Nonhomogeneous asymmetric cellular division in a discrete-time, size-structured model of growth in the chemostat

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Abstract

We extend a discrete-time size-structured model of growth in the chemostat to the case of nonhomogeneous and asymmetric cellular division, *i.e.*, cells dividing with unequal biomass and into unequally sized daughters. We show that previous results concerning this type of system still hold, and investigate numerically some of the properties of the size spectrum.

Introduction

Discrete-time models can successfully describe the complex phenomena involved in the life sciences [4, Chapters 1 and 3]. However, in the context of the chemostat this approach has seldom been used. Gage *et al* [5] introduced a model that describes the growth of a size-structured population in the chemostat. Later, Smith [10] showed using the mass conservation property that this model admits a globally asymptotically stable non trivial equilibrium, which he characterized. In a previous work [2], the model of Gage *et al* was extended to describe nonhomogeneous cellular division, *i.e.*, division of cells with different sizes. By showing that the resulting system verified the mass conservation principle, we were able to apply Smith's analysis and thus obtain a satisfactory mathematical description of its behavior. The purpose of the present work is to go even further and describe asymmetric cellular division.

The first motivation for such a level of detail is a point raised in a previous paper. Indeed, considering that the smallest cell in the model is of size b, [2] allows for a fourfold increase of the biomass, *i.e.*, a biomass in the interval $[b, 4b]$. While this is quite an improvement of the model of [5] where the biomass can only double, it is still quite far from the experimentally observed biomass spectra. For example, the data used in [1, 2] covers a 2.5 multiplication of the cellular diameter, which, if using biovolume as an indicator of the cellular biomass, corresponds to a 16 fold increase of the biomass.

Here, we investigate one of the possible ways to work around this limitation: introduction of division yielding cells of unequal size, *i.e.*, *asymmetric cellular division*. This has been considered in continuous time PDE models: in the case of *Daphnia* by Metz and Diekmann [8]. In models relative to cellular population dynamics, this has been the focus of quite a lot of interest, as reviewed in Arino and Sanchez [3]. We know however of no model taking the two processes into account: the nonhomogeneous size at division of [8] (in the chemostat context) and the nonhomogeneous division. Our aim here is to study the impact of asymmetry on the size spectrum, in the case of a population living in a chemostat.

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Cellular division is a very complex process. A phenomenological description of division involves several steps. The initiation step takes place for a cell of a given biomass. When division is finished, the mother cell has been replaced by several daughter cells. In most cases, there are two daughter cells, but there can sometimes be more (see, *e.g.*, hypothesis (iv) [12, p. 232]). We restrict ourselves to the case of two daughter cells. However, we consider *asymmetric cellular division* [6], treated in the chemostat context by Diekmann and Heijmans [8, Chapter 6]: a mother cell divides into two daughter cells, where the individual biomass of the daughters is not necessarily equal. We consider the case where the outcome of division is static: a dividing cell yields two daughter cells, one small and one large, and the proportion of the mother cell represented by the small and the large cell is a constant. We will show that although this results in a model that is quite complex, it has no influence on the global behaviour of the system, which can again be shown to admit a globally stable non trivial equilibrium, the difference with the models of [2, 5, 10] residing in the nature of the equilibrium distribution.

In essence, our model is very close to a model of Koch and Schaechter [7], even though the latter derives from a statistical approach.

This paper is organised as follows. Section 1 considers a simplistic model of asymmetric cellular division, which is used to introduce various concepts and notations. In Section 2, we give the general formulation of the mathematical model under consideration. Section 3 is devoted to the description of the various cellular processes modelled. Examples are then given in Section 4.

1   A naive introductory model

We begin by giving an example using a very simple model. We use this as a means of justifying our approach as well as introducing various concepts which will be used throughout the text.

It is generally assumed that a cell doubles its biomass, then divides. To investigate the role that variability in the symmetry of division plays in the size spectrum of cells, consider the naive model that follows. Suppose that we have a unique cell at generation 0. This cell grows from a biomass $b/2$ to a biomass b, then divides into two daughter cells. These two cells follow the same evolution, from a biomass $b/2$ to a biomass b, then divide, etc. If for simplicity, we assume that there is no overlapping of generations, we have at generation N at total number of 2^N cells; each one of these cells is born with a biomass $b/2$ and divides when its biomass is b.

Now suppose that instead of splitting evenly, the division of a mother cell of size b' yields one small daughter cell of size $\alpha b'$ and one large daughter cell of size $(1-\alpha)b'$, with $0 \leq \alpha \leq 1/2$ (the cases $\alpha = 0$ and $\alpha = 1/2$ correspond to an absence of division; they are included for completeness of the argument only). Let us define the *asymmetry* of a division as the quantity

$$\delta = 1 - \frac{\alpha}{1-\alpha} \tag{1}$$

Since $\alpha \in [0, \frac{1}{2}]$ we have that $\delta \in [0, 1]$. Furthermore, the transformation $\alpha \mapsto \delta$ is one-to-one for $\alpha \in [0, \frac{1}{2}]$, and thus a value $\delta \in [0, 1]$ defines uniquely an $\alpha = (\delta - 1)/(\delta - 2)$. This implies that it is strictly equivalent to speak of division into α and $1 - \alpha$ sized daughters, and to speak of division with *asymmetry* δ. From now on, we will in general use the latter term.

