

CHEMOSTATS AND EPIDEMICS: COMPETITION FOR NUTRIENTS/HOSTS

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Dedicated to Carlos Castillo-Chavez on the Occasion of his 60th Birthday

ABSTRACT. In a chemostat, several species compete for the same nutrient, while in an epidemic, several strains of the same pathogen may compete for the same susceptible hosts. As winner, chemostat models predict the species with the lowest break-even concentration, while epidemic models predict the strain with the largest basic reproduction number. We show that these predictions amount to the same if the per capita functional responses of consumer species to the nutrient concentration or of infective individuals to the density of susceptibles are proportional to each other but that they are different if the functional responses are nonproportional. In the second case, the correct prediction is given by the break-even concentrations. In the case of nonproportional functional responses, we add a class for which the prediction does not only rely on local stability and instability of one-species (strain) equilibria but on the global outcome of the competition. We also review some results for nonautonomous models.

1. Introduction. The system

$$\begin{aligned} S' &= \Lambda - DS - \sum_{j=1}^n f_j(S)I_j, \\ I_j' &= f_j(S)I_j - D_j I_j, \quad j = 1, \dots, n, \end{aligned} \tag{1.1}$$

can be interpreted as a chemostat model with n species of consumers I_j that compete for a limiting substrate S or as an epidemic model for the spread of an infectious pathogen that comes in n different strains and converts susceptible hosts S into hosts I_j infected with strain j . The epidemic model can also be understood as a competition model where various pathogen strains compete for the host as only resource [53].

In the chemostat setting, $D > 0$ is the dilution or washout rate of substrate, while in the epidemics setting it is the natural per capita death rate of the host. Λ is the

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rate at which fresh substrate is pumped into the chemostat or new susceptibles are being recruited into the host population, respectively.

$$S^\circ = \Lambda/D \tag{1.2}$$

is the equilibrium concentration of the substrate without consumers or the equilibrium population size of the host population without the disease. In a chemostat, the rates $D_j > 0$ are the removal rates of the j^{th} species. If the j^{th} species is subject to a death rate, $D_j > D$. If a filter slows the washout of the j^{th} species but not the substrate, $D_j < D$.

In an epidemic model, typically $D_j > D$ and $D_j - D$ are the per capita removal rates of strain j infectives by disease death, isolation, or recovery from the disease. Chemostat models typically also have yield constants for every species, but these can be made 1 by appropriate scaling if they are constant.

The functions f_j are the substrate uptake rates by species j or the per capita rate at which strain j infectives transfer the disease to susceptible hosts. For chemostat models, they are often taken in Michaelis-Menten form,

$$f_j(S) = \frac{\kappa_j S}{1 + b_j S}, \quad S \geq 0, \tag{1.3}$$

with $\kappa_j > 0$ and $b_j \geq 0$. The special case $b_j = 0$ provides the so-called density-dependent (or mass action) incidence for epidemic models. Next to frequency-dependent (alias standard) incidence $\frac{\kappa_j S I_j}{S + \sum_{j=1}^n I_j}$, it is the most commonly used incidence in epidemic models though incidences with a nonlinear dependence on S (like S^α with $0 < \alpha < 1$) have also been proposed early on in the history of epidemic modeling [16, 73] (see [15, Ch.3] and [40, 41] for surveys).

More generally we assume that $f_j : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ are locally Lipschitz and

$$f_j(0) = 0, \quad f_j(S) > 0, \quad S > 0, \quad j = 1, \dots, n. \tag{1.4}$$

The assumptions guarantee that solutions of initial value problems with nonnegative initial data remain nonnegative, exist for all $t \geq 0$, and are bounded. The latter follows since $S + \sum_j I_j$ satisfies a simple linear differential inequality.

Aside from chemostats or epidemics, the model represents the indirect competition between a collection of agents for a common resource, available in limited quantity, wherein each agent, having no direct interaction with its competitors, merely consumes the common resource so that it may reproduce and offset losses due to removal or mortality. It is the simplest form of competition, and as such it is crucially important to understand its dynamics.

For the chemostat model, it is obvious that substrate that has been consumed by one species can no longer be consumed by any other. For the epidemic model, the form of our system involves two assumptions that are not self-evident at all, namely absolute cross-protection and cross-immunity: Infection with one strain excludes infection by others (no superinfection and no coinfection), and it conveys complete and permanent immunity to all strains after recovery.

Under these assumptions, the principle of competitive exclusion should hold that only one competitor can survive on a single resource. So only one consumer species or one pathogen strain should persist, and all others die out. However, epidemic and chemostat modelers have suggested different threshold parameters that determine the winner.

