a model for temperature-controlled, self-sustained glycolytic oscillations in a closed reactor. It has been shown that this simple model reproduces key features observed in the experiments with temperature growth: (i) exponentially decreasing period of oscillations; (ii) reversal of relative duration leading and tail fronts. The applied model also reproduces the modulations of oscillations induced by the periodic temperature change.

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I. INTRODUCTION

Glycolysis is one of the most important metabolic processes and a typical example of biochemical oscillations. It is argued [1] that oscillating behavior can have benefits over steady states in the sense of efficiency of glucose utilization and cell's energy charge. At the same time, the glycolysis is discussed as a promising way of biofuel production; see, for example, the Ref. [2]. This induces the question about external regulation of oscillating glycolytic reaction.

The usual method of regulation is a temperature control due to the well-known Arrhenius law for rate constant of chemical reaction. Actually, the temperature dependence for a period of glycolytic oscillations was detected in the first experimental studies of them [3,4]. The interplay of temperature variation as well as other regulators was also investigated experimentally [5]. However, the most detailed experimental study was evaluated relatively recently [6,7]. The experiments were performed with cell-free yeast extract in a closed reactor, and the following has been obtained: (i) detailed tracing of the dependence “period versus temperature,” demonstrating its Arrhenius character and (ii) the significant temperature influence on a shape of oscillations.

There are several theoretical attempts to take into account the mentioned temperature dependence. The model [8] has considered the set of eight rate equations for the key processes of glycolytic path. A correspondence to the early experimental estimations [3,4] was found. Note that these works, as well as the further detailed study [6], deal principally with oscillations connected with the activity of a key enzyme, phosphofructokinase (PFK). For this reason, current theoretical research [9] operates with the allosteric Goldbeter-Lefever model [10], describing the conversion of substrate [adenosine-5'-triphosphate (ATP)] into product [adenosine diphosphate (ADP)] in the presence of PFK. The authors of Ref. [9] have obtained the plot “period vs. temperature” satisfactory, corresponding to the experiment in Ref. [6].

But two considered models are quite complex. This makes difficult an analytical estimation of period as a function of temperature, as well as an explanation of phenomena founded experimentally in Refs. [6,7]. From this point of view, the more simple approach based on the Selkov model [11] looks

more promising. This model recently showed its power as an explanation of phase reversal [12] and spatial modulations [13] of glycolytic traveling waves in yeast extract filling an open spatial reactor with inhomogeneous influx.

Thus, the main goal of this work is to incorporate the temperature dependence into the Selkov-based mathematical model of glycolytic oscillations in the form of the generalized Rayleigh equation and to apply the obtained system for reproducing experimental dependences described in Ref. [6].

II. MODEL

The original Selkov model [11] describing the autocatalytic conversion of substrate (ATP) x into product (ADP) y reads in dimensionless form as

$$\frac{dx}{dt} = \nu - xy^2, \quad (1)$$

$$\frac{dy}{dt} = -wy + xy^2, \quad (2)$$

where substrate influx ν and product outflow w into the sphere of reaction are considered constant parameters.

In the case of a closed vessel, as has been shown in Ref. [14], ν actually means the initial quantity of substrate taking place within a vessel. Therefore, it can be considered only as an “influx” into the reaction not in the vessel. In other words, it is a source of the substrate. Thus, its value unidirectionally decreases with time. But this leads to divergence of the solutions of Eqs. (1)–(2), conversely to the experimentally detected decay of oscillations. To correct this, Merkin-Needham-Scott proposed to incorporate into Eqs. (1)–(2) terms linearly depended on substrate concentration.

Additionally, we need to consider the incorporating of temperature dependence into these two reaction terms. There is experimental evidence (e.g., Ref. [15]) that enzyme-catalyzed (via PFK) autocatalytic Selkov's term xy^2 actually has this dependence governed by the Arrhenius equation:

$$\beta(T) = \beta_0 \exp(-k/T). \quad (3)$$

On the other hand, the Merkin-Needham-Scott term, αx , corresponds to extremely slow catalyzing process. Moreover, the authors of Ref. [14] refer to it as “uncatalyzed term.” Biochemically, it can correspond to a number of additional reactions proceeding in parallel with the PFK-catalyzed autocatalytic reaction (cubic term). However, in the sense of

