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Mathematical Biosciences 177&178 (2002) 127–145

Mathematical Biosciences

www.elsevier.com/locate/mbs

A size-structured, non-conservative ODE model of the chemostat

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Received 15 December 2000; received in revised form 19 November 2001; accepted 15 December 2001

Abstract

We study a class of size-structured, ODE models of growth in the chemostat, that take into account cell maintenance and substrate dependent cell mortality. Unlike most classical chemostat models, they are supposed to be non-conservative, in the sense that they do not verify the *mass conservation principle*. However, using a change of time scale, we are able to obtain qualitative results. Then, using a Lyapunov functional, we prove the global stability of the non-trivial equilibrium. Some examples of the possible structure of the models are given to finish with.

Keywords: Chemostat; Size-structured models; Non-conservative models; Cellular death; Maintenance

1. Introduction

Consider the classical two-dimensional Monod model [1]

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \mu(s)x - dx, \tag{1a}$$

$$\frac{\mathrm{d}s}{\mathrm{d}t} = -\mu(s)x + d(s_{\mathrm{in}} - s), \tag{1b}$$

which describes the growth of a species (bacteria, phytoplankton) whose concentration is noted x, feeding on a substrate at a concentration s, in a device called a *chemostat*. The latter is a

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0025-5564/02/$ - see front matter
PII: S0025-5564(02)00084-6

continuous culture experimental apparatus consisting of a well-mixed closed vessel, inside which the organisms are located. Nutrients are fed into this vessel at a rate d (called the *dilution rate*) and a concentration s_{in}. In order to keep the volume of liquid constant in the vessel, there is an outflow of matter. Hence organisms and substrate alike are washed out of the device at the dilution rate d. Inside the culture vessel, organisms absorb the nutrient to grow. In the Monod model, this uptake of nutrient is supposed to take place at a rate $\mu(s)$, which is called the *uptake rate* (a non-linear function of s). This uptake results in the growth of organisms at the same rate (this equality assumes that the units for the organisms and the substrate are the same, as will be discussed later).

There have been numerous modifications and improvements [1] of this basic model. Most classical chemostat analysis rely on the fact that systems like (1a) and (1b) verify a property called the *mass conservation principle*: in (1a) and (1b) and its sequels, the sum of the biomass and substrate is governed by the differential equation

$$\frac{\mathrm{d}(x+s)}{\mathrm{d}t} = d(s_{\text{in}} - (x+s)).$$

Using this property, one can show that the sum of the biomass and of the substrate tends to a fixed quantity (the input nutrient concentration s_{in}). Hence the non-linearity of the system is 'tamed', rendering the analysis easier. Indeed, in the ω-limit set, one can substitute (for example) s by $s_{\text{in}} - x$, thereby reducing (1a) and (1b) to a one-dimensional system.

From a biological point of view, however, the Monod model is a little too simple. Indeed, it describes the total biomass in the system, without any distinction between cells. While this is sufficient if the goal of the analysis is, for example, the prediction of the total biomass that will result of the use of a certain dilution rate or input substrate concentration, it comes short for the description of more specific cellular processes. One of the shortcomings is the description of the size of the cells. Indeed, nowadays much of the data obtained, be it from laboratory chemostats or in the sea, is size-structured, because of the prevailing use of optical particle counters, which are able to produce structured data of good quality in almost continuous time (see e.g., the device described in [2]). As the data is size-structured, and that manipulations of the data can yield errors [3], it is therefore important to use it in models able to generate the same sort of 'output', i.e., in size-structured models.

However, there have been very few attempts to describe a chemostat using physiologically structured population models. Most of these works use partial differential equations [1,4–6]. There have also been works using a discrete-time model [7–9]. All of these models verify the mass conservation principle, and use it in a fundamental way in the proofs. There are several points that we want to assess in this paper. First, we wish to introduce a system of ordinary differential equations modelling a size-structured population growing in a chemostat. The use of a system of ODEs to model a structured population is usually restricted to stage-structured populations description [10]. Hofmann in [11] briefly discusses size-structured ODE models of phytoplankton–zooplankton interaction in the sea. However, these models are simulatory models, onto which no thorough mathematical analysis has been conducted.

The second point that we wish to consider here is the *metabolic activity* (or *maintenance*) of cells. The $\mu(s)$ terms that appear in (1a) and (1b) result from two assumptions: x and s are evaluated using the same units (for example using the mass of carbon atoms), hence no conversion

coefficient is needed; and all of the substrate that is uptaken by a cell is used for its growth. While the first assumption is not a problem, the second one is less obvious. Indeed, in order to 'stay alive', cells indulge in activities other than growth, respiration being the most vital. Kooijman defines [12, p. 76] maintenance as "the (mean) energy requirement of an organism, excluding the production processes of growth, reproduction and development". The Dynamic Energy Budgets approach of Kooijman [12] is very detailed, but produces models that are hard to analyse mathematically.

Finally, we will consider *cell mortality*. Some authors (e.g., [13]) have shown (using Lyapunov stability theory) that using different dilution rates for the substrate and the biomass to account for cell mortality (using different values of d in (1a) and (1b), say respectively d_1 and d_0, with $d_1 \geqslant d_0$), does not fundamentally modify the behaviour of the system provided the mortality is not too important. Here, we will show that substrate dependent mortality can be dealt with.

The model that we introduce thus has the following characteristics: it is size-structured, accounts for cell maintenance and substrate dependent cell mortality. Therefore, it does not verify the mass conservation principle. However, using an approach different of the one used when mass conservation is present, we are able to study it.

This paper is organised as follows. In Section 2, we state the model. We then study it in Section 3, the main result of this paper being stated in Section 3.2. Finally, in Section 4, we give a few examples of possible applications of the method: a model with simple cellular division, a model with inhomogeneous cellular division and a model with asymmetric cellular division.

2. Model formulation

Let us begin by a few notational conventions. Uppercase letters are used throughout this text for vectors, vector-valued functions and matrices; $^{\mathrm{T}}$ is the transpose operator. Lowercase letters denote real values or real valued functions. If $V \in \mathbb{R}^n$ is a vector, then $\mathbb{1}^{\mathrm{T}}V$ (with $\mathbb{1} = (1,\ldots,1)^{\mathrm{T}}$) is the sum of the elements of V (and a norm of V), while $\mathbb{1}^{\mathrm{T}}M$ is the column sum of the $n \times n$-matrix M. Concerning order relations on $\mathbb{R}^n$, we use the standard notations (see e.g., [14]). Let V and W be two vectors in $\mathbb{R}^n$. We note $V \leqslant W$ if $v_i \leqslant w_i$ for all i, $V < W$ if $V \leqslant W$ and $v_i < w_i$ for some i, and $V \ll W$ if $v_i < y_i$ for all i. If a vector V is such that $V \gg 0$ (i.e., that $V \in \operatorname{int}\mathbb{R}^n_+$), one says that it is *strongly positive*.

We suppose that the system under consideration is a well-stirred chemostat. We consider the structured model (2a) and (2b), where $X \in \mathbb{R}^n$ and $s \in \mathbb{R}$ are the state variables, $X = (x_1,\ldots,x_n)^{\mathrm{T}}$ representing the total cellular biomass in each of n size classes, and s the substrate concentration.