The biomass production number of species j or disease reproduction number of strain j at substrate/host level S is given by

$$\mathcal{R}_j(S) = \frac{f_j(S)}{D_j}, \quad (1.5)$$

with $1/D_j$ being the time available and $f_j(S)$ being the per unit rate at which biomass can be acquired at substrate level S or secondary infections can be generated from S susceptibles.

The *basic (re)production number* for species or strain j is given by

$$\mathcal{R}_j^\circ = \mathcal{R}_j(S^\circ), \quad S^\circ = \Lambda/D, \quad (1.6)$$

because S° is the equilibrium level to which the substrate or host population dynamics tend when there are no consumers or no pathogens. The *break even concentrations* S_j are defined as those concentration where

$$\mathcal{R}_j(S_j) = 1, \quad (1.7)$$

i.e.,

$$f_j(S_j) = D_j. \quad (1.8)$$

We will not generally assume in this paper that a break even concentration S_j is well-defined or is unique except for $j = 1$. For the sake of exposition, we assume in this introduction and in Section 2 that we have break even concentrations $S_j < S^\circ$ for all j and also assume

$$f_j(S) < f_j(S_j), \quad S \in [0, S_j), \quad f_j(S) > f_j(S_j), \quad S \in (S_j, S^\circ). \quad (1.9)$$

This last condition is tacitly assumed whenever we mention a break even concentration for species or strain j .

Our assumption that $S_j < S^\circ$ is motivated by the fact that if $f_j(S) < D_j$, $0 < S < S^\circ$, then species (strain) j would die out even without competition (Proposition 4.2).

As early as 1977, Hsu, Hubbell, and Waltman showed that the species with the smallest break-even constant outcompetes the others if $D_j = D$ for all $j = 1, \dots, m$, and the functional responses f_j are of Michaelis-Menton form [33]. This result was extended to differential $D_j > 0$ and Michalis-Menten form in 1978 by Hsu [32]. Arbitrary increasing functional responses and $D_j = D$ were dealt with by Armstrong and McGehee also in 1980 [6], while more general functional responses and $D_j = D$ were treated by Butler and Wolkowicz in 1985 [14]. See [67] for a comprehensive presentation of these works. Further progress was made for arbitrary functional responses and differential $D_j > 0$ by various authors [45, 76, 77] in the nineties, but seems to have stalled after 2000 such that a definitive answer seems still to be missing. In particular, it is remarkable that competitive exclusion has not been proved in the case of monotone functional response and differential $D_j > 0$!

For density-dependent incidence, i.e., $f_j(S) = \kappa_j S$, Anderson and May [4] argued in the early eighties that evolution would maximize the basic reproduction number, i.e., in model (1.1), the strain with the largest basic reproductive number outcompetes the others. Apparently, this seemed so evident to them that no mathematical proof was given, but it would have followed from Hsu's 1978 paper [32].

2. Break-even concentrations or \mathcal{R}_0 ? Basic reproduction numbers and break-even constants predict the same winners if $f_j(S) = \kappa_j g(S)$ with the same monotone increasing function $g : \mathbb{R}_+ \rightarrow \mathbb{R}_+$. By (1.5) and (1.6),

$$\mathcal{R}_j^\diamond = g(S^\diamond) \tilde{\mathcal{R}}_j, \quad \tilde{\mathcal{R}}_j = \frac{\kappa_j}{D_j}, \quad (2.1)$$

and, by (1.8),

$$S_j = g^{-1}(1/\tilde{\mathcal{R}}_j). \quad (2.2)$$

The basic reproduction number is the largest and the break-even constant the smallest if $\tilde{\mathcal{R}}_j$ is the largest.

We now construct an example with general Michaelis-Menten functions (1.3) and $D_j = D$ where the break-even concentrations give the correct prediction and the basic reproduction numbers the wrong one.

We first consider equation (1.8),

$$\frac{\kappa_j S_j}{1 + b_j S_j} = D, \quad 0 < S_j < S^\diamond, \quad (2.3)$$

and then also consider (1.5) and (1.6),

$$1 < \mathcal{R}_j^\diamond = \frac{\kappa_j S^\diamond}{1 + b_j S^\diamond} \frac{1}{D}.$$

We set

$$x_j = \frac{S_j}{S^\diamond}.$$

Then the equations become

$$\frac{(\kappa_j/D) S^\diamond x_j}{1 + b_j S^\diamond x_j} = 1, \quad 0 < x_j < 1,$$

and

$$1 < \mathcal{R}_j^\diamond = \frac{(\kappa_j/D) S^\diamond}{1 + b_j S^\diamond}.$$

