On Stability and Stabilization for Chemostats with Many Limiting Nutrients

Frédéric Mazenc   Michael Malisoff

Abstract— We study models of chemostats where the species compete for multiple limiting nutrients. We first consider cases where the input nutrient concentrations, nutrient flow, and species removal rates are all given positive constants. For such cases, we use Brouwer degree theory to find conditions guaranteeing that the models admit globally asymptotically stable componentwise positive equilibria, starting from all componentwise positive initial states. Then we use our results to prove stabilization results for controlled chemostats with two or more limiting nutrients. When the dilution rate and input nutrient concentrations can be taken as controls, we show that many possible componentwise positive equilibrium points can be rendered globally asymptotically stable. This extends existing control results for chemostats with one limiting nutrient. We illustrate our methods in simulations.

Key Words—Chemostats, degree theory methods, resource competition, stability and stabilization

I. INTRODUCTION

Chemostats play a key role in bioengineering and population biology. The chemostat is a type of bioreactor where fresh medium is continuously added and culture liquid is continuously removed. Hence, the culture volume remains constant. It has many industrial applications, such as the commercial production of genetically altered organisms. Chemostat models also play a role in experimentally reproducing and understanding the behavior of interacting species in lakes and waste-water treatment plants. See [5], [6], [8], [16], [17], [18], [32], [37] for an overview of the chemostat literature and its role in microbial ecology. Competitive exclusion [2] states that in well mixed chemostats with one limiting substrate, only one species can persist generically. This motivated a large literature that explains the discrepancy between the competitive exclusion principle, and the fact that multiple competing species typically survive in nature on one limiting substrate [4], [21], [24]-[27], [29]-[30], [33].

Fewer studies have been devoted to models with two or more limiting nutrients. Chemostats with two species and two limiting nutrients were studied by MacArthur, Tilman, and others using graphical approaches, leading to resource competition theory [19], [22], [23], [31], [38], [39]. One key testable prediction of the theory states that the number

of coexisting species cannot exceed the number of limiting resources generically, which is an extension of the competitive exclusion principle. The predictions of resource competition theory have been validated in experiments. There are also several global stability results for chemostats with two competing species and two limiting substrates. For example, stable periodic solutions were found for Monod kinetics [11] and later for interacting resources [3], [34]. Other numerical studies for chemostats with more than two competing species and more than two limiting nutrients illustrate the possibility of chaotic or oscillatory dynamics [14], [15]. See also [13] for the existence of heteroclinic cycles in winnerless chemostats with multiple species competing for several limiting nutrients. However, to the best of our knowledge, a full theoretical stability and stabilization analysis for equilibria in chemostats with more than two limiting nutrients is not available.

In this note, we report our new results for the chemostat model [7]

$$
\begin{cases}
\dot{s}_j = D_j^s(s_j^{in} - s_j) - \sum_{i=1}^{N} \mathcal{G}_{i,j}(S)x_i \, , \ 1 \le j \le M \\
\dot{x}_i = \left[-D_i^x + \sum_{j=1}^{M} \eta_{i,j}\mathcal{G}_{i,j}(S) \right] x_i \, , \ 1 \le i \le N
\end{cases}
\tag{1}
$$

for N species competing for M resources, where $S = (s_1, s_2, \ldots, s_M)$, s_j is the concentration of the jth substrate, x_i is the concentration of the ith species, $D_j^s > 0$ is the constant input rate from the feed bottle containing the jth substrate, $D_i^x > 0$ is the constant removal rate of the ith species, the constant $s_j^{in} > 0$ denotes the concentration of substrate j at the inlet (i.e., the jth substrate feed concentration), $\mathcal{G}_{i,j} : [0, \infty)^M \to \mathbb{R}$ is the consumption rate of substrate j by species i per unit of biomass of species i, and $\eta_{i,j} > 0$ is the constant yield coefficient for converting substrate j into biomass of species i for all i and j.

Determining the set of all componentwise nonnegative equilibrium points for (1) in the closure of $\mathcal{X} = (0, \infty)^{M+N}$ is difficult in general, because we must ensure that the $\dot{s}_j$'s are zero, and that some of the terms in brackets are zero. The extended competitive exclusion principle leads us to first consider the case where $M = N$. In Section III, we use Brouwer degree theory [10], [35] to prove existence of componentwise positive equilibrium points for (1) when $M = N$, under general assumptions. In Section IV, we prove the existence of a globally asymptotically stable equilibrium point for certain families of growth functions $\mathcal{G}_{i,j}$, where stability is understood relative to componentwise positive

initial states. Our growth functions are very different from those of [13], which are based on the law of the minimum. While our global asymptotic stability result holds for cases where $M \neq N$, it only applies when the componentwise nonnegative equilibria are known, which is not in general guaranteed. In Section V, we merge the results of Sections III and IV to prove global asymptotic stability of componentwise positive equilibria for chemostats where $N = M$.

Our stability theorems require more structure for the $\mathcal{G}_{i,j}$'s than we need for existence of componentwise positive equilibria. However, we can show global asymptotic stability of equilibria under Monod uptake functions, which are widely used in the chemostat literature. In addition, when a suitable componentwise nonnegative equilibrium point is known, we can allow the constants D_j^s and D_i^x to be distinct. This differs from [36], which shows stability properties of coexistence equilibria when $N = 2$ or $N = 3$ under the assumption $D_j^s = D_i^x = D$ for all $i, j \in \{1, 2, \ldots, N\}$. See also [40] for coexistence of multiple species in chemostats with one limiting substrate in which the species levels do not necessarily converge to an equilibrium point but are guaranteed to stay between two given positive bounds; and [1] for coexistence of any number of species along a periodic orbit with four limiting resources.

