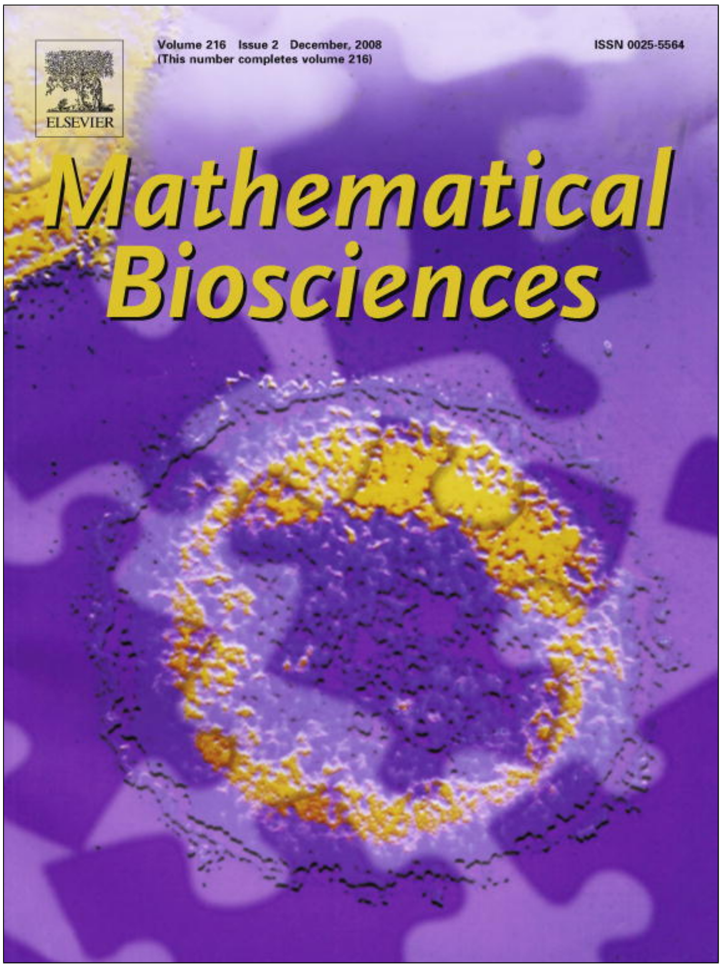
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Yakubovich's oscillatority of circadian oscillations models ☆

Denis V. Efimov *, Alexander L. Fradkov

Control of Complex Systems Laboratory, Institute of Problem of Mechanical Engineering, Bolshoi Avenue, 61, V.O., St-Petersburg 199178, Russia

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ABSTRACT

The testing procedure of Yakubovich's oscillatority property is presented. The procedure is applied for two models of circadian oscillations [J.C. Leloup, A. Goldbeter, A model for circadian rhythms in *Drosophila* incorporating the formation of a complex between the PER and TIM proteins, J. Biol. Rhythms, 13 (1998) 70–87; J.C. Leloup, D. Gonze, A. Goldbeter, Limit cycle models for circadian rhythms based on transcriptional regulation in *Drosophila* and *Neurospora*. J. Biol. Rhythms, 14 (1999) 433–448]. Analytical conditions of these models oscillatority are established and bounds on oscillation amplitude are calculated.

1. Introduction

During recent years an interest in studying more complex behavior of the systems related to oscillatory and chaotic modes has grown significantly. It was founded that important and useful concept for studying irregular oscillations in dynamical systems is "oscillatority" introduced by V.A.Yakubovich in 1973 [14]. Frequency domain conditions for oscillatority were obtained for Lurie systems, composed on linear and nonlinear parts [12,14,15]. Oscillation analysis and design methods for generic nonlinear systems were proposed in [5]. The result of [5] was developed in [6] for nonlinear time delay systems. In [6] the proposed results were applied to several biological systems, which models can be described by nonlinear dynamical equations with delays. Among them the model of circadian rhythms in *Drosophila* from works [8,9] was analyzed. The considered model from [8] has dimension of five. In work [10] more detailed model of circadian oscillations was proposed (with dimension 10), that incorporates the formation of a complex between the PER and TIM proteins. In paper [11] it was noted that circadian oscillations in *Drosophila* and *Neurospora* are closely related by the nature of the feedback loop that governs circadian rhythmicity, even if they differ by the identity of the molecules involved in the regulatory circuit. The simple model of circadian oscillation in *Neurospora* was presented in [11] (with dimension 3).