We introduce the dimensionless parameters

$$\alpha_j = \frac{\kappa_j S^\diamond}{D}, \quad \beta_j = b_j S^\diamond.$$

Then

$$\frac{\alpha x_j}{1 + \beta_j x_j} = 1, \quad 0 < x_j < 1,$$

and

$$1 < \mathcal{R}_j^\diamond = \frac{\alpha_j}{1 + \beta_j}.$$

We solve for x_j ,

$$x_j = \frac{1}{\alpha_j - \beta_j}, \quad 0 < x_j < 1,$$

$$1 < \mathcal{R}_j^\diamond = \frac{\alpha_j}{1 + \beta_j}.$$

The basic reproduction numbers would falsely predict that the second species (strain) wins while the break-even concentrations would correctly predict that the first species (strain) wins if

$$1 < \mathcal{R}_1^\diamond < \mathcal{R}_2^\diamond, \quad x_1 < x_2.$$

This is equivalent to

$$1 + \beta_1 < \alpha_1,$$

$$\alpha_1 \frac{1 + \beta_2}{1 + \beta_1} < \alpha_2 < \alpha_1 - \beta_1 + \beta_2.$$

The following can now be easily shown.

Theorem 2.1. *Let $1 + \beta_1 < \alpha_1$ and $\beta_1 > \beta_2$. Then*

$$\alpha_1 \frac{1 + \beta_2}{1 + \beta_1} < \alpha_1 - \beta_1 + \beta_2.$$

Choose α_2 strictly between those two numbers. Then the basic reproduction numbers wrongly predict that the second species (strain) wins while the break-even concentrations correctly predict that the first species wins.

That the break-even concentrations correctly predict the winner follows from the result of [32].

3. Proportional functional responses. If the functional responses are proportional to each other, competitive exclusion can be shown under nonautonomous time regimes. This is based on the following rather elementary results.

Lemma 3.1. *For $j = 1, 2$, let $\kappa_j > 0$ and let $x_j : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ be positive solutions of*

$$x_j' = [\kappa_j g(t) + h_j(t)]x_j, \tag{3.1}$$

where $g, h_j : \mathbb{R}_+ \rightarrow \mathbb{R}$ are continuous. Assume that

$$\frac{1}{\kappa_2} \int_0^t h_2(s)ds - \frac{1}{\kappa_1} \int_0^t h_1(s)ds \rightarrow -\infty, \quad t \rightarrow \infty.$$

Then the following hold:

- (a) *If x_1 is bounded on \mathbb{R}_+ , then $x_2(t) \rightarrow 0$ as $t \rightarrow \infty$.*
- (b) *If $\liminf_{t \rightarrow \infty} x_1(t) < \infty$, then $\liminf_{t \rightarrow \infty} x_2(t) = 0$.*

Notice that if the equations (3.1) are part of a larger system, g and h_j are allowed to depend not only on the independent variable t but also on the dependent variables x_1 and x_2 and any other dependent variables of the system.

Proof. Notice that

$$\frac{1}{\kappa_j} \frac{x_j'}{x_j} - \frac{1}{\kappa_j} h_j = g.$$

We integrate from 0 to t and find that

$$\frac{1}{\kappa_j} \ln \frac{x_j(t)}{x_j(0)} - \frac{1}{\kappa_j} \int_0^t h_j(s)ds$$

does not depend on j . We exponentiate,

$$\left(\frac{x_2(t)}{x_2(0)} \right)^{1/\kappa_2} = \left(\frac{x_1(t)}{x_1(0)} \right)^{1/\kappa_1} \exp \left(\frac{1}{\kappa_2} \int_0^t h_2(s)ds - \frac{1}{\kappa_1} \int_0^t h_1(s)ds \right),$$

and the assertion follows. □

This proof is the time-heterogeneous version of the one given in [13] and [17]. Alternatively [1, 2], one can derive a differential equation for $\phi = I_2^{\xi_2} I_1^{-\xi_1}$ with arbitrary ξ_j and then discover that $\xi_j = 1/\kappa_j$ is a good choice to get rid of g .

We consider the following time-heterogeneous version of a system considered in [17],

$$\begin{aligned}
 I &= (I_1, \dots, I_n), & R &= (R_1, \dots, R_n), & P &= (S, I, R), \\
 S' &= \Lambda(t, P) - D(t)S - g(t, P) \sum_{j=1}^n \kappa_j I_j + \sum_{j=1}^n \rho_j(t, P) R_j, \\
 \left. \begin{aligned}
 I_j' &= g(t, P) \kappa_j I_j - [D(t) + \mu_j(t) + \gamma_j(t)] I_j \\
 R_j' &= \gamma_j(t) I_j - [D(t) + \rho_j(t, P)] R_j
 \end{aligned} \right\} & j &= 1, \dots, n.
 \end{aligned} \tag{3.2}$$

In an infectious disease model, R_j represents the individuals that have recovered from a strain- j -infection, γ_j is the per capita rate at which strain- j -infectious individuals recover, and ρ_j is the per capita rate at which they lose their protection against a reinfection and become susceptible again. In a chemostat model, R_j is the part of the dead consumer biomass that can be recycled into substrate, $\mu_j + \gamma_j$ is the death rate with $\gamma_j/(\mu_j + \gamma_j)$ be the portion of the dead biomass that can be recycled into nutrient substrate with ρ_j being the rate at which this actually happens. (For related chemostat models with nutrient recycling see [25, 64].)

