Pergamon

Nonlinear Analysis, Theory, Methods & Applications, Vol. 22, No. 8, pp. 1017–1031, 1994

0362-546X/94 $7.00 + .00

COMPETITION IN THE GRADOSTAT: THE GLOBAL STABILITY PROBLEM†

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(*Received* 15 *June* 1992; *received in revised form* 26 *October* 1992; *received for publication* 2 *June* 1993)

Key words and phrases: Gradostat, equilibria, competition, stability.

1. INTRODUCTION

IN THIS PAPER we show that the general two vessel gradostat with "Monod" and more general growth functions is globally stable. However, for other growth functions, multiple stable equilibria are possible. Examples with multiple stable equilibria are also constructed in three vessel gradostats with Monod growth functions.

The original gradostat is a linearly connected chain of n vessels each of which is a chemostat. The model takes the form (cf. [1, 2])

$$\begin{cases} \dot{S}_i = (S_{i-1} - 2S_i + S_{i+1})d - \dfrac{u_i}{y_u} f(S_i) - \dfrac{v_i}{y_v} g(S_i) \\ \dot{u}_i = (u_{i-1} - 2u_i + u_{i+1})d + u_i f(S_i) \qquad (i = 1, \dots, n) \\ \dot{v}_i = (v_{i-1} - 2v_i + v_{i+1})d + v_i g(S_i) \end{cases} \tag{1.1}$$

where $S_0 = S^{(0)} > 0$ is the concentration of the input nutrient (substrate) to the first vessel and $d > 0$ is the washout rate. S_i, u_i and v_i denote the concentration of the nutrient and the two competing micro-organism species in vessel i (with the convention that $u_0 = v_0 = 0$ and $S_{n+1} = u_{n+1} = v_{n+1} = 0$). The functions

$$f(S) = \frac{m_u S}{a_u + S} \qquad \text{and} \qquad g(s) = \frac{m_v S}{a_v + S} \tag{1.2}$$

are the nutrient uptake (growth) functions of the two competing species. The quantities m_u, a_u, y_u are the maximal growth rate, the Michaelis–Menton (half saturation) constant and the yield constant of one of the species and similarly m_v, a_v and y_v of the other. Since $\lim_{t\to\infty} S_i(t) + (1/y_u)u_i(t) + (1/y_v)v_i(t) = c_i$, where $c_i = (1 - i/(n + 1))S_0$, (1.1) reduces to

$$\begin{cases} \dot{u}_i = (u_{i-1} - 2u_i + u_{i+1})d + u_i f(c_i - (u_i + v_i)) \\ \dot{v}_i = (v_{i-1} - 2v_i + v_{i+1})d + v_i g(c_i - (u_i + v_i)) \end{cases} \qquad (i = 1, \dots, n) \tag{1.3}$$

on $X = \{(u, v) \in \mathbb{R}_+^{2n} \mid u + v \le c\}$. We have assumed that $y_u = y_v = 1$, which can be achieved by a suitable rescaling.

† Research partially supported by the Natural Sciences and Engineering Research Council of Canada, grant number NSERC OGP36475 and by the Austrian Fonds zur Förderung der wissenschaftlichen Forschung, project P8043. This paper is dedicated to Paul Waltman on the occasion of his 60th birthday.

One also considers more general nutrient uptake functions. They are assumed to satisfy

$$f(0) = g(0) = 0, \qquad f'(S), g'(S) > 0 \tag{1.4}$$

and usually also

$$f''(S), g''(S) < 0. \tag{1.5}$$

In [3], it is also assumed that the two uptake functions are related to each other by a relation of the form

$$g(S) = \beta f(\alpha S) \tag{1.6}$$

for some positive constants α, β, as is the case for Monod functions (1.2). Although it is not clear why the two growth functions should be related in this way, we will also discuss this special case for completeness.

The above linear configuration has been extended to a more general situation. The following description is taken from [4]. Let E_{ij} be the volumetric flow rate from vessel j to i ($i \neq j$), with the convention $E_{ii} = 0$ and let E be the n by n matrix (E_{ij}). Let V_i be the volume of the ith vessel, D_i the flow rate from an input reservoir to vessel i, $S_i^{(0)}$ the concentration of the substrate in the input reservoir feeding vessel i and C_i the flow rate from vessel i to a receiving reservoir. The rate of change of the vector $S(t) := (S_1(t), \ldots, S_n(t))$ when there is no consumption is given by

$$[\mathrm{diag}\{V_i\}]\dot{S} = \bar{A}S + \bar{e} \tag{1.7}$$

where

$$\bar{A} = E - \mathrm{diag}\{C_i\} - \mathrm{diag}\left\{\sum_h E_{hi}\right\} \qquad \text{and} \qquad \bar{e} = (D_1 S_1^{(0)}, \ldots, D_n S_n^{(0)}).$$

Moreover, since the volume V_i is a constant, the volumetric in and out flow rates must be the same, i.e.

$$\sum_j E_{ij} + D_i = \sum_h E_{hi} + C_i.$$

If we multiply (1.7) throughout by $\mathrm{diag}\{V_i^{-1}\}$ and denote $e = [\mathrm{diag}\{V_i^{-1}\}]\bar{e}$ and $A = [\mathrm{diag}\{V_i^{-1}\}]\bar{A}$, then (1.7) becomes

$$\dot{S} = AS + e.$$

We will assume that $S_i^{(0)} > 0$ for some i so that $e > 0$. Moreover, $A_{ii} < 0$, $A_{ij} \geq 0$ ($i \neq j$) and $\sum_j A_{ij} = -V_i^{-1}D_i \leq 0$, with strict inequality for some i. The matrix A will also be assumed to be irreducible. The full system (with consumption) now becomes

$$\begin{cases} \dot{S} = e + AS - F(S)u - G(S)v \\ \dot{u} = Au + F(S)u \\ \dot{v} = Av + G(S)v \end{cases} \tag{1.8}$$

where $F(S) = \mathrm{diag}\{f(S_1), \ldots, f(S_n)\}$ and $G(S) = \mathrm{diag}\{g(S_1), \ldots, g(S_n)\}$.

It can be shown that (cf. [4, lemma 3.1]) $\lim_{t\to\infty} S(t) + u(t) + v(t) = c$, where $c \gg 0$ is the unique solution of $Ac = -e$. Using this fact, (1.8) can be reduced to

$$\begin{cases} \dot{u} = [A + F(c - u - v)]u \\ \dot{v} = [A + G(c - u - v)]v \end{cases} \tag{1.9}$$

on $X = \{(u, v) \in \mathbb{R}_+^{2n} \mid u + v \leq c\}$.