In this paper the theory developed in [5,6] is applied to the models of circadian oscillations in *Drosophila* and *Neurospora* from papers [10] and [11] to derive conditions of oscillations arising in the systems. This topic of research dealing with conditions of oscillatority of various circadian rhythms models is very popular in the last years [16–19] (just to mention the latest papers). Mainly the researches in this field are oriented on developing conditions of *periodical* oscillations existence that results to rather complex and local analysis of the models. The concept of Yakubovich's oscillatority covers any types of irregular oscillations as well as periodical ones (without distinguishing the type of periodicity of oscillating modes). Such relaxation allows one to simplify the testing conditions, additionally, the conditions provide the restrictions on all admissible values of parameters ensuring oscillatority for the model (in contrast with bifurcation approach [16], where existence of oscillations are guaranteed only locally in the vicinity of bifurcation point, while values of parameters of real biological processes can be far beyond the bifurcation).

In the following section some definitions and notations from [5] are introduced and the procedure for oscillatority property establishing is formulated. In section 3 the model of circadian oscillations in *Drosophila* from [11] is considered. In section 4 the complex model of circadian rhythms in *Drosophila* from [10] is analyzed.

2. Preliminaries

Let us consider the following model of nonlinear dynamical system:

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \tag{1}$$

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* Corresponding author. Present address: Montefiore Inst., B28 Université de Liège, 4000, Belgium.

E-mail addresses: efde@mail.ru (D.V. Efimov), alf@control.ipme.ru (A.L. Fradkov).

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where $\mathbf{x} \in R^n$ is the state space vector; $\mathbf{f}$ is locally Lipschitz continuous function on R^n, $\mathbf{f}(0) = 0$. Solution $\mathbf{x}(\mathbf{x}_0, t)$ of the system (1) with initial condition $\mathbf{x}_0 \in R^n$ is defined at the least locally for $t \leqslant T$ (further we will simply write $\mathbf{x}(t)$ if initial conditions are clear from the context). If $T = +\infty$ for all initial conditions, then such system is called forward complete.

As usual, function $\rho: R_+ \to R_+$ belongs to class K, if it is strictly increasing and $\rho(0) = 0; \rho \in K_\infty$ if $\rho \in K$ and $\rho(s) \to \infty$ for $s \to \infty; R_+ = \{\tau \in R: \tau \geqslant 0\}$. Notation $DV(\mathbf{x})\mathbf{F}(\cdot)$ stands for directional derivative of function V with respect to vector field $\mathbf{F}$ if function V is differentiable and for Dini derivative in the direction of $\mathbf{F}$

$$DV(\mathbf{x})\mathbf{F}(\cdot) = \lim_{t \to 0^+} \inf \frac{V(\mathbf{x} + t\mathbf{F}(\cdot)) - V(\mathbf{x})}{t}$$

if function V is Lipschitz continuous.

Definition 1 [5]. Solution $\mathbf{x}(\mathbf{x}_0, t)$ with $\mathbf{x}_0 \in R^n$ of system (1) is called $[\pi^-, \pi^+]$-oscillation with respect to output $\psi = \eta(\mathbf{x})$ (where $\eta: R^n \to R$ is a continuous monotonous with respect to all arguments function) if the solution is defined for all $t \geqslant 0$ and

$$\underline{\lim}_{t \to +\infty} \psi(t) = \pi^-; \overline{\lim}_{t \to +\infty} \psi(t) = \pi^+; -\infty < \pi^- < \pi^+ < +\infty.$$

Solution $\mathbf{x}(\mathbf{x}_0, t)$ with $\mathbf{x}_0 \in R^n$ of system (1) is called **oscillating**, if there exist some output ψ and constants π^-, π^+ such, that $\mathbf{x}(\mathbf{x}_0, t)$ is $[\pi^-, \pi^+]$-oscillation with respect to the output ψ. Forward complete system (1) is called **oscillatory**, if for almost all $\mathbf{x}_0 \in R^n$ solutions of the system $\mathbf{x}(\mathbf{x}_0, t)$ are oscillating. Oscillatory system (1) is called **uniformly oscillatory**, if for almost all $\mathbf{x}_0 \in R^n$ for corresponding solutions $\mathbf{x}(\mathbf{x}_0, t)$ there exist output ψ and constants π^-, π^+ non-depending on initial conditions.

