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Steady state in a biological system: global asymptotic stability

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SEZIONE III

(Botanica, zoologia, fisiologia e patologia)

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Biologia matematica. — *Steady state in a biological system: global asymptotic stability.* Nota di MARIA ADELAIDE SNEIDER, presentata (*) dal Socio G. FICHERA.

ABSTRACT. — A suitable Liapunov function is constructed for proving that the unique critical point of a non-linear system of ordinary differential equations, considered in a well determined polyhedron K, is globally asymptotically stable in K.
The analytic problem arises from an investigation concerning a steady state in a particular macromolecular system: the visual system represented by the pigment rhodopsin in the presence of light.

KEY WORDS: Steady state; Global asymptotic stability; Biological system.

RIASSUNTO. — *Stato stazionario in un sistema biologico: stabilità asintotica in grande.* Mediante la costruzione di una opportuna funzione di Liapunov si dimostra che l'unico punto critico relativo ad un sistema differenziale non lineare, considerato in un determinato poliedro K, è globalmente asintoticamente stabile in K. Il problema analitico è originato dallo studio dello stato stazionario di un particolare sistema macromolecolare che interessa il pigmento rodopsina.

In [1] (1) a question is considered regarding the behaviour of the visual system represented by the pigment rhodopsin in the presence of light.

The problem studied in [1], suggested by Jeffries Wyman, is, according to his opinion, of considerable broader interest because of its bearing in other light controlled reactions, as well as in the kinetics of macromolecules generally, especially those of enzymes.

The problem investigated in [1] amounts, from the mathematical point of view, to proving the existence of only one critical point ξ of a certain autonomous nonlinear system of three ordinary differential equations in a well determined polyhedron K of R^3 (2) and to demonstrating the asymptotic stability of ξ.

In [1] the asymptotic stability of ξ has been proved *in the small.* Only by assuming a special hypothesis on the coefficients of the system this asymptotic stability has been proved to hold *globally* in K (see [1]). On the other hand con-

(*) Nella seduta del 20 novembre 1987.
(1) Results in [1] have been presented in [2].
(2) See Sect. 1 of the present paper.

siderations suggested by macromolecular Biology require that the asymptotic stability of ξ should be proved to hold globally in K, without any further assumption.

This problem is the one solved in the present Note.

1. The system of ordinary differential equations considered in [1] is the following:

$$
\begin{aligned}
\dot{x}_1 &= Lc_1^2 - (\varrho_1 + 2Lc_1 + Qc_2)x_1 + (P - 2Lc_1)x_2 - Lc_1x_3 + Lx_1^2 + \\
&\quad + (2L + Q)x_1x_2 + (L + Q)x_1x_3 + Lx_2^2 + Lx_2x_3,
\end{aligned}
$$

$$
\begin{aligned}
(1) \quad \dot{x}_2 &= Qc_2x_1 - \varrho_2x_2 + Nc_1x_3 - Qx_1x_2 - (N + Q)x_1x_3 - Qx_2x_3, \\
\dot{x}_3 &= Mc_1c_2 - Mc_2x_1 + [\varrho_2 - P - M(c_1 + c_2)]x_2 - [\varrho_3 + Nc_1 + M(c_1 + c_2)]x_3 + \\
&\quad + Mx_1x_2 + (M + N)x_1x_3 + Mx_2^2 + (2M + N)x_2x_3 + Mx_3^2.
\end{aligned}
$$

The real constants ϱ_1, ϱ_2, ϱ_3, L, M, N, P, Q, c_1, c_2 are assumed positive and satisfying the only condition $\varrho_2 > P$.

Let K be the polyhedron of R^3 defined by the following conditions:

if $c_2 \geqslant c_1$: $x_1 \geqslant 0$, $x_2 \geqslant 0$, $x_3 \geqslant 0$, $c_1 - x_1 - x_2 - x_3 \geqslant 0$;

if $c_2 < c_1$: $x_1 \geqslant 0$, $x_2 \geqslant 0$, $x_3 \geqslant 0$, $c_1 - x_1 - x_2 - x_3 \geqslant 0$, $c_2 - x_2 - x_3 \geqslant 0$.

In [1] the system (1) has been investigated in polyhedron K. We refer the reader to [1] for the connections between the analysis of the system (1) in K and the problem of macromolecular Biology proposed by J. Wyman.

We denote by $x(t)$ the 3-vector $(x_1(t), x_2(t), x_3(t))$ and by $F(x) = (F_1(x), F_2(x), F_3(x))$ the 3-vector whose components are the right hand sides of (1).