A possible chemostat choice for the function g is the Beddington functional response

$$g(t, S, I, R) = \frac{S}{1 + b_0(t)S + \sum_{k=1}^n b_k(t)I_k + \sum_{j=1}^n a_j(t)R_j}; \tag{3.3}$$

as for epidemics, standard or frequency dependent incidence is included by

$$g(t, S, I, R) = \frac{S}{S + \sum_{j=1}^n (I_j + R_j)}. \tag{3.4}$$

To apply Lemma 3.1, set $g(t) = g(t, P(t))$ and

$$h_j(t) = D(t) + \mu_j(t) + \gamma_j(t).$$

We introduce the time averages,

$$\bar{h}_j(t) = \frac{1}{t} \int_0^t h_j(s) ds. \tag{3.5}$$

Assume that the time averages have positive limits $\bar{h}_j^\infty = \lim_{t \rightarrow \infty} \bar{h}_j(t)$. This is the case, e.g., if D , μ_j , and γ_j are almost periodic. We define the relative reproduction numbers,

$$\tilde{\mathcal{R}}_j = \frac{\kappa_j}{\bar{h}_j^\infty}. \tag{3.6}$$

If $\tilde{\mathcal{R}}_2 < \tilde{\mathcal{R}}_1$, the assumptions of Lemma 3.1 are satisfied. Of course, the same argument applies for $j = 2, \dots, n$ in system (3.2).

Theorem 3.2. *Assume that $I_1 : \mathbb{R}_+ \rightarrow \mathbb{R}_+$ is positive and bounded and $\tilde{\mathcal{R}}_j < \tilde{\mathcal{R}}_1$ for $j = 2, \dots, n$. Then $I_j(t) \rightarrow 0$ as $t \rightarrow \infty$ for $j = 2, \dots, n$.*

4. Nonproportional response functions and Lyapunov functions. The system (1.1) always has the consumer (disease) free equilibrium $x^\diamond = (S^\diamond, 0, \dots, 0)$. Throughout this section, we assume that the first species persists if it is on its own,

$$f_1(S^\diamond) > D_1. \tag{4.1}$$

The following result is similar to results in [5, 76].

Theorem 4.1. *For all solutions of (1.1) with $I_1(0) > 0$ there exists some $r \geq 0$ such that $S(t) < S^\diamond$ for all $t \geq r$.*

Proof. Since $S' \leq D(S^\diamond - S)$, $\limsup_{t \rightarrow \infty} S(t) \leq S^\diamond$. Assume that $S(t) \geq S^\diamond$ for all $t \geq 0$. Then S is decreasing and $S(t) \rightarrow S^\diamond$ as $t \rightarrow \infty$ and, by (4.1), there exists some $s \geq 0$ such that $I_1'(t) \geq 0$ for all $t \geq s$. Since $I_1(0) > 0$, $I_1(t) > 0$ for all $t \geq 0$ and $I_1(t) \geq I_1(s) > 0$ for $t \geq s$. This implies that

$$\limsup_{t \rightarrow \infty} S'(t) \leq -f_1(S^\diamond)I_1(s) < 0$$

and $S(t) \rightarrow -\infty$ as $t \rightarrow \infty$. Thus there exists some $r \geq 0$ such that $S(r) < S^\diamond$. Since $S'(t) < 0$ for any $t \geq r$ such that $S(t) = S^\diamond$, we conclude that $S(t) < S^\diamond$ for all $t \geq r$. \square

The next result is also known in similar form [67, 76]; since it is fundamental, we include the short proof.