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a Selkov-like equation, they simply mean small additional influx/outflow in the sphere of reaction like $-wy$ term; see also the discussion in Ref. [16]. Therefore, their temperature dependence can be neglected. Thus, α is a constant. Summarizing these assumptions, we get the system:

$$\frac{dx}{dt} = v - \alpha x - \beta(T)xy^2, \quad (4)$$

$$\frac{dy}{dt} = -wy + \alpha x + \beta(T)xy^2, \quad (5)$$

$$\frac{dv}{dt} = -\varepsilon v, \quad (6)$$

where Eq. (6) describes the substrate consumption of a closed reactor. It is separated from Eqs. (4)–(5) and can be solved explicitly:

$$v(t) = v_0 \exp(-\varepsilon t). \quad (7)$$

Therefore, the substitution of Eq. (7) into Eq. (4) leads to the system of two differential equations.

For theoretical analysis, it is convenient to represent the system of Eqs. (4)–(6) with the coefficients of Eqs. (3)–(7) in the form of a generalized Rayleigh equation, introduced for the Selkov system and discussed in recent works (Refs. [12,17]). Following the strategy described in the cited works, we introduce new variable ξ in such a way that

$$x = \frac{z_0 w - v + w\xi + \dot{\xi}}{w}, \quad y = \frac{v - \dot{\xi}}{w},$$

and

$$z_0 = \frac{w^3 v + \beta v^3 + \alpha v w^2}{\beta v^2 w + \alpha w^3}$$

is an equilibrium full concentration of reagents. As a result, we finally get the single second-order differential equation:

$$\ddot{\xi} + \lambda \dot{\xi} + \lambda'' \dot{\xi}^2 + \lambda' \dot{\xi}^3 + [\alpha w + \beta \Omega^2 (1 - v^{-1} \dot{\xi})^2] \xi = 0, \quad (8)$$

where the coefficients are $\lambda = [3v^2\beta + w^2(w + \alpha) - 2\beta v w z_0]/w^2$, $\lambda' = \beta/w^2$, $\lambda'' = \beta(z_0 w - 3v)/w^2$, $\Omega = v/\sqrt{w}$.

III. RESULTS

The form of the generalized Rayleigh equation allows to analysis of basic properties of self-sustained oscillation in the most direct way. First of all, the range of their existence is determined by a value of the coefficient λ . The equality $\lambda = 0$ corresponds to the Hopf bifurcation. It can be shown that there exist two roots $v_{1,2}$ corresponding to the equation $\lambda(v) = 0$, which is a biquadratic equation relatively to v , and the oscillations are observed within the interval bounded by its two roots. As a result, when v decreases because Eq. (7) is smaller than the smallest value of $v_{1,2}$, the oscillations will decay. As well, the change of β value also effects the speed of approaching the lower Hopf bifurcation point. Therefore, colder reactor medium corresponds to smaller number of realized oscillations. Additionally, the decay of substrate source in a closed vessel leads to the decrease of mean product concentration with a time: all plots in Fig. 1 have negative mean

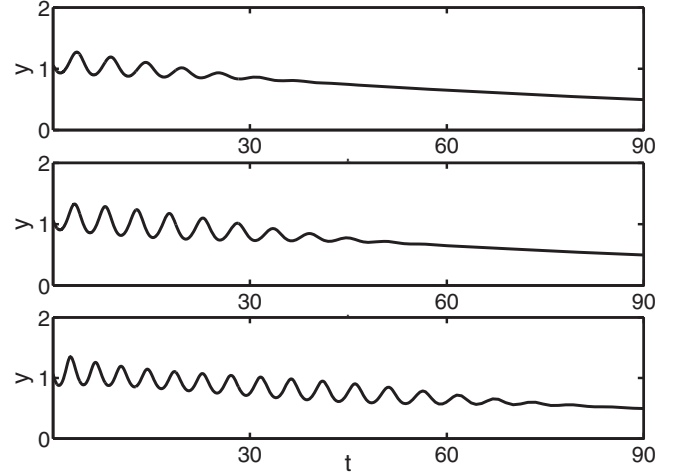


FIG. 1. Examples of decaying oscillations corresponding to various temperatures: (a) 290 K ($\beta = 0.26$); (b) 295 K ($\beta = 0.45$); (c) 305 K ($\beta = 1$). Parameter determining substrate decay: $\varepsilon = 0.009$.

slope. Both these effects have been found experimentally [7]. The illustration of the calculated numerical solutions of (8) for three various temperatures is presented in the Fig. 1. The set of dimensionless parameters used for this and all other figures: $k = 4.73 \times 10^3$, $\beta_0 = 5.53 \times 10^6$, $w = 2$, $v_0 = 2.23$, $\alpha = 0.24$. The initial values are $\xi(0) = 0.3$, $\dot{\xi}(0) = 0.1$.