Note that term "almost all solutions" is used to emphasize that generally system (1) has a nonempty set of equilibrium points, thus, there exists a set of initial conditions with zero measure such, that corresponding solutions are not oscillations. It is worth to stress, that constants π^- and π^+ are exact asymptotic bounds for output ψ. Conditions of oscillation existence in the system are summarized in the following theorem.

Theorem 1 [5]. *Let system (1) have two continuous and locally Lipschitz Lyapunov functions V_1 and V_2 satisfying for all $\mathbf{x} \in R^n$ and $t \in R_+$ inequalities:*

$$\upsilon_1(|\mathbf{x}|) \leqslant V_1(\mathbf{x}, t) \leqslant \upsilon_2(|\mathbf{x}|), \upsilon_3(|\mathbf{x}|) \leqslant V_2(\mathbf{x}, t) \leqslant \upsilon_4(|\mathbf{x}|),$$

for $\upsilon_1, \upsilon_2, \upsilon_3, \upsilon_4 \in K_\infty$ and

$$\partial V_1/\partial t + DV_1(\mathbf{x}, t)\mathbf{f}(\mathbf{x}) > 0 \text{ for } 0 < |\mathbf{x}| < X_1 \text{ and } \mathbf{x} \notin \Xi;$$

$$\partial V_2/\partial t + DV_2(\mathbf{x}, t)\mathbf{f}(\mathbf{x}) < 0 \text{ for } |\mathbf{x}| > X_2 \text{ and } \mathbf{x} \notin \Xi,$$

$$X_1 < \upsilon_1^{-1} \circ \upsilon_2 \circ \upsilon_3^{-1} \circ \upsilon_4(X_2),$$

where $\Xi \subset R^n$ is a set with zero Lebesgue measure, and $\Omega \cap \Xi$ is empty set, $\Omega = \{\mathbf{x} : \upsilon_2^{-1} \circ \upsilon_1(X_1) < |\mathbf{x}| < \upsilon_3^{-1} \circ \upsilon_4(X_2)\}$. Then the system is oscillatory.

Note, that the set Ω determines lower bound for value of π^- and upper bound for value of π^+.

Like in [15] one can consider Lyapunov function for linearized near the origin system (1) as a function V_1 to prove local instability of the system solutions. Instead of existence of Lyapunov function V_2 one can require just boundedness of the system solution $\mathbf{x}(t)$ with known upper bound. It can be obtained using another approach not dealing with time derivative of Lyapunov function analysis. In this case Theorem 1 transforms into Theorem 3.4 from [7].

Conditions of above theorem are rather general and define the class of systems, which oscillatory behavior can be investigated by the approach. Namely systems, which have in state space attracting compact set containing oscillatory movements of the systems. For such systems Theorem 1 gives the useful tool for testing oscillating behavior and obtaining estimates for the amplitude of oscillations. It is possible to show that for a subclass of uniformly oscillating systems proposed conditions are also necessary.

Theorem 2 [4]. *Let system (1) be uniformly oscillatory with respect to the output $\psi = \eta(\mathbf{x})$ (where $\eta: R^n \to R$ is a continuous monotonous with respect to all arguments function), and for all $\mathbf{x} \in R^n$ the following relations are satisfied:*

$$\chi_1(|\mathbf{x}|) \leqslant \eta(\mathbf{x}) \leqslant \chi_2(|\mathbf{x}|), \chi_1, \chi_2 \in K_\infty;$$

the set of initial conditions for which system is not oscillating consists in just one point $\Xi = \{\mathbf{x}: \mathbf{x} = 0\}$. Then there exist two continuous and locally Lipschitz Lyapunov functions $V_1: R^{n+1} \to R_+$ and $V_2: R^{n+1} \to R_+$ such, that for all $\mathbf{x} \in R^n$ and $t \in R_+$ inequalities hold:

$$\upsilon_1(|\mathbf{x}|) \leqslant V_1(\mathbf{x}, t) \leqslant \upsilon_2(|\mathbf{x}|),$$

$$\upsilon_3(|\mathbf{x}|) \leqslant V_2(\mathbf{x}, t) \leqslant \upsilon_4(|\mathbf{x}|), \upsilon_1, \upsilon_2, \upsilon_3, \upsilon_4 \in K_\infty;$$

$$\partial V_1/\partial t + DV_1(\mathbf{x}, t)\mathbf{f}(\mathbf{x}) > 0 \text{ for } 0 < |\mathbf{x}| < \chi_2^{-1}(\pi^-);$$

$$\partial V_2/\partial t + DV_2(\mathbf{x}, t)\mathbf{f}(\mathbf{x}) < 0 \text{ for } |\mathbf{x}| > \chi_1^{-1}(\pi^+).$$