Suppose that the asymmetry δ is constant, $\delta \in (0, 1)$, and equal for all dividing cells, *i.e.*, that division is always asymmetric. To simplify and without loss of generality, suppose that $b = 1$. Then we have the following.

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Generation	Begining of generation	End of generation
0	1 cell of $1/2$	1 cell of 1
1	1 cell of α	1 cell of 2α
	1 cell of $(1-\alpha)$	1 cell of $2(1-\alpha)$
2	1 cell of $2\alpha^2$	1 cell of $4\alpha^2$
	2 cells of $2\alpha(1-\alpha)$	2 cells of $4\alpha(1-\alpha)$
	1 cell of $2(1-\alpha)^2$	1 cell of $4(1-\alpha)^2$
$\vdots$		
N	For $k=0,\dots,N,$	For $k=0,\dots,N,$
	C_N^k cells of $2^{N-1}\alpha^{N-k}(1-\alpha)^k$	C_N^k cells of $2^N\alpha^{N-k}(1-\alpha)^k$

where the values for generation N result of the binomial theorem. To simplify, let us consider the mean biomass of cells in each generation. Then, at generation N, for each $k=0,\dots,N$ we have C_N^k cells with biomass

$$\frac{3}{2}2^{N-1}\alpha^{N-k}(1-\alpha)^k$$

Plotting the total biomass in a size class as a function of the mass, this very simple model gives distributions as shown in Figure 1(a).
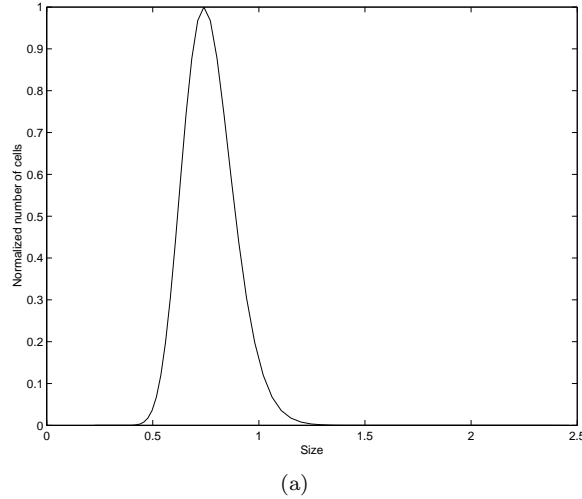

(a)

Figure 1: Simple division model, with 60 generations and a small asymmetry of $\delta = 0.039$.

Asymmetry of the division thus is clearly responsible for the spread of the cellular size distribution. But of course, this model cannot be taken at face value. Its main shortcomings are now summarized.

- The maximum cellular size is unbounded. Indeed, since the largest daughter cell never disappears, its division yields a yet larger daughter cell. The mean biomass of the largest cell during generation N is bounded below by $3\beta^{N-1}/2$, where $\beta > 1$ for a nonzero dissymmetry.

- Cellular growth is unlimited and is supposed to always lead in one generation to a doubling of the cellular biomass.

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The objectives of the present paper are to address these shortcomings, by proposing a dynamical model of the evolution of such a cell population, in the chemostat context. A discrete-time model for the chemostat is presented in Section 2, and the description of the cellular processeses is done in Section 3.

2   The general chemostat model

We refer to [11] for an extensive survey of mathematical models of the chemostat. A general assumption, to which we adhere here, is that the culture vessel of the chemostat is well mixed, so that spatial aspects can be neglected.

2.1   The mathematical model

The following is a discrete-time, size-structured model of growth in a chemostat. Its construction is treated in [1, 2, 5, 10] so we simply state it here. The system under consideration is, for $t \geq 0$,

$$
\begin{aligned}
\mathbf{x}_{t+1} &= (1 - E)A(S_t)\mathbf{x}_t & \text{(2a)} \\
S_{t+1} &= (1 - E)[S_t - f(S_t)X_t] + ES^0 & \text{(2b)}
\end{aligned}
$$

Equation (2a) describes the evolution of the cellular biomass in the chemostat, denoted by the variable $\mathbf{x}_t \in \mathbb{R}^n_+$. For now, it suffices to think of the biomass as a continuous variable spanning a finite segment. This segment is, for the purpose of observation, split into a finite number r of *size classes*. We denote $x_i(t)$ the biomass content of size class i at time t, $\mathbf{x}_t = (x_1(t), \ldots, x_r(t))^T$ and $X_t = \mathbb{1}^T\mathbf{x}_t$ (with $\mathbb{1} = (1, \ldots, 1)^T$), total organic biomass in the system at time t. We indifferently say that a cell belongs to (biomass) class i or that it has a certain biomass (meaning that it has a biomass making it a member of class i). We suppose that the size classes are ordered by increasing index, and therefore speak equivalently of smaller (resp. larger) index or of smaller (resp. larger) cell. Equation (2b) then describes the evolution of $S_t \in \mathbb{R}_+$, the substrate concentration in the chemostat at time t.

The model being time-discrete, we define an iteration period (or time step) Δ_T. We furthermore scale the time step so that $t + \Delta_T$ is $t + 1$, which leads to the indexes of the left-hand side in (2). Every rate used hereafter should then be understood as rates per time step. To begin with, we define E, the dilution proportion. E is not strictly speaking a rate: indeed, it represents the proportion of cells in the chemostat that are affected by dilution ($1 - E$ representing the complementary proportion of unaffected cells).

