МАТЕМАТИЧКИ ВЕСНИК
49 (1997), 115–122

UDK 517.938
оригинални научни рад
research paper

# A TIME-DEPENDENT BIOCHEMICAL SYSTEM

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**Abstract.** Following Selgrade [1] we consider a model of a positive feedback biochemical system in a periodic environment. Results of existence, uniqueness and stability for solutions of such systems are presented.

## 1. A positive feedback biochemical system

We consider the system

$$\left| \begin{aligned} &\dot{x}_1 = f(x_n) - \alpha_1 x_1 \\ &\dot{x}_i = x_{i-1} - \alpha_i x_i, \quad 2 \le i \le n, \end{aligned} \right. \tag{1}$$

where the coefficients $\alpha_i$, $1 \le i \le n$, are positive. The dot above means a derivative with respect to time $t$. Dynamical systems of this type describe some enzyme biochemical processes. For more details on the interpretation of (1) one may see Selgrade [1] and the references therein. In addition we assume that the model reflects $\Omega$-periodic influence of the environment. More precisely, we will assume that all the coefficients $\alpha_i$ are $\Omega$-periodic time-dependent. Since all the variables $x_i$ size up real quantities it is natural to look only for positive solutions of (1). Our approach to consider periodic nonautonomous modifications of classical dynamical systems is similar to the one employed in the papers [2], [3], [4] and [5].

For the sake of brevity we will reduce our considerations mostly to the case $n = 3$ since it illustrates entirely the general one. So, we consider the system

$$\left| \begin{aligned} &\dot{x} = f(z) - \alpha x \\ &\dot{y} = x - \beta y \\ &\dot{z} = y - \gamma z \end{aligned} \right. \tag{2}$$

where $\alpha$, $\beta$ and $\gamma$ are $\Omega$-periodic functions. We will look for strictly positive $\Omega$-periodic solutions of (2) in accordance with the natural significance of this system. For any $\Omega$-periodic function $g$ we denote

$$[g] = \frac{1}{\Omega} \int_0^{\Omega} g(\tau)\, d\tau \quad \text{and} \quad \{g\} = g(t) - [g].$$

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*AMS Subject Classification*: 92 C 45

Let

$$D_\alpha^- = \min_{0\le t,s\le\Omega} e^{-\int_{t-s}^{t}\{\alpha\}(\tau)d\tau}, \quad D_\alpha^+ = \max_{0\le t,s\le\Omega} e^{-\int_{t-s}^{t}\{\alpha\}(\tau)d\tau};$$

$$D_\beta^- = \min_{0\le t,s\le\Omega} e^{-\int_{t-s}^{t}\{\beta\}(\tau)d\tau}, \quad D_\beta^+ = \max_{0\le t,s\le\Omega} e^{-\int_{t-s}^{t}\{\beta\}(\tau)d\tau};$$

$$D_\gamma^- = \min_{0\le t,s\le\Omega} e^{-\int_{t-s}^{t}\{\gamma\}(\tau)d\tau}, \quad D_\gamma^+ = \max_{0\le t,s\le\Omega} e^{-\int_{t-s}^{t}\{\gamma\}(\tau)d\tau}.$$

THEOREM 1. *Suppose that the function $f:[0,\infty)\to[0,\infty)$ is continuous and that $\alpha$, $\beta$ and $\gamma$ are continuous $\Omega$-periodic functions with $[\alpha]>0$, $[\beta]>0$ and $[\gamma]>0$. Let there exist constants $B>0$ and $k_\infty>0$ for which*

$$f(u)\le k_\infty u \quad \text{for} \quad u\ge B \quad \text{and} \quad k_\infty < \frac{[\alpha][\beta][\gamma]}{D_\alpha^+ D_\beta^+ D_\gamma^+}. \tag{3}$$

*Let also, in the case $f(0)=0$, there exist constants $A>0$ and $k_0$ such that*

$$f(u)\ge k_0 u \quad \text{for} \quad 0<u\le A \quad \text{and} \quad k_0 > \frac{[\alpha][\beta][\gamma]}{D_\alpha^- D_\beta^- D_\gamma^-}. \tag{4}$$

*Then system (2) has strictly positive $\Omega$-periodic solutions.*

THEOREM 2. *Suppose the conditions of Theorem 1 hold and $f\in C^2(0,\infty)$. Let in addition $f'(z)\ge 0$ and $f''(z)<0$ for every $z>0$. Then system (2) has just one strictly positive $\Omega$-periodic solution.*

These results show the sensibility of the system (2); in other words that it reacts to a periodic environment or to an outside periodic influence.