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \mu(s)AX - d_1(s)X \tag{2a}$$

$$\frac{\mathrm{d}s}{\mathrm{d}t} = -\mu(s)\Gamma^{\mathrm{T}}X + d_0(s_{\mathrm{in}} - s) \tag{2b}$$

where $d_1(s)$ is the dilution rate that apply to cells, A is a $n \times n$-matrix describing the fluxes of biomass between the different size classes, and Γ is a vector denoting the consumption of substrate resulting of cell growth. We use $d_1(s)$ as a combination of dilution and mortality, defining

$$d_1(s) = d_0 + \delta(s)$$

where $\delta(s) \geqslant 0$ is the mortality rate, which we suppose to be a decreasing monotone function of s: $\delta(0) = \delta_{\max}$, $\mathrm{d}\delta/\mathrm{d}s < 0$, and $\lim_{s\to\infty} \delta(s) = \delta_{\min} \geqslant 0$. To avoid the case of a chemostat in *batch* mode, we suppose that the dilution rate $d_0 > 0$.

The specific growth rate $\mu(s)$ is such that $\mu(0) = 0$, $\mathrm{d}\mu/\mathrm{d}s > 0$ and $\lim_{s\to\infty} \mu(s) = \mu_{\max}$.

In order to remain as general as possible, we do not give a precise form of the flow matrix A. We do however make a few structural hypotheses. We suppose that it is irreducible (i.e., that its associated connection graph is strongly connected, one can move from one class to any other in a finite number of steps). We furthermore suppose that A is *quasi-positive* (as termed in [14], or *essentially non-negative*, as termed in [15]): its off-diagonal elements are non-negative. The last assumption we make concerning A is the following:

$$\mathbb{1}^{\mathrm{T}} A \leqslant \Gamma^{\mathrm{T}} \tag{3}$$

Remember that s and X are measured using the same units. This assumption says that the substrate that is uptaken by cells is not entirely allocated to cell growth: there is a disappearance due to cell maintenance.

Considering (2a), one realizes that we make the assumption that the growth rate $\mu(s)$ is a factor of all possible flows. This is the strongest hypothesis in this model, and will be discussed in Section 5.

Examples of the type of application that we bear in mind introducing such a system, in particular, forms of the transition matrix A, are given in Section 4.

3. Model behaviour

Since mass conservation is not verified by system (2a) and (2b), we cannot apply the classical framework of chemostat analysis. We will however be able to study the system. The steps that we follow in order to do so are:

- Begin by considering a new system, consisting of a sort of 'proportion ratio' obtained by normalising the original system.
- This new system can be shown to have the same asymptotic behaviour as the linear system $\xi' = (A - \lambda I)\xi$, where λ is the dominant eigenvalue of A.
- Since the matrix A is irreducible, the behaviour of the linear system is governed by the Perron root of A.
- Then we study the two-dimensional system consisting of the normed 'sum' of the cellular biomass, and of the substrate. We show that the non-trivial equilibrium of this system is globally stable, using a Lyapunov function.
- Finally, plugging this knowledge into the original system, we are able to deduce the behaviour of (2a) and (2b).

Before we proceed to this analysis, we need to establish two technical results concerning system (2a) and (2b), that will be used later.

Lemma 3.1. *The closed positive orthant is positively invariant for the flow of* (2a) and (2b). *Furthermore, solutions of* (2a) and (2b) *are bounded.*

Proof. First let us show that the positive orthant is positively invariant for the flow of (2a) and (2b).

Suppose that $\exists t_1 \geqslant 0$ such that $s(t_1) = 0$. Two cases are possible: $t_1 = 0$ and $t_1 > 0$. If $t_1 = 0$, then we have $\mathrm{d}s(0)/\mathrm{d}t = d_0 s_{\mathrm{in}} > 0$, so for small $t > 0$, $s(t) > 0$. Now suppose that $s_0 > 0$ and that $t_1 > 0$ is the first t such that $s(t) = 0$. Then we have $\mathrm{d}s(t_1)/\mathrm{d}t = d_0 s_{\mathrm{in}} > 0$, but also that

$$\frac{\mathrm{d}s}{\mathrm{d}t}(t_1) = \lim_{\substack{t \to t_1 \\ t < t_1}} \frac{s(t_1) - s(t)}{t_1 - t} \leqslant 0$$

which is a contradiction. Therefore, there cannot exist a $t_1 > 0$ such that $s(t_1) = 0$.

Now since A is quasi-positive, the components of X can be written, for all $i = 1, \ldots, n$,

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \mu(s) \sum_{j=1,\, j \neq i}^{n} \alpha_{i,j} x_j - \mu(s)\alpha_{i,i} x_i - d_1(s) x_i$$

with $\alpha_{i,j} \geqslant 0$ for all i and j. Therefore for all $i = 1, \ldots, n$, $\mathrm{d}x_i/\mathrm{d}t \geqslant 0$.

Therefore, the closed positive orthant is invariant for the flow of (2a) and (2b). Hence the variables X and s are positive for positive initial conditions X_0 and s_0.

Let us now show that the solutions of (2a) and (2b) are bounded

$$\begin{aligned}
\frac{\mathrm{d}(\mathbb{1}^{\mathrm{T}} X + s)}{\mathrm{d}t} &= \mu(s)\left[\mathbb{1}^{\mathrm{T}} A X - \Gamma^{\mathrm{T}} X\right] - d_1(s)\mathbb{1}^{\mathrm{T}} X + d_0(s_{\mathrm{in}} - s) \\
&= \mu(s)\left[\mathbb{1}^{\mathrm{T}} A X - \Gamma^{\mathrm{T}} X\right] + d_0\big(s_{\mathrm{in}} - (\mathbb{1}^{\mathrm{T}} X + s)\big) - \delta(s)\mathbb{1}^{\mathrm{T}} X \\
&\leqslant d_0\big(s_{\mathrm{in}} - (\mathbb{1}^{\mathrm{T}} X + s)\big). \qquad (4)
\end{aligned}$$

The last inequality results from inequality (3). Hence the total mass is bounded uniformly with respect to time. Remark that this last inequality is linked to the mass conservation principle (which would hold if both quantities were equal). □

Now we can (and need to) be a little more precise concerning s. This is the object of the following lemma.

Lemma 3.2. *There exists an* $\varepsilon > 0$ *such that for all* (X_0, s_0), *there exists a* $\tau \geqslant 0$ *such that for all* $t \geqslant \tau$, $s(t) > \epsilon$.