Proposition 4.2. *If $j \neq 1$ and $f_j(S) < D_j$ for all $S \in (0, S^\diamond)$, then $I_j(t) \rightarrow 0$ as $t \rightarrow \infty$ for all solutions of (1.1) with $I_1(0) > 0$.*

Proof. By Theorem 4.1, after a shift in time, we can assume that $S(t) < S^\diamond$ for all $t \geq 0$. This implies that I_j is decreasing and has a limit I_j^∞ . By the fluctuation lemma ([31], [69, Prop.A.22]), there exists a sequence $t_j \rightarrow \infty$, $S(t_j) \rightarrow S^\infty = \limsup_{t \rightarrow \infty} S(t)$, $S'(t_j) \rightarrow 0$ as $j \rightarrow \infty$. So

$$0 \leq \Lambda - DS^\infty - f_j(S^\infty)I_j^\infty.$$

Assume that $I_j^\infty > 0$. Then $S^\infty < S^\diamond$ and $\sup S(\mathbb{R}_+) < S^\diamond$. This implies that $\sup_{t \geq 0} f_j(S(t)) < D_j$ and $I_j(t) \rightarrow 0$, a contradiction. \square

In addition to (4.1), we assume that the first species has a break-even concentration $S_1 \in (0, S^\diamond)$ in the sense that

$$f_1(S) < f_1(S_1) = D_1, \quad S < S_1, \quad f_1(S) > f_1(S_1), \quad S_1 < S < S^\diamond. \tag{4.2}$$

Then there is at least one more equilibrium $x_1 = (S_1, I_1^*, 0, \dots, 0)$ with

$$I_1^* = \frac{D(S^\diamond - S_1)}{D_1}, \tag{4.3}$$

and it is the only one of this form.

Finally, we assume that

$$f_j(S) < D_j, \quad 0 < S \leq S_1. \tag{4.4}$$

Under the extra condition that f_1 is differentiable at S_1 and $f_1'(S_1) > 0$, (4.4) implies that the equilibrium $(S_1, I_1^*, 0, \dots, 0)$ is locally asymptotically stable.

Easy contradiction arguments show that

$$\liminf_{t \rightarrow \infty} S(t) \leq S_1 \leq \limsup_{t \rightarrow \infty} S(t) \quad \text{if } I_1(0) > 0. \tag{4.5}$$

For almost all (D_1, \dots, D_n) , all other equilibria of the system (1.1) are of the form $(S_j, 0, \dots, 0, I_j^*, 0, \dots, 0)$, $j = 2, \dots, n$, with $f(S_j) = D_j$ and appropriate I_j^* . By (4.4), we have $S_j > S_1$, and these equilibria are unstable by (4.5).

In order to show that $(S_1, I_1^*, 0, \dots, 0)$ attracts all solutions of (1.1), Lyapunov functions have played a central role in the analysis of chemostat models from an early stage [32, 45, 64, 65, 67, 76]. See [35] for a synopsis. Lyapunov functions have also been used to study invasions in chemostat foodwebs [74], competition for multiple resources [8, 9], and predation-mediated persistence in chemostats [75].

Compared with this, the successful use of Lyapunov functions on a large scale in epidemic models has started relatively late, mainly in the last decade ([10, 26], [39]–[44], [54, 60, 62, 68]). See [24] for an excellent survey. Recently, even large epidemic systems have been successfully treated by Volterra Lyapunov functions, first systems with an arbitrary number of disease stages, both finite [3, 28, 36, 37, 55] and distributed [50, 51] [56]–[59], and then systems with an arbitrary, but finite number of subpopulations [24, 29, 30, 46, 47], and finally combinations of both [48], and with infinite-dimensional population structure [70].

The Lyapunov functions used in both chemostat and epidemic models are mainly adaptations of the classical Lyapunov function $V(x) = x - a \ln(x/a)$ which has worked so well for Lotka-Volterra systems [27]. This function has been discovered by Volterra himself [72, p.15] who shows that a linear combination of functions of this form is constant along the solutions of the Lotka-Volterra predator-prey system.

We consider the following candidate for a Lyapunov function,

$$V = \int_{S_1}^S \frac{f_1(s) - f_1(S_1)}{f(s)} ds + \left(I_1 - I_1^* \ln \frac{I_1}{I_1^*} \right) + \sum_{j=2}^n c_j I_j, \quad (4.6)$$

with a function $f : [0, S^\circ) \rightarrow (0, \infty)$ and nonnegative constants c_2, \dots, c_n . The orbital derivative is

$$\begin{aligned} \dot{V} &= \frac{f_1(S) - f_1(S_1)}{f(S)} \left(\Lambda - DS - \sum_{j=1}^n f_j(S) I_j \right) \\ &\quad + (I_1 - I_1^*) (f_1(S) - D_1) + \sum_{j=2}^n c_j [f_j(S) - D_j] I_j. \end{aligned}$$

We substitute the equilibrium equations for the equilibrium $(S_1, I_1^*, 0, \dots, 0)$,

$$\begin{aligned} \dot{V} &= \frac{f_1(S) - f_1(S_1)}{f(S)} \left(DS_1 + f_1(S_1) I_1^* - DS - \sum_{j=1}^n f_j(S) I_j \right) \\ &\quad + (I_1 - I_1^*) (f_1(S) - f_1(S_1)) + \sum_{j=2}^n c_j [f_j(S) - D_j] I_j. \end{aligned}$$