We will need the following important and well-known fact about monotone flows (cf. [5, theorem 10.5; 6, lemma 2.1; 7, remark 1.2] for the second part of the statement).

LEMMA 1.1. Consider the autonomous ordinary differential equation

$$\dot{x} = f(x) \tag{1.10}$$

defined on a closed, convex set $U \subset \mathbb{R}^n$. Assume $f \in C^1(U)$, U is positively invariant under the flow $\pi(\cdot, t)$ defined by (1.10) and there exist $m_i = 0$ or 1 $(i = 1, \ldots, n)$ such that all the off-diagonal entries of $PDf(x)P$ are nonnegative for every $x \in U$, where $P = \text{diag}\{(-1)^{m_1}, \ldots, (-1)^{m_n}\}$. Define the cone

$$K = \{x \in \mathbb{R}^n : (-1)^{m_i} x_i \geq 0, \text{ for all } 1 \leq i \leq n\}$$

and the ordering

$$x <_K y \qquad \text{if and only if } y - x \in K\backslash\{0\}.$$

Then π preserves the ordering $<_K$ (i.e. π is K-monotone) in the sense that $x <_K y$ implies $\pi(x, t) <_K \pi(y, t)$ for all $t \geq 0$. Moreover, if E_1, E_2 are two equilibria of (1.10) with $E_1 <_K E_2$, then one of the following holds.

(i) There is an increasing (under $<_K$) orbit connecting E_1 to E_2.
(ii) There is a decreasing orbit connecting E_2 to E_1.
(iii) There is a third equilibrium E_3 of (1.10) such that $E_1 <_K E_3 <_K E_2$.

For equation (1.9), if we let $m_i = 0$ for $i = 1, \ldots, n$ and $m_i = 1$ for $i = n + 1, \ldots, 2n$, then the cone K above is given by

$$K = \{(u, v) \in \mathbb{R}^{2n} \mid u_i \geq 0 \text{ and } v_i \leq 0 \text{ for all } i = 1, \ldots, n\}$$

and lemma 1.1 is applicable to (1.9) on X.

We summarize some of the known facts about (1.9) in the following theorem (cf. [4, Sections 4, 5]).

THEOREM 1.2. (I) The flow defined by (1.9) is K-monotone on X and is strongly K-monotone on $\text{int}(X)$.

(II) If v were absent, i.e. for $v \equiv 0$ in (1.9), we have:

(i) if the stability modulus $s(A + F(c)) \leq 0$, then $\lim_{t\to\infty} u(t) = 0$ provided $0 \leq u(0) \leq c$;

(ii) if $s(A + F(c)) > 0$, then there exists (unique) $\hat{u} \gg 0$ such that $\lim_{t\to\infty} u(t) = \hat{u}$ provided $0 < u(0) < c$.

Similarly, if u were absent and $s(A + G(c)) > 0$ we have $\tilde{v} \gg 0$ satisfying the analogous properties.

(III) Let $E_0 = (0, 0)$, $\hat{E} = (\hat{u}, 0)$ and $\tilde{E} = (0, \tilde{v})$. Let also Σ be the set of equilibrium points of (1.9). We have:

(i) if $\Sigma = \{E_0\}$, then E_0 is a global attractor for (1.9);

(ii) if $\Sigma = \{E_0, \hat{E}\}$, then $\hat{E}$ attracts all solutions $(u(t), v(t))$ in X with $u(0) > 0$. There is an analogous statement when $\Sigma = \{E_0, \tilde{E}\}$;

(iii) if $\Sigma = \{E_0, \hat{E}, \tilde{E}\}$, then either $\lim_{t\to\infty}(u(t), v(t)) = \hat{E}$ for all solutions in X with $u(0) > 0$, or $\lim_{t\to\infty}(u(t), v(t)) = \tilde{E}$ for all solutions in X with $v(0) > 0$.

(IV) If an equilibrium point of the form $E^* = (u^*, v^*)$ $(u^* > 0,\ v^* > 0)$ exists, then $\tilde{E} \ll_K E^* \ll_K \hat{E}$. Moreover, for every solution $(u(t), v(t))$ in X that does not converge to one of the boundary fixed points $E_0, \hat{E}, \tilde{E}$, there is a t_0 such that $(u(t), v(t)) \in]\tilde{E}, \hat{E}[$ for $t > t_0$.

Note that the uniqueness and global stability of $\hat{u}$ and $\tilde{v}$ in theorem 1.2 II (ii) follows from the monotonicity of the growth functions f and g (cf. [8, theorem 2.1; 9, theorem 6; 10, theorem 2.3]). Statement III (iii) also follows from a modification of lemma 1.1.

The global dynamics of (1.9) when an interior equilibrium E^* exists is an open question. In the case of two vessels (i.e. $n = 2$), we will show in theorems 2.1 and 3.1 that if E^* exists, then it is unique and is globally stable, provided (roughly speaking) the graphs of f and g intersect transversely at only one positive value $\bar{S}$. This generalizes theorems 5.6 and 6.1(d) from [2] on the standard two vessel gradostat (1.1). On the other hand, if f and g intersect at more than one positive value, then it is possible to produce examples with unstable E^* (see Section 3). In Section 4, we show that it is also possible to have an unstable interior equilibrium E^* for a general three vessel gradostat even if f and g are Monod. This is carried out for the tridiagonal case ($a_{13} = a_{31} = 0$) as well as for the cyclically linked case ($a_{13} = a_{21} = a_{32} = 0$). Some concrete numerical examples illustrating the results in Sections 3 and 4 are given in Section 5.