Proof. From (4) in the proof of Lemma 3.1, we deduce that

$$(\mathbb{1}^{\mathrm{T}} X + s)(t) \leqslant s_{\mathrm{in}} + \mathrm{e}^{-d_0 t}\left[(\mathbb{1}^{\mathrm{T}} X_0 + s_0) - s_{\mathrm{in}}\right] = (1 - \mathrm{e}^{-d_0 t}) s_{\mathrm{in}} + \mathrm{e}^{-d_0 t}(\mathbb{1}^{\mathrm{T}} X_0 + s_0) \qquad (5)$$

and therefore

$$(\mathbb{1}^{\mathrm{T}} X + s)(t) \leqslant \max(s_{\mathrm{in}}, \mathbb{1}^{\mathrm{T}} X_0 + s_0). \qquad (6)$$

Let us suppose that $\mathbb{1}^{\mathrm{T}}X_0 + s_0 \leqslant 2s_{\mathrm{in}}$. Inequality (6) implies that $(\mathbb{1}^{\mathrm{T}}X + s)(t) \leqslant 2s_{\mathrm{in}}$ is true for all $t > 0$. Therefore for all $t > 0$, $\mathbb{1}^{\mathrm{T}}X(t) \leqslant 2s_{\mathrm{in}}$. Hence we can deduce a lower bound for $\mathrm{d}s/\mathrm{d}t$ in Eq. (2b)

$$\frac{\mathrm{d}s}{\mathrm{d}t} \geqslant -2k\mu(s)s_{\mathrm{in}} + d_0(s_{\mathrm{in}} - s),$$

where k is defined, from the equivalence of norms in $\mathbb{R}^n$, by $\Gamma^{\mathrm{T}}X \leqslant k\mathbb{1}^{\mathrm{T}}X$ for $X \geqslant 0$.

Therefore, since $\mu(s)$ is continuous and $\mu(0) = 0$, there exists an $\varepsilon > 0$ such that $\forall s$, $0 \leqslant s \leqslant \varepsilon$, $d_0(s_{\mathrm{in}} - s) - 2k\mu(s)s_{\mathrm{in}} > 0$. As a consequence

$$\forall s(t) \in [0, \varepsilon],\ \frac{\mathrm{d}s}{\mathrm{d}t} > 0$$

and thus the solution exits $[0, \varepsilon]$ at some time τ, and cannot reenter this interval for all later times.

Now using inequality (5) allows us to settle the case of 'large' initial conditions. Indeed, suppose that $\mathbb{1}^{\mathrm{T}}X_0 + s_0 > 2s_{\mathrm{in}}$. Then (5) implies that $\exists\tau > 0$ such that for all $t > \tau$, $(\mathbb{1}^{\mathrm{T}}X + s)(t) \leqslant 2s_{\mathrm{in}}$, which takes us back to the previously treated case. □

These lemmas being stated, we now turn to system (2a) and (2b), concerning which we can then formulate the following proposition, the main result of this section.

Proposition 3.1. *Let $v_{\mathrm{p}}^{\mathrm{l}}$ be a left eigenvector corresponding to the eigenvalue of A with maximal real part λ_{p}. Then, for all solutions of* (2a) *and* (2b) *such that $X_0 \geqslant 0$, we have*

$$\frac{X}{v_{\mathrm{p}}^{\mathrm{lT}}X} \to v_{\mathrm{p}}^{\mathrm{r}} \quad \text{as } t \to \infty, \tag{7}$$

where $v_{\mathrm{p}}^{\mathrm{r}}$ is a right eigenvector of A corresponding to the eigenvalue λ_{p} with maximal real part, chosen such that $\mathbb{1}^{\mathrm{T}}v_{\mathrm{p}}^{\mathrm{r}} = 1$ and $v_{\mathrm{p}}^{\mathrm{lT}}v_{\mathrm{p}}^{\mathrm{r}} = 1$.

Proof. Let $v_{\mathrm{p}}^{\mathrm{lT}}$ be a left eigenvector of A corresponding to the eigenvalue λ_{p} with maximal real part, i.e., a vector such that

$$v_{\mathrm{p}}^{\mathrm{lT}}A = \lambda_{\mathrm{p}}v_{\mathrm{p}}^{\mathrm{lT}}. \tag{8}$$

Since A is quasi-positive and irreducible, we know from a corollary of the Perron–Frobenius theorem [14, Corollary 3.2, p. 60], that $v_{\mathrm{p}}^{\mathrm{l}} \gg 0$. We state here the normalisation choice, although it will only be used later: we suppose that the right eigenvector $v_{\mathrm{p}}^{\mathrm{r}} \gg 0$ associated to λ_{p} is such that $\mathbb{1}^{\mathrm{T}}v_{\mathrm{p}}^{\mathrm{r}} = 1$, and that both these eigenvectors verify $v_{\mathrm{p}}^{\mathrm{lT}}v_{\mathrm{p}}^{\mathrm{r}} = 1$.

Let us introduce the following variable:

$$Z = \frac{X}{v_{\mathrm{p}}^{\mathrm{lT}}X}. \tag{9}$$

We have $Z \in \mathbb{R}^n$. Of course, Z is only defined if $X \neq 0$. We have

$$v_{\mathrm{p}}^{\mathrm{lT}}Z = 1. \tag{10}$$

Then taking the derivative of Z, we have

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \frac{X'}{v_{\mathrm{p}}^{\mathrm{lT}}X} - \frac{X(v_{\mathrm{p}}^{\mathrm{lT}}X)'}{(v_{\mathrm{p}}^{\mathrm{lT}}X)^2} = \frac{X'}{v_{\mathrm{p}}^{\mathrm{lT}}X} - \frac{Zv_{\mathrm{p}}^{\mathrm{lT}}X'}{v_{\mathrm{p}}^{\mathrm{lT}}X}. \tag{11}$$

Now substituting (2a) in (11) and using (10) and (8) yields

$$\begin{aligned}\frac{\mathrm{d}Z}{\mathrm{d}t} &= \mu(s)AZ - d_1(s)Z - Zv_{\mathrm{p}}^{\mathrm{lT}}\frac{\mu(s)AX - d_1(s)X}{v_{\mathrm{p}}^{\mathrm{lT}}X} \\ &= \mu(s)\left[AZ - Zv_{\mathrm{p}}^{\mathrm{lT}}AZ\right] + d_1(s)Zv_{\mathrm{p}}^{\mathrm{lT}}Z - d_1(s)Z = \mu(s)\left[AZ - \lambda_{\mathrm{p}}Z\right] = \mu(s)[A - \lambda_{\mathrm{p}}I]Z,\end{aligned} \tag{12}$$

where I is the identity matrix. Hence the dynamics of Z is independent of $d_1(s)$. Furthermore, $\mu(s)$ is in factor of the term in Z. From Lemma 3.2, one can find a positive quantity ε such that, after an eventual short time τ, the substrate concentration s is strictly superior to ε. Since μ is continuous and increasing, we therefore have $\mu(s) > \mu(\varepsilon)$ after an eventual short time τ.

Therefore, using a *change in velocity* ([16, p. 92], stated as Theorem A.1 in Appendix A), one concludes that the following linear system:

$$\frac{\mathrm{d}\xi}{\mathrm{d}t} = (A - \lambda_{\mathrm{p}}I)\xi, \tag{13}$$

with $\xi(t) \in \mathbb{R}^n$, has the same asymptotic behaviour and the same geometric phase portrait as (12).

