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COMPETITION MODELS IN THE GRADOSTAT WITH GENERAL NUTRIENT UPTAKE FUNCTIONS

BETTY TANG

Dedicated to Paul Waltman on the occasion of his 60th birthday

ABSTRACT. Mathematical models of two competing microbial species in the gradostat have been studied extensively in recent years. Much analysis of the model is based on the assumption that the nutrient uptake function is the Michaelis-Menten term in the Monod growth model. This paper shows that previous results, especially for uniform persistence and coexistence, can also be applied to models assuming more general nutrient uptake functions.

1. Introduction. In this paper we study mathematical models of two species competing for a single growth-limiting nutrient in the gradostat assuming general nutrient uptake functions.

The gradostat is a laboratory device simulating an ecosystem with nonuniform spatial distribution of nutrient supply. The original system was used by Wimpenny and Lovitt to study the effects of nutrient gradients on microbial growth [**10, 22, 23**]. Mathematical models of microbial growth and competition in the gradostat have been studied extensively [**8, 9, 17, 18, 19**]. While conditions for uniform persistence of the two species have been established, coexistence equilibrium as a global attractor of trajectories of the model equations has only been established for a very special case of a two-vessel gradostat using the Michaelis-Menten nutrient uptake function proposed by Monod [**12**].

The Michaelis-Menten nutrient uptake function is a prototype of monotonically increasing, bounded, and concave functions. Even though the Monod model is a popular model for microbial growth, other functions with similar properties are better approximations to some experimental data [**1**, Figure 2]. It is also possible that the function may not even be concave. From a mathematical point of view, it is desirable to study a model which can describe a wider class of nutrient

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uptake functions. We examine here the extent of how nutrient uptake functions can be generalized to obtain the same results in [**8, 18**].

A summary of previous results on the gradostat competition model with Michaelis-Menten nutrient uptake function is given in Section 2. The analysis of the general n-vessel gradostat model can be carried out with a $2n$-dimensional nonautonomous system

$$X' = \mathcal{F}(X,t)$$

which is asymptotically autonomous: $\mathcal{F}(X,t) \to \mathcal{F}(X)$ as $t \to \infty$. The limit autonomous system

$$X' = \mathcal{F}(X)$$

is strongly monotone and the global behavior of its trajectories can be analyzed using the theory of monotone dynamical systems developed by Hirsch [**5, 6, 7**], Smith [**14**], etc. It is clarified here that the sufficient conditions given in [**18**] for almost all trajectories of the limit autonomous system converging to some positive equilibrium only guarantees the uniform persistence of the two competing species in the original nonautonomous system. If there is a strictly positive equilibrium of the limit autonomous system which is a global attractor, then using a theorem of Markus [**11**] one can show that there is a unique coexistence equilibrium which is also the global attractor of the nonautonomous system. This procedure has been successfully carried out previously only with a very special case of a two-vessel gradostat [**8**].

In Section 3 we examine the particular properties of the nutrient uptake function that are required to establish the results summarized in Section 2. This enables us to show that monotone increasing, bounded, and concave nutrient uptake functions are sufficient to obtain uniform persistence results for the general n-vessel gradostat. If $n = 2$, it is shown that the concavity assumption can be removed to obtain uniform persistence, and a certain class of monotone increasing, bounded concave or sigmoidal functions is sufficient for the stronger result of uniqueness of the coexistence equilibrium in any two-vessel gradostat. The trade-off of such generalizations is that the result may not hold for a set of measure zero in the parameter space.

The following is a list of definitions and notations used throughout the paper. The partial ordering on $\mathbf{R}^n$ defined by a cone K with nonempty interior is denoted by the subscript $K : x \leq_K y$ if $y - x \in K$, $x <_K y$ if $x \leq_K y$ and $x \neq y$, $x \ll_K y$ if $y - x \in \overset{\circ}{K}$. The subscript K is omitted if K is the nonnegative cone $\mathbf{R}^n_+ = \{x = (x_1, \dots, x_n) \in \mathbf{R}^n \mid x_i \geq 0, 1 \leq i \leq n\}$. The interval $[x, y]_K$ is the set $\{z \in \mathbf{R}^k \mid x \leq_K z \leq_K y\}$. The trajectory of the solution of the system

$$x' = \mathcal{F}(x, t)$$

satisfying $x(0) = x_0$ is denoted by $\pi(t; x_0)$.