In Sections III-V, we assume that D_i^x, D_j^s, and s_{in}^j are given constants, in which case there are no controls, but our results for constant D_i^x, D_j^s, and s_{in}^j lead to results for the controlled case. Specifically, we show how if the dilution rate and input nutrient concentrations are controllers, then many different componentwise positive equilibria are globally asymptotically stabilizable; see Section VI. This extends [21],[24]-[27],[29]-[30] on ways to generate coexistence of multiple competing species in well mixed chemostats with one limiting substrate. We demonstrate our work in simulations. For complete proofs of all results to follow, see [28].

II. DEFINITIONS AND NOTATION

We omit arguments of functions when no confusion would result. We call a point $(z_1, \ldots, z_n) \in \mathbb{R}^n$ *weakly positive* provided $z_i \geq 0$ for all $i \in \{1, 2, \ldots, n\}$, and *positive* provided $z_i > 0$ for all $i \in \{1, 2, \ldots, n\}$. We use the convention $\{p, \ldots, q\} = \varnothing$ when $p > q$, and $\mathcal{B}_\varepsilon(y)$ is the radius $\varepsilon > 0$ open ball centered at y in a Euclidean space whose dimension will be clear from the context. We use C^1 to mean continuously differentiable. By C^1 of a function h being defined on a closed set $\mathcal{S}$, we mean C^1 on some open set containing $\mathcal{S}$. For functions f and h with the same domain, $f \equiv h$ means that they agree throughout the domain, and $\partial \mathcal{G}$ is the boundary of any set $\mathcal{G}$.

Take any system $\dot{x} = \mathcal{F}(x)$ with state space $\mathcal{X} = (0, \infty)^p$ for some $p \in \mathbb{N}$, where $\mathcal{F}$ is locally Lipschitz on the closure $\text{clos}(\mathcal{X})$ of $\mathcal{X}$, and a weakly positive equilibrium point Y_* (meaning, $Y_* \geq 0$ and $\mathcal{F}(Y_*) = 0$). We call Y_* *globally asymptotically stable relative to* $\mathcal{X}$ provided (i) for each constant $\varepsilon > 0$, there is a constant $\delta > 0$ such that all trajectories for the system starting in $\mathcal{X} \cap \mathcal{B}_\delta(Y_*)$ remain in $\mathcal{B}_\varepsilon(Y_*)$ for all nonnegative times and (ii) all trajectories for

the system starting in $\mathcal{X}$ converge to Y_* asymptotically.

Consider any non-negative real number ξ_*. If $\xi_* > 0$, then we define the function $\varphi_{\xi_*} : (-\xi_*, \infty) \to \mathbb{R}$ by

$$\varphi_{\xi_*}(\xi) = \xi - \xi_* \ln\left(1 + \{\xi/\xi_*\}\right) \tag{2}$$

and we define $\varphi_0 : (0, \infty) \to \mathbb{R}$ by $\varphi_0(\xi) = \xi$. Then the φ_{ξ_*}'s are C^1, and they are radially unbounded (i.e., $\lim_{\xi \to +\infty} \phi_{\xi_*}(\xi) = \lim_{\xi \to -\xi_*} \phi_{\xi_*}(\xi) = +\infty$ for all $\xi_* > 0$, and $\lim_{\xi \to +\infty} \phi_0(\xi) = +\infty$). Also, the φ_{ξ_*}'s for $\xi_* > 0$ are all positive definite (meaning 0 at 0, and positive at all other points in their domains). We also use the positive points

$$\begin{aligned} \nu &= (1, \ldots, 1)^\top \in \mathbb{R}^N, \quad \Delta = \left(D_1^x, \ldots, D_N^x\right)^\top, \\ \text{and} \quad \Theta &= \left(D_1^s s_1^{in}, \ldots, D_M^s s_M^{in}\right)^\top. \end{aligned} \tag{3}$$

Given any $a, b \in \mathbb{R}^N$, we use $a \leq b$ to mean that $a_i \leq b_i$ for all $i \in \{1, 2, \ldots, N\}$. For all $i \in \{1, 2, \ldots, N\}$, we define $P_i : \mathbb{R}^N \to \mathbb{R}^N$ by $P_i(a) = (p_1^i(a), \ldots, p_N^i(a))$ where the components are $p_k^i(a) = 0$ if $k \neq i$ and $p_i^i(a) = a_i$ for all $a = (a_1, \ldots, a_N) \in \mathbb{R}^N$. We define $Q_i : \mathbb{R}^N \to \mathbb{R}^N$ by $Q_i(a) = a - P_i(a)$. We also use $C = [c_{i,j}]$ to denote the matrix with generic entry $c_{i,j}$ in row i and column j for all i and j. We also use Brouwer degree theory [10], [35, pp.101-107]. We let $d(f, p, \mathcal{S})$ denote the degree of a C^1 function $f : \text{clos}(\mathcal{S}) \to \mathbb{R}^n$ that is defined on the closure of a bounded open set $\mathcal{S} \subseteq \mathbb{R}^n$, relative to a point p. If $d(f, p, \mathcal{S}) \neq 0$, then $f(x) = p$ has a solution $x \in \mathcal{S}$.

III. EXISTENCE OF POSITIVE EQUILIBRIUM POINTS

A. Statement of Result

We begin with the special case

$$\begin{cases} \dot{s}_j = D_j^s(s_j^{in} - s_j) - \sum_{i=1}^{N} \mathcal{G}_{i,j}(S)x_i, & 1 \leq j \leq N \\ \dot{x}_i = \left[-D_i^x + \sum_{j=1}^{N} \eta_{i,j}\mathcal{G}_{i,j}(S)\right]x_i, & 1 \leq i \leq N \end{cases} \tag{4}$$

of (1) where $N = M$. We assume:

Assumption 1: For all $i, j, k \in \{1, 2, \ldots, N\}$, the function $\mathcal{G}_{i,j}$ is C^1 on $[0, \infty)^N$, $\mathcal{G}_{i,j}(0) = 0$, $\mathcal{G}_{i,j}(S) > 0$ for all $S \in (0, \infty)^N$, $(\partial \mathcal{G}_{i,j}/\partial s_k)(S) \geq 0$ for all $S \in [0, \infty)^N$, and $(\partial \mathcal{G}_{i,i}/\partial s_i)(mP_i(\nu)) > 0$ for all $m > 0$. $\square$