We regroup,

$$\begin{aligned} \dot{V} &= \frac{f_1(S) - f_1(S_1)}{f(S)} \left[D(S_1 - S) + f_1(S_1) I_1^* - f_1(S) I_1 + f(S) (I_1 - I_1^*) \right] \\ &\quad + \sum_{j=2}^n \left(c_j [f_j(S) - D_j] - \frac{f_1(S) - f_1(S_1)}{f(S)} f_j(S) \right) I_j. \end{aligned} \quad (4.7)$$

An obvious choice to make the first term on the right hand side nonpositive is $f = f_1$. An analogous choice, in a more general model with variable yields, is made

in [65]. Alternatively, one can observe that $f_1(S_1)I_1^* = D(S^\circ - S_1)$. So the term in brackets becomes

$$[\cdot] = D(S^\circ - S) - f_1(S)I_1 + f(S)I_1 - f(S)I_1^*. \tag{4.8}$$

This suggests to choose f as in [76] such that the first and last term eliminate each other,

$$f(S) = \frac{D}{I_1^*}(S^\circ - S) = f_1(S_1)\frac{S^\circ - S}{S^\circ - S_1}. \tag{4.9}$$

Then

$$[\cdot] = I_1 f_1(S_1) \left(\frac{S^\circ - S}{S^\circ - S_1} - \frac{f_1(S)}{f_1(S_1)} \right). \tag{4.10}$$

If $0 \leq S < S_1$, $\frac{S^\circ - S}{S^\circ - S_1} > 1 > \frac{f_1(S)}{f_1(S_1)}$ and if $S_1 < S \leq S^\circ$, the inequalities are reversed. This implies that the first term on the right hand side of (4.7) is always nonpositive and zero only if $S = S_1$ or $I_1 = 0$.

Recall that for all solutions with $I_1(0) > 0$ there exists some $r > 0$ such that $S(t) < S^\circ$ for all $t \geq r$. Thus, focusing on the second term on the right side of (4.7), we try to find $c_j > 0$ such that

$$c_j[f_j(S) - D_j]f(S) - [f_1(S) - f_1(S_1)]f_j(S) < 0, \quad S \in (0, S^\circ). \tag{4.11}$$

As already observed in [65] for increasing f_1 , the choice (4.9) will give more general conditions than the choice $f = f_1$ because it provides a function that is strictly decreasing on $[0, S^\circ]$. It gives competitive exclusion for certain functional responses of sigmoidal or inhibitory type (see [76] for details).

The choice $f = f_1$ has a nice symmetry, though, and we will stick with that one. In this case, the sign of the second term on the right side of (4.7) is negative provided:

$$c_j[f_j(S) - D_j]f_1(S) - [f_1(S) - f_1(S_1)]f_j(S) < 0, \quad S \in (0, S^\circ). \tag{4.12}$$

A more natural way to write (4.12) is to divide through by $f_1(S)f_j(S)$ to get:

$$c_j \left(1 - \frac{1}{\mathcal{R}_j(S)} \right) - \left(1 - \frac{1}{\mathcal{R}_1(S)} \right) < 0, \quad S \in (0, S^\circ).$$

We note that in case it is assumed that the break-even concentrations S_j exist and that f_j satisfies (1.9), then the inequality above holds for any $c_j > 0$ on $[S_1, S_j]$.

The first species (strain) out-competes the others if it has larger reproduction numbers at all relevant substrate levels S .

Theorem 4.3. *Let $\mathcal{R}_j(S) < \mathcal{R}_1(S)$ for all $S \in (0, S^\circ)$. Then all solutions with $I_1(0) > 0$ go to the equilibrium $(S_1, I_1^*, 0, \dots, 0)$.*

Proof. (4.12), with $c_j = 1$, may be written as:

$$\mathcal{R}_j(S) - \mathcal{R}_1(S) < 0, \quad 0 < S < S^\circ. \quad \square$$

Theorem 4.3 gives another proof that competitive exclusion holds in the case of proportional functional response $f_j(S) = \kappa_j g(S)$, $j \geq 1$ satisfying (4.2) and (4.4). In this case, $f_j(S_1) < D_j$ is equivalent to $\mathcal{R}_j(S) < \mathcal{R}_1(S)$ for all $S \in (0, S^\circ)$.

We consider functional responses that are of generalized Michaelis-Menten type. While it is nice to formulate results in terms of break-even concentrations, this concept is only needed for the winning species.