In the chemostat chamber, the organisms consume the nutrient at a rate f, which is a function of the available nutrient concentration S_t at time t. This consumption results in growth of the organisms by an equivalent amount. We will suppose that f is such that $f(0) = 0$, $f'(S) > 0$ and $f''(S) < 0$, and denote $m = \lim_{S \to \infty} f(S)$. Remark that the classical Michaelis-Menten growth function that is used for saturating but unhibitory growth of algae satisfies these conditions.

Finally, the transition matrix A depends on the substrate concentration S_t, and describes the evolution of the biomass between the different size classes. Depending on the precise nature of $A(S)$, various processes can be described. Obtaining a form suitable for our goal is the main purpose of this article, and is the object of Section 3.

2.2 Model behavior

It is not the purpose of this paper to further the mathematical analysis carried out by Smith [10]. We are only concerned here with the introduction of a model that makes an advanced description of the division process. As a consequence, we will limit our mathematical discussion of the analysis of the system behavior to those concepts that are necessary to establish Theorem 2.1. The latter states that designing a transition matrix that describes cellular division is worthwhile, as system (2) converges to an equilibrium distribution of biomass (a size spectrum) provided certain conditions are met. We refer the reader interested by the mathematical analysis to [10].

We say that matrix $A(S_t)$ is *of mass conservation for system* (2) if, and only if, it is such that $X_t + S_t \to S^0$ when $t \to \infty$, *i.e.*, that the *mass conservation principle* holds asymptotically. From [10], a sufficient condition for matrix A to be of mass conservation for system (2) is that for all S, $A(S)$ be such that

$$\mathbb{1}^T A(S) = (1 + f(S), \dots, 1 + f(S))$$

In mathematical terms, this means that $\mathbb{1}^T$ is a left eigenvector of $A(S)$ associated to the eigenvalue $1 + f(S)$. Let then S^* be the solution, if it exists, of $f(S^*) = E$. The following result establishes that the vector $\mathbf{x}^*$ tends to an equilibrium distribution.

Theorem 2.1. *Suppose that $(1 - E)(1 + f(S^0)) > 1$ and that, further from being of mass conservation for system (2), the sequence of nonnegative matrices $A(S)$ admits a limit as $S \to S^*$, denoted $A(S^*)$, which is a primitive matrix.*

Then, if $X_0 > 0$, system (2) admits one globally asymptotically stable non trivial equilibrium $(\mathbf{x}^*, S^*)$, with

$$\mathbf{x}^* = \frac{e}{X^*}$$

where $X^* = \mathbb{1}^T \mathbf{x}^*$ always exists and e is the Perron-Frobenius eigenvector of $A(S^*)$.

Note that we only require that the limit matrix $A(S^*)$ be primitive. Thus, under quite general conditions, we are assured that there exists an equilibrium distribution $\mathbf{x}^*$. Furthermore, this equilibrium is independent of initial conditions, and can be obtained by computing the Perron-Frobenius eigenvector of $A(S^*)$, *i.e.*, the eigenvector associated to the eigenvalue of $A(S^*)$ with highest magnitude; note that because of the structure of the matrix $A(S^*)$, we know that this eigenvector will only consist of positive entries.

The remainder of this paper will be devoted to the construction of a particular matrix $A(S^*)$ that is a) a satisfactory description of the cellular division process, and b) such that the conditions of Theorem 2.1 hold.

3 Modelling cellular processes

In the preceding section, a precise description of cellular size and its evolution was left out, since the dynamical system can be formulated and analyzed without this information. To deal with the biology, these blanks must now be filled. Hence we need adequate ways of describing the size (biomass) of a cell, the way this biomass evolves, the onset of division as well as its outcome. Refining this list of tasks, we can outline the following points to be addressed (the section in which they are treated is indicated):

i) cellular size (Section 3.1),

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ii) evolution of cellular size (Section 3.2),

iii) onset of division (Section 3.3),

iv) possible outcomes of division (Section 3.4),

v) link between division and birth (Section 3.5),

Points *i)* and *ii)* were thoroughly treated in [5, 10] as well as in [1, 2] where the growth process is derived using another method. Together with point *iii)*, which was the object of [2], they are included here in a shortened version for the completeness of the exposition. Points *iv)* and *v)* are specific to asymmetric division.

3.1 Description of cellular size

To describe cellular size, we proceed as follows. Assume that in an unlimiting environment (*i.e.*, if the nutrient concentration is high), cellular growth is exponential. To describe exponential growth, a constant noted M is used. Without going into details, suppose that $r_\delta \leq r$ is *the number of classes that a cell has to span for its biomass to double*. Define consequently M as

$$M = 2^{1/r_\delta} \tag{3}$$

Then, supposing that b_{min} is the smallest possible birth biomass, and defining the mean biomass of a cell in class $i \leq r$ to be

$$M^{i-1}b_{min}$$

allows the simultaneous description of cellular size and growth (the latter in unlimiting conditions).

3.2 Description of cellular growth

In practice, however conditions are never unlimiting. Therefore the speed with which a cell progresses among size classes is not exponential. This implies the definition of a second quantity: the *proportion of moving cells*. Here again, we do not detail, referring to the previous works on the subject for a derivation of the growth equation. It suffices to say that, at time t, the proportion of cells moving from one size class to the next is given as a function of the substrate concentration by

$$P_t = \frac{f(S_t)}{M-1} \tag{4}$$

and hence the proportion of biomass staying in the same size class is $1 - P_t$.