2. THE GENERAL TWO VESSEL GRADOSTAT WITH MONOD GROWTH FUNCTIONS

When there are only two vessels, (1.9) becomes

$$\begin{cases} \dot{u}_1 = a_{11}u_1 + a_{12}u_2 + u_1 f(S_1) \\ \dot{u}_2 = a_{21}u_1 + a_{22}u_2 + u_2 f(S_2) \\ \dot{v}_1 = a_{11}v_1 + a_{12}v_2 + v_1 g(S_1) \\ \dot{v}_2 = a_{12}v_1 + a_{22}v_2 + v_2 g(S_2) \end{cases} \tag{2.1}$$

where $S_i = c_i - (u_i + v_i) \geq 0$ and $c = (c_1, c_2)$ is a positive vector. In this section, we will always assume that f and g are Monod functions as given in (1.2). Let A be the two by two matrix (a_{ij}). From the assumptions in Section 1, we know that

$$a_{12}, a_{21} > 0, \qquad a_{ii} < 0\ (i = 1, 2) \qquad \text{and} \qquad \det(A) > 0. \tag{2.2}$$

The Jacobian matrix of (2.1) is given by

$$J = \begin{pmatrix} a_{11} + f(S_1) - u_1 f'(S_1) & a_{12} & -u_1 f'(S_1) & 0 \\ a_{21} & a_{22} + f(S_2) - u_2 f'(S_2) & 0 & -u_2 f'(S_2) \\ -v_1 g'(S_1) & 0 & a_{11} + g(S_1) - v_1 g'(S_1) & a_{12} \\ 0 & -v_2 g'(S_2) & a_{21} & a_{22} + g(S_2) - v_2 g'(S_2) \end{pmatrix}. \tag{2.3}$$

According to (2.1), $f(S_1) = -(a_{11}u_1 + a_{12}u_2)/u_1$, etc. at an interior equilibrium and J becomes

$$J = \begin{pmatrix} -\frac{a_{12}u_2}{u_1} - u_1 f'(S_1) & a_{12} & -u_1 f'(S_1) & 0 \\ a_{21} & -\frac{a_{21}u_1}{u_2} - u_2 f'(S_2) & 0 & -u_2 f'(S_2) \\ -v_1 g'(S_1) & 0 & -\frac{a_{12}v_2}{v_1} - v_1 g'(S_1) & a_{12} \\ 0 & -v_2 g'(S_2) & a_{21} & -\frac{a_{21}v_1}{v_2} - v_2 g'(S_2) \end{pmatrix}. \tag{2.4}$$

The determinant of this matrix turns out to be (after some tedious calculation)

$$\det(J) = \frac{a_{12}a_{21}}{u_1u_2v_1v_2}(u_1v_2 - u_2v_1)(u_1^2v_2^2 f'(S_1)g'(S_2) - u_2^2v_1^2 f'(S_2)g'(S_1)). \tag{2.5}$$

For Monod growth functions f and g, their derivatives can be expressed as

$$f'(S) = \frac{a_u}{m_u S^2} f(S)^2 \quad \text{and} \quad g'(S) = \frac{a_v}{m_v S^2} g(S)^2.$$

Inserting these into (2.5), we obtain

$$\begin{aligned} \det(J) &= \frac{a_u a_v a_{12} a_{21}}{m_u m_v S_1^2 S_2^2 u_1 u_2 v_1 v_2}(u_1v_2 - u_2v_1)(u_1^2v_2^2 f(S_1)^2 g(S_2)^2 - u_2^2v_1^2 f(S_2)^2 g(S_1)^2) \\ &= \frac{a_u a_v a_{12} a_{21}}{m_u m_v S_1^2 S_2^2 u_1 u_2 v_1 v_2}(u_1v_2 f(S_1)g(S_2) + u_2v_1 f(S_2)g(S_1))(u_1v_2 - u_2v_1) \\ &\quad \times (u_1v_2 f(S_1)g(S_2) - u_2v_1 f(S_2)g(S_1)). \end{aligned} \tag{2.6}$$

Again using the equilibrium equations of (2.1), the expression of $\det(J)$ in (2.6) can be rewritten as

$$\begin{aligned} \det(J) &= \frac{a_u a_v a_{12} a_{21}}{m_u m_v S_1^2 S_2^2 u_1 u_2 v_1 v_2}(u_1v_2 f(S_1)g(S_2) + u_2v_1 f(S_2)g(S_1))(u_1v_2 - u_2v_1) \\ &\quad \times ((a_{11}u_1 + a_{12}u_2)(a_{21}v_1 + a_{22}v_2) - (a_{21}u_1 + a_{22}u_2)(a_{11}v_1 + a_{12}v_2)) \\ &= \frac{a_u a_v a_{12} a_{21}}{m_u m_v S_1^2 S_2^2 u_1 u_2 v_1 v_2}(u_1v_2 f(S_1)g(S_2) + u_2v_1 f(S_2)g(S_1)) \det(A)(u_1v_2 - u_2v_1)^2. \end{aligned} \tag{2.7}$$

Note that the last equality follows from the product formula for determinants. Based on (2.2), this shows that at any interior equilibrium $E^* = (u_1^*, u_2^*, v_1^*, v_2^*)$, $\det(J) > 0$ holds as long as $u_1^*v_2^* \neq u_2^*v_1^*$.

Remark. Another way to derive the above result would be to eliminate the diagonal terms a_{11} and a_{22} from the equilibrium equations of (2.1)

$$a_{12}\frac{u_2}{u_1} + f(S_1) = a_{12}\frac{v_2}{v_1} + g(S_1)\ (= -a_{11})$$
$$a_{21}\frac{u_1}{u_2} + f(S_2) = a_{21}\frac{v_1}{v_2} + g(S_2)\ (= -a_{22}). \tag{2.8}$$

If we express $g(S_1)$ and $g(S_2)$ in terms of $f(S_1)$ and $f(S_2)$ using (2.8) and insert them into the last line of (2.6), we obtain

$$\det(J) = \frac{a_u a_v a_{12} a_{21}}{m_u m_v S_1^2 S_2^2 u_1 u_2 v_1 v_2}(u_1 v_2 f(S_1)g(S_2) + u_2 v_1 f(S_2)g(S_1))(u_1 v_2 - u_2 v_1)^2$$
$$\times \left(f(S_1)f(S_2) + a_{21} f(S_1)\frac{u_1}{u_2} + a_{12} f(S_2)\frac{u_2}{u_1}\right). \tag{2.9}$$

This again shows $\det(J) \geq 0$ and $\det(J) = 0$ if and only if $u_1^*/v_1^* = u_2^*/v_2^*$.

Similarly (and much easier), one shows that the other leading principal minors of J alternate in sign. For example, the leading 3 by 3 principal minor of J is given by

$$-\frac{a_{12}}{u_1 u_2 v_1}(u_1^2 u_2^2 v_2 f'(S_1)f'(S_2) + a_{21} u_1^3 v_2 f'(S_1) + a_{12} u_2^3 v_2 f'(S_2) + u_2^3 v_1^2 f'(S_2)g'(S_1))$$

which is always negative, provided f and g satisfy (1.4). Therefore, a well-known stability criterion for quasipositive matrices (cf. [9, lemma 1; 6, theorem 2.7]) implies the stability of E^*.