For the uniformly oscillatory systems with single equilibrium point at the origin Theorems 1 and 2 give necessary and sufficient conditions of oscillations existence. According to the results of works [8–11] the circadian rhythms in *Drosophila* and *Neurospora* are the nice examples of uniformly oscillating systems. In this case application of proposed in Theorems 1 and 2 theory to the circadian oscillation models is natural for deriving conditions of oscillations existence. That is more expressions for time derivatives of Lyapunov functions V_1 and V_2 can provide *analytical* parametric conditions for oscillations existence.

Finally, let us describe the testing procedure of oscillatority property presence in dynamical nonlinear systems:

(1) calculation of *equilibrium points coordinates*;
(2) determining *boundedness of the system trajectories property* (using function V_2 or applying another approach);
(3) confirmation of *local instability property in an equilibrium* (applying function V_1 or using the first approximation of the system dynamics in the equilibrium);
(4) the form of set Ω calculation and verification of the *equilibrium points absence* in that set.

If all four steps are successfully passed, then the system is oscillatory in the sense of Yakubovich (Definition 1). Let us apply the above procedure to circadian oscillations models in *Drosophila* and *Neurospora*.

3. Circadian oscillations in *Neurospora*

Following [11] let us consider the following model of the oscillations:

$$\dot{M} = \upsilon_s \frac{K_I^n}{K_I^n + F_N^n} - \upsilon_m \frac{M}{K_m + M}; \tag{2}$$

$$\dot{F}_c = k_s M - \upsilon_d \frac{F_c}{K_d + F_c} - k_1 F_c + k_2 F_N; \tag{3}$$

$$\dot{F}_N = k_1 F_c - k_2 F_N, \tag{4}$$

where variables M, F_c and F_N denote, respectively, the concentrations (defined with respect to the total cell volume) of the *frq* mRNA and of the cytosolic and nuclear forms of FRQ.

According to proposed procedure let us start with coordinates of equilibrium calculation for system (2)–(4). Equating to the zero the right-hand side of the system we obtain the following system of nonlinear equations:

$$F_c^0 = k_2 k_1^{-1} F_N^0; \quad M^0 = \frac{v_d k_2 F_N^0}{k_s (K_d k_1 + k_2 F_N^0)}; \quad v_s \frac{K_I^n}{K_I^n + (F_N^0)^n} = v_m \frac{M^0}{K_m + M^0}, \tag{5}$$

where M^0, F_c^0, F_N^0 are coordinates of possible equilibriums. It is clear that for any positive values of the system (2)–(4) parameters the first two equations in Eq. (5) have the single positive solutions. The third equation also admits only single positive solution since the function on the left-hand side is strictly decreasing to zero, while the function on the right-hand side is strictly increasing from zero. Thus, the system has the single equilibrium with positive coordinates (strictly bigger than zero) for positive values of the parameters. For $n \leqslant 3$ it is possible to analytically calculate the values of M^0, F_c^0, F_N^0 as functions of the system parameters, for $n > 3$ only numerical solution is possible in generic case.

As the second step let us base the global boundedness of the system trajectories property using the following propositions.

Proposition 1. *Let $v_s \geqslant v_m$. Then there exists $\delta \in (0,1)$ such, that if for some $t_0 > 0$ it holds that*

$$F_N(t_0) \geqslant \varepsilon, F_c(t_0) \geqslant k_2 k_1^{-1} \varepsilon,$$
$$M(t_0) \geqslant 2\frac{v_d}{k_s}, \varepsilon = K_I \sqrt[n]{\frac{v_s}{v_m}\left(1 + K_m \frac{k_s}{\delta v_d}\right) - 1},$$

then there exists time instant $t_1 \geqslant t_0$ such, that

$$F_N(t) \leqslant \varepsilon, F_c(t) \leqslant k_2 k_1^{-1} \varepsilon, M(t) \leqslant 2\frac{v_d}{k_s} \textit{for all } t \geqslant t_1.$$

Note that the case $v_s < v_m$ can be considered in the same way as it was analyzed for the five order model in paper [1].