Assumption 2: There are constants

$$B \in \left(0, \min_{j \in \{1, 2, \ldots, N\}} s_j^{in}\right) \quad \text{and} \quad \epsilon \in (0, B) \tag{5}$$

for which

$$\sum_{j=1}^{N} \eta_{i,j}\mathcal{G}_{i,j}\left(BP_i(\nu)\right) > D_i^x \quad \text{and} \tag{6}$$

$$\sum_{j=1}^{N} \eta_{i,j}\mathcal{G}_{i,j}\left(BQ_i(\nu) + \epsilon P_i(\nu)\right) < D_i^x \tag{7}$$

hold for all $i \in \{1, 2, \ldots, N\}$. Also,

$$\sum_{i=1, i \neq k}^{N} \frac{\mathcal{G}_{i,k}(S)D_i^s(s_i^{in} - \epsilon)}{\mathcal{G}_{i,i}(S)} < D_k^s(s_k^{in} - B) \tag{8}$$

holds for all $k \in \{1, 2, \ldots, N\}$ and all $S \in [\epsilon, B]^N$. $\square$

In [28], we prove:

Theorem 1: If (4) satisfies Assumptions 1-2, then it admits a positive equilibrium point. $\square$

Remark 1: Conditions (6)-(7) roughly say that the growth of each species x_i primarily depends on the substrate s_i. Also, (8) roughly says that each substrate s_i is mainly consumed by species x_i because $\mathcal{G}_{i,i}$ is larger relative to $\mathcal{G}_{i,k}$ for $i \neq k$. This fact suggests that coexistence occurs for any system (4) that satisfies Assumptions 1-2. Theorem 1 is based on a rigorous proof of this intuition. $\square$

B. Sketch of Proof of Theorem 1

The main steps of the proof are as follows. First we prove that there is a point $S^s = (s_1^s, \ldots, s_N^s) \in (\epsilon, B)^N$ for which

$$\sum_{j=1}^{N} \eta_{i,j} \mathcal{G}_{i,j}(S^s) \;=\; D_i^x \quad \forall i \in \{1, 2, \ldots, N\} . \tag{9}$$

Then we show that the linear system

$$\sum_{i=1}^{N} \mathcal{G}_{i,j}(S^s) x_i + D_j^s s_j^s \;=\; D_j^s s_j^{in}, \quad 1 \leq j \leq N \tag{10}$$

has a solution $X^s = (x_{s1}, x_{s2}, \ldots, x_{sN}) \in (0, \infty)^N$. This yields the positive equilibrium $Z^s = (S^s, X^s)$ of (4).

First Step. *Existence of S^s.* Take the compact set $\mathcal{C} = [\epsilon, B]^N$ and the C^1 function $H : \mathcal{C} \times [0,1] \to \mathbb{R}^N$ defined by $H(S,l) = (H_1(S,l), \ldots, H_N(S,l))^\top$, where

$$H_i(S,l) = \sum_{j=1}^{N} \eta_{i,j} \mathcal{G}_{i,j} \big(l Q_i(S) + P_i(S) \big) . \tag{11}$$

One easily checks that there does not exist a pair $(S, l) \in (\partial\mathcal{C}) \times [0,1]$ for which $H(S,l) = \Delta$, where Δ is from (3). To see why, note that if $S_a = (s_{a1}, \ldots, s_{aN}) \in \partial\mathcal{C}$ and $i \in \{1, 2, \ldots, N\}$ were such that $s_{ai} = \epsilon$, then

$$l Q_i(S_a) + P_i(S_a) \;\leq\; B Q_i(\nu) + \epsilon P_i(\nu) \tag{12}$$

for all $l \in [0,1]$. Since the $\mathcal{G}_{i,j}$'s are non-decreasing in each component of S, we conclude from (7) that $H_i(S_a, l) < D_i^x$. Therefore, $H_i(S_a, l) \neq \Delta$. Next, consider a point $S_b = (s_{b1}, \ldots, s_{bN}) \in \partial\mathcal{C}$ for which there is an index $i \in \{1, 2, \ldots, N\}$ such that $s_{bi} = B$. Then we can use (6) and the fact that the $\mathcal{G}_{i,j}$'s are non-decreasing in each component to conclude that $H_i(S_b, l) > D_i^x$, so $H(S_b, l) \neq \Delta$.

Since there is no pair $(S, l) \in (\partial\mathcal{C}) \times [0,1]$ for which $H(S,l) = \Delta$, we can use the homotopy invariance property [10], [35, p. 103] to check that the Brouwer degrees satisfy

$$d\big(H(\cdot,0), \Delta, (\epsilon, B)^N\big) = d\big(H(\cdot,1), \Delta, (\epsilon, B)^N\big) . \tag{13}$$

Also, $H(S,0) = (\gamma_1(s_1), \ldots, \gamma_N(s_N))^\top$, where

$$\gamma_i(m) = \sum_{j=1}^{N} \eta_{i,j} \mathcal{G}_{i,j}(m P_i(\nu)) \tag{14}$$

for $i = 1, 2, \ldots, N$. Using Assumption 1 and (6)-(7), we can show that the equation $H(S, 0) = \Delta$ admits a unique solution $S_p \in (\epsilon, B)^N$, and that $d(H(\cdot, 0), \Delta, (\epsilon, B)^N) = 1$. We conclude from (13) that there is a solution $S^s \in (\epsilon, B)^N$ of the equation $H(S, 1) = \Delta$, and this satisfies (9).