For $n \times n$ matrices $M = \{M_{ij}\}$, $M \leq N$ ($M < N$) if $M_{ij} \leq N_{ij}$ ($M_{ij} < N_{ij}$) for all (i, j). A diagonal matrix with d_i being the i-th diagonal element is denoted by $\operatorname{diag}(d_1, \dots, d_n)$. M is quasipositive if $M_{ij} \geq 0$ whenever $i \neq j$. The Perron-Frobenius theory on quasipositive irreducible matrices [**2**] is very useful for the analysis of the model. For such matrices M, the stability modulus

$$s(M) = \max\{\operatorname{Re} \lambda \mid \lambda \text{ is an eigenvalue of } M\}$$

is a simple eigenvalue and the only eigenvalue of M with a corresponding eigenvector $w \gg 0$. If N is another quasipositive matrix, $M \leq N$, $M \neq N$ and $M + N$ is irreducible, then $s(M) < s(N)$.

2. The model based on Monod growth kinetics. Let $S = (S_1, \dots, S_n)$, $u = (u_1, \dots, u_n)$, $v = (v_1, \dots, v_n)$, $b = (b_1, \dots, b_n)$, where S_i, u_i and v_i are respectively the concentration of the growth-limiting nutrient and the two competing species, referred to as the u-species and the v-species, in the i-th vessel of the gradostat, and b_i is the (constant) concentration of nutrient supply into the i-th vessel. Model equations describing competition in the gradostat between the two species are of the following form

$$\begin{aligned} S' &= AS - F_u(S)u - F_v(S)v + b \\ u' &= Au + F_u(S)u \\ v' &= Av + F_v(S)v \\ S(0) = S_0, &\qquad u(0) = u_0, \qquad v(0) = v_0. \end{aligned} \tag{2.1}$$

A is an $n \times n$ matrix, the elements of which represent the flow rates between different vessels, and $F_u(S) = \operatorname{diag}(f_u(S_1), \dots, f_u(S_n))$

$(F_v(S) = \operatorname{diag}(f_v(S_1), \dots, f_v(S_n)))$, where $f_u(S_i)$ $(f_v(S_i))$ is the per-capita nutrient uptake rate of the u-species (v-species) in the i-th vessel and is the same as the specific growth rate upon nutrient consumption of the species (after appropriate scaling) in that vessel.

Based on practical considerations in a gradostat experiment, the matrix A must satisfy the following considerations:

(a) $A_{ii} < 0$,

(b) $A_{ij} \geq 0$, $i \neq j$,

(c) $\sum_{j=1}^{n} A_{ij} \leq 0$, with strict inequality holds for some i,

(d) A is irreducible.

These constraints render A a quasipositive and irreducible matrix, and $s(A) < 0$. Hence $-A$ is an M-matrix, and $-A^{-1}$ has positive entries [**18**]. For the original gradostat described by Wimpenny and Lovitt [**10, 22, 23**], A is of the form

$$A = \mathcal{A}_{n\times n} \begin{pmatrix} -2 & 1 & 0 & 0 & \cdots & \\ 1 & -2 & 1 & 0 & \cdots & \\ \vdots & & & & & \\ 0 & \cdot & \cdot & \cdot & 1 & -2 \end{pmatrix}.$$

(Readers are referred to [**18**] for detailed derivatives of (2.1).) We are primarily interested in solutions of (2.1) with initial values $S_0 \geq 0$, $u_0 > 0$ and $v_0 > 0$.

Mathematical analysis of (2.1) has been carried out in [**8, 18**] incorporating the Monod growth model [**12**]: the function $f(S)$ is given by Michaelis-Menten enzyme kinetics and is of the form $f(S) = mS/(a+S)$, where m and a are positive constants interpreted as respectively the maximal growth rate and the half-saturation constant. (The subscript u or v is dropped for convenience's sake.) The constants m and a are species specific and depend on the limiting nutrient under consideration. Since the competing species are genetically distinct, it is biologically reasonable to assume that either $m_u \neq m_v$ or $a_u \neq a_v$.

The following is a summary of results in [**8, 18**] concerning the solutions of (2.1) assuming Monod growth kinetics.

Theorem 2.1. $\mathbf{R}_+^{3n}$, *as well as the boundaries* $u = 0$ *and* $v = 0$, *are positively invariant sets with respect to the dynamical system generated by the equations in* (2.1).