The factor at the last term in (8) plays a role of a squared variable frequency:

$$\omega^2 = \alpha w + \beta \Omega^2 (1 - v^{-1} \dot{\xi})^2. \quad (9)$$

However, it should be pointed out that the presence of small variable term $v^{-1} \dot{\xi}$ does not affect sufficiently the value of weak nonlinear oscillations; see the discussion in Ref. [12]. Therefore, the frequency is principally determined by the temperature [Eq. (3)] and the substrate depletion [Eq. (7)]. The latter effect is visible in the Fig. 1: the period of oscillations is larger near the stop of oscillations. The first effect is more specific in the considered case of oscillations in a closed vessel. Figure 2 demonstrates frequency of oscillations on

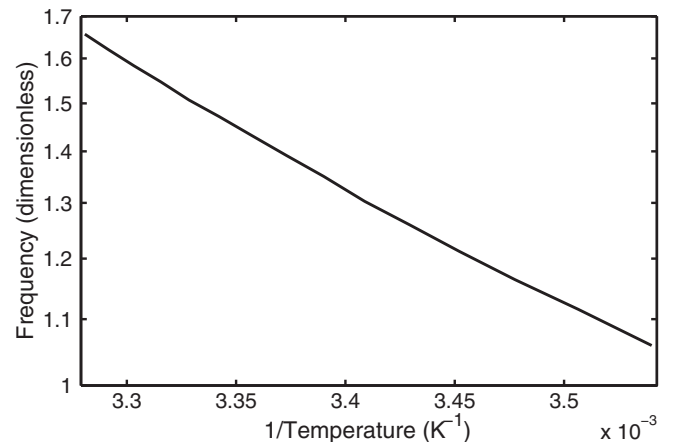


FIG. 2. The dependence of oscillations' frequency on temperature in semilogarithmic co-ordinates. Here, $\varepsilon = 0$ is taken, with the goal of period stability during the oscillations.

the inverse temperature, i.e., the semilogarithmic Arrhenius plot. Its behavior corresponds to Fig. 2(b) in Ref. [6], where frequency-temperature dependence is approximated by the Arrhenius law. At the same time, it could be pointed out that the presence of the constant term α in Eq. (9) slightly differs from the actual frequency-temperature dependence from a pure Arrhenius exponential case for small inverse temperatures. Deviations of experimental results from the fitting line are detected in this region in Fig. 2(b) in Ref. [6]. However, one needs to take into account an experimental error. Thus, the detailed experimental test of this could be stated as a problem for future experiments.

The next significant property of glycolytic oscillations, which was first found in the experiment of Ref. [6], is the change of individual oscillation shape. It has been observed that low-temperature relaxation oscillations grow from the magnitude's minimum to the maximum steeper than decay from maximum to minimum and visa versa for high-temperature oscillations. In general, the lines presenting the lengths of the first and second phases cross around 292 K