Hence we now turn our attention to system (13). Since A is an irreducible quasi-positive matrix, $A - \lambda_{\mathrm{p}}I$ is also an irreducible, quasi-positive matrix. Therefore, still from [14, Corollary 3.2, p. 60], it admits a dominant eigenvalue, that is equal to 0 since λ_{p} is the dominant eigenvalue of A. We denote by $v_{\mathrm{p}}^{\mathrm{r}}$ the associated strictly positive eigenvector of $A - \lambda_{\mathrm{p}}I$. Note that $v_{\mathrm{p}}^{\mathrm{r}}$ is also the eigenvector associated to λ_{p}, and remember that we chose $v_{\mathrm{p}}^{\mathrm{r}}$ such that $\mathbb{1}^{\mathrm{T}}v_{\mathrm{p}}^{\mathrm{r}} = 1$ and that $v_{\mathrm{p}}^{\mathrm{lT}}v_{\mathrm{p}}^{\mathrm{r}} = 1$.

Then we have

$$\frac{\xi}{v_{\mathrm{p}}^{\mathrm{lT}}\xi} \to v_{\mathrm{p}}^{\mathrm{r}} \quad \text{as } t \to \infty$$

because A is irreducible and quasi-positive, and therefore

$$\frac{X}{v_{\mathrm{p}}^{\mathrm{lT}}X} \to v_{\mathrm{p}}^{\mathrm{r}} \quad \text{as } t \to \infty. \tag{14}$$

This concludes the proof. □

Using this, we will be able to derive the behaviour of the system in the ω-limit set, provided that we study the behaviour of $v_{\mathrm{p}}^{\mathrm{lT}}X$.

3.1. The two-dimensional system

We now consider the system in $v_{\mathrm{p}}^{\mathrm{lT}}X$ and s. For convenience, we note $\zeta(t) \overset{\mathrm{def}}{=} v_{\mathrm{p}}^{\mathrm{lT}}X(t) \in \mathbb{R}_+$. In the ω-limit set, Eq. (14) implies that we have $X(t) = \zeta(t)v_{\mathrm{p}}^{\mathrm{r}}$. Hence in the ω-limit set, the system is written

$$\frac{\mathrm{d}\zeta}{\mathrm{d}t} = \mu(s)v_{\mathrm{p}}^{\mathrm{lT}}A\zeta v_{\mathrm{p}}^{\mathrm{r}} - d_1(s)\zeta, \tag{15a}$$

$$\frac{ds}{dt} = -\mu(s)\Gamma^{T}\zeta v_{p}^{r} + d_0(s_{in} - s). \tag{15b}$$

Now since v_p^l is a left eigenvector of A, we have $v_p^{lT}A = \lambda_p v_p^{lT}$. We can choose v_p^l such that $v_p^{lT}v_p^r = 1$. So (15a) is equivalent to

$$\frac{d\zeta}{dt} = \mu(s)\lambda_p\zeta - d_1(s)\zeta. \tag{16}$$

Hence the system under consideration is

$$\frac{d\zeta}{dt} = \mu(s)\lambda_p\zeta - d_1(s)\zeta, \tag{17a}$$

$$\frac{ds}{dt} = -\mu(s)\Gamma^{T}v_{p}^{r}\zeta + d_0(s_{in} - s). \tag{17b}$$

Theorem 3.1. *Consider the two-dimensional system* (17a) *and* (17b). *Then either one of the following holds.*

1. *If one of the following conditions is verified*:
   (a) $\lambda_p\mu_{max} \leqslant d_0 + \delta_{min}$,
   (b) s^*, *unique solution of the equation* $d_1(s) = \lambda_p\mu(s)$, *is such that* $s^* \geqslant s_{in}$,

   then the system (17a) *and* (17b) *admits a single, globally asymptotically stable trivial equilibrium* $(0, s_{in})$.
2. *Suppose that* $\lambda_p\mu_{max} > d_0 + \delta_{min}$, *and that* s^*, *unique solution of the equation* $d_1(s) = \lambda_p\mu(s)$, *is such that* $s^* < s_{in}$. *Then the system* (17a) *and* (17b) *admits two equilibrium points*: *an unstable trivial equilibrium* $(0, s_{in})$; *a globally asymptotically stable non-trivial equilibrium, given by*

$$\left(\frac{d_0\lambda_p}{d_1(s^*)\Gamma^{T}v_{p}^{r}}(s_{in} - s^*), s^*\right), \tag{18}$$

where s^* *is the unique solution of* $d_1(s) = \lambda_p\mu(s)$.

Proof. The nullclines of (17a) are given by $\zeta = 0$ and $d_1(s)/\mu(s) = \lambda_p$. Using $\zeta = 0$ in (17b) yields $s = s_{in}$, which is the trivial equilibrium of (17a) and (17b). Now consider

$$d_1(s) = \lambda_p\mu(s).$$

Since d_1 is monotonically decreasing and μ is monotonically increasing on $\mathbb{R}_+$, if there exists a s^* verifying this relation, it is unique. Fig. 1 illustrates the two possible cases. If such a value of s does not exist, i.e., if $\lambda_p\mu_{max} \leqslant d_0 + \delta_{min}$, then we are back in the trivial equilibrium case. This is condition (a) of Case 1. Note that the case $\lambda_p \leqslant 0$ is part of this case: $\lambda_p\mu(s)$ is decreasing and $\lambda_p\mu(s) < 0$ since $\mu(0) = 0$.

Now suppose that condition (a) of Case 1 is violated, i.e., that such a s^* exists. Then substituting $\mu(s^*) = d_1(s^*)/\lambda_p$ in (17b) gives

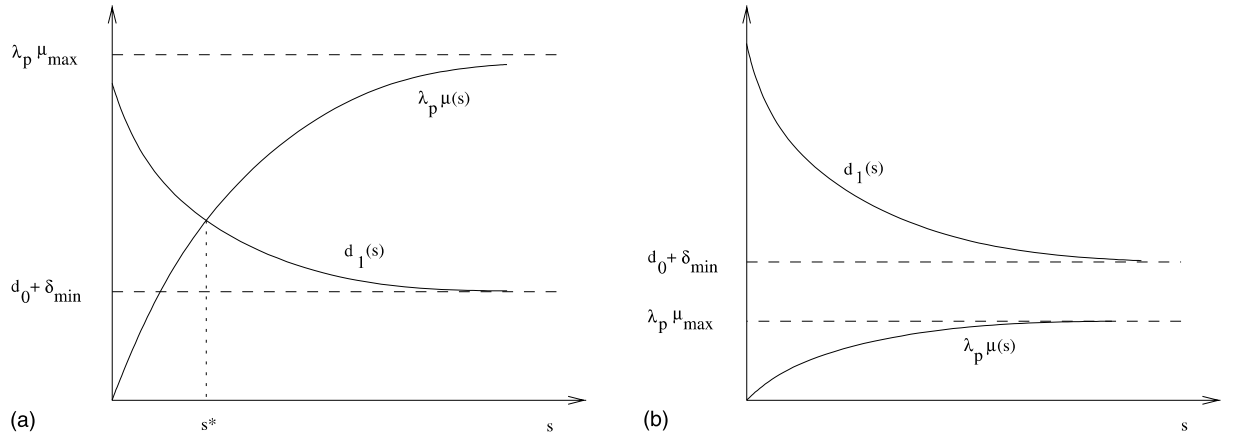

Fig. 1. The two possible cases: (a) s^* exists; (b) s^* does not exist.

$$\zeta^* = \frac{d_0\lambda_p}{d_1(s^*)\Gamma^T v_p^r}(s_{in} - s^*).$$

For this equilibrium to be meaningful, we must have $s^* < s_{in}$, hence condition (b) of Case 1, or 2.