REMARK 1. By the nature of the proofs that will be given later on, one can immediately see that completely analogous results are valid for system (1).

EXAMPLE 1. Consider the Griffith 3-dimensional model (see [1]) for which

$$f(z)=\frac{z^m}{1+z^m}.$$

When $0<m<1$, all the conditions of the above theorems are satisfied for all the positive values of $[\alpha]$, $[\beta]$ and $[\gamma]$ since

$$\lim_{z\to 0}\frac{f(z)}{z}=\infty \quad \text{and} \quad \lim_{z\to\infty}\frac{f(z)}{z}=0.$$

When $m=1$ we have $k_0=1$ and $\lim_{z\to\infty} f(z)/z=0$. In this case the conditions of Theorems 1–2 turn out to be

$$\frac{[\alpha][\beta][\gamma]}{D_\alpha^- D_\beta^- D_\gamma^-}<1.$$

EXAMPLE 2. Consider the Othmer-Tyson model (see [1]) for which

$$f(z)=\frac{1+z^m}{K+z^m}, \quad K>1.$$

For every $0 < m \leq 1$, all the conditions of our theorems (see also the remark above) are satisfied for all the positive values of $[\alpha]$, $[\beta]$ and $[\gamma]$ since $f(0) \neq 0$ and $\lim_{z\to\infty} f(z)/z = 0$.

REMARK 2. Suppose one requires $f$ to be time-dependent and $\Omega$-periodic, i.e. $f = f(t,u)$ and $f(t,u) \equiv f(t+\Omega,u)$. Then the conditions for $f$ in (3) and (4) have to be replaced with $\max_t f(t,u) \leq k_\infty u$ and $\min_t f(t,u) \geq k_0 u$.

The proofs of the theorems are based on the theory of completely continuous and positive vector fields presented by Krasnosel'skii in [6] and [7].

## 2. A numerical example

Here we will present an illustrative example for the case $n = 2$. Consider the system

$$\left|\begin{aligned} \dot{x} &= \frac{\sqrt{y}}{1+\sqrt{y}} - x \\ \dot{y} &= x - \cos^2 t\, y \end{aligned}\right.$$

that essentially satisfies all the requirements of Theorems 1–2. A $\pi$-periodic solution is found near the initial data $x(0) = 0.5124$ and $y(0) = 0.9631$. The calculations give

$$|x(0) - x(\pi)| + |y(0) - y(\pi)| < 0.000046.$$

In Fig. 1 below its phase form is shown.

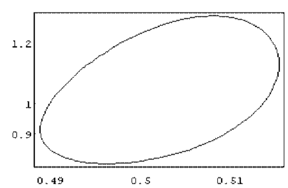


Fig. 1

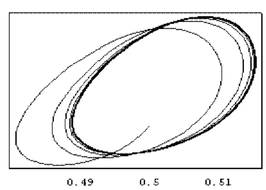


Fig.2

In Fig. 2 the phase curve that begins at the point $(0.5, 0.9)$ is traced for $t \in [0, 33\pi]$. Obviously this curve comes near to the periodic one. This solution seems to be stable.