3.3 Nonhomogeneous cellular division

In the model of [5, 10], it is assumed that all cells are born with a biomass b and divide (if they survive to that point) when their biomass is $2b$. As in [2], in order to relax the equal division biomass hypothesis, we introduce three types of biomass, *birth, growth* and *division* biomass. To understand this, consider Figure 2, and suppose for now that we are dealing with a continuous size variable, and that cellular division is symmetric. If mature cells divide when their size is between $2b$ and $2c$, then their offsprings have a size between b and c. Recall that the interval of cellular biomass has been split, for the purpose
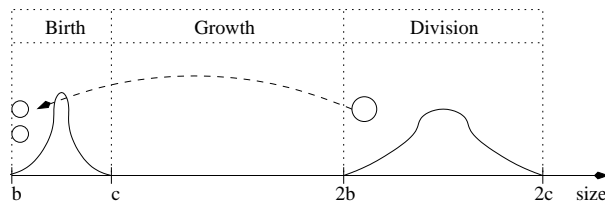
Figure 2: Symmetric nonhomogeneous cellular division. The three types of classes are illustrated. To a given interval for which cell division occurs corresponds an interval of size 1/2 in which cells are born. Similarly, a distribution of division sizes maps to a distribution of birth sizes. Growth classes are "intert" classes in which no division related event occurs.

of observation, into a certain number of size classes. Provided a little care is used when doing so, it is then possible to classify the underlying biomass classes as belonging to one of the three types. We note the respective numbers of such classes as r_b, r_g and r_d. Hence $r = r_b + r_g + r_d$. In the case of symmetric division, it was shown in [2] that choosing $r_b = r_d$ enabled a good description of this process. In the case of asymmetric division, the situation is more complicated, as discussed in Section 3.4.

Here, we are only concerned by what happens to cells that are in the division part of Figure 2. Division is an event that occurs for cells of different sizes. Therefore, we suppose that cells in a given division class (*i.e.*, with a certain biomass) and whose growth is sufficient, can either progress to the next size class or undergo division. We furthermore suppose that the proportion of cells undergoing division, in a given division class, is function of the substrate concentration. Therefore, we have size and substrate dependent division. For example, one can assume that larger cells are less sensitive to low substrate concentrations than smaller cells.

Let us denote $D_i(S)$ the proportion of cells in division class i that undergo division when the substrate concentration is S. Then $1 - D_i(S)$ is the proportion of cells which continue growing, instead of dividing. For now, we will not be explicit on the type of substrate dependence that we assume. Precise examples will be given in Section 4. Some hypotheses are however necessary for the mathematical analysis.

In order to put an explicit bound on the cellular size, we suppose that in the last division class, all cells divide, *i.e.*, that $D_{r_d}(S) = 1$ for all S.

3.4 Asymmetric cellular division

Here, unlike in [2], the number of division classes is not equal to the number of birth classes. One of the main difficulties that we encounter is then to obtain values of r_b and r_g that are suitable for the description of cell birth, growth and division. The derivation of these numbers from the knowledge of α, r_d and b is the object of the following sections.

We also need to obtain a law describing the way a cell dividing in division class d yields two cells, with s (respectively g) the index of the class containing the small cell (respectively big cell) resulting from division.

For clarity we decompose, the birth of unequally sized daughter cells into two steps. First, we establish the possible results of division (which we call *potential birth classes*). This static process can be thought of as an initial condition of the system. In a second step, we describe the *effective* repartition of the progeny among the potential birth classes. This is a dynamical process which depends of the state of the
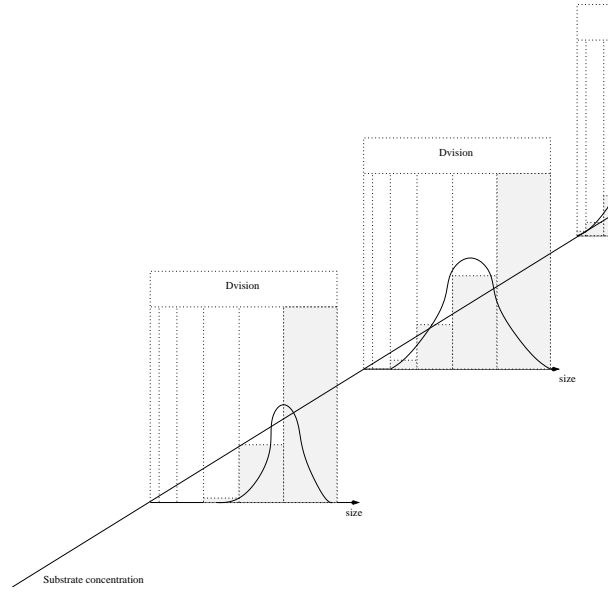
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Figure 3: Proportion of dividing cells in several division classes, for different values of the substrate concentration.
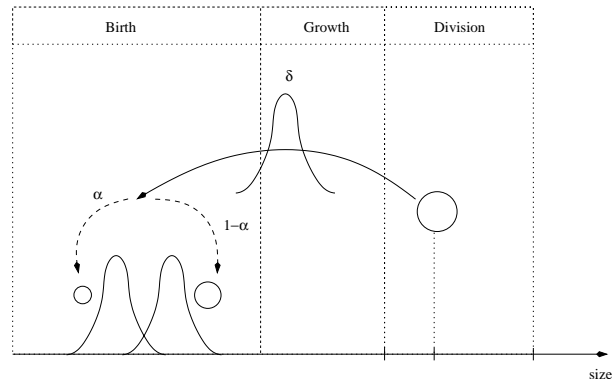

Figure 4: Asymmetric cellular division.