We now turn to the question of the stability of these equilibria. To show the stability of the interior equilibrium and the instability of the trivial equilibrium, we make use of a Lyapunov function used in the predator–prey context by Harrison [17]. Indeed, a chemostat can be considered as a predator–prey system, the substrate being the prey and the organisms the predator. For readability, we postpone the proof of this result to Appendix B. □.

3.2. The result for the general system

We can now turn our attention back to the general system (2a) and (2b), using the preceding results. We have the following theorem, which is the main result of this paper.

Theorem 3.2. *Consider the general* $(n+1)$*-dimensional system* (2a) *and* (2b). *Then either one of the following two cases holds.*

1. *If one of the following conditions is verified*:
   (a) $\lambda_p\mu_{max} \leqslant d_0 + \delta_{min}$,
   (b) s^*, *unique solution of the equation* $d_1(s) = \lambda_p\mu(s)$, *is such that* $s^* \geqslant s_{in}$,

   then the system (2a) *and* (2b) *admits a single, globally asymptotically stable trivial equilibrium* $(0,\ldots,0,s_{in})$.
2. *Suppose that* $\lambda_p\mu_{max} > d_0 + \delta_{min}$, *and that* s^*, *unique solution of the equation* $d_1(s) = \lambda_p\mu(s)$, *is such that* $s^* < s_{in}$. *Then the system* (2a) *and* (2b) *admits two equilibria*: *an unstable trivial equilibrium* $(0,\ldots,0,s_{in})$; *a globally asymptotically stable, non-trivial equilibrium, given by*

$$X^* = \frac{d_0\lambda_p}{d_1(s^*)\Gamma^T v_p^r}(s_{in} - s^*)v_p^r \tag{19}$$

and

$$s = s^*,$$

where $v_{\mathrm{p}}^{\mathrm{r}}$ *is the strongly positive eigenvector associated to the dominant eigenvalue* λ_{p} *of* A.

Proof. Theorem 3.1 rules the behaviour of the two-dimensional limit system of (2a) and (2b), namely (17a) and (17b). Depending on the behaviour of the limit system (17a) and (17b), the behaviour of the $(n+1)$-dimensional system (2a) and (2b) can be deduced.

Case 1. The two-dimensional system has the unique trivial equilibrium $(0, s_{\mathrm{in}})$. Since $v_{\mathrm{p}}^{\mathrm{l}} \gg 0$, we have $v_{\mathrm{p}}^{\mathrm{lT}} X = 0$ if, and only if, $X \equiv 0$.

Case 2. The equation $d_1(s) = \lambda_{\mathrm{p}} \mu(s)$ admits a unique solution $s^* < s_{\mathrm{in}}$. Therefore Case 2 of Theorem 3.1 holds, and the two-dimensional system (17a) and (17b) admits a globally asymptotically stable non-trivial equilibrium, and a trivial, unstable equilibrium. The value of the trivial equilibrium follows from Case 1. Concerning the non-trivial, positive equilibrium, we have from Eq. (14) that $X^* = \zeta^* v_{\mathrm{p}}^{\mathrm{r}}$. Thus (19).

The original system (2a) and (2b) can be equivalently written under the form of a system in $(Z(t), \zeta(t), s(t))$. Under the conditions of the theorem, Case 2, we have proved that Z converges to $v_{\mathrm{p}}^{\mathrm{r}}$, and that (ζ, s) has the globally (in the positive orthant) asymptotically stable equilibrium (ζ^*, s^*). Using results such as [18, p. 263], we then have that the system in Z, ζ and s has the globally (in the positive orthant) asymptotically stable non-trivial equilibrium (Z^*, ζ^*, s^*). From the equivalence to system (2a) and (2b), we thus have the result. □

4. A few examples

Up to now, we have discussed the system in its general form (2a) and (2b). In particular, we have not given any example of the nature of the transition matrix A. In this section, we give three possible characterisations of this matrix, corresponding to the description of three rather different phenomena, depending on the type of description of the cellular division process that we make. Before proceeding with the examples, let us discuss briefly the use of size-structured models in the context of the chemostat, and more specifically, the use of size-structured models for the description of cellular division, since this will be the object of the three following examples. We mentioned in the introduction the low number of papers devoted to the description of size-structured chemostats. Among this already low number, the only examples that we know of that consider cellular division process are the continuous time, continuous structure models in Metz and Diekmann [4], as well as the models derived from these works [5,6]. Other PDE models [1], as well as most discrete-time models [7–9], suppose that cell division occurs for cells of a predetermined, constant size, and yields two equally sized daughter cells.

It is our purpose here to show that ODEs can be used for the description of quite complex division processes. The purpose of this paper is not to formulate precisely such models, but to show that were such models precisely formulated, they could be studied. Hence what follows are

rough approximations of the type of transition matrices that are intended as applications of the method. A complete description of the process would require the precise definition of the size classes, as well as of the growth function, the division proportions and so on. We refer the reader to [19] where one derivation is done in the discrete-time discrete-structure case.

In all three cases, we suppose that the biomass of cells in the chemostat ranges from b_1 to b_2. We divide the cells in size classes, i.e., that we divide the biomass into n biomass classes. Hence $x_i(t)$ is the biomass of cells in biomass class i at time t. Suppose that the size classes are chosen so that all cell growth in class i is immediately reported to class $i+1$. Therefore, the diagonal elements of A are -1. This biomass then enters class $i+1$ at a rate $1+\gamma_i$, which is diminished of an amount $m_i \in [0,1]$ because of maintenance. Maintenance thus acts as follows: if m_i is small (close to 0), then only a small fraction of the uptaken nutrient is allocated to cellular growth, while as m_i tends to 1, most of the uptaken nutrient is allocated to growth.

4.1. Simple cellular division

In this first example, we suppose that cell division only occurs for cells in the last size class, yielding two equally sized cells in the first class: we call this *homogeneous*—with respect to the size of cells when they divide—*symmetric*—with respect to the size of the daughter cells—cellular division. The structure of the system is then as depicted in Fig. 2. A version of this system with a continuous size variable is given in [1], while a discrete-time, discrete-structure version can be found in [7–9].

Matrix A then has the form

$$\begin{bmatrix} -1 & 0 & & 0 & (1+\gamma_n)m_n \\ (1+\gamma_1)m_1 & -1 & 0 & & 0 \\ & \ddots & \ddots & & \\ & & & -1 & 0 \\ & & & (1+\gamma_{n-1})m_{n-1} & -1 \end{bmatrix} \tag{20}$$

and the consumption vector is given by $\Gamma = (\gamma_1, \ldots, \gamma_n)^{\mathrm{T}}$.