## 3. Proof of Theorem 1

One can easily check out the validity of

LEMMA 1. *Let $\epsilon$ and $\phi$ be continuous $\Omega$-periodic functions and $[\epsilon] > 0$. Then there exists a unique $\Omega$-periodic solution to the equation*

$$\dot{x} = -\epsilon(t)x + \phi(t)$$

*for which we have the representation*

$$x(t)=\int_0^\Omega \frac{e^{-[\epsilon]s}}{1-e^{-[\epsilon]\Omega}}e^{-\int_{t-s}^t\{\epsilon\}(\tau)d\tau}\phi(t-s)\,ds.$$

By Lemma 1, the problem for the $\Omega$-periodic solutions of (2) reduces to the problem for the solutions to the following operator system

$$\begin{aligned}
x(t)&=\int_0^\Omega \frac{e^{-[\alpha]s}}{1-e^{-[\alpha]\Omega}}e^{-\int_{t-s}^t\{\alpha\}(\tau)d\tau}f(z(t-s))\,ds,\\
y(t)&=\int_0^\Omega \frac{e^{-[\beta]s}}{1-e^{-[\beta]\Omega}}e^{-\int_{t-s}^t\{\beta\}(\tau)d\tau}x(t-s)\,ds,\\
z(t)&=\int_0^\Omega \frac{e^{-[\gamma]s}}{1-e^{-[\gamma]\Omega}}e^{-\int_{t-s}^t\{\gamma\}(\tau)d\tau}y(t-s)\,ds.
\end{aligned}$$

Denote

$$\begin{aligned}
\mathcal{G}_\alpha(\Theta)(t)&=\int_0^\Omega \frac{e^{-[\alpha]s}}{1-e^{-[\alpha]\Omega}}e^{-\int_{t-s}^t\{\alpha\}(\tau)d\tau}\Theta(t-s)\,ds,\\
\mathcal{G}_\beta(\Theta)(t)&=\int_0^\Omega \frac{e^{-[\beta]s}}{1-e^{-[\beta]\Omega}}e^{-\int_{t-s}^t\{\beta\}(\tau)d\tau}\Theta(t-s)\,ds,\\
\mathcal{G}_\gamma(\Theta)(t)&=\int_0^\Omega \frac{e^{-[\gamma]s}}{1-e^{-[\gamma]\Omega}}e^{-\int_{t-s}^t\{\gamma\}(\tau)d\tau}\Theta(t-s)\,ds.
\end{aligned}$$

Let $C(\Omega)$ be the Banach space of the real continuous $\Omega$-periodic functions defined over the whole axes and provided with the usual maximum norm. Let also $C_+(\Omega)\subset C(\Omega)$ be the cone of the nonnegative functions. The linear operators $\mathcal{G}_\alpha$, $\mathcal{G}_\beta$ and $\mathcal{G}_\gamma$ are completely continuous in $C(\Omega)$ and positive with respect to $C_+(\Omega)$. It is not difficult to see that for $\Theta\in C_+(\Omega)$ we have

$$\begin{aligned}
\min_t \mathcal{G}_\alpha\Theta &\geq \frac{D_\alpha^-}{D_\alpha^+}e^{-[\alpha]\Omega}\max_t \mathcal{G}_\alpha\Theta,\\
\min_t \mathcal{G}_\beta\Theta &\geq \frac{D_\beta^-}{D_\beta^+}e^{-[\beta]\Omega}\max_t \mathcal{G}_\beta\Theta,\\
\min_t \mathcal{G}_\gamma\Theta &\geq \frac{D_\gamma^-}{D_\gamma^+}e^{-[\gamma]\Omega}\max_t \mathcal{G}_\gamma\Theta,
\end{aligned}$$

as well as

$$\begin{aligned}
D_\alpha^-\frac{[\Theta]}{[\alpha]} &\leq \Big[\mathcal{G}_\alpha\Theta\Big]\leq D_\alpha^+\frac{[\Theta]}{[\alpha]},\\
D_\beta^-\frac{[\Theta]}{[\beta]} &\leq \Big[\mathcal{G}_\beta\Theta\Big]\leq D_\beta^+\frac{[\Theta]}{[\beta]},\\
D_\gamma^-\frac{[\Theta]}{[\gamma]} &\leq \Big[\mathcal{G}_\gamma\Theta\Big]\leq D_\gamma^+\frac{[\Theta]}{[\gamma]}.
\end{aligned}$$

Similar estimates one may find in Krasnosel'skii, Lifshic and Sobolev [6].