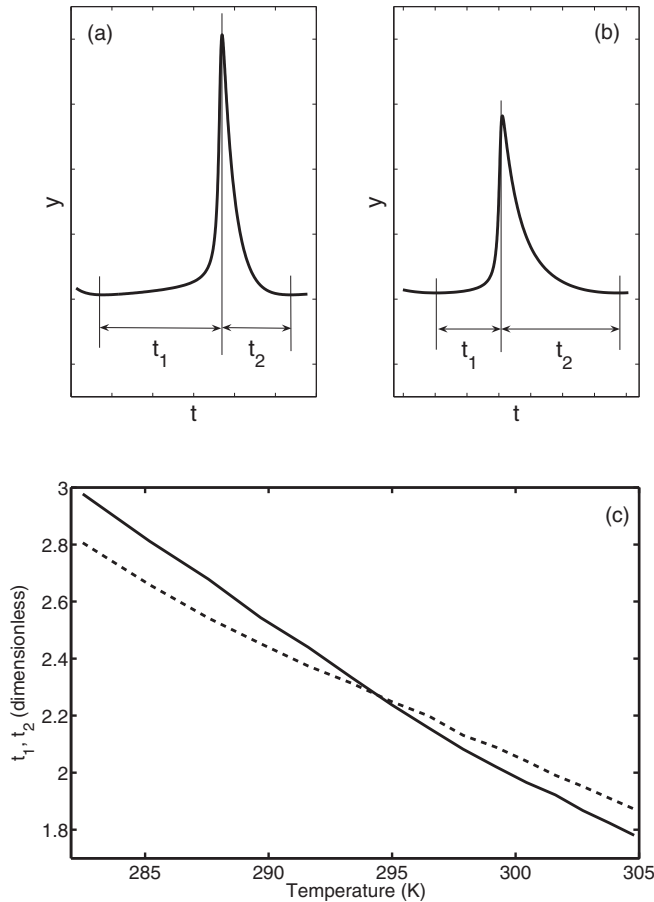


FIG. 3. Temperature dependence for the leading edge and tail of an individual oscillation: (A) 280 K ($\beta = 0.26$); (B) 305 K ($\beta = 1$) (time scales are different for A and B); (C) evolution of the times for the first (t_2 defined as the time interval from the minimal magnitude, solid line) and second (t_1 , from the maximum to the minimum, dashed line) phases of oscillations as a function of temperature. Here, $\varepsilon = 0$ is taken, with the goal of period stability during the oscillations.

(19° C) (see Fig. 3). Our numerical solution of Eqs. (4)–(5) demonstrates a similar picture; see Fig. 3. It is natural that the simple model of the individual oscillation (see inset in Fig. 3, Ref. [6]). However, it reproduces its crucial feature: temperature-dependent ratio of the leading edge and tail, see Figs. 3(a) and 3B. Moreover, the tracing of this ratio with the temperature change [see Fig. 3(c)] clearly demonstrate the desired cross-section of phase lengths around the same temperature as in the experiment. Note that the emergence of cross-section is mainly based on the tail's prolongation.

Finally, let us consider the influence of periodic temperature variations. Figure 4 represents three examples of modulated shapes of ADP oscillations emerging due to temperature oscillations of media (compare with Fig. 5 in Ref. [6]). For simplicity of consideration, we modulate directly β , since it is a reciprocated function of temperature. Naturally, as it was discussed above, the simple model (4)–(5) cannot reproduce the exact shape of experimental curves, but we can reveal the key mechanism of such a behavior. The periodic difference between heights of concentration peaks is connected with the fact that these oscillations take place around one of Hopf bifurcation points. When the value of temperature corresponds to $\lambda > 0$, the oscillations decay, and visa versa, temperatures corresponding to $\lambda < 0$ leads to the sustained oscillations. This process repeats periodically. The relation of time-length for these two phases determines the position of curve's depth and the shape of resulting oscillations: from alternation of high and low individual peaks [Fig. 4(a)] through the cavity within an individual peak [Fig. 4(b)] to a sequence of wave trains [Fig. 4(c)].

IV. SUMMARY AND DISCUSSION

We have considered the temperature control of glycolytic self-sustained oscillations via incorporation of the Arrhenius

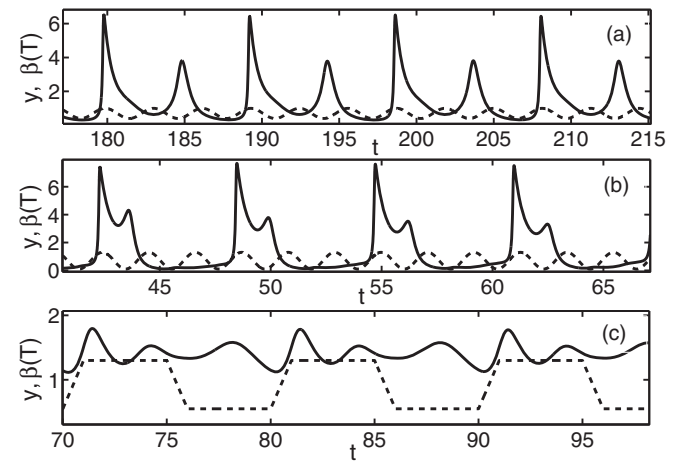


FIG. 4. Modulations of oscillations (solid line) induced by periodic temperature variations (dashed line): (A) $\beta = \beta_0 + 0.3 \sin(2t)$, (B) $\beta = \beta_0 + 0.3 \sin(3t)$, (C) β is a piecewise-constant function with the period 10 with the mean β_0 and lower and higher values 0.55 and 1.33, correspondingly. The common parameters for all cases: $\beta_0 = 0.7$, $\nu_0 = 2.85$, $w = 2$, $\alpha = 0.05$, $\varepsilon = 0$. The corresponding value of bifurcation point (larger of two) is $\nu_2 = 3.246$, and the period of oscillations corresponding to the constant β_0 is 6.7.