The following theorems are demonstrated in [1]:

I. *Let* x° *be a point of* K *and* $x(t)$ *the solution of the problem*

$$(1) \quad \dot{x} = F(x), \qquad (2) \quad x(0) = x^\circ,$$

then

i) $x(t)$ *is defined for every* $t \in [0, +\infty)$;

ii) $x(t) \in K - \partial K$ *for* $t > 0$.

(See theor. 7.1 of [1]).

II. *If* $\xi = (\xi_1, \xi_2, \xi_3)$ *is a critical point for* (1) *and if* $\xi \in K$, *then* ξ *is asymptotically stable* (3).

(See theor. 5.1 of [1]).

(3) We recall that ξ is a *critical point* for the system (1) whenever $F(\xi) = 0$. The critical point ξ is *stable* if given $\epsilon > 0$ there exists $\delta_\epsilon > 0$ such that, if $x(t)$ is any solution of (1) for which $|x(0) - \xi| < \delta_\epsilon$, then $|x(t) - \xi| < \epsilon$ for $t \in [0, +\infty)$.
The point σ is *asymptotically stable* if it is stable and $\gamma > 0$ exists such that, if $|x(0) - \xi| < \gamma$, then $\lim_{t \to +\infty} x(t) = \xi$.
(See, for instance, [3], p. 78).

III. *The system* (1) *has exactly one critical point* ξ *in* K *and* $\xi \in K - \partial K$.
(See theor. 6.VII of [1]).

In the present paper the following theorem will be proved:

THEOREM: *The critical point* $\xi \in K - \partial K$ *of the system* (1) *is globally asymptotically stable in* K.

By saying that ξ is globally asymptotically stable in K we mean that:
i) ξ is stable;
ii) if $x^\circ \in K$ and if $x(t)$ is the solution of the problem (1), (2), then

$$\lim_{t \to +\infty} x(t) = \xi. \tag{3}$$

2. Let $\xi = (\xi_1, \xi_2, \xi_3)$ be the unique critical point of the system (1) contained in $K - \partial K$.

Let us define the following closed domains of the space R^3:

$$A_1 \equiv \{x = (x_1, x_2, x_3), (x_1 - \xi_1)(x_3 - \xi_3) \geqslant 0\},$$

$$A_2 \equiv \{x = (x_1, x_2, x_3), (x_1 - \xi_1)(x_3 - \xi_3) \leqslant 0\}.$$

We have: $R^3 = A_1 \cup A_2$.

The two sets A_1 and A_2 have in common only points of their boundaries.

Let us define in R^3 the following function:

$$V(x) \begin{cases} = |x_1 - \xi_1 + x_2 - \xi_2| + |x_2 - \xi_2 + x_3 - \xi_3| + |x_1 - \xi_1| + |x_3 - \xi_3| & \text{for } x \in A_1, \\ = |x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3| + |x_1 - \xi_1| + |x_2 - \xi_2| + |x_3 - \xi_3| & \text{for } x \in A_2. \end{cases}$$

The function $V(x)$ is continuous in $A_h (h = 1, 2)$.

The partial derivatives $V_{x_i} (i = 1, 2, 3)$ exist almost everywhere in R^3, are piece-wise constant in R^3 and assume the only values -2, 0, 2.

Set, for any x of R^3 where all the V_{x_i} exist,

$$W(x) = \sum_{i=1}^{3} V_{x_i}(x) F_i(x).$$

The function $W(x)$ is piece-wise continous in R^3.

Let us now consider the following closed domains of R^3:

$$B_1 \equiv \{x = (x_1, x_2, x_3),\ x_1 - \xi_1 \geqslant 0,\ x_3 - \xi_3 \geqslant 0,\ x_1 - \xi_1 + x_2 - \xi_2 \geqslant 0,\ x_2 - \xi_2 + x_3 - \xi_3 \geqslant 0\},$$

$$B_2 \equiv \{x = (x_1, x_2, x_3),\ x_1 - \xi_1 \geqslant 0,\ x_3 - \xi_3 \geqslant 0,\ x_1 - \xi_1 + x_2 - \xi_2 \leqslant 0,\ x_2 - \xi_2 + x_3 - \xi_3 \geqslant 0\},$$

$$B_3 \equiv \{x = (x_1, x_2, x_3),\ x_1 - \xi_1 \geqslant 0,\ x_3 - \xi_3 \geqslant 0,\ x_1 - \xi_1 + x_2 - \xi_2 \geqslant 0,\ x_2 - \xi_2 + x_3 - \xi_3 \leqslant 0\},$$