At this point the problem for $\Omega$-periodic solutions of (2) turns into the following operator form

$$\left|\begin{array}{l} x = \mathcal{G}_\alpha f(z) \\ y = \mathcal{G}_\beta x \\ z = \mathcal{G}_\gamma y \end{array}\right.$$

which is equivalent to one scalar operator equation $z = \mathcal{G}_\gamma \mathcal{G}_\beta \mathcal{G}_\alpha f(z)$. Denote $\mathcal{G} = \mathcal{G}_\gamma \mathcal{G}_\beta \mathcal{G}_\alpha$. Obviously $\mathcal{G}$ is completely continuous in $C(\Omega)$ and positive with respect to $C_+^\circ(\Omega)$. Then our problem gets the form

$$z = \mathcal{G} f(z), \quad z \in C_+^\circ(\Omega), \quad z \not\equiv 0,$$

where $C_+^\circ(\Omega) \subset C_+(\Omega)$ is the subcone for which

$$\min_t z(t) \geq \frac{D_\gamma^-}{D_\gamma^+} e^{-[\gamma]\Omega} \max_t z(t).$$

In order to prove Theorem 1 we will use the next theorem that is extracted from Krasnosel'skii and Zabrejko [7] in a form convenient for us.

Theorem 3. [7] *Let $Y$ be a real Banach space with a cone $Q$ and $L\colon Y \to Y$ be a completely continuous and positive with respect to $Q$ operator. Then the following propositions are valid.*

(i) *Let $L(0) = 0$ and suppose that for every sufficiently small $r > 0$ there is no $y \in Q$ for which*

$$\|y\|_Y = r \quad \text{and} \quad y \overset{\circ}{\geq} L(y).$$

*Then* $\operatorname{ind}(0, L; Q) = 0$.

(ii) *Suppose that for every sufficiently large $R$ there is no $y \in Q$ for which*

$$\|y\|_Y = R \quad \text{and} \quad y \overset{\circ}{\leq} L(y).$$

*Then* $\operatorname{ind}(\infty, L; Q) = 1$.

(iii) *Let $L(0) = 0$ and suppose that* $\operatorname{ind}(0, L; Q) \neq \operatorname{ind}(\infty, L; Q)$. *Then $L$ has nontrivial fixed points in $Q$.*

(iv) *Let $L(0) \neq 0$ and suppose that* $\operatorname{ind}(\infty, L; Q) \neq 0$. *Then $L$ has nontrivial fixed points in $Q$.*

Here $\operatorname{ind}(\cdot, L; Q)$ denotes an index of a point with respect to $L$ and $Q$, which is always supposed to exist. The sign "$\overset{\circ}{\leq}$" denotes the semiordering generated by $Q$.

At first we will find the $\operatorname{ind}(0, \mathcal{G}; C_+^\circ(\Omega))$ in the case $f(0) = 0$. Here we intend to use part (i) of Theorem 3. By a contradiction argument, assume that there exists $\tilde{z} \in C_+^\circ(\Omega)$ for which

$$\tilde{z} \geq \mathcal{G} f(\tilde{z}), \quad 0 < \|\tilde{z}\| \leq A.$$

After integrating over the interval $[0,\Omega]$ one gets the inequality

$$\left[\tilde{z}\right] \geq k_0 \frac{D_\beta^-}{[\beta]}\frac{D_\gamma^-}{[\gamma]}\frac{D_\alpha^-}{[\alpha]}\left[\tilde{z}\right], \quad \left[\tilde{z}\right] > 0,$$

which contradicts condition (4). Then $\operatorname{ind}(0,\mathcal{G};C_+^\circ(\Omega)) = 0$.

