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Yakubovich's oscillatority of circadian oscillations models ☆

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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:

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

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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:

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

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

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