Let $z(t) = S(t) + u(t) + v(t)$. Since $z' = Az + b$, analysis of (2.1) can be carried out with the $2n$-dimensional nonautonomous system

$$
\begin{aligned}
u' &= Av + F_v(z(t) - u - v)u \\
v' &= Av + F_v(z(t) = u - v)v \\
u(0) = u_0 &> 0, \qquad v(0) = v_0 > 0.
\end{aligned}
\tag{2.2}
$$

Since $s(A) < 0$, $z(t) \to \omega = -A^{-1}b \gg 0$ as $t \to \infty$, solutions of (2.1) with initial conditions in $\mathbf{R}_+^{3n}$ are bounded, and (2.2) is an asymptotically autonomous system. Markus shows that the omega limit set W^+ of a trajectory $\pi(t; u_0, v_0)$ of (2.2) is nonempty, compact and connected, and $\pi(t; u_0, v_0)$ approaches W^+ as $t \to \infty$ [**11**]. The following theorem, also due to Markus [**11**], shows that under certain conditions the asymptotic behavior of trajectories of (2.2) can be obtained by analyzing the limit equations:

$$
\begin{aligned}
U' &= AU + F_u(\omega - U - V)U \\
V' &= AV + F_v(\omega - U - V)V
\end{aligned}
\tag{2.3}
$$

in $\mathbf{R}_+^{2n}$.

Markus's Theorem [**11**]. *Let* E *be a locally asymptotically stable compact invariant set of* (2.3). *If the omega limit set of a trajectory* $\pi(t; u_0, v_0)$ *of* (2.2) *intersects the basin of attraction of* E, *then* $\pi(t; u_0, v_0)$ *approaches* E *as* $t \to \infty$.

Actually in the original version of Markus's theorem, E is a locally asymptotically stable equilibrium point, but the extension to a locally asymptotically stable compact invariant set is straightforward.

The analyses in [**8, 18**] are focused on system (2.3). Most of the results also apply to system (2.1) using Markus's theorem but are not explicitly stated. We will clarify that here and also point out those results that cannot be directly applied to (2.1).

It is easy to see that the omega limit set of all trajectories $\pi(t; U_0, V_0)$ of (2.3) is contained in the set $P = \{(U, V) \in \mathbf{R}^{2n}_{+} \mid U + V \leq \omega\}$, so the analysis of (2.3) can be restricted to P. In the interior of P, (2.3) is a strongly monotone dynamical system with respect to the partial ordering induced by the cone $K = \mathbf{R}^n_+ \times \mathbf{R}^n$: if $(U_0, V_0) <_K (\overline{U}_0, \overline{V}_0), \pi(t; U_0, V_0) \ll_K \pi(t; \overline{U}_0, \overline{V}_0)$.

First consider the equations of (2.3) on the boundary $V = 0$:

$$U' = AU + F_u(\omega - U)U, \qquad U(0) = U_0,\ \omega \geq U_0 > 0, \tag{2.4}$$

which is a cooperative and strongly monotone system.

Theorem 2.2. *If* $s(A + F_u(\omega)) \leq 0$, $U(t) \to 0$ *as* $t \to \infty$.

Theorem 2.3. *If* $s(A+F_u(\omega)) > 0$, *there exists a unique equilibrium* $\hat{u}, \omega \gg \hat{u} \gg 0$, *and all trajectories of* (2.4) *approach* $\hat{u}$ *as* $t \to \infty$.

The sign of $s(A + F_u(\omega))$ determines the local stability of the equilibrium 0 for system (2.4). Direct application of Markus's theorem shows that, on the boundary $v = 0$, if $s(A+F_u(\omega)) \leq 0$, all trajectories $\pi(t; S_0, u_0, 0)$, $S_0 \geq 0$, $u_0 > 0$, of (2.1) approach the equilibrium $(\omega, 0, 0)$ as $t \to \infty$, and if $s(A + F_u(\omega)) > 0$, there exists a unique equilibrium $(\omega - \hat{u}, \hat{u}, 0)$, $\omega \gg \hat{u} \gg 0$, such that $\pi(t; S_0, u_0, 0)$ approaches $(\omega - \hat{u}, \hat{u}, 0)$ as $t \to \infty$. Similarly, on the boundary $v = 0$, if $s(A + F_v(\omega)) \leq 0$, all trajectories $\pi(t; S_0, 0, v_0)$, $S_0 \geq 0$, $v_0 > 0$ of (2.1) approach the equilibrium $(\omega, 0, 0)$ as $t \to \infty$, and if $s(A + F_u(\omega)) > 0$, there exists a unique equilibrium $(\omega - \tilde{v}, \tilde{v}, 0)$, $\omega \gg \tilde{v} \gg 0$, such that $\pi(t; S_0, 0, v_0)$ approaches $(\omega - \tilde{v}, \tilde{v}, 0)$ as $t \to \infty$. Note that $\hat{u}$ and $\tilde{v}$ must satisfy respectively $s(A + F_u(\omega - \hat{u})) = 0$ and $s(A + F_v(\omega - \tilde{v})) = 0$.