Now let us find $\operatorname{ind}(\infty,\mathcal{G};C_+^\circ(\Omega))$. Here we will use part (ii) of Theorem 3. Let $R$ be fixed and sufficiently large so that

$$R\frac{D_\gamma^-}{D_\gamma^+}e^{-[\gamma]\Omega} \geq B.$$

Then $f(z(t)) \leq k_\infty z(t),$, for every $t$ whenever $z \in C_+^\circ(\Omega)$ and $\|z\| \geq R$ because

$$\min_t z \geq \frac{D_\gamma^-}{D_\gamma^+}Re^{-[\gamma]\Omega} \geq B.$$

By a contradiction argument, assume that there exists $\tilde{z} \in C_+^\circ(\Omega)$ for which $\tilde{z} \leq \mathcal{G}(\tilde{z})$, $\|\tilde{z}\| \geq R$. Integrating over $[0,\Omega]$ one gets

$$\left[\tilde{z}\right] \leq k_\infty \frac{D_\beta^+}{[\beta]}\frac{D_\gamma^+}{[\gamma]}\frac{D_\alpha^+}{[\alpha]}\left[\tilde{z}\right], \quad \left[\tilde{z}\right] > 0,$$

which contradicts condition (3). Therefore $\operatorname{ind}(\infty,\mathcal{G};C_+^\circ(\Omega)) = 1$.

Thus in the case $f(0) = 0$ we have

$$1 = \operatorname{ind}(\infty,\mathcal{G};C_+^\circ(\Omega)) \neq \operatorname{ind}(0,\mathcal{G};C_+^\circ(\Omega)) = 0.$$

Now the parts (iii)–(iv) of Theorem 3 imply that $\mathcal{G}$ has nontrivial fixed points in $C_+^\circ(\Omega)$ independently of whether or not $f(0) = 0$.

## 4. Proof of Theorem 2

One may immediately check out that all the requirements of §46.2[7] are satisfied with respect to our solution operator $\mathcal{G}$. This remark is sufficient for the proof of Theorem 2.

## 5. Stability examination

Here we will prove a simple result to throw some light over this important question. First of all notice that one can immediately find a proof of the following

Lemma 2. *Suppose that the conditions of Theorem 2 hold. Then there exists a unique positive root $\hat{\xi}$ of the equation*

$$f(\xi) = \frac{[\alpha][\beta][\gamma]}{D_\alpha^- D_\beta^- D_\gamma^-}\xi.$$

*Moreover, for every* $\eta$ *with* $0<\eta<\hat{\xi}$ *there exists a constant* $k_\eta$ *for which*

$$f(u)\geq k_\eta u \quad \text{for} \quad 0<u\leq k_\eta \quad \text{and} \quad k_\eta>\frac{[\alpha][\beta][\gamma]}{D_\alpha^- D_\beta^- D_\gamma^-}.$$

By using Lemma 2 one can obtain the following useful corollary.

LEMMA 3. *Suppose the conditions of Theorem* 2 *hold. Then for the positive* $\Omega$*-periodic solution* $(\tilde{x},\tilde{y},\tilde{z})$ *of* (2) *it holds* $\max_t \tilde{z}(t)\geq\hat{\xi}$ *and therefore*

$$\min_t \tilde{z}(t)\geq\frac{D_\gamma^-}{D_\gamma^+}\hat{\xi}e^{-[\gamma]\Omega}.$$

*Proof.* In the case $f(0)=0$ this assertion follows straightforwardly from Lemma 2 and from the way used in the proof of Theorem 1. This approach covers also the case $f(0)\neq 0$ which is easier than the first one. ∎

THEOREM 4. *Suppose that the conditions of Theorem* 2 *hold and let*

$$D=f'\left(\frac{D_\gamma^-}{D_\gamma^+}\hat{\xi}e^{-[\gamma]\Omega}\right).$$

*If*

$$\frac{DD_\alpha^+ D_\beta^+ D_\gamma^+}{[\alpha][\beta][\gamma]}<1,$$

*then the solution existence and uniqueness of which are provided by Theorem* 2 *is locally asymptotically stable.*

*Proof.* Let $(\tilde{x},\tilde{y},\tilde{z})$ be the positive $\Omega$-periodic solution of (2). To obtain stability we will consider the linearization of (2) in a neighborhood of $(\tilde{x},\tilde{y},\tilde{z})$

$$\left|\begin{aligned} \dot{u}&=f'(\tilde{z})w-\alpha u\\ \dot{v}&=u-\beta v\\ \dot{w}&=v-\gamma w\end{aligned}\right. \tag{5}$$