Second Step. *Existence of X^s.* Take the compact set $\mathcal{E} = [0, A]^N$, where A is any constant such that $A > \mathcal{M}$ and

$$\mathcal{M} = \max_{m \in \{1, 2, \ldots, N\}} \frac{D_m^s s_m^{in}}{\mathcal{G}_{m,m}(S^s)}. \tag{15}$$

Choose the function $F : \mathcal{E} \times [0,1] \to \mathbb{R}^N$ defined by $F(X, l) = (F_1(X, l), \ldots, F_N(X, l))^\top$, where

$$F_k(X, l) = \sum_{i=1, i \neq k}^{N} l \mathcal{G}_{i,k}(S^s) x_i + \mathcal{G}_{k,k}(S^s) x_k + D_k^s s_k^s \tag{16}$$

for $k = 1, 2, \ldots, N$ and $X = (x_1, \ldots, x_N)$. We proceed by contradiction. Let Θ be the constant vector in (3).

Suppose that there existed a pair $(k, l) \in \{1, 2, \ldots, N\} \times [0, 1]$, and a point $X_e \in \mathcal{E}$ whose kth component is equal to A, for which $F(X_e, l) = \Theta$. Since Assumption 1 ensures that $\mathcal{G}_{k,k}(S^s) > 0$, it follows from (15) that

$$F_k(X_e, l) \;\geq\; \mathcal{G}_{k,k}(S^s) A \;>\; D_k^s s_k^{in}. \tag{17}$$

Therefore $F(X_e, l) \neq \Theta$. Next suppose that there were a pair $(k, l) \in \{1, 2, \ldots, N\} \times [0, 1]$, and a point $X_f = (x_{f1}, \ldots, x_{fN}) \in \mathcal{E}$ whose kth component is 0, such that $F(X_f, l) = \Theta$. Then

$$F_k(X_f, l) \;=\; \sum_{i=1, i \neq k}^{N} l \mathcal{G}_{i,k}(S^s) x_{fi} + D_k^s s_k^s \quad \text{and} \tag{18}$$

$$D_m^s s_m^{in} \;=\; F_m(X_f, l) \;\geq\; \mathcal{G}_{m,m}(S^s) x_{fm} + D_m^s s_m^s \tag{19}$$

for all $m \in \{1, 2, \ldots, N\} \setminus \{k\}$. Since $S^s \in (\epsilon, B)^N$, we can use Assumption 1 to get

$$F_k(X_f, l) \;\leq\; \sum_{i=1, i \neq k}^{N} \mathcal{G}_{i,k}(S^s) \frac{D_i^s s_i^{in} - D_i^s \epsilon}{\mathcal{G}_{i,i}(S^s)} + D_k^s B . \tag{20}$$

Hence, (8) gives $F_k(X_f, l) < D_k^s s_k^{in}$, so $F(X_f, l) \neq \Theta$, and there is no pair $(X, l) \in (\partial\mathcal{E}) \times [0, 1]$ such that $F(X, l) = \Theta$.

We deduce from the homotopy invariance property that

$$d\big(F(\cdot, 0), \Theta, (0, A)^N\big) = d\big(F(\cdot, 1), \Theta, (0, A)^N\big) . \tag{21}$$

We can easily check that the equation $F(X, 0) = \Theta$ admits exactly one solution in $(0, A)^N$. Arguing as we did in the first step of our proof, we can prove that $d(F(\cdot, 0), \Theta, (0, A)^N) = 1$, so (21) implies that $d(F(\cdot, 1), \Theta, (0, A)^N) = 1$. Hence, (10) has a solution $X^s \in (0, A)^N$, as claimed.

Remark 2: The proof of Theorem 1 actually shows that for each constant $\delta > 0$, there is an equilibrium point (S^s, X^s) in $(\epsilon, B)^N \times (0, \mathcal{M} + \delta]^N$, where ϵ and B are from Assumption 2 and $\mathcal{M}$ is defined in (15).

IV. LYAPUNOV APPROACH TO PROVE GLOBAL ASYMPTOTIC STABILITY

A. Assumptions and Result

We next give a global asymptotic stability result for a specific class of systems (1). We do not assume that $N = M$. Instead, we assume that (i) a certain stability condition holds for a known weakly positive equilibrium point for (1), (ii) all of the functions $\mathcal{G}_{i,j}$ are Monod, depending only on s_j and (iii) the coefficients $\eta_{i,j}$ are all equal to 1 (but see [28] for extensions to cases where the yield factors are not necessarily

all equal to 1). In particular, we assume throughout this section that the resources are non-interacting.

Hence, we take

$$\mathcal{G}_{i,j}(S) = \frac{c_{i,j}s_j}{1+g_j s_j} \tag{22}$$

where $g_j > 0$ and $c_{i,j} > 0$ are constants for all i and j. This produces the system

$$\begin{cases} \dot{s}_j = D_j^s(s_j^{in} - s_j) - \sum_{i=1}^{N} c_{i,j}\frac{s_j x_i}{1+g_j s_j}, \ 1 \le j \le M \\ \dot{x}_i = \left[-D_i^x + \sum_{j=1}^{M} c_{i,j}\frac{s_j}{1+g_j s_j} \right] x_i, \ 1 \le i \le N \ . \end{cases} \tag{23}$$

To help in the analysis of the stability properties for (23), we introduce additional notation. Take the functions

$$\Gamma_k(S) = D_k^x - \sum_{l=1}^{M} c_{k,l}\frac{s_l}{1+g_l s_l}, \quad 1 \le k \le N \ , \tag{24}$$

so $\dot{x}_i = -\Gamma_i(S)x_i$ for all i. Let L_k denote the kth row of $C = [c_{i,j}] \in \mathbb{R}^{N \times M}$ and $C_{j_1,\dots,j_a}^{\flat}$ denote the submatrix of C that is obtained by removing all rows of C except for the rows $L_{j_1}, \dots, L_{j_a}$. For example,

$$C_{1,2}^{\flat} = \left[\begin{array}{c} L_1 \\ L_2 \end{array} \right] \ .$$

We give sufficient conditions for (23) to have a weakly positive globally asymptotically stable equilibrium point relative to $(0,\infty)^{M+N}$. In what follows, a *bipartition* $\{E_1, E_2\}$ of $\{1, 2, \dots, N\}$ is any pair of sets E_1 and E_2 (one of which could be empty) such that $E_1 \cup E_2 = \{1, 2, \dots, N\}$ and $E_1 \cap E_2 = \emptyset$. Also, a matrix M is *right invertible* provided there is a matrix T such that MT is an identity matrix. Instead of Assumption 1-2, we now assume:

Assumption 3: There are a weakly positive equilibrium point $E_* = (S_*, X_*) \in \mathbb{R}^M \times \mathbb{R}^N$ for (23) and a bipartition $\{E_1, E_2\}$ of $\{1, 2, \dots, N\}$ such that (i) $\Gamma_k(S_*) = 0$ for all $k \in E_1$, and $\Gamma_k(S_*) > 0$ for all $k \in E_2$ and (ii) the matrix $C_{j_1,\dots,j_q}^{\flat}$ with $E_1 = \{j_1, \dots, j_q\}$ is right invertible. □

In [28], we prove:

Theorem 2: Let (23) satisfy Assumption 3. Then E_* is a globally asymptotically stable equilibrium point for (23) relative to $(0,\infty)^{M+N}$. □

Remark 3: If Assumption 3 holds, and if we set $S_* = (s_{1*}, \dots, s_{M*})$, then $s_{j*} > 0$ for all $j \in \{1, 2, \dots, M\}$, because $D_j^s s_j^{in} > 0$ for all $j \in \{1, 2, \dots, M\}$. Also, since $\Gamma_k(S_*) > 0$ and $\dot{x}_k = -\Gamma_k(S)x_k$ hold for all $k \in E_2$, we have $x_{k*} = 0$ for all $k \in E_2$. Simulations can help determine whether Assumption 3 holds. If simulations suggest that (23) has a globally asymptotically stable equilibrium relative to $(0,\infty)^{M+N}$, then they suggest where approximatively the equilibrium is in the closed positive orthant. Then one can guess what the corresponding sets E_1 and E_2 would be and then check whether Assumption 3 holds for this bipartition. □

B. Sketch of Proof of Theorem 2

By renumbering the species as needed without relabeling, we assume without loss of generality that there is a $q \in$ $\{1, 2, \dots, N\}$ such that $E_1 = \{1, 2, \dots, q\}$ and $E_2 = \{q+1, \dots, N\}$. We define the functions $K_j : [0, \infty) \to \mathbb{R}$ by

$$K_j(p) = D_j^s + \sum_{i=1}^{N} c_{i,j}\frac{x_{i*}}{1+g_j s_{j*}}\frac{1}{1+g_j p}, \ 1 \le j \le M. \tag{25}$$

Set $\tilde{x}_j = x_j - x_{j*}$ for $j = 1, \dots, N$; $\tilde{X} = (\tilde{x}_1, \dots, \tilde{x}_N)$; $\tilde{s}_j = s_j - s_{j*}$ for $j = 1, 2, \dots, M$; and $\tilde{S} = (\tilde{s}_1, \dots, \tilde{s}_M)$. Since E_* is an equilibrium point of (23), we have

$$\begin{aligned} \dot{\tilde{s}}_j &= -D_j^s \tilde{s}_j + \sum_{i=1}^{N} c_{i,j}\left(x_{i*}\frac{s_{j*}}{1+g_j s_{j*}} - x_i\frac{s_j}{1+g_j s_j} \right) \\ &= -K_j(s_j)\tilde{s}_j - \sum_{i=1}^{N} c_{i,j}\frac{s_j}{1+g_j s_j}\tilde{x}_i \end{aligned} \tag{26}$$

for all $j \in \{1, 2, \dots, M\}$. Hence, simple calculations give

$$\begin{aligned} \dot{\tilde{s}}_j &= -K_j(s_j)\tilde{s}_j - \sum_{i=1}^{N} c_{i,j}\frac{s_j \tilde{x}_i}{1+g_j s_j}, \ 1 \le j \le M \ , \\ \dot{\tilde{x}}_k &= \left[-\Gamma_k(S_*) + \sum_{l=1}^{M} \frac{c_{k,l}}{1+g_l s_{l*}}\frac{\tilde{s}_l}{1+g_l s_l} \right] x_k, \ 1 \le k \le N. \end{aligned} \tag{27}$$

Set

$$U_f(\tilde{S}, \tilde{X}) = \sum_{j=1}^{M} \frac{1}{1+g_j s_{j*}}\varphi_{s_{j*}}(\tilde{s}_j) + \sum_{k=1}^{N} \varphi_{x_{k*}}(\tilde{x}_k) \ , \tag{28}$$

where the functions $\varphi_{\xi*}$ are defined in (2). Then U_f is C^1 on its domain $\mathcal{X} = \{(\tilde{S}, \tilde{X}) : \tilde{s}_i > -s_{i*} \ \forall i \in \{1, 2, \dots, M\}$ and $\tilde{x}_m > -x_{m*} \ \forall m \in \{1, 2, \dots, N\}\}$. Also, $\mathcal{X}$ is a positively invariant set for (27) because $(0,\infty)^{M+N}$ is positively invariant for (23). The time derivative of U_f along all trajectories of (27) in $\mathcal{X}$ is