$$B_4 \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \geqslant 0,\ \ x_3 - \xi_3 \geqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 \leqslant 0,\ \ x_2 - \xi_2 + x_3 - \xi_3 \leqslant 0\},$$

$$B_5 \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \leqslant 0,\ \ x_3 - \xi_3 \leqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 \leqslant 0,\ \ x_2 - \xi_2 + x_3 - \xi_3 \leqslant 0\},$$

$$B_6 \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \leqslant 0,\ \ x_3 - \xi_3 \leqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 \geqslant 0,\ \ x_2 - \xi_2 + x_3 - \xi_3 \leqslant 0\},$$

$$B_7 \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \leqslant 0,\ \ x_3 - \xi_3 \leqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 \leqslant 0,\ \ x_2 - \xi_2 + x_3 - \xi_3 \geqslant 0\},$$

$$B_8 \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \leqslant 0,\ \ x_3 - \xi_3 \leqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 \geqslant 0,\ \ x_2 - \xi_2 + x_3 - \xi_3 \geqslant 0\},$$

$$B_9 \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \geqslant 0,\ \ x_2 - \xi_2 \geqslant 0,\ \ x_3 - \xi_3 \leqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3 \geqslant 0\},$$

$$B_{10} \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \geqslant 0,\ \ x_2 - \xi_2 \geqslant 0,\ \ x_3 - \xi_3 \leqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3 \leqslant 0\},$$

$$B_{11} \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \leqslant 0,\ \ x_2 - \xi_2 \leqslant 0,\ \ x_3 - \xi_3 \geqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3 \leqslant 0\},$$

$$B_{12} \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \leqslant 0,\ \ x_2 - \xi_2 \leqslant 0,\ \ x_3 - \xi_3 \geqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3 \geqslant 0\},$$

$$B_{13} \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \leqslant 0,\ \ x_2 - \xi_2 \geqslant 0,\ \ x_3 - \xi_3 \geqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3 \geqslant 0\},$$

$$B_{14} \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \leqslant 0,\ \ x_2 - \xi_2 \geqslant 0,\ \ x_3 - \xi_3 \geqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3 \leqslant 0\},$$

$$B_{15} \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \geqslant 0,\ \ x_2 - \xi_2 \leqslant 0,\ \ x_3 - \xi_3 \leqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3 \leqslant 0\},$$

$$B_{16} \equiv \{x = (x_1, x_2, x_3),\ \ x_1 - \xi_1 \geqslant 0,\ \ x_2 - \xi_2 \leqslant 0,\ \ x_3 - \xi_3 \leqslant 0,\ \ x_1 - \xi_1 + x_2 - \xi_2 + x_3 - \xi_3 \geqslant 0\}.$$

The two sets B_h and B_k, if $h \neq k$, $(h, k = 1, 2, \ldots, 16)$ have in common only points of their boundaries.

We have:

$A_1 \equiv B_1 \cup B_2 \cup B_3 \cup B_4 \cup B_5 \cup B_6 \cup B_7 \cup B_8$,

$A_2 \equiv B_9 \cup B_{10} \cup B_{11} \cup B_{12} \cup B_{13} \cup B_{14} \cup B_{15} \cup B_{16}$.

The function $V(x)$ is continuously differentiable in each open domain $B_h - \partial B_h (h = 1, 2, \ldots, 16)$ and each of its first derivatives coincides with a continuous function in B_h, i.e. V is continuously differentiable in the closed domain B_h.

The following theorem proves that $V(x)$ is a "Liapunov function" for the system (1).

IV. *The non-negative function* $V(x)$ *enjoys the following properties:*

a) $V(x)$ *is continuous in* R^3 *and is continuously differentiable in each closed domain* B_h;

b) $V(x)$ *vanishes when and only when* $x \equiv \xi$;

c) $W(x)$ *is continuous in* $B_h - \partial B_h$ *and in this set coincides with a function* $W^{(h)}(x)$ *which is continuous in* B_h, *vanishes for* $x \equiv \xi$ *and is strictly negative in* $(B_h \cap K)/\{\xi\}$ $(h = 1, 2, ..., 16)$.

We postpone the proof of theor. IV to the next Section.

From theor. IV one easily deduces the proof of the main THEOREM of Sect. 1. Although the arguments are standard, we report them here for the convenience of the reader.

We already know that ξ is stable (see theor II and footnote (3)). We need only to prove that, if $x(t)$ is the solution of (1), (2) with $x^\circ \in K$, then (3) holds.

Suppose $\min \lim\limits_{t \to +\infty} |x(t) - \xi| = 2\alpha > 0$.