Now we consider the "degenerate" case when there is an interior equilibrium E^* with $u_1^* v_2^* = u_2^* v_1^*$, i.e. $v^* = ku^*$ for some constant $k > 0$. By (2.8), $f(S_i^*) = g(S_i^*)$ for $i = 1, 2$. If the Monod functions f and g are not identical, then either

(a) $f(S) \neq g(S)$ for all $S > 0$ and there is no interior equilibrium, or

(b) f and g intersect at a single positive value $\bar{S}$ and, hence, $S_1^* = S_2^* = \bar{S}$.

In case (b), $-f(\bar{S})$ $(= -g(\bar{S}))$ coincides with the spectral modulus, $s(A)$, of A and there is a continuum, $\mathcal{E}$, of equilibria given by

$$\mathcal{E} = \{(\lambda u^*, (1 + k - \lambda)u^*) \mid 0 \leq \lambda \leq 1 + k)\}$$

which connects the two boundary equilibria, $\hat{E} = (u^* + v^*, 0) = ((1 + k)u^*, 0)$ and $\tilde{E} = (0, u^* + v^*)$ of (2.1). If f and g were identical, the situation is even more degenerate and there is a (two-dimensional) quadrilateral of equilibria.

THEOREM 2.1. Assume f, g are Monod as in (1.2) and f is not identical to g. Let $\bar{S} > 0$ be such that $f(\bar{S}) = g(\bar{S})$.

(i) If $-f(\bar{S}) \neq s(A)$, then there is a unique globally attracting equilibrium. In particular, if an interior equilibrium exists, it must be unique and is globally stable.

(ii) If $-f(\bar{S}) = s(A)$ (and $\bar{S} < c_1, c_2$), then there is a line of equilibria $\mathcal{E}$ which is globally attracting in the sense that every interior orbit of (2.1) converges to one of the equilibria in $\mathcal{E}$.

Proof. (i) The case of no interior equilibrium has been completely analysed in [3, theorems 5.2 and 5.4], see theorem 1.2.III above.

If an interior equilibrium E^* exists, then $\tilde{E} \ll_K E^* \ll_K \hat{E}$. Since any interior equilibrium is asymptotically stable, lemma 1.1 implies uniqueness of E^* and the existence of two monotone solutions $\gamma_1(t)$, $\gamma_2(t)$ such that $\lim_{t\to\infty} \gamma_i(t) = E^*$ and $\lim_{t\to-\infty} \gamma_1(t) = \tilde{E}$, $\lim_{t\to-\infty} \gamma_2(t) = \hat{E}$. If (u_0, v_0) lies in the (open) order interval $]\tilde{E}, \hat{E}[$, then one can find t_0 such that $\gamma_1(t_0) <_K (u_0, v_0) <_K \gamma_2(t_0)$. Hence, by comparison, the solution $(u(t), v(t))$ through (u_0, v_0) converges to E^*.

(ii) It follows from theorem 9.7 (and its proof) in [5], that every orbit in the open order interval $]\tilde{E}, \hat{E}[$ converges to one of the fixed points on the line $\mathcal{E}$. But then theorem 1.2 (IV) implies the assertion. ■

3. MORE GENERAL UPTAKE FUNCTIONS FOR THE TWO VESSEL GRADOSTAT

We first give another proof for theorem 2.1, which extends to more general uptake functions satisfying the assumption (1.4).

THEOREM 3.1. Suppose that f and g are such that f'/g' is a monotonic function, and f is not identical to g on any interval $[0, c]$, $c > 0$. Then the assertions of theorem 2.1 again hold for (2.1).

Proof. It is sufficient to show that (2.5) is again positive, whenever $u_1^* v_2^* - u_2^* v_1^* \neq 0$, since the rest of the proof of theorem 2.1 works in general. For this we rewrite (2.5) as

$$\det(J) = \frac{a_{12}a_{21}}{u_1 u_2 v_1 v_2}(u_1 v_2 - u_2 v_1)(u_1^2 v_2^2 f'(S_1)g'(S_2) - u_2^2 v_1^2 f'(S_2)g'(S_1))$$

$$= \frac{a_{12}a_{21} v_1^2 v_2^2 g'(S_1)g'(S_2)}{u_1 u_2}\left(\frac{u_1}{v_1} - \frac{u_2}{v_2}\right)\left(\frac{u_1^2}{v_1^2}\frac{f'(S_1)}{g'(S_1)} - \frac{u_2^2}{v_2^2}\frac{f'(S_2)}{g'(S_2)}\right). \tag{3.1}$$

Without loss of generality we may assume that f'/g' is monotonically increasing. Then (ignoring the trivial case when $f(S) \neq g(S)$ for all $S > 0$) there is a unique value $\bar{S} > 0$ such that $f(S) \lesseqgtr g(S)$ for $S \lesseqgtr \bar{S}$. (The possibility of a continuum of intersection points, i.e. $f = g$ on an interval $[a, b]$ would imply $f = g$ on $[0, b]$ which is ruled out by the assumptions.)

First consider the case where $u_1^*/v_1^* > u_2^*/v_2^*$ (i.e. $u_1^*/u_2^* > v_1^*/v_2^*$). Then

$$f(S_1^*) = -a_{11} - a_{12}\frac{u_2^*}{u_1^*} > -a_{11} - a_{12}\frac{v_2^*}{v_1^*} = g(S_1^*)$$

and

$$f(S_2^*) = -a_{22} - a_{21}\frac{u_1^*}{u_2^*} < -a_{22} - a_{21}\frac{v_1^*}{v_2^*} = g(S_2^*).$$

This implies $S_1^* > \bar{S} > S_2^*$, so that $f'(S_1^*)/g'(S_1^*) \geq f'(S_2^*)/g'(S_2^*)$ and $(u_1^{*2}/v_1^{*2})(f'(S_1^*)/g'(S_1^*)) > (u_2^{*2}/v_2^{*2})(f'(S_2^*)/g'(S_2^*))$. Hence, the last two factors for (3.1) are positive.

Similarly, in the case where $u_1^*/v_1^* < u_2^*/v_2^*$, all inequality signs are reversed so that the last two factors of (3.1) are negative.

In either case $\det(J)$ is positive and the proof is complete. ■

To apply theorem 3.1 to uptake functions related by (1.6) we need the following lemma.

LEMMA 3.2. Let $\phi: \mathbb{R}^+ \to \mathbb{R}^+$. Then $\phi(\alpha x)/\phi(x)$ is monotone increasing in x for $0 < \alpha < 1$ and monotone decreasing in x for $\alpha > 1$ if and only if

$$\phi(x)\phi'(x) + x\phi(x)\phi''(x) - x\phi'(x)^2 \leq 0 \tag{3.2}$$

holds for all $x \geq 0$.

