

# Global Qualitative Behavior of a Class of Nonlinear Biological Systems; Application to the Qualitative Validation of Phytoplankton Growth Models

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***Global qualitative behavior of a class of nonlinear  
biological systems; application to the qualitative  
validation of phytoplankton growth models.***

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THÈME 4



***Rapport  
de recherche***



# Global qualitative behavior of a class of nonlinear biological systems; application to the qualitative validation of phytoplankton growth models.

Olivier Bernard\* , Jean-Luc Gouzé †

Thème 4 — Simulation et optimisation  
de systèmes complexes  
Projet Comore

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**Abstract:** In this paper we propose a methodology to analyze the global qualitative behavior of a class of nonlinear differential systems with respect to their structure. This class of loop structured systems with monotonous interactions encompasses numerous biological models. We show that, independently of the parameters values or of the analytical formulation of the system, the possible successions with respect to time of some qualitative events that characterize the transients of state variables are strongly related to the signs of the Jacobian matrix (structure of the model). We propose a procedure to derive the transition graph; this graph summarizes the set of possible qualitative features for the state according to the structure of the model. The comparison of the graph with experimental (even noisy) data allows to validate directly this structure. The method is illustrated with a set of models usually used to describe phytoplanktonic growth in the chemostat. The corresponding transition graph is derived and compared with experimental data.

**Key-words:** Qualitative behavior, nonlinear systems, robust validation, biological modeling, bioreactors.

\* CESAME, UCL, 4, Av. G. Lemaitre, B-1348 Louvain-La-Neuve, Belgium, email [bernard@auto.ucl.ac.be](mailto:bernard@auto.ucl.ac.be)

† Projet COMORE, email [gouze@sophia.inria.fr](mailto:gouze@sophia.inria.fr)

# Comportement qualitatif global de systèmes biologiques non linéaires ; application à la validation qualitative de modèles de croissance phytoplanctonique.

**Résumé :** On propose une méthodologie pour analyser le comportement qualitatif global d'une classe de systèmes différentiels non-linéaires : les systèmes en boucle et à interactions monotones, qui décrivent de nombreux modèles en biologie. Nous montrons que, indépendamment de la formulation analytique du modèle ou de la valeur des paramètres, la succession temporelle de certains événements qualitatifs est reliée aux signes de la matrice jacobienne (structure du modèle). Nous construisons le graphe de transition, qui décrit l'ensemble des comportements globaux possibles pour une structure donnée. La comparaison de ce graphe avec les données expérimentales permet de valider cette structure. Cette méthode est illustrée par une application à des modèles de croissance de phytoplancton en chemostat. On trace le graphe de transition et on le compare aux mesures.

**Mots-clés :** Comportement qualitatif, systèmes non-linéaires, validation, modélisation biologique, bioréacteurs.

# 1 Introduction

In the biological and ecological fields, models are constructed often in order to test hypotheses on the functioning of a given living system. Hence, the comparison between experiments and simulations of such a phenomenological model is used to test if the way the biological system works accords the hypotheses. The construction of these models results generally of a multiple steps analysis during which the modeler has to formulate several hypotheses. As a first step, he has to determine the involved variables, which dynamics he wants to represent in the model. Then he must identify the scheme of interaction between these variables, corresponding to the hypotheses on the possible mechanisms in the biological system. After these steps, the modeler has to formalize the relation between the state variables. For this he can either use a law defined for a similar problem or postulate himself for a relation consistent with the empirical data. In this last case, he will use his biological knowledge and knowing for example that the death rate due to predation increases when the predator concentration increases, he will look after an increasing function linking death rate and predator concentration. Processing in that way, the biologist constructs a model relying on rather simple hypotheses generally having for result monotonous interactions between states variables.

To test and validate the model, he has now no other possibilities than to identify the parameters. At this point, he is faced with one of the major difficulty characterizing the biological field: few measurements perturbed by a high level of noise. Model calibration with such data will therefore give rise to a great uncertainty in the parameters values.