Theorem 3.2 can obviously be applied to this system. Indeed, the matrix A is quasi-positive and irreducible, has $\mu(s)$ in factor of all flows, and inequality (3) holds. Writing the equation for the left eigenvector,

$$v_{\mathrm{p}}^{\mathrm{lT}} A = \lambda_{\mathrm{p}} v_{\mathrm{p}}^{\mathrm{lT}}$$

and noting $v_{\mathrm{p}}^{\mathrm{lT}} = (v_1^{\mathrm{l}}, \ldots, v_n^{\mathrm{l}})$, one finds that

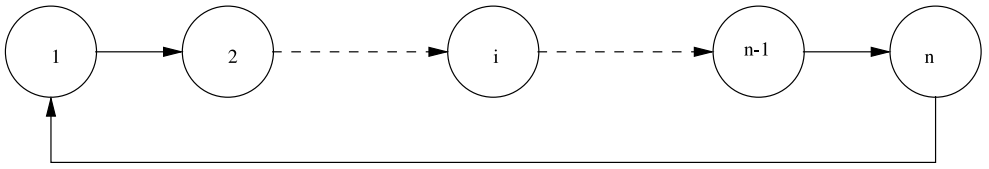

Fig. 2. The simplest structure, with homogeneous and symmetric division.

$$v_1^{\mathrm{l}} = \frac{\prod_{i=1}^{n}(1+\gamma_i)m_i}{(1+\lambda_{\mathrm{p}})^n} v_1^{\mathrm{l}}.$$

We thus have an expression of λ_{p} as a function of the γ_is

$$\lambda_{\mathrm{p}} + 1 = \left(\prod_{i=1}^{n}(1+\gamma_i)m_i \right)^{1/n}. \tag{21}$$

This expression can be evaluated if the γ_is and the m_is are known, giving the sign of λ_{p}. If $\lambda_{\mathrm{p}} \leqslant 0$, we need to proceed no further, since the only equilibrium of the system is the trivial one. If $\lambda_{\mathrm{p}} > 0$, then, from the equation for the right eigenvector, which we note $v_{\mathrm{p}}^{\mathrm{r}} = (v_1^{\mathrm{r}}, \ldots, v_n^{\mathrm{r}})^{\mathrm{T}}$, we obtain after some manipulations that

$$v_i^{\mathrm{r}} = \frac{\prod_{j=0}^{i-1}(1+\gamma_j)m_j}{(1+\lambda_{\mathrm{p}})^i} v_n^{\mathrm{r}}, \tag{22}$$

where indices are considered modulo n, i.e., that $\gamma_0 = \gamma_n$ and $m_0 = m_n$. Using the fact that $\mathbb{1}^{\mathrm{T}} v_{\mathrm{p}}^{\mathrm{r}} = 1$, we also have that

$$\sum_{i=1}^{n}(1+\gamma_i)m_i v_i^{\mathrm{r}} = 1 + \lambda_{\mathrm{p}}. \tag{23}$$

Using (22) in (23), we thus obtain that

$$v_n^{\mathrm{r}} = \frac{1+\lambda_{\mathrm{p}}}{\sum_{i=1}^{n}(1+\gamma_i)m_i \frac{\prod_{j=0}^{i-1}(1+\gamma_j)m_j}{(1+\lambda_{\mathrm{p}})^i}}. \tag{24}$$

This expression can be evaluated since all its terms are known. Then the right eigenvector can be expressed using (22), finally allowing one to express the non-trivial equilibrium point.

4.1.1. A simplified case

An interesting special case of the preceding model is the one where all the rates are equal: for all $i = 1, \ldots, n$, $\gamma_i = \gamma$ and $m_i = m$. Indeed, in this case, we obtain from (21) that

$$\lambda_{\mathrm{p}} = (1+\gamma)m - 1.$$

This eigenvalue is positive if and only if

$$\gamma > \frac{1-m}{m}. \tag{25}$$

Remark 4.1. From a biological point of view, if m is small (close to 0), then cells use a large part of the uptaken nutrient for maintenance activities. The rate of passage of the biomass from one class to the next then has to be high in order to avoid extinction of the population.

If (25) is not verified, then we are in the case where $\lambda_{\mathrm{p}} \leqslant 0$, and only the trivial equilibrium exists. Let us now suppose that (25) be verified. Substituting the value of λ_{p} that we have found

into the system of equations resulting from the right eigenvalue equation, one finds that all elements of $v_{\mathrm{p}}^{\mathrm{r}}$ are necessarily equal. Since we choose $v_{\mathrm{p}}^{\mathrm{r}}$ such that $\mathbb{1}^{\mathrm{T}} v_{\mathrm{p}}^{\mathrm{r}} = 1$, this implies that

$$v_{\mathrm{p}}^{\mathrm{r}} = \begin{pmatrix} 1/n \\ \vdots \\ 1/n \end{pmatrix}.$$

Since $\Gamma = \gamma\mathbb{1}$, we have $\Gamma^{\mathrm{T}} v_{\mathrm{p}}^{\mathrm{r}} = n(\gamma/n) = \gamma$. Thus by Theorem 3.2, the non-trivial equilibrium is given by s^* such that

$$\lambda_{\mathrm{p}}\mu(s^*) = d_1(s^*)$$

and X^* such that

$$X^* = \frac{((1+\gamma)m - 1)d_0}{n\gamma d_1(s^*)}(s_{\mathrm{in}} - s^*)\mathbb{1}.$$

Hence the distribution of biomass is equal in all size classes.

Remark 4.2. The equilibrium that we have obtained is (to a constant) the same as the one obtained by Gage et al. in their paper [7]. This is not surprising if one compares both systems. Indeed, the progression of cells amongst the size classes is only function of the substrate, and division only occurs for cells in the last size class. This is exactly the same hypotheses as the ones used in [7].

4.2. Inhomogeneous cellular division

Now another type of transition matrix which could be considered would be one describing *inhomogeneous* cellular division.

Consider Fig. 3. It supposes that the various cell sizes can be classified into three different types of classes: classes where cells are born, classes where they grow, and finally, classes in which they undergo division. Therefore, the matrix A given as a previous example is a particular case of this, with the number of division and birth classes being equal to one. The transition matrix then has the structure shown in Table 1, and the consumption vector is still $\Gamma = (\gamma_1, \ldots, \gamma_n)^{\mathrm{T}}$.

In the matrix of Table 1, the p_is, with $p_i \in [0, 1]$, represent the proportion of cells in a given division class that undergo division, so that the remaining $1 - p_i$ cells continue growing. The last p_i

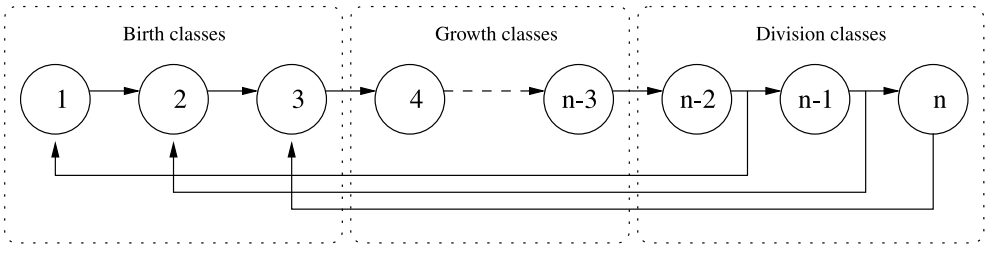

Fig. 3. A size-structured model with inhomogeneous cell size at division. Here there are three division and three birth classes.