As the third step let us investigate the conditions of the equilibrium instability using the first approximation of the system near the equilibrium:

$$\mathbf{x} = \mathbf{A}(M^0, F_c^0, F_N^0)\mathbf{x}, \mathbf{A}(M^0, F_c^0, F_N^0) = \begin{bmatrix} -v_m \frac{K_m}{(K_m+M^0)^2} & 0 & \frac{-v_s (K_I F_N^0)^n}{(K_I^n + (F_N^0)^n)^2} \frac{n}{F_N^0} \\ k_s & \frac{-v_d K_d}{(K_d + F_c^0)^2} - k_1 & k_2 \\ 0 & k_1 & -k_2 \end{bmatrix}, \tag{6}$$

where $\mathbf{x} = (\delta M, \delta F_c, \delta F_N)^T$ is vector of the system state deviations from the equilibrium and $\mathbf{A}$ is the first approximation matrix dependent on the model parameters. The characteristic polynomial of the matrix $\mathbf{A}$ has form

$$p(s) = s^3 + a_1 s^2 + a_2 s + a_3,$$
$$\begin{pmatrix} a_3 \\ a_2 \\ a_1 \end{pmatrix} = \begin{pmatrix} \frac{K_m k_2 v_m}{(K_m+M_0)^2}\left(2k_1 + \frac{K_d v_d}{(F_c^0+K_d)^2}\right) - \frac{k_1 k_s n v_s (F_N^0 K_I)^n}{F_N^0[(F_N^0)^n + K_I^n]^2} \\ \left(k_1 + \frac{K_d v_d}{(F_c^0+K_d)^2}\right)\left(k_2 + \frac{K_m v_m}{(K_m+M_0)^2}\right) + k_1 k_2 + \frac{K_m k_2 v_m}{(K_m+M_0)^2} \\ k_1 + k_2 + \frac{K_d v_d}{(F_c^0+K_d)^2} + \frac{K_m v_m}{(K_m+M_0)^2} \end{pmatrix}.$$

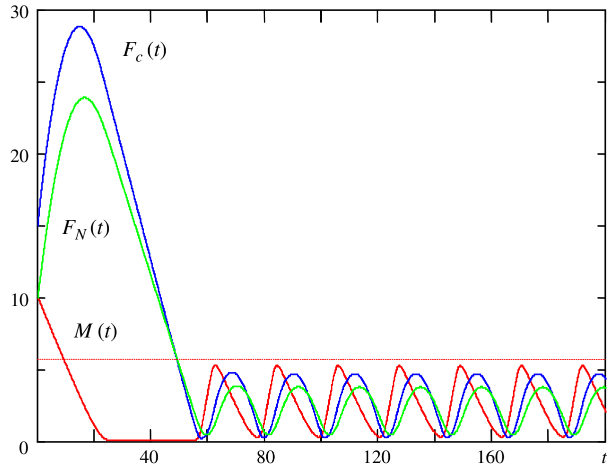

Fig. 1. Oscillations in model (2)–(4).

Applying Hurwitz criterion to the third order system (6) we obtain that, if the following inequalities are satisfied, then the matrix $\mathbf{A}$ has all eigen-values with negative real parts:

$$a_1 > 0, \quad a_1 a_2 - a_3 > 0, \quad a_3 > 0.$$

For any positive values of the parameters we have $a_1 > 0$, $a_2 > 0$, straightforward calculations show $a_1 a_2 - a_3 > 0$ (opening the brackets we obtain that all items have positive signs), thus the single possibility to lose the stability for Eq. (6) comes from coefficient a_3. The condition $a_3 < 0$ (which ensures for matrix $\mathbf{A}$ the presence of eigen-values with positive real parts) can be rewritten as follows:

$$k_2 v_m K_m [v_d K_d + 2k_1 (F_c^0 + K_d)^2] F_N^0 (K_I^n + (F_N^0)^n)^2 \ll k_1 k_s n v_s (K_I F_N^0)^n (F_c^0 + K_d)^2 (K_m + M_0)^2. \tag{7}$$

Inequality (7) is a function of the system parameters and the equilibrium coordinates F_N^0, F_c^0, M^0, which are the solution of equations (5). For $n \leqslant 3$ equations (5) have analytical solutions, substituting which in Eq. (7) it is possible to obtain system instability condition dependent on the parameters only.