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system.

3.4.1 Potential birth classes

Let us consider a cell in division class i, and suppose that it undergoes a division with dissymmetry δ. Consider another cell in the same division class i undergoing division at the exact same instant as the former, but with a different dissymmetry δ'. Cells in other division classes can have a totally different division behaviour. For example, we could suppose that smaller cells undergoing division are premature (with respect to the division process), giving birth to very dissimilar progeny, while larger cells would tend to nearly always divide into two equally sized parts.

Considered on the population level, this means that cells reaching a given division class i and undergoing division (the proportion of which is given by the division proportions of Section 3.3), give birth to daughter cells in several birth classes. In order to model this, we introduce the following notations. We suppose that in a given division class $i = 1, \ldots, r_d$, there are $n(i)$ possible values of δ:

$$0 = \delta_{n(i),i} < \delta_{n(i)-1,i} < \cdots < \delta_{2,i} < \delta_{1,i} < 1 \tag{5}$$

Note that we always allow at least the eventuality of a symmetric division. From (5) we can similarly obtain $0 < \alpha_{1,i} < \cdots < \alpha_{n(i),i} = 1/2$, that describe the fractions of the biomass undergoing division in class i that are "allocated" to small daughter cells, and the fraction of the biomass undergoing division in class i that is allocated to large daughter cells $1/2 = 1 - \alpha_{n(i),i} < \cdots < 1 - \alpha_{1,i} < 1$. Therefore, there are *at most* $2n(i) - 1$ *potential* birth classes corresponding to the division class i.

At this point, it is possible to compute the number of birth and growth classes necessary to the description of these hypotheses. As mentioned earlier, the numbers r_b and r_g of birth and growth classes are functions of several parameters (r_d, r_δ, as well as of the nature of the $\alpha_{i,j}$'s). Before stating the result giving these numbers, remark the following.

Remark– The smallest possible birth biomass b_{min} is not necessarily the result of the division of a cell in the first division class, with the smallest division ratio. Indeed, suppose that the number r_d of division classes is large. Then the difference between the mean biomass of cells in two consecutive classes is small. Suppose then that for some reason, cells in the first division class divide only in symmetrically, while cells in the second division class split into two very unequal parts, with $\alpha_{1,2} \ll 0.5$. In this case the smallest birth biomass is the result of a division in division class 2. In order to be able to determine the number of classes in the system, this information is needed. Note that supposing that symmetric division is always an option saves us from the same considerations for the large daughter cells. The value of $r_{\min}$, index of the division class giving the smallest daughter cells, is the index of the division class i such that $\alpha_{1,i} M M^{r_b+r_g+i-1}$ is minimal. Since $M^{r_b+r_g}$ is strictly positive for all values of r_b and r_g, $r_{\min}$ is the index of the division class making the quantity $\alpha_{1,i} M^i$ minimal. In a more formal way, $r_{\min}$ is the minimal element of the subset Θ of indexes, defined by

$$\Theta = \{i = 1, \ldots, r_d; \ \ \alpha_{1,i} M^i \le \alpha_{1,j} M^j, \ \ \forall j = 1, \ldots, r_d, \ \ j \ne i\} \tag{6}$$

Then the number of birth and of growth classes is given by the following proposition.

Proposition 3.1. *Let r_δ be the number of classes that a cell has to span to double its biomass, and r_{min} be the index of the division class producing the smallest daughter cell. Then*

- *the number of* birth *classes is given by*

$$r_b = r_d - r_{min} + 1 + \frac{r_\delta}{\ln 2} \ln \frac{1 - \alpha_{1,r_d}}{\alpha_{1,r_{min}}} \tag{7}$$

- *the number of* growth *classes is given by*

$$r_g = -r_d - 1 - \frac{r_\delta}{\ln 2} \ln(1 - \alpha_{1,r_d}) \tag{8}$$

The proof of this Proposition is given in Appendix A. Note that we have to make sure that the number of birth and growth classes is positive (we furthermore require that the number of birth classes be at least 1). From equations (7) and (8), we thus obtain that r_δ must satisfy the following inequality:

$$r_\delta \geq \max\left((r_d - r_{\min}) \ln 2 \left(\ln \frac{\alpha_{1,r_{\min}}}{1 - \alpha_{1,r_d}} \right)^{-1} \;\; ; \;\; -\frac{\ln 2}{\ln(1 - \alpha_{1,r_d})}(r_d + 1) \right) \tag{9}$$

3.4.2 The dynamical part of division

To complete the description of the division process, we now have to make explicit the mechanism which *effectively* determines how the population of cells in a given division class i are split between the $2n(i) - 1$ potential birth classes. Note that this is a dynamic process: it is function of the substrate concentration.

In order to do so, let us define the functions $\pi_{i,j}(S_t)$ such that, for all $S \geq 0$ and all $i = 1, \ldots, r_d$:

$$\forall j = 1, \ldots, n(i), \;\; 0 \leq \pi_{j,i}(S) \leq 1 \tag{10}$$

and

$$\sum_{k=1}^{n(i)} \pi_{k,i}(S) = 1 \tag{11}$$

These functions define, for each division class i and as a function of the quantity of substrate available in the chemostat, the proportion of cells undergoing division that divide into daughters of sizes $\alpha_{j,i}$ and $1 - \alpha_{j,i}$.