Competition results can be classified based on Σ, the set of equilibrium points of (2.3). Obviously, the elements of Σ change as the parameters of (2.3) change.

Lemma 2.4. (a) $E_0 = (0, 0)$ *always exists*;

(b) $E_u = (\hat{u}, 0)$ *exists if and only if* $s(A + F_u(\omega)) > 0$;

(c) $E_v = (0, \tilde{v})$ *exists if and only if* $s(A + F_v(\omega)) > 0$;

(d) *if there exists an equilibrium* $E^+ = (u^+, v^+)$ *in* $\overset{\circ}{\mathbf{R}}{}^{2n}_+$*, then* $E^+ \in \overset{\circ}{P}$*,* E_u *and* E_v *exist, and* $E_u \gg_K E^+ \gg_K E_v$.

Theorem 2.5. (a) *If* $\Sigma = \{E_0\}$*,* E_0 *is the global attractor for* (2.3).

(b) *If* $\Sigma = \{E_0, E_u\}$ *or* $\{E_0, E_v\}$*, then the positive equilibrium point is the global attractor for* (2.3).

(c) *If* $\Sigma = \{E_0, E_u, E_v\}$*, then either* E_u *(if* $s(A + F_v(\omega - \hat{u})) < 0$*) or* E_v *(if* $s(A + F_u(\omega - \tilde{v})) < 0$*) is the global attractor for* (2.3).

The sign of $s(A + F_v(\omega - \hat{u}))$ and of $s(A + F_u(\omega - \tilde{v}))$ determines respectively the local stability of E_u and E_v for system (2.3). If E is an equilibrium point of (2.3), denote by $\overline{E}$ the corresponding point of (2.1), e.g., $\overline{E}_u = (\omega - \hat{u}, \hat{u}, 0)$. Markus's theorem immediately implies that all trajectories $\pi(t; S_0, u_0, v_0)$, $S_0 \geq 0$, $u_0 > 0$, $v_0 > 0$, of (2.1) converge to $\overline{E}_0$ as $t \to \infty$ in case (a) of Theorem 2.5; to $\overline{E}_u$ or $\overline{E}_v$ in case (b), depending on whether E_u or E_v exists, (if a species cannot survive without competition, then it also will not survive when the competitor is present); and to $\overline{E}_u$ or $\overline{E}_v$ in case (c), depending on whether E_u or E_v is a local attractor for system (2.3). Note that in the last case $s(A + F_v(\omega - \hat{u}))$ and $s(A + F_u(\omega - \tilde{v}))$ cannot both be negative.

Theorem 2.6. (a) Σ *contains an equilibrium point* E^+ *in* $\overset{\circ}{\mathbf{R}}{}^{2n}_+$ *only if the graphs of the functions* $f_u(S)$ *and* $f_v(S)$ *intersect at some* S*,* $0 < S < \max(\omega_1, \omega_2)$.

(b) *If* E_u *and* E_v *exist and* $s(A + F_v(\omega - \hat{u})) > 0$ *and* $s(A + F_u(\omega - \tilde{v})) > 0$*, then there exist equilibrium points* E^* *and* E^{**} *in* $\overset{\circ}{P}$ *satisfying* $E_v \ll_K E^* \leq_K E^{**} \ll_K E_u$*, and the omega limit set of all trajectories* $\pi(t; u_0, v_0)$*,* $u_0 > 0$*,* $v_0 > 0$*, of* (2.3) *is contained in the set* $\Lambda = \overset{\circ}{P} \cap [E^*, E^{**}]_K$*. Moreover, almost all of these trajectories approach an equilibrium point in* Λ *as* $t \to \infty$.

If $(u_0, v_0) \in \bar{\Lambda}$, monotonicity implies that $E^* = \pi(t; E^*) \leq_K \pi(t; u_0, v_0) \leq_K \pi(t; E^{**}) = E^{**}$ for $t > 0$, so $\bar{\Lambda}$ is an attracting compact invariant set. Markus's theorem then implies that, under the hypotheses of Theorem 2.6, all trajectories $\pi(t; S_0, u_0, v_0)$, $S_0 \geq 0$, $u_0 > 0$, $v_0 > 0$, of (2.1) approach the set

$$\Delta = \{(\omega - u - v, u, v) \in \overset{\circ}{\mathbf{R}}{}_{+}^{3n} \mid (u, v) \in \bar{\Lambda}\}$$

as $t \to \infty$. Whether almost all of these trajectories approach an equilibrium in Δ is an open question. In other words, Theorem 2.6(b) gives sufficient conditions only for the uniform persistence of the two competing species in system (2.1).