factor into the autocatalytic term of the Merkin-Needham-Scott version of the Selkov system. To the analysis of control parameter influence, we reduced the considered system to the generalized Rayleigh equation. Such a form has allowed us to argue that the frequency of oscillation decreasing with the temperature growth is mainly determined by the autocatalytic term. This representation could be used also for further analysis of stages in complicated cascades of chemical and biochemical reactions, where a temperature compensation is detected [9,18]. Furthermore, the mathematical form can allow to plan experiments on nontemperature, say, chemical, regulation of enzyme activity [19] and to explain their results.

At the same time, the slow catalyzed Merkin-Needham-Scott term could be considered as a constant and provides two

main features: (i) the damping of oscillations via the Hopf bifurcation and (ii) the deviation from Arrhenius law in the range of high temperatures. The presence of two Hopf bifurcation points in this dynamical system provides the explanation of the shape of experimentally found [6] oscillations. They are determined as a result of sequential crossing of bifurcation point that leads to decaying and sustained oscillations. The second effect has partial confirmation in Ref. [6] but needs more detailed further experiments with reduced error of curve determination.

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- [1] P. Richard, *FEMS Microb. Rev.* **27**, 547557 (2003).
 [2] A. J. Ragauskas *et al.*, *Science* **311**, 484 (2006).
 [3] B. Chance, R. W. Estabrook, and A. Ghosh, *Proc. Natl. Acad. Sci. USA* **51**, 1244 (1964).
 [4] A. Betz and B. Chance, *Arch. Biochem. Biophys.* **109**, 579 (1965).
 [5] J. Das and H.-G. Busse, *J. Biochem.* **97**, 719 (1985).
 [6] T. Mair, C. Warnke, K. Tsuji, and S. C. Müller, *Biophys. J.* **88**, 639 (2005).
 [7] C. Warnke, Master's thesis, Otto-von-Guericke-Universität Magdeburg, Institut für Experimentelle Physik-Abteilung Biophysik (2003).
 [8] P. Ruoff, M. K. Christensen, J. Wolf, and R. Heinrich, *Biophys. Chem.* **106**, 179 (2003).
 [9] S. Sen, S. S. Riaz, and D. S. Ray, *J. Theor. Biol.* **250**, 103 (2008).
 [10] A. Goldbeter and R. Lefever, *Biophys. J.* **12**, 1302 (1972).
 [11] E. Sel'kov, *Eur. J. Biochem.* **4**, 79 (1968).
 [12] A. I. Lavrova, L. Schimansky-Geier, and E. B. Postnikov, *Phys. Rev. E* **79**, 057102 (2009).
 [13] A. I. Lavrova, S. Bagyan, T. Mair, M. J. B. Hauser, and L. Schimansky-Geier, *BioSystems* **97**, 127 (2009).
 [14] J. H. Merkin, D. J. Needham, and S. K. Scott, *Proc. R. Soc. London A* **406**, 299 (1986).
 [15] S. L. Tai, P. Daran-Lapujade, M. A. H. Luttkik, M. C. Walsh, J. A. Diderich, G. C. Krijger, W. M. van Gulik, J. T. Pronk, and J.-M. Daran, *J. Biol. Chem.* **282**, 10243 (2007).
 [16] B. F. Gray and S. K. Scott, *J. Chem. Soc., Faraday Trans. 1* **81**, 1563 (1985).
 [17] A. I. Lavrova, E. B. Postnikov, and Y. M. Romanovsky, *Phys. Usp.* **52**, 1239 (2009).
 [18] K. Rajan and L. F. Abbott, *Phys. Rev. E* **75**, 022902 (2007).
 [19] J. A. Cornish-Bowden, *Principles of Enzyme Kinetics* (Newnes-Butterworth, London, 1976).