Proof. Let $\phi(\alpha x)/\phi(x)$ be monotone increasing in x for $0 < \alpha < 1$ and monotone decreasing in x for $\alpha > 1$. By differentiating $\phi(\alpha x)/\phi(x)$ we have

$$\alpha\phi'(\alpha x)\phi(x) - \phi(\alpha x)\phi'(x) \geq 0 \qquad (0 < \alpha < 1)$$

$$\alpha\phi'(\alpha x)\phi(x) - \phi(\alpha x)\phi'(x) \leq 0 \qquad (\alpha > 1)$$

for all $x > 0$ which simplifies to

$$\frac{\alpha x\phi'(\alpha x)}{\phi(\alpha x)} \geq \frac{x\phi'(x)}{\phi(x)} \qquad (0 < \alpha < 1)$$

$$\frac{\alpha x\phi'(\alpha x)}{\phi(\alpha x)} \leq \frac{x\phi'(x)}{\phi(x)} \qquad (\alpha > 1).$$

This implies that $x\phi'(x)/\phi(x)$ is monotone decreasing. Hence, by differentiating again,

$$\phi(x)\phi'(x) + x\phi(x)\phi''(x) - x\phi'(x)^2 \leq 0.$$

Since the above argument can be reversed, this completes the proof. ■

Applying lemma 3.2 to the function $\phi(x) = f'(x)$ yields the following corollary.

COROLLARY 3.3. Let f and g satisfy (1.4) and (1.6) and let furthermore

$$f'(S)f''(S) + Sf'(S)f'''(S) - Sf''(S)^2 < 0, \tag{3.3}$$

then the assertion of theorem 2.1 holds for (2.1).

This confirms the conjecture in [3, p. 218] under the additional assumption (3.3). That it is not true in general will be shown in the rest of this section. Note that for the Monod function $f(x)$ given in (1.2), the left-hand side of (3.3) simplifies to $-2m_u^2a_u^3/(a_u + S)^6$, which is indeed negative.

The assumption in theorem 3.1 implies that the two growth functions f and g have only one positive intersection point. In contrast, we will now show that if f and g intersect at more than one positive value, then it is possible to choose the other parameters in (2.1) to produce an unstable interior equilibrium. The monotonicity of the flow implies then that there will be at least two stable equilibria in system (2.1)—either in the interior or on the boundary.

Recall from Section 2 that the determinant of the Jacobian J of (2.1) evaluated at an interior equilibrium is given by (3.1). If we can construct an interior equilibrium $E^* = (u^*, v^*)$ for (2.1) such that (3.1) is negative, then E^* is unstable and we are done. We will first present the general construction of such examples and give a concrete example in Section 5 to convince the sceptical reader.

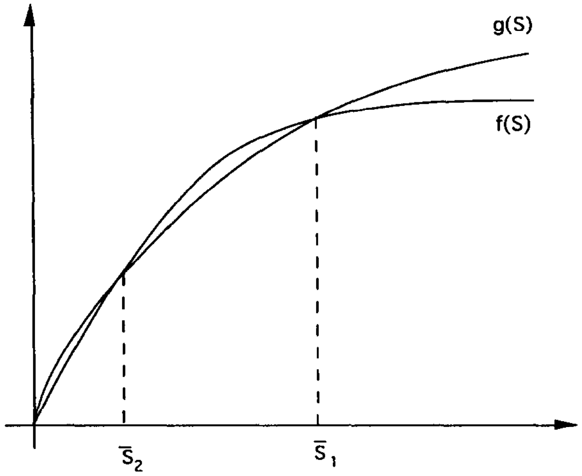

Fig. 1.

Let f and g be two arbitrary functions satisfying (1.4). Assume that f and g intersect at two positive values, i.e. there exists $0 < \bar{S}_2 < \bar{S}_1$ such that $f(\bar{S}_i) = g(\bar{S}_i)$. Let furthermore $\alpha_i = f'(\bar{S}_i)/g'(\bar{S}_i)$ $(i = 1, 2)$ be such that $\alpha_1 < 1 < \alpha_2$. Note that this assumption is automatically satisfied at two consecutive transverse intersection points of the graphs of f and g, maybe after interchanging f and g (cf. Fig. 1).

Let $S_i^* = \bar{S}_i - \varepsilon_i$ $(0 < \varepsilon_i \ll 1,\ i = 1, 2)$. Then $f(S_1^*) > g(S_1^*)$ and $f(S_2^*) < g(S_2^*)$.

Let $E^* = (u_1^*, u_2^*, v_1^*, v_2^*)$ be an interior equilibrium of (2.1) corresponding to the given S_1^*, S_2^*. By (2.1)

$$\begin{aligned} \frac{u_1^*}{u_2^*} &= -\frac{a_{22} + f(S_2^*)}{a_{21}} = -\frac{a_{12}}{a_{11} + f(S_1^*)} \\ \frac{v_1^*}{v_2^*} &= -\frac{a_{22} + g(S_2^*)}{a_{21}} = -\frac{a_{12}}{a_{11} + g(S_1^*)} \end{aligned} \tag{3.4}$$

so that $u_1^*/u_2^* > v_1^*/v_2^*$. Hence, if we choose S_i^* sufficiently close to $\bar{S}_i$ and less that $\bar{S}_i$ $(i = 1, 2)$, then $u_2^*/v_2^* < u_1^*/v_1^* < u_2^*/v_2^*(\alpha_2/\alpha_1)^{1/2}$ and the determinant in (3.1) is negative.

Since the construction of a general gradostat (1.8) with general diffusion matrix A is now rather easy, we will be more ambitious and construct an "original" gradostat (1.1). Hence, let $a_{11} = a_{22} = -2d$ and $a_{12} = a_{21} = d$. (We have assumed that $y_u = y_v = 1$.)