Theorem 2.7. *Under the same hypotheses in Theorem* 2.6, *if any equilibrium* $E^+ = (u^+, v^+)$, $u^+ \gg 0$, $v^+ \gg 0$, *of* (2.3) *is locally asymptotically stable, then* $E^* = E^{**}$ *and is the global attractor for system* (2.3).

Proof. The set Λ is the global attractor for (2.3). Suppose $E^* \neq E^{**}$, then $E^* \ll_K E^{**}$ by strong monotonicity. Since E^* and E^{**} are both locally asymptotically stable, there exists $E^\dagger$, $E^* \ll_K E^\dagger \ll_K E^{**}$, which is unstable [**13**, Proposition 3.7], a contradiction. Hence $E^* = E^{**}$. □

If the hypotheses in Theorem 2.7 are satisfied, then Markus's theorem implies a stronger coexistence result for system (2.1): there exists a unique $\overline{E}^* \in \overset{\circ}{\mathbf{R}}{}_{+}^{3n}$ and all trajectories $\pi(t; S_0, u_0, v_0)$, $u_0 > 0$, $v_0 > 0$, approach $\overline{E}^*$ as $t \to \infty$. Although in numerical simulations this scenario holds for $n \geq 2$, only one special case for $n = 2$ has been proved so far:

Lemma 2.8 [**8**]. *If* $n = 2$, $A = \mathcal{A}_{2\times 2}$, *and* $b = c(1, 0)$, $c > 0$, *then any interior equilibrium* $E^+ = (u^+, v^+)$, $u^+ \gg 0$, $v^+ \gg 0$, *of* (2.3) *is locally asymptotically stable.*

In [**17**], a two-vessel gradostat corresponding to which A is of the form

$$\begin{pmatrix} -D - e & e \\ e & -D - e \end{pmatrix}$$

is considered, and it was pointed out that the above lemma also applies.

Theorem 2.9. *Assume the same hypotheses in Lemma* 2.8 *and suppose* E_u *and* E_v *exist.*

(a) *If* E_u (E_v) *is a local attractor for system* (2.3), *then there is no interior equilibrium and* $\overline{E}_u$ $(\overline{E}_v)$ *is the global attractor for system* (2.1).

(b) *A necessary condition for the two species to coexist in system* (2.1) *is* $s(A + F_v(\omega - \hat{u})) \geq 0$ *and* $s(A + F_u(\omega - \tilde{v})) \geq 0$, *and a sufficient condition for coexistence is* $s(A + F_v(\omega - \hat{u})) > 0$ *and* $s(A + F_u(\omega - \tilde{v})) > 0$. *Moreover, in the latter case all trajectories* $\pi(t; S_0, u_0, v_0)$, $S_0 \geq 0$, $u_0 > 0$, $v_0 > 0$, *of* (2.1) *approach a unique coexistence equilibrium* $\overline{E}^* = (\omega - u^* - v^*, u^*, v^*)$ *in* $\overset{\circ}{\mathbf{R}}{}^6_+$.

3. Model equations with general nutrient uptake function. The nutrient uptake term in the Monod growth model is a prototype of functions $f = mg(S/a)$, where g is a C^1 function defined on an open interval containing $\mathbf{R}_+$ with the following properties:

(P1) $g(0) = 0$, $0 \leq g'(0) < \infty$, $g^{(k)}(0) > 0$ for some $k < \infty$.

(P2) $g'(S) > 0$, i.e., g is monotonically increasing, for $S \geq 0$.

(P3) $\lim_{S \to \infty} g(S) = 1$.

(The subscript u or v is dropped.)

Properties (P1)–(P3) are characteristic of microbial nutrient uptake rate observed experimentally (see, for example, [**21**, Figure 2]). As far as the analysis is concerned, (P2) is the most important property: much of the analysis is based on the fact that systems (2.3) and (2.4) are monotone dynamical systems, a direct consequence of (P2).

Besides the Michaelis-Menten term, other examples of uptake function include the exponential term $g(S) = 1 - \exp(-S \ln 2)$ proposed by Teissier [**20**], and the hyperbolic tangent term $\tanh((S \ln 3/2))$ proposed by Bleecken [**3**]. These functions are all concave and agree reasonably well with experimental data. However, data for very low nutrient concentration is not available, leaving open the possibility that the function can change concavity for low S, for example, a sigmoidal function. We will examine whether the assumption of the Michaelis-

Menten term, i.e., $g = S/(1+S)$, in the various theorems in the last section can be generalized to concave and sigmoidal functions. Some generalizations have already been mentioned in [**16**] for the one-species case.