Table 1
Transition matrix for a model with inhomogeneous, symmetric cellular division

$$\begin{bmatrix}
-1 & 0 & & & p_1(1+\gamma_{n-2})m_{n-2} & 0 & 0 \\
(1+\gamma_1)m_1 & -1 & 0 & & 0 & p_2(1+\gamma_{n-1})m_{n-1} & 0 \\
0 & (1+\gamma_2)m_2 & -1 & & 0 & 0 & (1+\gamma_n)m_n \\
 & 0 & (1+\gamma_3)m_3 & -1 & & & \\
 & & & \ddots & \ddots & & \\
 & & & & -1 & 0 & \\
 & & & & (1-p_1)(1+\gamma_{n-2})m_{n-2} & -1 & 0 \\
 & & & & 0 & (1-p_2)(1+\gamma_{n-1})m_{n-1} & -1
\end{bmatrix}$$

Here we suppose that there are three size classes in which cellular division can occur, and three classes in which cells are born.

(here p_3) is equal to one: all cells divide in the last class. A discrete-time version of this model was analysed in [20].

4.3. Asymmetric cellular division

Suppose now that cell division is homogeneous, but *asymmetric*, i.e., that the division of a mother cell produces two daughter cells with a biomass (size) that is not necessarily equal. Then one has the sort of structure that is shown in Fig. 4: the division of a cell in class n can yield either two cells of equal mass in class 2, or one smaller cell in class 1 and one larger cell in class 3.

To model this behaviour, one could use a transition matrix of the same form as (20), but where the last column would be the following vector:

$$\begin{pmatrix}
\pi_1(1+\gamma_n)m_n \\
\pi_2(1+\gamma_n)m_n \\
(1-\pi_1)(1+\gamma_n)m_n \\
0 \\
\vdots \\
0 \\
-1
\end{pmatrix}.$$

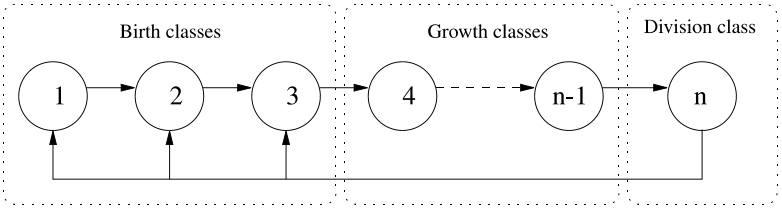

Fig. 4. A size-structured model with homogeneous, asymmetric cellular division. Here there are three birth classes.

Instead of being allocated to the first element of this vector, the result of the division of cells in class n is spread among the different birth classes (three in the case of the figure).

4.4. More complex cases

We shall not treat here the more general case consisting of a combination of inhomogeneous and asymmetric cellular division. We refer the reader to [19] where this is done in the discrete-time context. As can be inferred from the preceding examples, numerous combinations and connection graphs can be devised to account for varied phenomenons.

5. Conclusion and discussion

We have considered here a very general model of growth in the chemostat. This size-structured model, formulated using ordinary differential equations, does not verify the mass conservation principle. Hence we were not able to use the classical approach of chemostat analysis, which consists in studying the system in its ω-limit set, where it is linear.

The system, or more precisely the class of system which was introduced here, accounts for maintenance and cell death. Direct analysis was not possible. However, we observed that a new system, consisting of a normed version of the original system, was almost linear. Thus, after ensuring that the quantity of substrate was positive, we were able to study the behaviour of the new system, by considering a change of time scale. Then, studying the two-dimensional system (substrate and normed cellular biomass) in the ω-limit set of the linear system, we concluded to the existence of a globally stable non-trivial equilibrium for it. This stability was proved using a Lyapunov functional introduced by Harrison [17] in the predator–prey context.

Finally with this knowledge, we could turn our attention back to the original $(n+1)$-dimensional non-linear system. We concluded about it that it also admitted a globally stable, non-trivial equilibrium point.

The very general form of the model allows for general hypotheses. As long as (1) the transition matrix A is quasi-positive and irreducible (2) the growth rate μ is a factor of this transition matrix; then the analysis developed herein is valid.

We illustrated the sort of biological systems that this class of system can account for, studying an example and giving two others. It has to be noted that a simplified version of the former, with division in only the last size class and with all fluxes occurring at the same rate, leads to the same equilibrium distribution as in a discrete-time model introduced by Gage et al. [7]. Analysis of the more complex examples was not carried out, but we expect to find the same sort of equilibrium size distribution as had been found in the discrete-time context in [19,20].

The assumption of size-independent cellular growth is the most crucial one, and it should be discussed. Although not very satisfactory, it should be noted that it is quite a common hypothesis in structured models of cellular growth to assume this independence. On the other hand, the introduction of size specific growth greatly complicates the analysis. Cazzador studied [21] a model of yeast growth in the chemostat, in which the yeast can be in two states: budded or unbudded. Each state has a specific growth rate. Therefore, he considers a three-dimensional system,

and shows that a Hopf bifurcation can occur for certain parameter ranges. Extension of his analysis to the $(n+1)$-dimensional case seems a complicated task.

While the assumption of homogeneous growth is a little bothersome, one can easily see that the description of the cellular division process that we can do can be quite complex. Indeed, a great deal of liberty exists with the various model parameters to play with the growth function. Consider, e.g., our first example. By using very different values for the γ_is and m_is depending on i (the size), it is possible to account for size specific differences in growth. The same way, it is possible, in the case of inhomogeneous or asymmetric cellular division, to make the division rates quite different depending on the cellular size.

Appendix A. Equivalence of flows

We use the following theorem of Hofbauer and Sigmund [16] several times in the text.

Theorem A.1. [16] *If two differential equations of the form*

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = f_i(x_1, \ldots, x_n)$$

and

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = f_i(x_1, \ldots, x_n) W(x_1, \ldots, x_n)$$

differ only by a positive factor W which does not depend on i, then these equations admit the same orbits.