If we keep in mind that the biological functions used to represent interactions between variables are poorly known, a drastic validation of model appears very difficult: the three level hypothesis (structure hypothesis, function hypothesis and parameters hypothesis) gives rise to a high level of uncertainty for the model. At this point we have to recall that the first information that the biologists want to have at first is the pertinence of the chosen structure to represent the system. In such condition it appears clearly that the classical comparison between uncertain output and noisy measures can rarely answer this question.

Recently a methodology has been proposed ([1, 2]) in order to compare the structure of a model with qualitative features, easy to derive even from noisy data, such as extrema with respect to time or crossing of equilibrium values. From the study of the extradiagonal terms of the Jacobian matrix of the system it can be derived two graphs called transition graphs. The first one summarizes for almost any trajectory the possible succession of extrema, and the other one consider the way the equilibria of the system are crossed for each state variable: bottom-up or top-down. This method allows therefore the modeler to test the structure of his model (i.e. extra diagonal signs of the Jacobian matrix) by comparing the observed succession of extrema [resp. equilibrium crossing] with this allowed by the transition graph. These studies have been developed for a broad class of biological models (loop structured systems with monotonous interactions), including gene regulation models, compartmental systems [3, 4], cellular growth [5], and development of stage structured populations [6]. We emphasize nevertheless that the analysis can also be applied to other models, provided that there are enough zeros in the Jacobian matrix.

The previous analysis is nevertheless not sufficient to test the whole interactions in the system, and particularly the sign of the diagonal terms in the Jacobian matrix. In this paper we extend the qualitative description of the dynamics of loop structured systems, by relating the qualitative events corresponding to extrema to these corresponding to crossing of equilibrium values. We use the diagonal signs of the Jacobian matrix to show that qualitative features

(tendencies of the state variables and positions toward the considered equilibrium) of any trajectory are restricted to a certain set. We propose a procedure to derive this set of possible qualitative features. This allow us to consider the domain  $\Omega$  as partitioned by different regions delimited by the nullclines and the hyperplanes associated to an equilibrium  $x^*$ . The transient behavior of the system can then be determined by a theorem giving the possible global behavior, and represented into a graph describing the transients in terms of extrema and equilibrium crossings, providing therefore a powerful way of validating the structure of the model without any precise knowledge of functions and parameters used.

Let us here make the remark that, for the sake of simplicity, we suppose the system to be autonomous and without inputs. We could also consider the following controlled system :

$$\left\{ \begin{array}{l} \dot{x} = f(x, u(t)) \end{array} \right.$$

with the input  $u(t)$  being constant on time intervals  $]t_i, t_{i+1}[$ . Of course, the whole analysis applies on each time interval.

An application is performed for a class of systems representing growth of phytoplankton in a continuous bioreactor (chemostat). The qualitative transient behavior is presented, and some results are derived. It is shown that, at the most one maximum, one minimum, one equilibrium crossing bottom-up and one top-down for each state variable is possible. The transition graph obtained is then compared to some experiments, and conclusions on the structure of the models usually used to describe phytoplanktonic growth are drawn.

## 2 Definitions

**Notations.** The notations  $x > 0$  for  $x = {}^t(x_1, \dots, x_n) \in \mathbf{R}^n$  means that for all  $i$ ,  $x_i > 0$ . For  $y \in \mathbf{R}$  we consider the function “sign”:

$$\text{sign}(x) = \begin{cases} -1 & \text{If } y < 0 \\ 0 & \text{If } y = 0 \\ 1 & \text{If } y > 0 \end{cases}$$

For  $x \in \mathbf{R}^n$ ,  $\text{sign}(x)$  is the vector with components  $\text{sign}(x_i)$ . The matrix  $\text{diag}(x)$  is the diagonal matrix having  $x \in \mathbf{R}^n$  on its main diagonal.

Let  $\Omega$  be an open convex domain of  $\mathbf{R}^n$  and  $f$  a  $C^1$  mapping from  $\Omega$  onto  $\mathbf{R}^n$ . We consider on  $\Omega$  the autonomous differential system :

$$(\Sigma) \left\{ \begin{array}{l} \dot{x} = f(x) \end{array} \right.$$

**Definition 1** A system  $(\Sigma)$  has a loop structure if  $f_i(x) = f_i(x_i, x_{i+1}) \forall i \in \{1, \dots, n\}$ .