(P1)–(P3) are obviously sufficient for Theorem 2.1, the boundedness of solutions of (2.1), and the equivalence of systems (2.1) and (2.2). Since, additionally, A is an irreducible matrix, systems (2.3) and (2.4) are strongly monotone dynamical systems in $\overset{\circ}{P}$ and $\{u \in \mathbf{R}^n_+ \mid 0 \ll u \ll \omega\}$, respectively.

The convergence of trajectories $\pi(t; U_0)$ of (2.4) to 0 in Theorem 2.2 is implied by (2.4) being a strongly monotone dynamical system and 0 being locally asymptotically stable, thus no additional property of g is required. An easy way to see this is to note that $A + F_u(\omega - u) \leq A + F_u(\omega)$ and use Kamke's comparison theorem [**4**]. On the other hand, convergence to $\hat{u} \gg 0$ in Theorem 2.3 hinges on the uniqueness of a positive equilibrium point of (2.4) [**6**, Theorem 5.6]. In [**14**] general cooperative systems are discussed and it is shown that a sufficient condition for this uniqueness result is g being a C^2 concave function:

$$\text{(P4)} \qquad\qquad g''(S) < 0, \qquad \text{for } S \geq 0.$$

The application of this for the gradostat equations is mentioned in [**16**]. We show in the following that, due to special properties of planar systems, concavity of g is not a necessary condition for $n = 2$; whether this holds for $n > 2$ is unknown.

Theorem 3.1. *For $n = 2$, Theorem* 2.3 *holds if g satisfies* (P1)–(P3).

Proof. If $n = 2$, $\pi(t; U_0)$ converges to some equilibrium point as $t \to \infty$ [**5**, Theorem 2.3]. Since $s(A + F_u(\omega)) > 0$ and $s(A + F_u(\omega))$ is the only eigenvalue of $A + F_u(\omega)$ with an eigenvector in $\overset{\circ}{R}{}^2_+$, 0 does not have a stable manifold which intersects $\overset{\circ}{R}{}^2_+$ and, therefore, cannot be the omega limit point of any trajectory satisfying $U_0 > 0$. Positive invariance of $\mathbf{R}^2_+$ implies that there exists an equilibrium $\hat{u} > 0$. Since all entries of $-A^{-1}$ are positive, $\hat{u} = [-A^{-1} F_u(\omega - \hat{u})]\hat{u}$ actually satisfies $\hat{u} \gg 0$. Suppose $\bar{u} \gg 0$ is another equilibrium point and, without loss of generality, assume $\bar{u}_1 \geq \hat{u}_1$. Then

$$\begin{aligned}\hat{u}_2 &= (-A_{11} - f_u(\omega_1 - \hat{u}_1))\hat{u}_1/A_{12}\\ &\leq (-A_{11} - f_u(\omega_1 - \bar{u}_1))\bar{u}_1/A_{12} = \bar{u}_2\end{aligned}$$

and so $\hat{u} < \bar{u}$. But that implies $0 = s(A + F_u(\omega - \hat{u})) < s(A + F_u(\omega - \bar{u})) = 0$, a contradiction. □

Thus (P1)–(P4) are sufficient for the same conclusions in Lemma 2.4 and Theorem 2.5 for $n \geq 2$, and (P4) can be dropped for $n = 2$. Results for interior equilibrium points of system (2.3) given by Theorems 2.6 and 2.7 are again consequences of (2.3) being a strongly monotone dynamical system in $\overset{\circ}{P}$ and require no additional assumption on g besides (P1)–(P3).

Lemma 2.8 for one particular case when $n = 2$ is proved in [**8**] using special forms of A and b as well as the Michaelis-Menten nutrient uptake term $g(S) = S/(1 + S)$. This is a crucial result enabling us to use Markus's theorem to obtain the global behavior of solutions of (2.1) as given in Theorem 2.9. The hypotheses of Lemma 2.8 can be generalized:

Theorem 3.2. *Suppose* $n = 2$, g *satisfies* (P1)–(P3), *and*

(P5) *for any* $c > 1$, $g'(cS)/g'(S)$ *is a strictly decreasing function of* S.