$$\begin{aligned} \dot{U}_f &= \sum_{j=1}^{M} \frac{1}{1+g_j s_{j*}}\frac{\tilde{s}_j \dot{\tilde{s}}_j}{s_j} + \sum_{k=1}^{N} \frac{\tilde{x}_k \dot{\tilde{x}}_k}{x_k} \\ &= -\sum_{j=1}^{M} \frac{K_j(s_j)}{(1+g_j s_{j*})s_j}\tilde{s}_j^2 \\ &\quad -\sum_{j=1}^{M} \frac{1}{1+g_j s_{j*}}\frac{\tilde{s}_j}{1+g_j s_j}\sum_{i=1}^{N} c_{i,j}\tilde{x}_i \\ &\quad -\sum_{k=1}^{N} \Gamma_k(S_*)\tilde{x}_k + \sum_{k=1}^{N}\tilde{x}_k\sum_{l=1}^{M} \frac{c_{k,l}}{1+g_l s_{l*}}\frac{\tilde{s}_l}{1+g_l s_l} \\ &= -\sum_{j=1}^{M} \frac{K_j(s_j)}{(1+g_j s_{j*})s_j}\tilde{s}_j^2 - \sum_{k=q+1}^{N} \Gamma_k(S_*)\tilde{x}_k \ , \end{aligned} \tag{29}$$

where the last equality holds because Assumption 3 and our renumbering give $\Gamma_k(S_*) = 0$ for all $k \in E_1 = \{1, 2, \dots, q\}$. As we saw in Remark 3,

$$x_{m*} = 0 \quad \forall m \in E_2 = \{q+1, \dots, N\} \ . \tag{30}$$

Using (29) and the forward invariance of $\mathcal{X}$ for (27), we then get $\dot{U}_f \le 0$ for all $t \ge 0$ along all trajectories of (27) starting in $\mathcal{X}$. Integrating $\dot{U}_f \le 0$ over $[0, t]$ for any $t \ge 0$ gives

$$U_f\big(\tilde{S}(t), \tilde{X}(t)\big) \le U_f\big(\tilde{S}(0), \tilde{X}(0)\big) \ . \tag{31}$$

We can then use Barbalat's Lemma and the right invertibility of $C_{1,\dots,q}^{\flat}$ to establish attractivity of E_*.

V. Globally Asymptotically Stable Positive Equilibrium

A. Statement of Result

We next combine Theorems 1-2 to show the existence of a globally asymptotically stable positive equilibrium for a family of systems of the form (23).

Theorem 3: Consider the system (23). Assume that $N = M$, that $C = [c_{i,j}]$ is invertible, and that there exist a constant $D > 0$ such that $D_j^s = D_i^x = D$ for all $i, j \in \{1, 2, \ldots, N\}$ and positive constants B and ϵ satisfying (5) such that

$$\frac{c_{i,i}B}{1+g_iB} > D \quad \forall i \in \{1, 2, \ldots, N\}, \tag{32}$$

$$\frac{c_{i,i}\epsilon}{1+g_i\epsilon} + \sum_{i \neq j}\frac{c_{i,j}B}{1+g_jB} < D \quad \forall i \in \{1, 2, \ldots, N\}, \text{ and} \tag{33}$$

$$\sum_{i=1, i \neq k}^{N}\frac{c_{i,k}(1+g_i\epsilon)}{c_{i,i}(1+g_kB)}\frac{s_i^{in}-\epsilon}{s_k^{in}-B} < \frac{\epsilon}{B} \quad \forall k \in \{1, 2, \ldots, N\}. \tag{34}$$

Then (23) admits a globally asymptotically stable positive equilibrium point relative to $(0, \infty)^{2N}$. $\square$

To prove Theorem 3, we first check Assumptions 1-2. Then Theorem 1 gives a positive equilibrium (S_*, X_*) for (23). Then we apply Theorem 2 to show that (S_*, X_*) is globally asymptotically stable relative to $(0, \infty)^{2N}$.

Remark 4: Under the assumptions of Theorem 3, we can use the formulas for the growth functions (22) to find the components of the positive equilibrium point for (23). In fact, we can use the formulas for $\dot{x}_i$ and the invertibility of C to solve for $s_l/\{1 + g_l s_l\}$ and therefore also for s_l for $l = 1, ..., N$ that make the terms in brackets in (23) all equal to zero. Putting these values in the formulas for $\dot{s}_j$ and again using the invertibility of C gives the equilibrium values of the x_i's that make all of the $\dot{s}_j$'s equal to zero. $\square$

B. Simulation for Theorem 3

The assumptions of Theorem 3 hold with $M = N = 3$,

$$D = 2, \quad s_k^{in} = \tfrac{17}{4} \quad \forall k \in \{1, 2, 3\}, \tag{35}$$

$$c_{k,k} = 2 \ \forall k \in \{1, 2, 3\}, \quad c_{i,k} = \tfrac{1}{12} \ \text{for} \ i \neq k,$$
$$g_k = \tfrac{1}{4} \ \forall k \in \{1, 2, 3\}, \quad B = 2, \quad \text{and} \quad \epsilon = \tfrac{1}{4}. \tag{36}$$

We simulated (23) with (35)-(36) and the initial state $(0.5, 1, 1.5, 0.5, 1, 1.5)$, and obtained the curves in Figure 1. Our simulation shows the rapid convergence of the species and nutrient levels to the positive equilibrium point guaranteed by Theorem 3.

VI. Regulation of Species and Nutrient Levels

A. Statement of Result

In the previous sections, we viewed the dilution rate and input nutrient concentrations as given positive constants and showed asymptotic stability properties of certain positive equilibrium points. However, if D and each s_j^{in} can be chosen as controls, then many different possible positive equilibrium points can be made globally asymptotically stable. In fact, we prove the following, where $\nu = (1, \ldots, 1)^\top \in \mathbb{R}^N$ as before [28]:
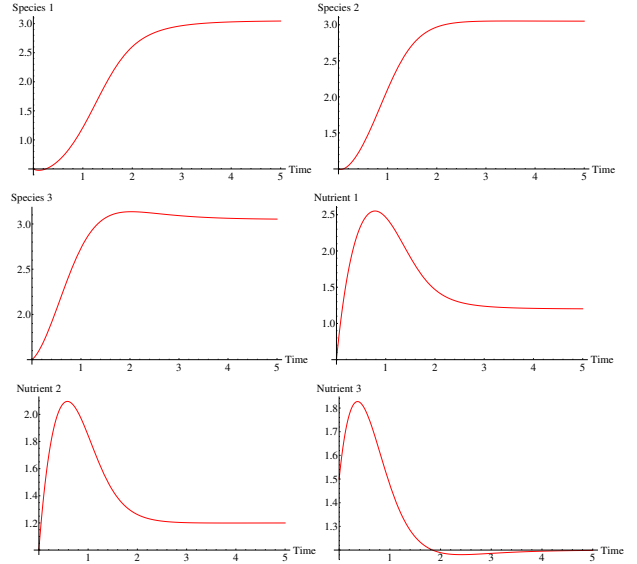

Fig. 1. Simulation of (23) with $N = M = 3$ and (35)-(36).