Denote $\bar{\lambda}_i = f(\bar{S}_i) = g(\bar{S}_i)$ $(i = 1, 2)$. Then

$$\begin{aligned} f(S_i) &\approx \bar{\lambda}_i - \varepsilon_i f'(\bar{S}_i) \\ g(S_i) &\approx \bar{\lambda}_i - \varepsilon_i g'(\bar{S}_i) \end{aligned} \qquad (i = 1, 2). \tag{3.5}$$

In order for (2.1) to have an interior equilibrium $E^* = (u_1^*, u_2^*, v_1^*, v_2^*)$, we need

$$\det\begin{pmatrix} a_{11} + f(S_1^*) & a_{12} \\ a_{21} & a_{22} + f(S_2^*) \end{pmatrix} = 0 = \det\begin{pmatrix} a_{11} + g(S_1^*) & a_{12} \\ a_{21} & a_{22} + g(S_2^*) \end{pmatrix} \tag{3.6}$$

which simplifies to

$$\begin{cases} d^2 = (-2d + f(S_1^*))(-2d + f(S_2^*)) \\ d^2 = (-2d + g(S_1^*))(-2d + g(S_2^*)) \end{cases} \tag{3.7}$$

or to

$$\begin{cases} d^2 \approx (-2d + \bar{\lambda}_1 - \varepsilon_1 f'(\bar{S}_1))(-2d + \bar{\lambda}_2 - \varepsilon_2 f'(\bar{S}_2)) \\ d^2 \approx (-2d + \bar{\lambda}_1 - \varepsilon_1 g'(\bar{S}_1))(-2d + \bar{\lambda}_2 - \varepsilon_2 g'(\bar{S}_2)). \end{cases} \tag{3.8}$$

These two equations are to be satisfied by one unknown d. However, we still have the choice of ε_1 and ε_2. For $\varepsilon_1 = \varepsilon_2 = 0$, these two equations coincide and have a unique solution $\bar{d}$, satisfying $2\bar{d} > \bar{\lambda}_i$ and $\bar{d}^2 = (-2\bar{d} + \bar{\lambda}_1)(-2\bar{d} + \bar{\lambda}_2)$. Therefore, we can expect that there is a C^1 curve in ε_1-ε_2-plane through the origin, where $d = d(\varepsilon_1, \varepsilon_2)$ satisfies both of the equations in (3.7). In the first approximation, this curve is given by

$$\varepsilon_1(f'(\bar{S}_1) - g'(\bar{S}_1))(2\bar{d} - \bar{\lambda}_2) = \varepsilon_2(g'(\bar{S}_2) - f'(\bar{S}_2))(2\bar{d} - \bar{\lambda}_1).$$

Therefore, we can choose such $\varepsilon_1 > 0$ and $\varepsilon_2 > 0$ as required in the beginning. The coordinate vectors of the equilibrium E^*, u^* and v^*, are then the positive eigenvectors of the quasipositive matrices in (3.6), and are determined from (3.4) up to multiples. The only further constraint to make this example an original gradostat is that $c_1 = 2c_2 > 0$, where $c_i = S_i^* + u_i^* + v_i^*$. This can be achieved as long as $S_1^* > 2S_2^*$ by using suitably large scalar multiples of u^* and v^*. Otherwise, if $S_1^* \le 2S_2^*$, we can at least achieve $c_1/2 < c_2 < 2c_1$ this way, so that the input vector satisfies $e = -Ac > 0$.

We conclude by showing that this is possible even if f and g are concave and related through (1.6). Suppose that for each choice of $\alpha, \beta > 0$ the equation $f(S) = g(S) = \beta f(\alpha S)$ has only one solution $S > 0$. Then $f(S)/f(\alpha S)$ must be strictly monotonic for each $\alpha \neq 1$. By lemma 3.2 this holds if and only if

$$f(S)f'(S) + Sf(S)f''(S) - Sf'(S)^2 < 0, \tag{3.9}$$

holds for all $S > 0$. It is not difficult to construct functions f satisfying (1.4)–(1.5), but violating (3.9). For example, one can take a smooth strictly concave perturbation of

$$f(S) = \begin{cases} \dfrac{S}{1+S} & 0 < S < 1 \\ \tfrac{1}{4}(1+S) & 1 \le S \le 2 \\ \dfrac{9S}{8(1+S)} & 2 < S, \end{cases} \tag{3.10}$$

and

$$g(S) = \tfrac{2}{3} f(2S)$$

then $f(\frac{1}{2}) = g(\frac{1}{2})$ and $f(1) = g(1)$. Moreover, $f(0) = 0$, $f'(S) > 0$ and $f''(S) \le 0$.

4. THE THREE VESSEL GRADOSTAT

In this section we show that for nonlinear uptake functions, the global stability result for the two vessel gradostat (theorems 2.1 and 3.1) does not generalize to the situation of more than two vessels.

More precisely we show the following.

THEOREM 4.1. Let f and g be bounded functions satisfying (1.4)–(1.5), such that there is a unique $\bar{S} > 0$ with $f(\bar{S}) = g(\bar{S})$. Suppose $f'(\bar{S}) > g'(\bar{S})$ so that $f(S) \lesseqgtr g(S)$ for $S \lesseqgtr \bar{S}$. Further assume that f'/g' is a strictly increasing function (or at least $(f'/g')(0) < (f'/g')(\bar{S}) < (f'/g')(\infty)$). Then there exists a three vessel gradostat as described in Section 1 with a linear configuration (i.e. $a_{13} = a_{31} = 0$) and intervessel flow rates $a_{12}, a_{32}, a_{21}, a_{23} > 0$ and certain input rates $e_i > 0$ such that (1.9) has an unstable interior equilibrium.

THEOREM 4.2. Under the same assumptions on f and g as in theorem 4.1, there exists a three vessel gradostat as described in Section 1 with a cyclic configuration (i.e. $a_{13} = a_{21} = a_{32} = 0$) and intervessel flow rates $a_{12}, a_{23}, a_{31} > 0$ and certain input rates $e_i > 0$ such that (1.9) has an unstable interior equilibrium.

As observed in Section 3, these assumptions on the uptake functions f and g are satisfied for Monod functions (1.2). The differential equations (1.9) can be written more explicitly as

$$\begin{aligned} \dot{u}_i &= \sum_{j=1}^{n} a_{ij}u_j + u_i f(S_i) \\ \dot{v}_i &= \sum_{j=1}^{n} a_{ij}v_j + v_i g(S_i) \end{aligned} \tag{4.1}$$

with $S_i = c_i - (u_i + v_i)$. The Jacobian matrix $J = (J(i,j))_{i,j=1,\ldots,2n}$ has a similar block form as in (2.3)

$$\begin{aligned} J(i,i) &= a_{ii} + f(S_i) - u_i f'(S_i), \\ J(i+n, i+n) &= a_{ii} + g(S_i) - v_i g'(S_i), \\ J(i,j) &= J(i+n, j+n) = a_{ij}, \\ J(i, i+n) &= -u_i f'(S_i), \\ J(i+n, i) &= -v_i g'(S_i), \\ J(i, j+n) &= J(i+n, j) = 0 \end{aligned} \tag{4.2}$$