The velocity of each variable only depends on the variable itself and on the next one (the indexes are counted modulo  $n$ ).

**Definition 2** The system  $(\Sigma)$  has monotonous interactions on  $\Omega$  if each partial derivative  $\partial f_i / \partial x_j(x)$  for  $i \neq j$  never cancels on  $\Omega$ .

Thereby the off-diagonal terms of the Jacobian matrix are of fixed sign on  $\Omega$ . The signs of the elements define what we call the structure of the system.

We will consider the set  $\mathcal{S}_n$  containing  $2^n$  elements:

$$\mathcal{S}_n \stackrel{\text{def}}{=} \left\{ \sigma^q = {}^t(\sigma_1^q, \dots, \sigma_n^q) ; \sigma_j^q \in \{-1, 1\}, q \in \{1, \dots, 2^n\} \right\}$$

Conventionally, we will denote  $\sigma^1 = {}^t(1, \dots, 1)$ .

**Definition 3** For  $x^* \in \Omega$  the system with monotonous interactions  $(\Sigma)$  is diagonally  $x^*$ -monotonous if for all  $j$  in  $\{1, \dots, n\}$ , for all  $q$  in  $\{1, \dots, 2^n\}$ , the sign of the partial derivative  $\partial f_j / \partial x_j(x)$  is fixed on each domain:

$$W_{\sigma^q}(x^*) \stackrel{\text{def}}{=} \{x \in \Omega; \text{diag}(\sigma^q)(x - x^*) > 0\}$$

The domains  $W_{\sigma^q}(x^*)$  are called the orthants of the  $x^*$ -deviation space or  $x^*$ -orthants. In the same way, we define the orthants of the velocity space or  $z$ -orthants:

$$Z_{\sigma^p} \stackrel{\text{def}}{=} \{x \in \Omega; \text{diag}(\sigma^p) f(x) > 0\}$$

We consider also the four following sets:

- For  $x^* \in \Omega$  the  $i^{\text{th}}$  hyperplane associated with  $x^*$ :

$$V_i(x^*) \stackrel{\text{def}}{=} \{x \in \Omega; x_i = x_i^*\}$$

- The  $i^{\text{th}}$  nullcline  $U_i$ :

$$U_i \stackrel{\text{def}}{=} \{x \in \Omega; f_i(x) = 0\}$$

- The union set of nullclines :  $U \stackrel{\text{def}}{=} \bigcup_{i=1}^n U_i$

- the union set of hyperplanes associated with  $x^*$  :  $V(x^*) \stackrel{\text{def}}{=} \bigcup_{i=1}^n V_i(x^*)$ .

For a fixed  $x^* \in \Omega$  and  $\sigma^q \in \mathcal{S}_n$  and a given application  $f$  we define the restriction of the application  $\text{sign}(f)$  to  $W_{\sigma^q}(x^*) - U$  that we denote  $\text{Sign}[f]_{\sigma^q}$ :

$$\text{Sign}[f]_{\sigma^q} : \begin{array}{ccc} W_{\sigma^q}(x^*) - U & \longrightarrow & \mathcal{S}_n \\ x & \longrightarrow & \text{Sign}[f]_{\sigma^q}(x) = \text{sign}(f(x)) \end{array}$$

Remark that this application has its image in  $\mathcal{S}_n$  because the nullclines have been removed from  $W_{\sigma^q}(x^*)$ , and therefore  $f_i(x) \neq 0$  for  $i \in \{1, \dots, n\}$ .



### 3 The set of possible qualitative events

In this section we will consider a monotonous (i.e with monotonous interactions) loop structured system  $(\Sigma)$  and we will suppose that there exists an (hyperbolic) equilibrium point  $x^* \in \Omega$  for which  $(\Sigma)$  is diagonally  $x^*$ -monotonous. We will then determine the set of orthants of the velocity space  $Z_{\sigma^q}$  compatible with a given orthant  $W_{\sigma^q}(x^*)$  of the  $x^*$ -deviation space. In other words the question is to determine all the possible signs of  $f(x)$  for  $x$  in a given  $x^*$ -orthant, i.e. the following set of signs :

$$\mathcal{F}^q \stackrel{\text{def}}{=} \mathcal{I}m(\text{Sign}[f]_{\sigma^q}) \quad (1)$$

First we will determine the elements of this set which are obtained locally around equilibrium  $x^*$ . Then we will determine the other elements by global considerations.