Theorem 4: Assume that the system (23) with $M = N$ is associated with an invertible matrix $C = [c_{i,j}]$, and define $k_1, \ldots, k_N \in \mathbb{R}$ by $C^{-1}\nu = (k_1, k_2, \ldots, k_N)^\top$. Assume that $k_i > 0$ for all $i \in \{1, 2, \ldots, N\}$. Let $\Xi_d = (\xi_1, ..., \xi_N) \in (0, +\infty)^N$ be given and choose any constant

$$D \in \left(0, \ \min_{j \in \{1,2,\ldots,N\}}\frac{1}{k_j g_j}\right) \tag{37}$$

and

$$\varpi_j = \frac{Dk_j}{1 - Dk_j g_j} \quad \forall j \in \{1, 2, \ldots, N\}. \tag{38}$$

Then (23) with the dilution rate $D_j^s \equiv D_i^x \equiv D$ and the constants

$$s_j^{in} = \varpi_j + k_j \sum_{i=1}^{N}c_{i,j}\xi_i, \quad j = 1, 2, \ldots, N \tag{39}$$

admits $(\varpi_1, ..., \varpi_N, \xi_1, ..., \xi_N)$ as a globally asymptotically stable positive equilibrium point relative to $(0, \infty)^{2N}$. $\square$

B. Simulation for Theorem 4

To illustrate Theorem 4, we again simulated (23) using the parameters (36), but instead of using the values (35) for the dilution rate and input nutrient concentration, we took $D = 4.333$ and $s_j^{in} = 5$ for $j = 1, 2, 3$. These controller values satisfy the requirements from Theorem 4 for stabilizing the species levels to $\xi_1 = \xi_2 = \xi_3 = 1$. We took the same initial states as in our first simulation. We obtained the curves in Figure 2 below. This illustrates the convergence of the species levels to the desired equilibrium states.

VII. Conclusions

Chemostat models are important in microbial ecology and typically contain more than two competing species and more than two limiting nutrients. We used Brouwer degree and Lyapunov methods to prove results on the existence and asymptotic stability of componentwise nonnegative equilibria for chemostats with multiple competing species and multiple limiting nutrients. Using control methods, we also showed
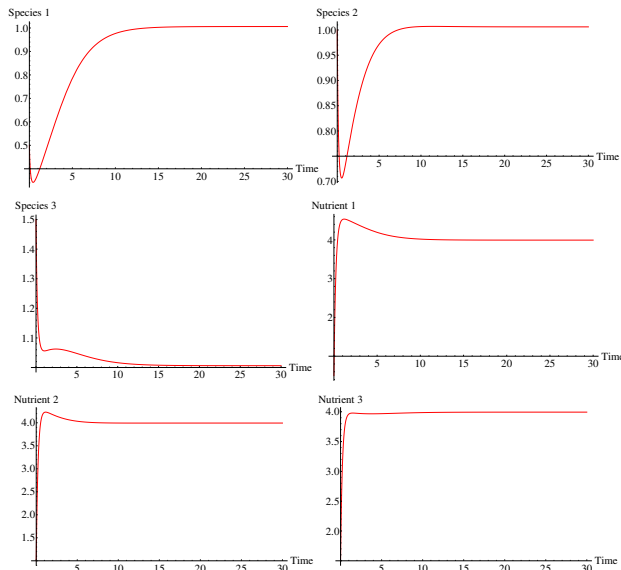
Fig. 2. Simulation of (23) with $N = M = 3$ using the Controllers $D = 4.333$ and $s_j^{in} = 5$ for $j = 1, 2, 3$ and the Parameters (36).

how many possible componentwise positive equilibria can be rendered globally asymptotically stable when the dilution rate and input nutrient concentrations are taken as the controls. Our results can inspire extensions to chemostats with multiple nutrients, nonmonotone uptake functions, time delays, and unknown perturbations.

REFERENCES

[1] R.A. Armstrong and R. McGehee. Coexistence of species competing for shared resources. *Theoretical Population Biology* 9(3):317-328, 1976.

[2] R.A. Armstrong and R. McGehee. Competitive exclusion. *American Naturalist* 115(2):151-170, 1980.

[3] G.J. Butler and G.S. Wolkowicz. Exploitative competition in a chemostat for two complementary, and possibly inhibitory, resources. *Mathematical Biosciences* 83(1):1-48, 1987.

[4] P. Gajardo, F. Mazenc, and H. Ramirez. Competitive exclusion principle in a model of chemostat with delay. *Dynamics of Continuous, Discrete, and Impulsive Systems Series A: Mathematical Analysis* 16(2):253-272, 2009.

[5] J-L. Gouzé and G. Robledo. Feedback control of a nonmonotone competition models in the chemostat. *Nonlinear Analysis: Real World Applications* 6(4):671-690, 2005.

[6] J-L. Gouzé and G. Robledo. Robust control for an uncertain chemostat model. *International Journal of Robust and Nonlinear Control* 16(3):133-155, 2006.

[7] J.P. Grover. *Resource Competition.* Chapman and Hall, London, UK, 1997.