$t_0 \geqslant 0$ exists such that, for $t > t_0$, $|x(t) - \xi| > \alpha$.

Because of the properties of $W(x)$ a positive number $\beta(\alpha)$ can be found such that $W^{(h)}(x(t)) < -\beta(\alpha)$ for $t > t_0$ $(h = 1, 2, ..., 16)$.

Since $V(x)$ is continuously differentiable in each B_h, if σ is a segment of straight line contained in $B_h \cap B_k$ and σ_1, σ_2, σ_3 are its direction cosines, we have in every point x of σ:

$$\sum_{i=1}^{3} V_{x_i}^{(h)}(x)\,\sigma_i = \sum_{i=1}^{3} V_{x_i}^{(k)}(x)\,\sigma_i\,, \tag{4}$$

where $V_{x_i}^{(h)}[V_{x_i}^{(k)}]$ is the partial derivative of V as defined in B_h [in B_k]; i.e. $V^{(h)}$ is the restriction of V to B_h.

On the other hand, given h and k, $h \neq k$ $(h, k = 1, 2, ..., 16)$, since $x(t)$ is an analytic function of t in $[0, T]$ for any $T > 0$, if the trajectory corresponding to $x(t)$ $(0 \leqslant t \leqslant T)$ does not completely belong to $B_h \cap B_k$, it has at most a finite number of points in common with this set.

For $t > t_0$ we have:

$$V(x(t)) = V(x(t_0)) + \int_{t_0}^{t} W(x(\tau))\,d\tau < V(x(t_0)) - \beta(\alpha)(t - t_0)\,,$$

where we assume $W = W^{(h)}$[or $W = W^{(k)}$] if $x(t) \in B_h \cap B_k$ $(0 \leqslant t < +\infty)$.

It follows that $\lim\limits_{t \to +\infty} V(x(t)) = -\infty$. This is impossible because $x(t) \in K$ for $t \geqslant 0$ (see theor. I) and $V(x)$ is bounded in K.

Hence:

$$\min \lim_{t \to +\infty} |x(t) - \xi| = 0\,. \tag{5}$$

Suppose now:

$$\max \lim_{t \to +\infty} |x(t) - \xi| = 2\lambda > 0\,. \tag{6}$$

Since ξ is stable, given ϵ such that $0 < \epsilon < \lambda$, there exists δ_ϵ such that, if $\tilde{x}(t)$ is any solution of (1) such that

$$|\tilde{x}(0) - \xi| < \delta_\epsilon, \tag{7}$$

then $|\tilde{x}(t) - \xi| < \epsilon$ for $t \geqslant 0$ (see footnote [3]).

Because of (5) some $\tilde{t} > 0$ exists such that $|x(\tilde{t}) - \xi| < \delta_\epsilon$.

Set $\tilde{x}(t) = x(t+\tilde{t})$. This is a solution of (1) which satisfies (7). Hence, for any $t \geqslant 0$, we have $|x(t+\tilde{t}) - \xi| < \epsilon < \lambda$. This contradicts (6).

The proof is now complete.

3. Let us now prove theor. IV.

We get the continuity of $V(x)$ in R^3 verifying, by inspection, that the definition of V in $B_h \cap B_k$ is the same either assuming $V = V^{(h)}$ or assuming $V = V^{(k)}$ ($h, k = 1, 2, \ldots, 16$). $V(x)$ is continuously differentiable in B_h since it coincides with a linear function in B_h.

Moreover it is also easy to verify that $V(\xi) = 0$ and $V(x)$ is strictly positive for $x \neq \xi$.

It is convenient to rewrite $F_i(x)$ ($i = 1, 2, 3$) as follows:

$$F_1(x) = L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3) + Px_2 - \varrho_1 x_1 - Qx_1(c_2 - x_2 - x_3),$$

$$F_2(x) = Qx_1(c_2 - x_2 - x_3) + Nx_3(c_1 - x_1 - x_2) - \varrho_2 x_2,$$

$$F_3(x) = M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3) + (\varrho_2 - P)x_2 - \varrho_3 x_3 - Nx_3(c_1 - x_1 - x_2).$$