This dependence on substrate can be interpreted as the preference that a given species may have for symmetric division in a substrate rich environment, and to its reaction to a stress (privation of substrate) by an asymmetric division. Furthermore, this process is also size-dependent. We can for example assume that more "mature" (larger) cells are more resistant to nutrient deprivation than smaller cells. Note that whereas there is evidence underlying nonhomogeneous division, we know of no evidence for asymmetric division, at least in the phytoplankton case.

3.5 Linking division and birth classes

The number of classes being determined, we now must describe the linkage between the different division and birth classes, *i.e.*, given a division class and a division ratio, we must determine in which one of the *potential* birth classes the daughter cells end up. This is the object of the following proposition.

Proposition 3.2. *Let d be the (division class relative) index of a division class. Then for all possible* $i = 1, \ldots, n(d)$ *division outcomes, the indexes of the birth class of the daughter cells are given by:*

- *for small daughter cells*

$$s = d + 1 - r_{min} + \frac{r_\delta}{\ln 2} \ln \frac{\alpha_{d,i}}{\alpha_{1,r_{min}}} \tag{12}$$

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- *for large daughter cells*

$$g = d + 1 - r_{min} + \frac{r_\delta}{\ln 2} \ln \frac{1 - \alpha_{d,i}}{\alpha_{1,r_{min}}} \tag{13}$$

Proof of this Proposition is given in Appendix B.

Let us now formulate a remark concerning the spread between "target" classes. It is indeed possible that different dissymetries lead to the same birth class. This is of course possible with cells originating from different division classes. But it is possible even for the progeny of one division class. Indeed, consider two division proportions, $\alpha_{d,i}$ and $\alpha_{d,i+1}$ (for cells in division class d). Then these dissymetries are linked to different birth classes if, and only if

$$\ln \frac{\alpha_{d,i+1}}{\alpha_{d,i}} \geq \frac{\ln 2}{r_\delta}$$

3.6 The transition matrix

The contents of sections 3.1 to 3.5 can now be assembled, in order to formulate the transition matrix $A(S_t)$ for our model. In the matrix $A(S)$, we use the notation $P_t = f(S_t)(M-1)^{-1}$ for clarity. Also, we write this matrix as a block matrix, for simplicity.

$$A(S) = \begin{bmatrix} B_G(S) & 0 & B_D(S) \\ J_1(S) & G(S) & 0 \\ 0 & J_2(S) & D(S) \end{bmatrix} \tag{14}$$

Matrices B_G and G have the same structure, except that B_G is a $r_b \times r_b$ matrix, whereas G is a $r_g \times r_g$ matrix. Their diagonals consists of elements $1 - P_t$, and the first subdiagonal consists of elements MP_t. The $r_g \times r_b$ matrix J_1 and the $r_d \times r_g$ matrix J_2 also have the same structure: all their elements are 0 except for the one in the upper right position ($(1, r_b)$ for J_1, $(1, r_g)$ for J_2), which is equal to MP_t. Matrix D, which is of size $r_d \times r_d$, has $1 - P_t$ on its main diagonal. Its first subdiagonal has elements $M(1 - D_i(S_t))P_t$ in the ith column, $i = 1, \ldots, r_d - 1$. Finally, the block B_D (of size $r_b \times r_d$) describes the outcome of division. Column q in $B_D(S_t)$ is given by

$$[B_D(S_t)]_q = \begin{bmatrix} \pi_{1,q}(S_t)\alpha_{1,q}MP_tD_q(S_t) \\ \vdots \\ \pi_{i,q}(S_t)\alpha_{i,q}MP_tD_q(S_t) \\ \vdots \\ \pi_{1,q}(S_t)MP_tD_q(S_t) \\ \vdots \\ \pi_{i,q}(S_t)(1 - \alpha_{i,q})MP_tD_q(S_t) \\ \vdots \\ \pi_{1,q}(S_t)(1 - \alpha_{1,q})MP_tD_q(S_t) \\ \vdots \end{bmatrix}$$
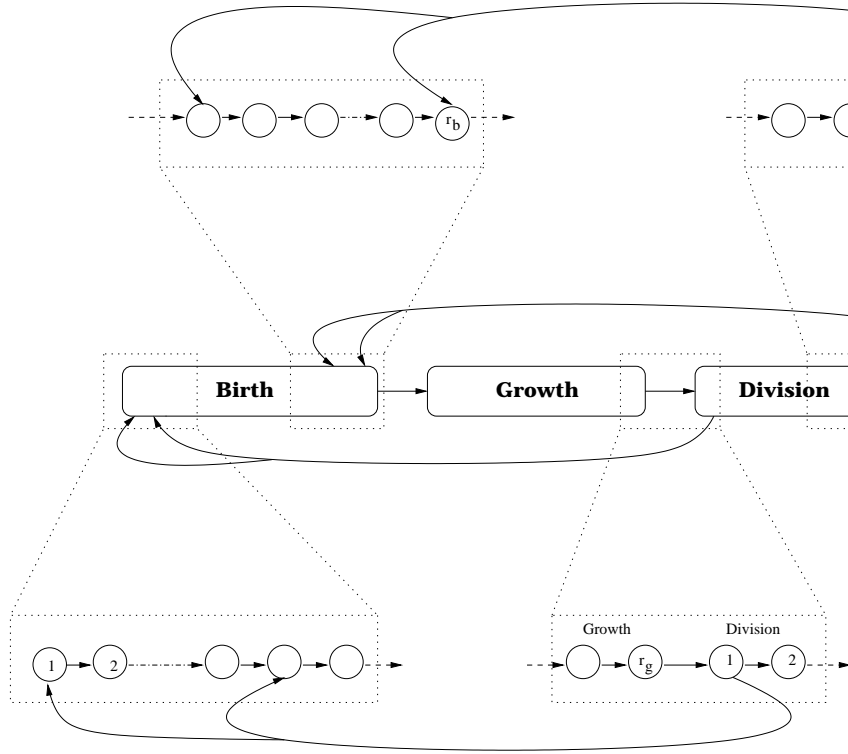
11