[8] S.R. Hansen and S.P. Hubbell. Single nutrient microbial competition: qualitative agreement between experimental and theoretical forecast outcomes. *Science* 207(4438):1491-1493, 1980.

[9] S.B. Hsu. Limiting behavior for competing species. *SIAM Journal on Applied Mathematics* 34(4):760-763, 1978.

[10] S.B. Hsu. *Ordinary Differential Equations with Applications.* World Scientific Publishing Company, Singapore, 2006.

[11] S.B. Hsu, K.S. Cheng, and S.P. Hubbell. Exploitative competition of microorganisms for two complementary nutrients in continuous cultures. *SIAM Journal on Applied Mathematics* 41(3):422-444, 1981.

[12] S.B. Hsu, S.P. Hubbell, and P. Waltman. A mathematical theory for single-nutrient competition in continuous cultures of micro-organisms. *SIAM Journal on Applied Mathematics* 32(2):366-383, 1977.

[13] S.B. Hsu, L. Ing and W. Roeger. Heteroclinic cycles in the chemostat models and the winnerless competition principle. *Journal of Mathematical Analysis and Applications* 360(2):599-608, 2009.

[14] J. Huisman and F.J. Weissing. Biodiversity of plankton by species oscillations and chaos. *Nature* 402(6760):407-410, 1999.

[15] J. Huisman and F.J. Weissing. Fundamental unpredictability in multi-species competition. *American Naturalist* 157(5):488-494, 2001.

[16] I. Karafyllis and C. Kravaris. Robust global stabilizability by means of sampled-data control with positive sampling rate. *International Journal of Control* 82(4):755-772, 2009.

[17] I. Karafyllis, C. Kravaris and N. Kalogerakis. Relaxed Lyapunov criteria for robust global stabilization of nonlinear systems. *International Journal of Control* 82(11):2077-2094, 2009.

[18] V. Lemesle and J-L. Gouzé. A simple unforced oscillatory growth model in the chemostat. *Bulletin of Mathematical Biology* 70(2):344–357, 2008.

[19] J.A. Léon and D.B. Tumpson. Competition between two species for two complementary or substitutable resources. *Journal of Theoretical Biology* 50(1):185-201, 1975.

[20] S.A. Levin. Community equilibria and stability, and an extension of the competitive exclusion principle. *American Naturalist* 104(939):413-423, 1970.

[21] C. Lobry and F. Mazenc. Effect of intra-specific competition on persistence in competition models. *Electronic Journal of Differential Equations* 2007(125):1-10, 2007.

[22] R.H. MacArthur. Species packing and competitive equilibria for many species. *Theoretical Population Biology* 1(1):1-11, 1970.

[23] R.H. MacArthur. *Geographical Ecology: Patterns in the Distribution of Species.* Princeton University Press, Princeton, NJ, 1972.

[24] F. Mazenc and Z-P. Jiang. Persistence for a chemostat with many species. *Dynamics of Continuous, Discrete and Impulsive Systems Series A: Mathematical Analysis* 17(6a):737-763, 2010.

[25] F. Mazenc and Z-P. Jiang. Global output feedback stabilization of a chemostat with an arbitrary number of species. *IEEE Transactions on Automatic Control* 55(11):2570-2575, 2010.

[26] F. Mazenc and M. Malisoff. Stabilization of a chemostat model with Haldane growth functions and a delay in the measurements. *Automatica* 46(9):1428–1436, 2010.

[27] F. Mazenc and M. Malisoff. Remarks on output feedback stabilization of two-species chemostat models. *Automatica* 46(10):1739-1742, 2010.

[28] F. Mazenc and M. Malisoff. Stability and stabilization for models of chemostats with multiple limiting substrates. *Preprint.*

[29] F. Mazenc, M. Malisoff, and P. De Leenheer. On the stability of periodic solutions in the perturbed chemostat. *Mathematical Biosciences and Engineering* 4(2):319-338, 2007.

[30] F. Mazenc, M. Malisoff, and J. Harmand. Stabilization in a two-species chemostat with Monod growth functions. *IEEE Transactions on Automatic Control* 54(4):855-861, 2009.

[31] T.E. Miller, J.H. Burns, P. Munguia, E.L. Walters, J.M. Kneitel, P.M. Richards, N. Mouquet, and H.L. Buckley. A critical review of twenty years' use of the resource-ratio theory. *American Naturalist* 165(4):439-448, 2005.

[32] M. Moisan, O. Bernard, and J-L. Gouzé. Near optimal interval observers bundle for uncertain bioreactors. *Automatica* 45(1):291-295, 2009.

[33] S. Pavlou. Microbial competition in bioreactors. *Chemical Industry and Chemical Engineering Quarterly* 12(1):71-81, 2006.

[34] S. Pilyugin, G.T. Reeves, and A. Narang. Predicting stability of mixed microbial cultures from single species experiments: 1. Phenomenological model. *Mathematical Biosciences* 192(2):85-109, 2004.

[35] S. Sastry. *Nonlinear Systems. Analysis, Stability and Control.* Springer, New York, 1999.

[36] H. Smith and B. Li. Competition for essential resources: A brief review. In *Dynamical Systems and Their Applications in Biology,* Fields Insitute Communications Volume 36. American Matematical Society, Providence, RI, 2003, pp. 213-227.

[37] H. Smith and P. Waltman. *The Theory of the Chemostat.* Cambridge University Press, Cambridge, UK, 1995.

[38] D. Tilman. Resources: A graphical-mechanistic approach to competition and predation. *American Naturalist* 116(3):362-393, 1980.

[39] D. Tilman. *Resource Competition and Community Structure.* Princeton University Press, Princeton, NJ, 1982.

[40] G.S.K. Wolkowicz and X-Q. Zhao. N-species competition in a periodic chemostat. *Differential Equations and Integral Equations* 11(3):465-491, 1998.