Theorem 4.4. *Let*

$$f_j(S) = \frac{\kappa_j g(S)}{1 + b_j g(S)}, \quad j = 1, \dots, n, \tag{4.13}$$

with a function $g : \mathbb{R}_+ \rightarrow \mathbb{R}$, $g(0) = 0$, $g(S) > 0$ for $S > 0$. Assume that there is some $S_1 \in (0, S^\circ)$ such that

$$f_1(S_1) = D_1, \quad f_j(S_1) < D_j, \quad j = 2, \dots, n,$$

and

$$g(S) < g(S_1), \quad 0 \leq S < S_1, \quad g(S) > g(S_1), \quad S_1 < S < S^\circ. \tag{4.14}$$

Then all solutions to (1.1) with $I_1(0) > 0$ converge to $(S_1, I_1^*, 0, \dots, 0)$.

Proof. Define

$$h_j(x) = \frac{\kappa_j x}{1 + b_j x}, \quad x \geq 0.$$

We will verify that suitable $c_j > 0$ may be found satisfying (4.12). Our hypotheses imply that $f_j(S) < D_j$ for $0 \leq S \leq S_1$, so if $f_j(S) < D_j$ for $S_1 < S < S^\circ$ then we may satisfy (4.12) by taking c_j suitably large.

Otherwise, we may suppose then that there exists $S_j \in (S_1, S^\circ)$ such that $f_j(S_j) = D_j$. Since $S_j > S_1$, our hypotheses imply that $g(S_1) < g(S_j)$. Now

$$f_j(S) - D_j = \frac{\kappa_j}{1 + b_j g(S_j)} \frac{g(S) - g(S_j)}{1 + b_j g(S)} = \frac{1}{1 + b_j g(S_j)} \frac{g(S) - g(S_j)}{g(S)} f_j(S).$$

So, to verify (4.12), our task is equivalent to finding $c_j > 0$ such that

$$\frac{c_j}{1 + b_j g(S_j)} \frac{g(S) - g(S_j)}{g(S)} - \frac{1}{1 + b_1 g(S_1)} \frac{g(S) - g(S_1)}{g(S)} < 0, \quad 0 < S < S^\circ.$$

With the choice of $c_j = \frac{1 + b_1 g(S_1)}{1 + b_j g(S_j)}$, this boils down to the condition $g(S_1) < g(S_j)$, $j \neq 1$, which we have already established. \square

(4.14) is automatically satisfied if g is strictly increasing on $(0, S^\circ)$. It is also satisfied if g is strictly increasing on $(0, S^*)$, decreasing on $(S^*, S^\circ]$, where $0 < S_1 < S^* < S^\circ$ and $g(S^\circ) > g(S_1)$.

Example 4.5. Theorem 4.4 covers functional responses such as

$$f_j(S) = \frac{\kappa_j S^\alpha}{1 + b_j S^\alpha}$$

with $\alpha > 0$.

More generally, let $g(S) = \frac{S^\alpha}{1 + cS^\beta}$ with $\alpha, \beta > 0$. Then g is strictly increasing if $\alpha \geq \beta > 0$ and unimodal if $0 < \alpha < \beta$. The associated f_j are of the form

$$f_j(S) = \frac{\kappa_j S^\alpha}{1 + cS^\beta + b_j S^\alpha}$$

with $\alpha, \beta > 0$. We can also take $g(S) = S^\alpha e^{-\beta S}$. Then

$$f_j(S) = \frac{\kappa_j S^\alpha}{e^{\beta S} + b_j S^\alpha}.$$

Here is a list of concave monotone functional responses for which, to our knowledge, competitive exclusion has not yet been shown,

$$\begin{array}{lll} f_j(S) = \kappa_j(1 - e^{-\beta_j S}) & \text{Ivlev} & [7, 38, 63] \\ f_j(S) = \kappa_j \ln(1 + \beta_j S) & \text{logarithmic} & [12] \\ f_j(S) = \kappa_j \min\{S, \beta_j\} & \text{Blackman} & [7, 11]. \end{array}$$

The second functional response is used in [12] not for the susceptibles, but for the per capita rate of being infected as a function of virus particles released after the death of infected insects.

We mention [45] that, if $S_1 < S_2 \leq \dots \leq S_n$ and

$$\frac{S_2 - S_1}{S^\diamond} > \frac{D}{D_{\min}} - \frac{D}{D_{\max}},$$

with D_{\min} and D_{\max} being the minimum and maximum of D, D_1, \dots, D_n , respectively, then competitive exclusion holds for general monotone functions and also for unimodal functional responses if $f_1(S) > D_1$ for $S \in (S_1, S^\diamond]$. This result was obtained by modifying the function (4.6) and improved an earlier result in [77].