The fourth step is obvious since the system (2)–(4) has only one equilibrium. Thus, the key condition of the system oscillatority is inequality (7). In [11] the model (2)–(4) was considered with the following values of parameters:

$$v_m = 0.505, \quad v_d = 1.4, \quad v_s = 1.6, \quad k_s = 0.5,$$
$$k_1 = 0.5, \quad k_2 = 0.6, \quad K_I = 1, \quad K_m = 0.5, \quad K_d = 0.13, \quad n = 4.$$

For these values system of equations (5) has the solution:

$$M_0 = 2.583, F_c^0 = 1.55, F_N^0 = 1.291,$$

for which inequality (7) is true. Therefore the system with these values of parameters is oscillatory. The results of the system simulation is shown in Fig. 1. The dash line corresponds to obtained in Proposition 1 bounds for oscillations amplitude $2k_s^{-1} v_d$.

4. Circadian oscillations in *Drosophila*

Let us consider the model from paper [10]:

$$\dot{M}_P = v_{sp}\frac{K_{IP}^n}{K_{IP}^n + C_N^n} - v_{mP}\frac{M_P}{K_{mP}+M_P} - k_d M_P; \quad (8)$$

$$\dot{P}_0 = k_{sP}M_P - V_{1P}\frac{P_0}{K_{1P}+P_0} + V_{2P}\frac{P_1}{K_{2P}+P_1} - k_d P_0; \quad (9)$$

$$\dot{P}_1 = V_{1P}\frac{P_0}{K_{1P}+P_0} - V_{2P}\frac{P_1}{K_{2P}+P_1} - -V_{3P}\frac{P_1}{K_{3P}+P_1} + V_{4P}\frac{P_2}{K_{4P}+P_2} - k_d P_1; \quad (10)$$

$$\dot{P}_2 = V_{3P}\frac{P_1}{K_{3P}+P_1} - V_{4P}\frac{P_2}{K_{4P}+P_2} - -k_3 P_2 T_2 + k_4 C - v_{dP}\frac{P_2}{K_{dP}+P_2} - k_d P_2; \quad (11)$$

$$\dot{M}_T = v_{sp}\frac{K_{IT}^n}{K_{IT}^n + C_N^n} - v_{mT}\frac{M_T}{K_{mT}+M_T} - k_d M_T; \quad (12)$$

$$\dot{T}_0 = k_{sT}M_T - V_{1T}\frac{T_0}{K_{1T}+T_0} + V_{2T}\frac{T_1}{K_{2T}+T_1} - k_d T_0; \quad (13)$$

$$\dot{T}_1 = V_{1T}\frac{T_0}{K_{1T}+T_0} - V_{2T}\frac{T_1}{K_{2T}+T_1} - -V_{3T}\frac{T_1}{K_{3T}+T_1} + V_{4T}\frac{T_2}{K_{4T}+T_2} - k_d T_1; \quad (14)$$

$$\dot{T}_2 = V_{3T}\frac{T_1}{K_{3T}+T_1} - V_{4T}\frac{T_2}{K_{4T}+T_2} - -k_3 P_2 T_2 + k_4 C - v_{dT}\frac{T_2}{K_{dT}+T_2} - k_d T_2; \quad (15)$$

$$\dot{C} = k_3 P_2 T_2 - k_4 C - k_1 C + k_2 C_N - k_{dC} C; \quad (16)$$

$$\dot{C}_N = k_1 C - k_2 C_N - k_{dN} C_N, \quad (17)$$

where M_P is cytosolic concentration of *per* mRNA; P_0, P_1, P_2 are unphosphorylated, monophosphorylated and bisphosphorylated concentrations of PER protein correspondingly; M_T is cytosolic concentration of *tim* mRNA; T_0, T_1, T_2 are unphosphorylated, monophosphorylated and bisphosphorylated concentrations of TIM protein correspondingly; C is PER-TIM complex concentration and C_N is nuclear form of PER-TIM complex. As in work [10] we will consider the following values of model (8)–(17) parameters:

$$K_{IP} = K_{IT} = v_{sT} = v_{sP} = 1, \quad v_{mP} = v_{mT} = 0.7,$$
$$K_{dP} = K_{dT} = K_{mP} = K_{mT} = 0.2, \quad k_{sP} = k_{sT} = 0.9,$$
$$v_{dP} = v_{dT} = 2, \quad V_{1P} = V_{1T} = V_{3P} = V_{3T} = 8,$$
$$K_{1P} = K_{1T} = K_{2P} = K_{2T} = K_{3P} = K_{3T} = K_{4P} = K_{4T} = 2,$$
$$k_1 = 0.6, \quad k_2 = 0.2, \quad k_3 = 1.2, \quad k_4 = 0.6, \quad n = 4,$$
$$k_d = k_{dC} = k_{dN} = 0.01, \quad V_{2P} = V_{2T} = V_{4P} = V_{4T} = 1.$$