Appendix B. Proof of the stability part of Theorem 3.1

Proof. So as to meet the requirements of the analysis of [17], the system has to be redimensionalised. Since $d_1(s) \geqslant d_0 > 0$, we can divide by $d_1(s)$, hence obtaining the system

$$\frac{\mathrm{d}\zeta}{\mathrm{d}t} = \frac{\mu(s)}{d_1(s)} \lambda_{\mathrm{p}} \zeta - \zeta \tag{A.1}$$

$$\frac{\mathrm{d}s}{\mathrm{d}t} = -\frac{\mu(s)}{d_1(s)} \Gamma^{\mathrm{T}} v_{\mathrm{p}}^{\mathrm{r}} \zeta + \frac{d_0}{d_1(s)} (s_{\mathrm{in}} - s) \tag{A.2}$$

which is dynamically equivalent to (17a) and (17b), in virtue of Theorem A.1. We then identify this system with the system studied in [17]:

$$\frac{\mathrm{d}H}{\mathrm{d}t} = a(H) - f(H) b(P)$$
$$\frac{\mathrm{d}P}{\mathrm{d}t} = n(H) g(P) + c(P).$$

In order to do so, consider the following functions, where s and ζ have been used for H and P, respectively,

$$a(s) = \frac{d_0}{d_1(s)}(s_{\text{in}} - s)$$

$$f(s) = \frac{\mu(s)}{d_1(s)}$$

$$b(\zeta) = \Gamma^{\text{T}} v_{\text{p}}^{\text{r}} \zeta$$

$$n(s) = \frac{\mu(s)}{d_1(s)}$$

$$g(\zeta) = \lambda_{\text{p}} \zeta$$

and finally

$$c(\zeta) = -\zeta.$$

Requirements of [17, Theorem 2.2] are that a/f and c/g be non-increasing functions with one of them being strictly decreasing, and that $[n(s) - n(s^*)][s - s^*] > 0$ and $[b(\zeta) - b(\zeta^*)][\zeta - \zeta^*] > 0$ for $s \neq s^*$ and $\zeta \neq \zeta^*$ respectively.

We have

$$\frac{c(\zeta)}{g(\zeta)} = -\frac{1}{\lambda_{\text{p}}}$$

and

$$\frac{a(s)}{f(s)} = \frac{d_0(s_{\text{in}} - s)}{\mu(s)}.$$

The latter is strictly decreasing if and only if

$$(s_{\text{in}} - s)\frac{\text{d}\mu}{\text{d}s} > -\mu(s).$$

From (4), we can deduce that in the vicinity of s^* we have $s < s_{\text{in}}$. Hence the function is indeed strictly decreasing.

Now $n(s)$ is a monotonically increasing function of s, so $[n(s) - n(s^*)][s - s^*] > 0$ for $s \neq s^*$, and $[b(\zeta) - b(\zeta^*)][\zeta - \zeta^*] = \Gamma^{\text{T}} v_{\text{p}}^{\text{r}} (\zeta - \zeta^*)^2 > 0$ for $\zeta \neq \zeta^*$.

Using these functions, the system is indeed of the needed form for the analysis of [17]. Define the following function:

$$V(s, \zeta) = \int_{s^*}^{s} \frac{n(u) - n(s^*)}{f(u)}\,\text{d}u + \int_{\zeta^*}^{\zeta} \frac{b(u) - b(\zeta^*)}{g(u)}\,\text{d}u \tag{A.3}$$

which, using the notation of our model, yields

$$V(s, \zeta) = s - s^* - \frac{\mu(s^*)}{d_1(s^*)} \int_{s^*}^{s} \frac{d_1(u)}{\mu(u)}\,\text{d}u + \frac{\Gamma^{\text{T}} v_{\text{p}}^{\text{r}}}{\lambda_{\text{p}}} \left(\zeta - \zeta^* \left(1 + \ln \frac{\zeta}{\zeta^*} \right) \right). \tag{A.4}$$

In (ζ^*, s^*), we have $V(\zeta^*, s^*) = 0$. The time derivative of V is given by

$$\frac{\mathrm{d}V}{\mathrm{d}t} = [n(s) - n(s^*)]\left[\frac{a(s)}{f(s)} - \frac{a(s^*)}{f(s^*)}\right] + [b(\zeta) - b(\zeta^*)]\left[\frac{c(\zeta)}{g(\zeta)} - \frac{c(\zeta^*)}{g(\zeta^*)}\right]$$

which in our model gives

$$\begin{aligned}\frac{\mathrm{d}V}{\mathrm{d}t} &= \left[\frac{\mu(s)}{d_1(s)} - \frac{\mu(s^*)}{d_1(s^*)}\right]\left[\frac{d_0}{\mu(s)}(s_{\mathrm{in}} - s) - \frac{d_0}{\mu(s^*)}(s_{\mathrm{in}} - s^*)\right] \\ &= d_0\left[\frac{\mu(s)}{d_1(s)} - \frac{\mu(s^*)}{d_1(s^*)}\right]\left[\frac{s_{\mathrm{in}} - s}{\mu(s)} - \frac{s_{\mathrm{in}} - s^*}{\mu(s^*)}\right]. \qquad \text{(A.5)}\end{aligned}$$

Now a few conditions have to be verified. To begin with, we seek s_{L}, s_{M}, ζ_{L} and ζ_{M}, the largest numbers such that

$$a(s) > b(\zeta^*)f(s) \quad \text{for } s_{\mathrm{L}} < s < s^* \qquad \text{(A.6)}$$

$$a(s) < b(\zeta^*)f(s) \quad \text{for } s^* < s < s_{\mathrm{M}} \qquad \text{(A.7)}$$

$$c(\zeta) \geqslant -n(s^*)g(\zeta) \quad \text{for } \zeta_{\mathrm{L}} < \zeta < \zeta^* \qquad \text{(A.8)}$$

$$c(\zeta) \leqslant -n(s^*)g(\zeta) \quad \text{for } \zeta^* < \zeta < \zeta_{\mathrm{M}}. \qquad \text{(A.9)}$$

Consider (A.6). Substituting their values for the functions, we seek the value of $s_{\mathrm{L}} < s^*$ such that

$$d_0(s_{\mathrm{in}} - s) > \frac{\mu(s)}{d_1(s)}\Gamma^{\mathrm{T}} v_{\mathrm{p}}^{\mathrm{r}} \zeta^*.$$

Now in s^* we have

$$d_0(s_{\mathrm{in}} - s^*) > \frac{\mu(s^*)}{d_1(s^*)}\Gamma^{\mathrm{T}} v_{\mathrm{p}}^{\mathrm{r}} \zeta^*.$$

Now consider a decreasing $s < s^*$. The left-hand side of the inequality is a decreasing function of s, thus increases if s decreases. On the contrary, the right-hand side is an increasing function of s, and thus decreases as s decreases. Therefore, the inequality is verified for all $s < s^*$, so $s_{\mathrm{L}} = 0$. Proceeding the same way, we can easily check that $s_{\mathrm{L}} = \zeta_{\mathrm{L}} = 0$ and $s_{\mathrm{M}} = \zeta_{\mathrm{M}} = \infty$.

Then defining

$$u = \min\{V(s^*, \zeta_{\mathrm{L}}), V(s^*, \zeta_{\mathrm{M}}), V(s_{\mathrm{L}}, \zeta^*), V(s_{\mathrm{M}}, \zeta^*)\}$$

we find $u = \infty$. Then Theorem 2.2 of [17] states that the domain of attraction of (s^*, ζ^*) includes the set

$$D_u = \{(s, \zeta) : V(s, \zeta) < u\}.$$

Hence the domain of attraction of the interior equilibrium is the whole positive quadrant $\mathbb{R}^2_+$. The interior equilibrium is thus globally stable. □

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