Except for a set of measure zero in the parameter space, any interior equilibrium $E^+ = (u^+, v^+)$, $u^+ \gg 0$, $v^+ \gg 0$, *of* (2.3), *if it exists, is locally asymptotically stable.*

Note that the hypotheses in the above theorem impose no extra condition on A and b. We first mention some properties of E^+ and the graphs of f_u and f_v that will be used in the proof of Theorem 3.2. By Theorem 2.6(a), existence of E^+ implies that the graphs of f_u and f_v must intersect at some S, $0 < S < \max(\omega_1, \omega_2)$. If there is a unique intersection point at $S = \sigma > 0$, either (i) $f_u(S) > f_v(S)$ for $S \in (0, \sigma)$ and $f_u(S) < f_v(S)$ for $S > \sigma$, or (ii) $f_u(S) < f_v(S))$ for $S \in (0, \sigma)$ and $f_u(S) > f_v(S))$ for $S > \sigma$. If (i) holds, $m_v > m_u$ and $m_u/(a_u)^k > m_v/(a_v)^k$, where $g^{(i)}(0) = 0$ for $i < k$ and $g^{(k)}(0) > 0$. The inequalities are reversed if (ii) holds. (The inequalities may not be strict ones, but the case of equalities corresponds to a set of measure zero in the parameter space.)

Denote $\omega - u^+ - v^+$ by S^+, $-A_{ii} - f_u(S_i^+)$ by α_i, $f'_u(S_i^+)u_i$ by β_i, $i = 1, 2$, and $-A_{ii} - f_v(S_i^+)$ by α_i, $f'_u(S_i^+)v_i$ by β_i, $i = 3, 4$.

Lemma 3.3. *If* $n = 2$ *and* g *satisfies* (P1)–(P3), *then any equilibrium point* $E^+ = (u^+, v^+)$ *of* (2.3), *if it exists, satisfy*

(a) $\alpha_i > 0$ *and* $\beta_i > 0$, $i = 1, 2, 3, 4$;

(b) $\alpha_a \alpha_2 = A_{12}A_{21} = \alpha_3 \alpha_4$;

(c) $u_2^+ = \alpha_1 u_1^+ / A_{12}$, $v_1^+ = \alpha_4 v_2^+ / A_{21}$;

(d) *except for a set of measure zero in the parameter space,* $S_1^+ \neq S_2^+$, *and either* $f_u(S_1^+) > f_v(S_1^+)$ *and* $f_u(S_2^+) < f_v(S_2^+)$, *or* $f_u(S_1^+) < f_v(S_1^+)$ *and* $f_u(S_2^+) > f_v(S_2^+)$.

Proof. (a) to (c) are obvious. To prove (d), first note that if E^+ exists, $s(A + F_u(S^+)) = 0 = s(A + F_v(S^+))$. Suppose $S_1^+ = S_2^+ = \mathcal{S}$. Then it must be the case that the graphs of f_u and f_v intersect at $S = \mathcal{S}$, and $f_u(\mathcal{S}) = f_v(\mathcal{S}) = -s(A)$, which happens only for a set of measure zero in the parameter space. Next, suppose that $f_u(S_i^+) > f_v(S_i^+)$, $i = 1, 2$. Then $0 = s(A+F_u(S^+)) > s(A+F_v(S^+)) = 0$, a contradiction. Therefore, either $f_u(S_1^+) > f_v(S_1^+)$ and $f_u(S_2^+) \leq f_v(S_2^+)$, or $f_u(S_1^+) \leq f_v(S_1^+)$ and $f_u(S_2^+) > f_v(S_2^+)$. Except for a set of measure zero in the parameter space, $f_u(S_i^+) \neq f_v(S_i^+)$, $i = 1, 2$, so generically all the inequalities are strict ones. The other inequalities can be shown similarly. $\square$

Lemma 3.4. *If* g *satisfies* (P1)–(P3) *and* (P5), *then the graphs of* $f_u(S)$ *and* $f_v(S)$ *intersect at most once for* $S > 0$.

Proof. Let $h(S) = f_u(S) - f_v(S)$, which is bounded for $S > 0$. Suppose without loss of generality that $h(S) > 0$ for S small. Then

$$h'(S) = \frac{m_u}{a_u} g'\left(\frac{S}{a_u}\right) - \frac{m_v}{a_v} g'\left(\frac{S}{a_v}\right)$$

is positive for S small and vanishes if and only if $g'(S/a_u)/g'(S/a_v) = m_v a_u / m_u a_v = q$. If $a_u < a_v$, put $S/a_v = x$ and $S/a_u = cx$ where

$c = a_v/a_u > 1$, and $Q = q$, otherwise put $S/a_u = x$ and $S/a_v = cx$, where $c = a_u/a_v > 1$, and $Q = 1/q$. Since $g'(cx)/g'(x)$ is strictly decreasing, $g'(cx)/g'(x) = Q$ has at most one solution for $x > 0$. This shows that the graph of $h(S)$ has at most one local extremum point for $S > 0$, and hence $h(S) = 0$ has at most one solution for $S > 0$. □