5. Coexistence. Since the work of Cushing [18] and de Mottoni and Schiaffino [19], it is known that two species can coexist in a periodic environment which would not coexist in a constant environment. However, in a chemostat or an epidemic model, competition is more specific than in a Lotka-Volterra competition model: The consumers compete for the substrate and the pathogen strains compete for the susceptibles. Nevertheless, in a chemostat, coexistence is possible even if the washout rate or the nutrient supply concentration is the only parameter that varies periodically [34, 66, 67, 78] which is the typical chemical engineering scenario. This requires the functional responses not to be proportional (Section 3).

In an epidemic model, since susceptible individuals typically do not recognize by which strain an infective individual is infected, functional responses can be expected to be proportional as functions of S . In this case, if the recruitment rate Λ and the natural death rate D were the only time-periodic parameters, there would be no coexistence (Section 3). In an epidemic model, however, it is also reasonable to assume that the incidence varies as a function of time with the seasons,

$$f_j(t, S) = \kappa_j(t)g(S), \quad t \geq 0, S \geq 0.$$

Again, if the κ_j are proportional functions of t , there is no coexistence (Section 3). However, if they are not, coexistence is possible [52]. But why should the κ_j not be proportional? After all, the strains face the same environmental conditions.

A possible scenario for non-proportional κ_j can result when a pathogen has a direct and an indirect route of infection.

As an illustration, we revisit a model [23] for an infectious disease which is spread both by direct (horizontal) transmission and by waterborne (or otherwise free-living) propagules released by infective hosts. As additional dependent variables, we add the amount of waterborne propagules, W_j , released by infectives with strain j .

Recast in the notation used above, the model in [23] takes the form

$$\begin{aligned} S' &= \Lambda - DS - S \sum_{j=1}^n (\hat{\kappa}_j(t)I_j + \tilde{\kappa}_j(t)W_j), \\ \left. \begin{aligned} I_j' &= S(\hat{\kappa}_j(t)I_j + \tilde{\kappa}_j(t)W_j) - D_j I_j \\ W_j' &= \sigma_j I_j - \nu_j W_j \end{aligned} \right\} \quad j = 1, \dots, n. \end{aligned} \quad (5.1)$$

The parameters σ_j are the per capita release rates of waterborne propagules and ν_j are their per unit destruction rates, for strain j . $\hat{\kappa}_j$ is the direct horizontal per capita infection rate, while $\tilde{\kappa}_j$ is the infection rate per capita host and per unit propagule. We assume that the parameters σ_j and ν_j are large compared with the other parameters, in other words, that the dynamics of waterborne pathogens are fast compared with the dynamics of the remaining system [71, 6.2.1]. Then a quasi-steady state approximation may be justified for the waterborne pathogens,

$$W_j \approx \frac{\sigma_j}{\nu_j} I_j.$$

We substitute this relation as an equality into the equations for I_j in (5.1) and obtain

$$I_j' = \kappa_j(t)SI_j - D_j I_j$$

with

$$\kappa_j(t) = \hat{\kappa}_j(t) + \tilde{\kappa}_j(t) \frac{\sigma_j}{\nu_j}.$$

Notice that even if the $\hat{\kappa}_j$ are proportional to each other and the $\tilde{\kappa}_j$ are proportional to each other,

$$\hat{\kappa}_j(t) = \hat{\eta}_j \phi(t), \quad \tilde{\kappa}_j(t) = \tilde{\eta}_j \psi(t),$$

the κ_j may no longer be proportional to each other if ϕ and ψ are not proportional to each other. For instance, one could be constant and the other periodic; then they can be tweaked to have the form of [52, Fig.1] where periodic coexistence of two strains is shown.

6. Epilog. Competition of consumer species for a substrate and of pathogen strains for susceptible hosts are special cases of a more general theme: subsistence of several species or variants of a single species in the same environment [20, 21, 61]. If the environmental conditions are given by the concentration or density of a single resource (here one homogeneous substrate or one unstructured host), competition favors the species or strain that can subsist under worse environmental conditions (at lower resource levels) than the others. Differently said, competition favors the species or strain that, when by itself, drives the resource to the lowest level (pessimization principle [21] [22, p.95]). If the functional response of strain j to the environmental variable separates in a multiplicative way, like $\kappa_j g(S)$ (proportional response), competition equivalently favors the strain with the largest basic reproduction number. If the response is nonproportional, competition still favors the species that can subsist at the worst environmental conditions, but not necessarily the one with the largest basic reproduction number. Competitive exclusion holds at equilibrium and, for proportional functional responses and some nonproportional functional responses, also dynamically: suboptimal strains die out as time tends to infinity. For general functional responses, dynamical competitive exclusion is still an open problem.

If the environment is time-periodically forced and the functional response is nonproportional, coexistence may occur, though not at equilibrium but in a time-oscillatory manner [34, 52, 66, 67, 78].

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