$(i, j = 1, \ldots, n, i \neq j)$. Again, when evaluating J at an equilibrium point E^* we can simplify the diagonal terms to

$$J(i,i) = -u_i^{-1} \sum_{j \neq i} a_{ij}u_j - u_i f'(S_i) \tag{4.3}$$

and similarly for $J(i+n, i+n)$. For a tridiagonal 3 by 3 matrix A the determinant of J can be expressed as follows

$$\det J = \frac{a_{12}a_{32}}{u_1 u_2 u_3 v_1 v_2 v_3} D$$

where

$$D = a_{21}(u_1 v_2 - v_1 u_2)(u_1^2 F_1 v_2^2 G_2 - u_2^2 F_2 v_1^2 G_1)(u_3^2 F_3 v_2 + u_2 v_3^2 G_3 + a_{32} u_2 v_2)$$
$$+ a_{23}(u_2 v_3 - v_2 u_3)(u_2^2 F_2 v_3^2 G_3 - v_2^2 G_2 u_3^2 F_3)(u_1^2 F_1 v_2 + u_2 v_1^2 G_1 + a_{12} u_2 v_2)$$
$$+ a_{21} a_{23}(u_1 v_3 - u_3 v_1) u_2 v_2 (u_1^2 F_1 v_3^2 G_3 - u_3^2 F_3 v_1^2 G_1). \tag{4.4}$$

We used the notations $F_i = f'(S_i)$ and $G_i = g'(S_i)$ for short. Each term in this expression which resembles (2.5) obviously would be positive if f and g are linear functions, or more generally f'/g' is constant. For more general functions, like Monod functions, at least one of the three terms in D may be negative, and it is not obvious at all whether $D \geq 0$ could still be true. The following construction shows that it is not true in general.

To simplify computations we assume $v_1 = v_2 = v_3 = v$. This is equivalent to defining the diagonal terms from the second set of the equilibrium equations of (4.1) as

$$a_{ii} = -\sum_{j \neq i} a_{ij} - g(S_i). \tag{4.5}$$

This automatically guarantees that the row sums of A will be negative, as required in Section 1. Inserting this into the first set of equilibrium equations of (4.1) gives

$$a_{12}\left(\frac{u_2}{u_1} - 1\right) = g(S_1) - f(S_1) \tag{4.6}$$

$$a_{21}\left(1 - \frac{u_1}{u_2}\right) + a_{23}\left(1 - \frac{u_3}{u_2}\right) = f(S_2) - g(S_2) \tag{4.7}$$

$$a_{32}\left(\frac{u_2}{u_3} - 1\right) = g(S_3) - f(S_3). \tag{4.8}$$

Since the diagonal terms a_{ii} do not occur in (4.4), conditions (4.6)–(4.8) are the only side conditions we have to take care of when analysing the sign of D.

Let us pick $S_1 < S_3 < \bar{S} < S_2$. Then from (4.6) and (4.8) $u_2 > u_1$ and $u_2 > u_3$. This makes the first two terms in (4.4) positive, since f'/g' is increasing in S. Therefore, we have to try to make the last term in (4.4) negative. Of course, this will be the case if

$$u_1 > u_3 \quad \text{and} \quad u_1^2 \frac{F_1}{G_1} < u_3^2 \frac{F_3}{G_3}. \tag{4.9}$$

Clearly (4.9) can be achieved by assuming $u_3 = q u_1$, where q is any number satisfying $((F_1/G_1)(G_3/F_3))^{1/2} < q < 1$. To complete the argument that the D in (4.4) can be made to be negative, we pick any u_2 such that $u_2 > u_1, u_3$ and compute $a_{12} > 0$ and $a_{32} > 0$ from (4.6) and (4.8). Next, we choose $a_{21}, a_{23} > 0$ such that (4.7) holds. Since $\lim_{S \to \infty} f'(S) = 0$ and $\lim_{S \to \infty} g'(S) = 0$, F_2 and G_2 and hence the first two terms of D can be made arbitrarily small if S_2 was only chosen large enough. Therefore, the negative third term in of D in (4.4) will dominate and $D < 0$. Finally we have to guarantee that the input vector $e = -Ac$ has positive components. Since $c = S + u + v$ and $Au, Av < 0$, this will hold if we only replace the vectors u, v by a large scalar multiple (note, that in (4.6)–(4.8) only the ratios of the u_i entered). More precisely, since also the vector S or its second component is large, we need $u, v \gg S_2$ to make $e > 0$. In order to keep the first two terms of D small (they are of higher order in u, v than the third term), we also need $F_2 u \ll 1$, etc. Now for Monod functions $F_2 = f'(S_2)$ is of order S_2^{-2} as $S_2 \to \infty$, so that we need $u, v \ll S_2^2$ to make the first two terms of D small. For more general functions the same idea works, since (1.4)–(1.5) imply that $\lim_{S\to\infty} Sf'(S) = 0$.

We will present a concrete numerical example in Section 5 to convince the sceptical reader.

Remark. Solving (4.6)–(4.8) with a bit more care, e.g. by taking S_1 close to 0 and S_3 close to $\bar{S}$ one can achieve any prescribed ratio of the intervessel flow rates, in particular one may choose them all equal: $a_{12} = a_{32} = a_{21} = a_{23} > 0$.

The discussion on the case of a cyclic three vessel gradostat is similar. The determinant of J can be expressed as

$$\det J = \frac{a_{12}a_{23}a_{31}}{u_1u_2u_3v_1v_2v_3} D,$$

where D stands now for

$$\begin{aligned} D = {} & a_{31}v_1u_1(u_2v_1 - u_1v_2)(F_2G_1v_3u_2^2v_1 - u_3v_2^2G_2F_1u_1) \\ & + (u_2v_1 - u_1v_2)u_3v_3(G_1F_3F_2u_3u_2^2v_1^2 - u_1^2v_2^2G_3G_2F_1v_3) \\ & + a_{23}u_3v_3(-v_3u_1 + u_3v_1)(F_3u_2G_1u_3v_1^2 - u_1^2G_3F_1v_2v_3) \\ & + (-v_3u_1 + u_3v_1)u_2v_2(G_2G_1F_3v_2u_3^2v_1^2 - u_1^2F_2v_3^2G_3F_1u_2) \\ & + a_{12}(v_2u_3 - u_2v_3)u_2v_2(-F_2G_3u_1v_3^2u_2 + G_2u_3^2F_3v_1v_2) \\ & + v_1u_1(-v_2u_3 + u_2v_3)(v_1F_2G_1G_3v_3^2u_2^2 - F_1v_2^2G_2u_3^2F_3u_1). \end{aligned} \tag{4.10}$$

Again, in the limit $S_3 \to \infty$ only the first term remains, which can be easily made negative. We skip the details and present only a numerical example in Section 5 to show that it is indeed possible for $\det(J)$ to be negative at an interior equilibrium.