Figure 5: Detail of the structure of the model. The enlarged parts correspond (top) to the division of a cell in the last division class and (bottom) to the division of a cell in the smallest division class. The indexes shown are class-type relative.

Each column vector $[\Pi(S_t)]_q$ has r_b rows, but only $2n(q) - 1$ nonzero elements with positions given by Proposition 3.2. An example $\Pi(S_t)$ is given in Section 4. Note that "defects" in the primitivity of the $A(S)$ matrices discussed following Theorem 2.1 originate from the possibility that $D_i(S) = 1$.

Remark– Various constraints were derived in [10] and generalized in [2] that ensure that the system remains well posed. In particular, care has to be taken to make sure that P_t stays in an admissible range of values (*i.e.*, $P_t \in [0,1]$). We refer the reader to the former papers for a statement of these constraints.

Our aim now is simply to prove that the conditions of Theorem 2.1 are verified. We can state the following result.

Proposition 3.3. *The transition matrix $A(S)$ defined by (14) is a matrix of mass conservation for system (2).*

Proof. Clearly the column sum of any of the $r_b + r_g$ first columns of matrix $A(S)$ is $1 - P_t + MP_t$. Since $P_t = f(S_t)/(M - 1)$, this gives $1 + f(S)$. For a given column $i = r_b + r_g + 1, \ldots, r - 1$, we have a column sum of

$$MP_t(1 - D_i(S_t)) + \sum_{k=1}^{n(i)} (\pi_{k,i}(S_t)\alpha_{k,i}MP_tD_i(S_t) + \pi_{k,i}(S_t)(1 - \alpha_{k,i})MP_tD_i(S_t))$$

$$= MP_t(1 - D_i(S_t)) + \sum_{k=1}^{n(i)} \pi_{k,i}(S_t)MP_tD_i(S_t)$$

$$= MP_t(1 - D_i(S_t)) + MP_tD_i(S_t)\sum_{k=1}^{n(i)} \pi_{k,i}(S_t) = MP_t$$

$\square$

Thus Theorem 2.1 applies, and we have existence of a globally asymptotically stable non trivial equilibrium.

4 Examples

For simplicity, we suppose throughout that $b_{min} = 1$.

4.1 Number of classes

Firstly, suppose that cellular division yields daughter cells that can be as unequal as 1/4 and 3/4 of the original mother biomass (a 1/3 dissymmetry), *i.e.*, that $\alpha_{i,r_{\min}} = 1/4$ (equal for all division classes). Suppose that $r_d = 20$ and $r_\delta = 100$. Hence considering the smallest size in a division class as b, the maximal size of a cell is $M^{19}b = 2^{\frac{19}{100}}b = 1.1408b$. The number of birth and growth classes is given by Proposition 3.1 as $r_b = 178$ and $r_g = 20$. Hence the total number of classes is 218, and the biomass spans a range of b to $2^{\frac{217}{100}}b = 4.5315b$.

Note that the multiplication of the biomass implied by the model is a function of the asymmetry of the division. Figure 4.1 illustrates this fact, with a value of r_δ chosen to be the smallest possible, when $r_d = 50$ and for varying division asymmetries. As noted in the Introduction, the model with inhomogeneous but symmetric cellular division allows for a maximum fourfold increase of the cellular biomass. This is obvious in this figure, as this corresponds to the case $\delta = 0$.
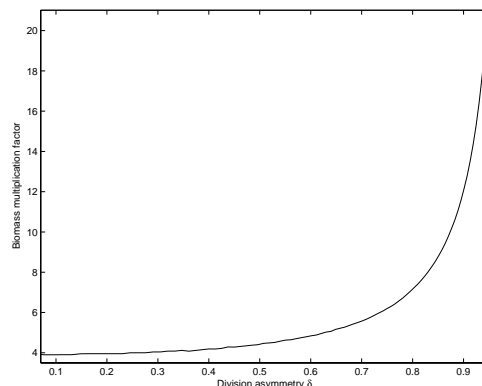
13

Figure 6: Biomass multiplication factor as a function of the division asymmetry, when $r_d = 50$.

5 Discussion

The model presented here provides a relatively realistic description of the cellular division process in the chemostat. In particular, it accounts for an asymmetric nonhomogeneous cell division. As special cases, it contains the model with symmetric homogeneous division of [5, 10] and the symmetric nonhomogeneous division model of [2].

The potentially huge number of parameters makes it very difficult to carry out an identification process, even in the equilibrium case. By making simplifying assumptions on the distributions of the different type of processes (*e.g.*, assuming that both division nonhomogeneity and division asymmetry are multidimensional Gaussian distributions depending on the size and the substrate concentration), we are able to drastically reduce the number of parameters. Still, the equilibrium eigenvector corresponding to the Perron-Frobenius eigenvalue of the transition matrix remains a highly nonlinear combination of the parameters.