We will show that the trivial solution of (5) is asymptotically stable and this will complete the proof. By a contradiction argument, suppose that the $\Omega$-periodic linear system (5) has a Floquet multiplier $\geq 1$. Notice that the multipliers of (5) are just the eigenvalues of the matrix $\mathcal{Q}(\Omega)$ where $\mathcal{Q}(\cdot)$ is the matrix-solution of (5) with $\mathcal{Q}(0)=\mathcal{I}$. It is not difficult to see that $\mathcal{Q}(\Omega)$ has positive elements. Therefore, its spectral radius is equal to its maximal *real* eigenvalue. Then the Floquet theory says that (5) should have a nontrivial solution of the form $\tilde{u}e^{\mu t}$, $\tilde{v}e^{\mu t}$, $\tilde{w}e^{\mu t}$ with $\Omega$-periodic $\tilde{u}$, $\tilde{v}$, $\tilde{w}$ and with a constant $\mu\geq 0$. In such case, it follows from (5) that

$$\left|\begin{aligned} \dot{\tilde{u}}&=f'(\tilde{z})\tilde{w}-(\alpha+\mu)\tilde{u}\\ \dot{\tilde{v}}&=\tilde{u}-(\beta+\mu)\tilde{v}\\ \dot{\tilde{w}}&=\tilde{v}-(\gamma+\mu)\tilde{w}\end{aligned}\right.$$

which one can reduce to the known operator form

$$\tilde{u} = \mathcal{G}_{\alpha+\mu} f'(\tilde{z})\tilde{w} = \int_0^{\Omega} \frac{e^{-([\alpha]+\mu)s}}{1-e^{-([\alpha]+\mu)\Omega}} e^{-\int_{t-s}^{t}\{\alpha\}(\tau)\,d\tau} f'(\tilde{z}(t-s))\tilde{w}(t-s)\,ds,$$

$$\tilde{v} = \mathcal{G}_{\beta+\mu}\tilde{u} = \int_0^{\Omega} \frac{e^{-([\beta]+\mu)s}}{1-e^{-([\beta]+\mu)\Omega}} e^{-\int_{t-s}^{t}\{\beta\}(\tau)\,d\tau} \tilde{u}(t-s)\,ds,$$

$$\tilde{w} = \mathcal{G}_{\gamma+\mu}\tilde{v} = \int_0^{\Omega} \frac{e^{-([\gamma]+\mu)s}}{1-e^{-([\gamma]+\mu)\Omega}} e^{-\int_{t-s}^{t}\{\gamma\}(\tau)\,d\tau} \tilde{v}(t-s)\,ds.$$

As before the last is equivalent to the scalar equation

$$\tilde{w} = \mathcal{G}_{\gamma+\mu}\mathcal{G}_{\beta+\mu}\mathcal{G}_{\alpha+\mu}\Big(f'(\tilde{z})\tilde{w}\Big). \tag{6}$$

Since $f'$ is decreasing, Lemma 3 gives $f'(\tilde{z}(t)) \le D$, for every $t$. Now (6) leads to the inequality

$$|\tilde{w}(t)| \le D\mathcal{G}_{\gamma+\mu}\mathcal{G}_{\beta+\mu}\mathcal{G}_{\alpha+\mu}\Big(|\tilde{w}(t)|\Big), \quad \text{for every } t.$$

Integrating over $[0,\Omega]$ one obtains

$$\Big[|\tilde{w}|\Big] \le \frac{DD_\alpha^+ D_\beta^+ D_\gamma^+}{([\alpha]+\mu)([\beta]+\mu)([\gamma]+\mu)}\Big[|\tilde{w}|\Big],$$

which implies that

$$\frac{DD_\alpha^+ D_\beta^+ D_\gamma^+}{[\alpha][\beta][\gamma]} \ge 1.$$

The last contradicts the assumption of Theorem 4.

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(received 07.11.1996.)

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