#### 3.1 Linear approach

As a first step, we will determine this set for the linearized of  $(\Sigma)$ . We suppose that the equilibrium point is hyperbolic. Around the point  $x^*$ , the system is equivalent to the linear system:

$$\Delta \dot{x} = Df(x^*) \Delta x \quad (2)$$

where  $Df(x)$  denotes the Jacobian matrix at point  $x$ , and  $\Delta x \stackrel{\text{def}}{=} x - x^*$ . We will denote  $\xi^{q+} \stackrel{\text{def}}{=} \text{diag}(\sigma^q) \Delta x$ , which is a positive vector for  $x \in W_{\sigma^q}$ .

We will consider the matrix  $\mathcal{M}^q \stackrel{\text{def}}{=} Df(x^*) \text{diag}(\sigma^q)$ , whose elements are denoted  $m_{kl}^q$  and whose signs are  $s_{kl}^q = \text{sign}(m_{kl}^q)$ . We denote  $M^q$  the linear application associated to the matrix  $\mathcal{M}^q$ .

The problem of determining the possible signs for  $Df(x^*) \Delta x$  when  $x \in W_{\sigma^q}(x^*)$  is then equivalent to the determination of the set

$$\mathcal{L}^q \stackrel{\text{def}}{=} \mathcal{I}m(\text{Sign}[M^q]_{\sigma^q}) = \{ \text{sign}(\mathcal{M}^q \xi), \xi \in \Omega^{+*} \} \quad (3)$$

with  $\Omega^{+*} \stackrel{\text{def}}{=} \{ \xi > 0, (\xi + x^*) \in \Omega \}$ .

We will determine the set  $\mathcal{L}^q$ , using two complementary lemma (remember that the  $s_{kl}^q$  take their values in  $\{-1, 0, 1\}$ ).

**Lemma 1** *Consider the linearized of a diagonally  $x^*$ -monotonous loop structured system  $(\Sigma)$ , at point  $x^* \in \Omega$ . For a given  $\sigma^q$ , if there exists an index  $k$  such that one of the two conditions is satisfied:*

1.  $s_{k,k}^q = 0$
2.  $s_{k,k}^q = s_{k,k+1}^q$

then

$$\mathcal{L}^q = \{ l^q = {}^t(l_1^q, \dots, l_n^q); l_j^q \in \{s_{j,j}^q \vee s_{j,j+1}^q\} \} \quad (4)$$

$1 \vee 1$	$\{1\}$
$-1 \vee 1$	$\{-1, 1\}$
$-1 \vee -1$	$\{-1\}$
$-1 \vee 0$	$\{-1\}$
$1 \vee 0$	$\{1\}$
$0 \vee 0$	$\{0\}$

Table 1: Table of rules for the qualitative sum  $\vee$ .

The table of the operator  $\vee$  (“qualitative sum”) is given in table 1.

**Proof:** Remark that  $\mathcal{L}^q \subset \mathcal{A}^q$ , where  $\mathcal{A}^q$  is the set of *a priori* possible signs:

$$\mathcal{A}^q \stackrel{\text{def}}{=} \{l^q; l_j^q \in \{s_{j,j}^q \vee s_{j,j+1}^q\}\}$$

Indeed, if  $\sigma \in \mathcal{L}^q$ , then there exists  $\xi \in \Omega^{+*}$  such that:  $\sigma = \text{sign}(\mathcal{M}^q \xi)$ . If we denote  $z = \mathcal{M}^q \xi$ , we have:

$$z_j = m_{j,j}^q \xi_j + m_{j,j+1}^q \xi_{j+1}$$

While  $\xi_j$  and  $\xi_{j+1}$  are positive, the possible signs  $\sigma_j$  for  $z_j$  are in the set  $\{s_{j,j}^q, s_{j,j+1}^q\}$  (remember that the sets  $z_j = 0$  have been removed by definition of  $\text{Sign}[M^q]_{\sigma^q}$ ). We will show that all the elements of  $\mathcal{A}^q$  have a preimage by  $\text{Sign}[M^q]_{\sigma^q}$ .