Note that our model gives a phenomenological description of the cellular division process. In this sense, it is much rougher description of the cellular cycle than the one given in [9], which studies numerically the evolution of a cell cycle structured population in the chemostat. However, what it lacks in the description of the cell cycle, it compensates by giving a more detailed description of the outcome of division (which is symmetric in [9]).

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A Proof of Proposition 3.1

The following relations must hold. Firstly, since the smallest possible birth size results from the smallest division ratio in division class $r_{\min}$,

$$\alpha_{1,r_{\min}} M M^{r_b+r_g+r_{\min}-1} b_{min} = b_{min} \tag{15}$$

Then, the largest possible birth biomass results of division in division class r_d (since we have supposed that symmetric division is always a possibility):

$$(1 - \alpha_{1,r_d}) M M^{r_b+r_g+r_d-1} b = M^{r_b-1} b \tag{16}$$

Equation (15) is equivalent to

$$\alpha_{1,r_{\min}} M^{r_b+r_g+r_{\min}} = 1 \tag{17}$$

and equation (16) can be written

$$(1 - \alpha_{1,r_d}) M M^{r_b+r_g+r_d-1} b = M^{r_b-1} b \quad \Leftrightarrow \quad (1 - \alpha_{1,r_d}) M^{r_b+r_g+r_d} = M^{r_b-1}$$
$$\Leftrightarrow \quad (1 - \alpha_{1,r_d}) M^{r_g+r_d+1} = 1 \tag{18}$$

Writing (17) as

$$M^{r_g+1} = \frac{1}{\alpha_{1,r_{\min}} M^{r_b+r_{\min}-1}} \tag{19}$$

and substituting this value in (18) yields

$$(1 - \alpha_{1,r_d})M^{r_g+r_d+1} = 1 \quad \Leftrightarrow \quad (1 - \alpha_{1,r_d})(\alpha_{1,r_{\min}}M^{r_b+r_{\min}-1})^{-1}M^{r_d} = 1$$

$$\Leftrightarrow \quad M^{r_b} = \frac{1 - \alpha_{1,r_d}}{\alpha_{1,r_{\min}}}M^{r_d-r_{\min}+1}$$

and thus

$$r_b = r_d - r_{\min} + 1 + \frac{\ln\frac{1-\alpha_{1,r_d}}{\alpha_{1,r_{\min}}}}{\ln M} \tag{20}$$

Now, taking the logarithm of (19), we have

$$r_g = -r_d - r_{\min} - \frac{\ln\alpha_{1,r_{\min}}}{\ln M}$$

which, using (20), gives

$$r_g = -r_d - 1 - \frac{\ln(1 - \alpha_{1,r_d})}{\ln M} \tag{21}$$

So finally, since $(\ln M)^{-1} = r_\delta/\ln 2$, we have Proposition 3.1.

B   Proof of Proposition 3.2

Let the triplet (s, g, d) denote the indexes of the birth classes where the small (s) and the large $(g \geq s)$ daughter cells resulting of the division of a mother cell in division class d fall.

Let us consider a dividing cell originating in division class d. According to our modelling hypotheses, it first grows of an amount M, then it divides into two daughter cells: one small cell, in a class that we will denote by s, and one big cell in class g.

Let us first express the fact that division (following growth) of a mother cell gives a certain biomass, and that there is no loss of biomass in the process, *i.e.*, that the whole biomass ends up in the daughter cells:

$$M^{s-1}b + M^{g-1}b = MM^{r_b+r_g+d-1}b \tag{22}$$

But the biomass of the two daughter cells are also linked. Indeed, for all $i = 1, \ldots, n(d)$, we must have

$$\frac{1 - \alpha_{d,i}}{\alpha_{d,i}}M^{s-1}b = M^{g-1}b \tag{23}$$

since the ratio of the mass of the small daughter cell and of the large daughter cell is function of the division proportion. Substituting (23) in (22) gives

$$(1 + \frac{1 - \alpha_{d,i}}{\alpha_{d,i}})M^{s-1} = M^{r_b+r_g+d}$$

$$\Leftrightarrow \quad (s-1)\ln M + \ln\frac{1}{\alpha_{d,i}} = (r_b + r_g + d)\ln M$$

$$\Leftrightarrow \quad s = 1 + r_b + r_g + d + \frac{\ln\alpha_{d,i}}{\ln M}$$

Now using Proposition 3.1 and the fact that $M = 2^{1/r_\delta}$, we thus obtain that

$$s = d + 1 - r_{\min} + \frac{r_\delta}{\ln 2} \ln \frac{\alpha_{d,i}}{\alpha_{1,r_{\min}}}$$

Solving (23) for g gives

$$g = s + \frac{\ln \frac{1 - \alpha_{d,i}}{\alpha_{d,i}}}{\ln M}$$

and thus

$$
\begin{aligned}
g &= d + 1 - r_{\min} + \frac{r_\delta}{\ln 2} \ln \frac{\alpha_{d,i}}{\alpha_{1,r_{\min}}} + \frac{r_\delta}{\ln 2} \ln \frac{1 - \alpha_{d,i}}{\alpha_{d,i}} \\
&= d + 1 - r_{\min} + \frac{r_\delta}{\ln 2} \ln \frac{1 - \alpha_{d,i}}{\alpha_{1,r_{\min}}}
\end{aligned}
$$

and we have Proposition 3.2.