Proof of Theorem 3.2. Let $A_{12} = r_1$, $A_{21} = r_2$. Existence of E^+ and the last lemma implies that there is a unique σ, $0 < \sigma < \max(\omega_1, \omega_2)$, at which the two graphs f_u and f_v intersect. The Jacobian matrix of (2.3) evaluated at E^+ is equivalent to

$$J = \begin{pmatrix} -\alpha_1 - \beta_1 & r_1 & \beta_1 & 0 \\ r_2 & -\alpha_2 - \beta_2 & 0 & \beta_2 \\ \beta_3 & 0 & -\alpha_3 - \beta_3 & r_1 \\ 0 & \beta_4 & r_2 & -\alpha_4 - \beta_4, \end{pmatrix}$$

and it is sufficient to show that the determinants of the principal minors, denoted by d_i, $i = 1, 2, 3, 4$, satisfy $\operatorname{sgn}(d_i) = (-1)^i$ [**13**, Proposition 3.4]. Obviously $d_1 = -\alpha_1 - \beta_1 < 0$. Direct computation shows that

$$d_2 = \beta_1\beta_2 + \alpha_1\beta_2 + \alpha_2\beta_1 > 0$$

and

$$d_3 = -(\alpha_2\alpha_3\beta_1 + \alpha_1\alpha_3\beta_2 + \alpha_3\beta_1\beta_2 + \alpha_1\beta_2\beta_3) < 0.$$

After simplification, d_4 an be written as

$$\begin{aligned} d_4 &= (\alpha_1\alpha_4 - r_1 r_2)\left(\beta_2\beta_3 - \frac{r_1 r_2}{\alpha_1\alpha_4}\beta_1\beta_4\right) \\ &= u_2^+ v_1^+ \frac{m_u m_v}{a_u a_v}(\alpha_1\alpha_4 - r_1 r_2)\left\{g'\left(\frac{S_2^+}{a_u}\right) g'\left(\frac{S_1^+}{a_v}\right)\right. \\ &\qquad \left. - \left[\frac{r_1 r_2}{\alpha_1\alpha_4}\right]^2 g'\left(\frac{S_1^+}{a_u} g'\left(\frac{S_2^+}{a_v}\right)\right\}. \end{aligned}$$

Denote the last term in the above expression by R. We will show that $\alpha_1\alpha_4 - r_1 r_2$ and R are of the same sign. First assume $S_2^+ < S_1^+$. If $f_u(S) > f_v(S)$ for $S \in (0, \sigma)$ and $f_v(S) > f_u(S)$ for $S > \sigma$, i.e., $m_v > m_u$ and $m_u/(a_u)^k > m_v/(a_v)^k$ for some $k > 0$, we have $f_u(S_1^+) < f_v(S_1^+)$ and $f_u(S_2^+) > f_v(S_2^+)$, and $a_v > a_u$. Then

$\alpha_4 > \alpha_2$ and hence $\alpha_1\alpha_4 > r_1r_2$. Let $x_i = S_i^+/a_v$, and write S_i^+/a_u as cx_i, where $c = a_v/a_u > 1$ and $i = 1, 2$. Then, since $x_2 < x_1$, $R > g'(x_1)g'(cx_2) - g'(x_2)g'(cx_1) > 0$. If $f_u(S) < f_v(S)$ for $S \in (0, \sigma)$ and $f_v(S) < f_u(S)$ for $S > \sigma$, it can be shown that $\alpha_1\alpha_4 < r_1r_2$ and $R < 0$. The case of $S_2^+ > S_1^+$ can be proved in a similar fashion. $\square$

Consequently, Theorem 2.9 (a) and (b) hold under the same hypotheses in Theorem 3.2. The Michaelis-Menten term, the exponential term, and the hyperbolic tangent term all satisfy (P5) besides (P1)–(P4). Some examples of sigmoidal functions satisfying (P1)–(P3) and (P5) are $1 - \exp(-s^2 \ln 2)$ and $S^2/(S^2+1)$. In fact, if we require g to be C^2, functions satisfying (P1)–(P3) and (P5) must be either concave or sigmoidal. This can be easily shown by noting that (P3) implies that $g''(\mathcal{S}) < 0$ for some $\mathcal{S} > 0$, then (P5) implies that, for any $c > 1$, $g''(c\mathcal{S}) < (g'(c\mathcal{S})/cg'(\mathcal{S}))g''(\mathcal{S}) < 0$, i.e., g is concave for all $S > \mathcal{S}$.

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DEPARTMENT OF MATHEMATICS, ARIZONA STATE UNIVERSITY, TEMPE, AZ 85287