We have:

$$\begin{aligned} W(x) = 2(F_1(x) + F_2(x) + F_3(x)) = 2[&L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3) \\ &+ M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3) - \varrho_1 x_1 - \varrho_3 x_3] \end{aligned}$$

$$\text{for } x \in B_1 - \partial B_1;$$

$$\begin{aligned} W(x) = 2F_3(x) = 2[&M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3) + (\varrho_2 - P)x_2 - \varrho_3 x_3 \\ &- Nx_3(c_1 - x_1 - x_2)] \end{aligned}$$

$$\text{for } x \in B_2 - \partial B_2;$$

$$\begin{aligned} W(x) = 2F_1(x) = 2[&L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3) + Px_2 - \varrho_1 x_1 \\ &- Qx_1(c_2 - x_2 - x_3)] \end{aligned}$$

$$\text{for } x \in B_3 - \partial B_3;$$

$$W(x) = -2F_2(x) = 2[\varrho_2 x_2 - Qx_1(c_2 - x_2 - x_3) - Nx_3(c_1 - x_1 - x_2)]$$

$$\text{for } x \in B_4 - \partial B_4;$$

$$\begin{aligned} W(x) = -2(F_1(x) + F_2(x) + F_3(x)) = 2[&\varrho_1 x_1 + \varrho_3 x_3 - L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3) \\ &- M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3)]; \end{aligned}$$

$$\text{for } x \in B_5 - \partial B_5;$$

$$\begin{aligned} W(x) = -2F_3(x) = 2[&\varrho_3 x_3 + Nx_3(c_1 - x_1 - x_2) - (\varrho_2 - P)x_2 \\ &- M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3)] \end{aligned}$$

$$\text{for } x \in B_6 - \partial B_6;$$

$$W(x) = -2F_1(x) = 2[\varrho_1 x_1 + Qx_1(c_2 - x_2 - x_3) - Px_2 - L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3)] \quad \text{for } x \in B_7 - \partial B_7;$$

$$W(x) = 2F_2(x) = 2[Qx_1(c_2 - x_2 - x_3) + Nx_3(c_1 - x_1 - x_2) - \varrho_2 x_2] \quad \text{for } x \in B_8 - \partial B_8;$$

$$W(x) = 2(F_1(x) + F_2(x)) = 2[L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3) + Nx_3(c_1 - x_1 - x_2) - (\varrho_2 - P)x_2 - \varrho_1 x_1] \quad \text{for } x \in B_9 - \partial B_9;$$

$$W(x) = -2F_3(x) = 2[\varrho_3 x_3 + Nx_3(c_1 - x_1 - x_2) - (\varrho_2 - P)x_2 - M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3)] \quad \text{for } x \in B_{10} - \partial B_{10};$$

$$W(x) = -2(F_1(x) + F_2(x)) = 2[\varrho_1 x_1 + (\varrho_2 - P)x_2 - Nx_3(c_1 - x_1 - x_2) - L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3)] \quad \text{for } x \in B_{11} - \partial B_{11};$$

$$W(x) = 2F_3(x) = 2[M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3) + (\varrho_2 - P)x_2 - \varrho_3 x_3 - Nx_3(c_1 - x_1 - x_2)] \quad \text{for } x \in B_{12} - \partial B_{12};$$

$$W(x) = 2(F_2(x) + F_3(x)) = 2[M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3) + Qx_1(c_2 - x_2 - x_3) - Px_2 - \varrho_3 x_3] \quad \text{for } x \in B_{13} - \partial B_{13};$$

$$W(x) = -2F_1(x) = 2[\varrho_1 x_1 + Qx_1(c_2 - x_2 - x_3) - Px_2 - L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3)] \quad \text{for } x \in B_{14} - \partial B_{14};$$

$$W(x) = -2(F_2(x) + F_3(x)) = 2[\varrho_3 x_3 + Px_2 - M(c_2 - x_2 - x_3)(c_1 - x_1 - x_2 - x_3) - Qx_1(c_1 - x_2 - x_3)] \quad \text{for } x \in B_{15} - \partial B_{15};$$

$$W(x) = 2F_1(x) = 2[L(c_1 - x_1 - x_2)(c_1 - x_1 - x_2 - x_3) + Px_2 - \varrho_1 x_1 - Qx_1(c_2 - x_2 - x_3)] \quad \text{for } x \in B_{16} - \partial B_{16}.$$

It is elementary to verify by inspection that the function $W(x)$ enjoys the properties c) of theor. IV.

REFERENCES

[1] FICHERA G., SNEIDER M.A., WYMAN J.: *On the existence of a steady state in a biological system*, Memorie Accad. Naz. dei Lincei, s. VIII, XIV, 1977, 1-26.

[2] Fichera G., Sneider M.A., Wyman J.: *On the existence of a steady state in a biological system*, Proc. Nat. Acad. Sci. U.S.A., 1974, 4182-4184.
[3] Lefschetz S., *Differential equations: geometric theory*, Interscience Publ. Inc., New York, 1957.