Let us start with equilibriums number and their coordinates calculations. As in the model (2)–(4) for $n = 4$ only numerical solutions of this problem is possible which shows that the system has the single equilibrium with coordinates:

$$M_P^0 = 1.513, \quad P_0^0 = 0.48, \quad P_1^0 = 0.469, \quad P_2^0 = 0.403,$$
$$M_T^0 = 1.513, \quad T_0^0 = 0.48, \quad T_1^0 = 0.469, \quad T_2^0 = 0.403,$$
$$C^0 = 0.305, \quad C_N^0 = 0.872.$$

As the second step to prove boundedness of the system (8)–(17) trajectories it is possible to use the following Lyapunov function:

$$V_2 = P_t + T_t + 2\frac{k_{sP}}{k_d}M_P + 2\frac{k_{sT}}{k_d}M_T,$$
$$P_t = P_0 + P_1 + P_2 + C + C_N, T_t = T_0 + T_1 + T_2 + C + C_N,$$

where P_t and T_t are total concentrations of PER and TIM proteins correspondingly. Time derivative of function V_2 admits the following upper estimate:

$$\dot{V}_2 \leqslant -0.5\kappa V_2 + 2\frac{k_{sP}}{k_d}v_{sP} + 2\frac{k_{sT}}{k_d}v_{sT}, \kappa = \min\{k_d, k_{dC}\},$$

which implies global boundedness of the system trajectories.

For the third step to establish local instability of the system equilibrium we use the first approximation of the system dynamics near the equilibrium. For the given values of the system parameters the matrix of the first approximation has two complex conjugate eigen-values with positive real parts, that confirms local instability property of the equilibrium (we exclude the expressions of the matrix and its eigen-values for brevity of presentation).

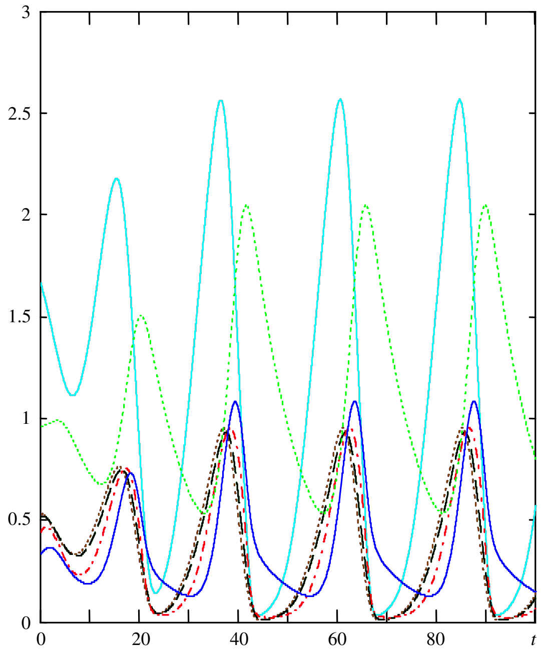

Fig. 2. Oscillations in model (8)–(17).

Since the system has only one equilibrium the fourth step in this example is redundant and the system is oscillatory. The result of the system computer simulation is shown in Fig. 2.

5. Conclusion

The proposed in papers [5,6] conditions of Yakubovich's oscillatority and presented here procedure of these conditions approving can be applied for wide range of biological systems (see examples in those papers and above). The approach also can be applied in adjacent areas like chemistry. The main advance of the solution comparing it with other approaches [2,3,13] consists in simplicity of its application for generic class of nonlinear systems. As a side of results the bounds on oscillation amplitude can be calculated. Oscillatority in the sense of Yakubovich covers wide range of nonlinear oscillation behavior (from periodical to chaotic oscillations). The conditions are necessary and sufficient for some classes of oscillating systems like models of circadian oscillations considered in the paper.

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