5. NUMERICAL EXAMPLES

In this section, we will show by means of numerical examples that the ideas presented in Sections 3 and 4 can be realized. More specifically, we will present numerical examples of

(I) a two vessel gradostat with f and g intersecting at two positive values,
(II) a tridiagonal three vessel gradostat with Monod f and g, and
(III) a cyclically connected three vessel gradostat with Monod f and g,

all of which possess an unstable interior equilibrium. All of these examples are found with the help of MAPLE, a software package designed by the Symbolic Computation Group at the University of Waterloo in Ontario, Canada.

(I) *A two vessel original gradostat*

Let f be the piecewise linear function

$$f(S) = \begin{cases} S & \text{for } 0 \le S \le 1 \\ 1 + \frac{1}{2}(S-1) & \text{for } 1 \le S \le 3 \\ 2 + \frac{1}{3}(S-3) & \text{for } 3 \le S \end{cases}$$

and let $g(S) = \beta f(\alpha S)$, where $\alpha = \frac{11}{6}$ and $\beta = \frac{15}{22}$. Then f and g intersect transversely at four positive values: $\frac{10}{11}$, $\frac{14}{11}$, $\frac{24}{11}$ and $\frac{42}{11}$. Let $\bar{S}_1 = \frac{42}{11}$ and $\bar{S}_2 = \frac{10}{11}$. It is easily verified that $(S_1^*, S_2^*, d) = (3.797477130, 0.8990909091, 1.713687059)$ is solution of (3.7). Moreover, $f(S_1^*) = 2.599159043$, $f(S_2^*) = 0.8990909091$, $g(S_1^*) = 2.264100319$, $g(S_2^*) = 0.9028409093$, $f'(S_1^*) = 1/3$, $f'(S_2^*) = 1$, $g'(S_1^*) = 5/12$ and $g'(S_2^*) = 5/8$. Now take $u_1^* = 52.38466620$ and $v_1^* = 10.48452334$. Then by (3.4), $u_2^* = [2 - f(S_1^*)/d]u_1^* = 7.117035300$ and $v_2^* = [2 - g(S_1^*)/d]v_1^* = 25.31720712$. One can easily verify that the determinant of the Jacobian matrix is -123.2453615 so that the interior equilibrium $E^* = (u_1^*, u_2^*, v_1^*, v_2^*)$ is unstable. Moreover, $c_1 = S_1^* + u_1^* + v_1^* = 200/3$ and $c_2 = S_1^* + u_2^* + v_2^* = 100/3$.

(II) *A tridiagonal three vessel general gradostat*

(i) Let $f(S) = S/(1 + S)$ and $g(S) = \frac{1}{2}S/(\frac{1}{3} + S)$. Then $\bar{S} = \frac{1}{3}$.

(ii) Let $S_1^* = \frac{1}{10}$, $S_2^* = 10000$ and $S_3^* = \frac{1}{5}$. Then $f(S_1^*) = \frac{1}{11}$, $f(S_2^*) = \frac{10000}{10001}$, $f(S_3^*) = \frac{1}{6}$, $g(S_1^*) = \frac{3}{26}$, $g(S_2^*) = \frac{15000}{30001}$ and $g(S_3^*) = \frac{3}{16}$. Also, $f'(S_1^*) = \frac{101}{121}$, $f'(S_2^*) = \frac{1}{100020001}$, $f'(S_3^*) = \frac{25}{36}$, $g'(S_1^*) = \frac{150}{169}$, $g'(S_2^*) = \frac{3}{1800120002}$ and $g'(S_3^*) = \frac{75}{128}$.

(iii) Let $u_1^* = 10$, $u_2^* = 11$, $u_3^* = 9$ and $v_1^* = v_2^* = v_3^* = 22000$. Then $c_1 = S_1^* + u_1^* + v_1^* = \frac{220101}{10}$, $c_2 = 32011$ and $c_3 = \frac{110046}{5}$.

Solving (4.6)–(4.8), we have $a_{23} = \frac{35}{143}$, $a_{32} = \frac{3}{32}$ and $a_{21} + 2a_{23} = \frac{1649945000}{300040001}$. If we choose $a_{23} = 1$, then $a_{21} = \frac{1049864998}{300040001}$. Using the second set of the equilibrium equations of (4.1), we obtain $a_{11} = -\frac{103}{286}$, $a_{22} = -\frac{1499919999}{300040001}$ and $a_{33} = -\frac{9}{32}$. One could easily verify that the first set of equilibrium equations of (4.1) are also satisfied and that the row sums of A are negative. Finally, one computes $\det(J)$ at E^* and it turns out to be the negative number

$$-\frac{534845439415186547414432081696656 25}{1838200446519660888909516980694272} \approx -29.096.$$

Hence, the interior equilibrium E^* is unstable and there are at least two stable equilibria. Moreover, the input vector $e = -Ac = (\frac{262703}{2860}, \frac{18302665105500}{300040001}, \frac{510249}{160})^T$ is positive.

(III) *A cyclically connected three vessel general gradostat with Monod growth functions*

Let

(i) $f(S) = S/(\frac{1}{100} + S)$ and $g(S) = 2S/(\frac{3}{100} + S)$,

(ii) $c_1 = \frac{5009}{1000}$, $c_2 = \frac{4009}{1000}$ and $c_3 = 13$, and

(iii) $a_{11} = -\frac{126}{247}$, $a_{12} = \frac{27}{247}$, $a_{22} = -\frac{123}{247}$, $a_{23} = \frac{9}{247}$, $a_{31} = \frac{999000}{1004003}$, $a_{33} = -\frac{3001000}{1004003}$ and $a_{13} = a_{21} = a_{32} = 0$.

Then

$$E^* = (S_1^*, S_2^*, S_3^*, u_1^*, u_2^*, u_3^*, v_1^*, v_2^*, v_3^*) = \left(\frac{9}{1000}, \frac{9}{1000}, 10, 4, 3, 2, 1, 1, 1\right)$$

is an interior equilibrium point and the determinant of the Jacobian matrix evaluated at E^* is the negative number

$$-\frac{70632079697353776142248000000000}{22981943417201469290323863097268 3} \approx -0.307.$$

Hence, E^* is unstable. Note also that $c = S + u + v = (\frac{5009}{1000}, \frac{4009}{1000}, 13)^T$ and the input $e = -Ac = (\frac{291513}{123500}, \frac{376107}{247000}, \frac{34009009}{1004003})^T$ is a positive vector.

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