If condition 1. or 2. is fulfilled for  $k$ ,  $\text{sign}(z_k) = s_{k,k+1}^q = s_{k,k+1}^q \vee s_{k,k}^q$ . We will fix  $\xi_k$  to an arbitrary positive value.

If we consider  $z_{k-1} = m_{k-1,k-1}^q \xi_{k-1} + m_{k-1,k}^q \xi_k$ , there exists two possibilities:

- i.* we have the case where one of the two conditions is fulfilled:  $s_{k-1,k-1}^q = 0$  or  $s_{k-1,k-1}^q = s_{k-1,k}^q$  and thus we can choose an arbitrary  $\xi_{k-1} > 0$ , we will have:

$$\text{sign}(z_{k-1}) = s_{k-1,k}^q = s_{k-1,k}^q \vee s_{k-1,k-1}^q$$

- ii.* in the other case,  $s_{k-1,k-1}^q = -s_{k-1,k}^q$ , and we choose:

$$\xi_{k-1} = -\epsilon \frac{m_{k-1,k}^q}{m_{k-1,k-1}^q} \xi_k \quad \text{with } \epsilon \in \left\{ \frac{1}{2}, \frac{3}{2} \right\}$$

Then  $z_{k-1} = (1 - \epsilon) m_{k-1,k}^q \xi_k$ . If we take  $\epsilon = \frac{1}{2}$  we have  $\text{sign}(z_{k-1}) = s_{k-1,k}^q$ , if we take  $\epsilon = \frac{3}{2}$  we obtain  $\text{sign}(z_{k-1}) = -s_{k-1,k}^q = s_{k-1,k-1}^q$ .

The same reasoning can be applied to  $z_{k-2}, \dots, z_{k+1}$ , hence  $\xi_{k-2}, \dots, \xi_{k+1}$  can be chosen so that the result follows.

The following lemma covers the remaining cases:

**Lemma 2** Consider the linearized of a diagonally  $x^*$ -monotonous loop structured system  $(\Sigma)$ , with  $x^* \in \Omega$ . If for every index  $k$ :  $s_{k,k}^q = -s_{k,k+1}^q$ , then

$$\mathcal{L}^q = \mathcal{S}_n - \mathcal{C}^q \tag{5}$$

with  $\mathcal{C}^q \stackrel{\text{def}}{=} \{-\text{sign}(\det[Df(x^*)]) \prod_{j=1}^n \sigma_j^q s_{j,j}^q D^q\}$ ,  $D^q \stackrel{\text{def}}{=} t(s_{1,1}^q, s_{2,2}^q, \dots, s_{n,n}^q)$ .

**Proof:** Recall that  $\det [Df(x^*)] \neq 0$  because the equilibrium is supposed to be hyperbolic.

We will show that among the set  $\mathcal{A}^q = \mathcal{S}_n$  corresponding to the set of *a priori* possible signs for  $z$  (see argue given in the proof of Lemma 1), one single element is not in  $\mathcal{I}m(\text{Sign}[M^q]_{\sigma^q})$ .

1. We will first assume that  $D^q = \sigma^1$  i.e. for every  $k$ :  $s_{k,k}^q = 1$ . The other cases are symmetrical and they will be detailed at the end of the proof.

We first show that it is possible to find  $\xi \in \Omega^{+\star}$  such that there exists  $k$  for which  $z_k z_{k+1} < 0$ . For the sake of clarity, we will first find such  $\xi$  ensuring  $z_1 < 0$  and  $z_n > 0$ . For a fixed  $\xi_2 > 0$ , it is possible to find  $\xi_3 > 0$  such that  $z_2$  is of desired sign (cf. proof of preceding lemma). In the same way  $\xi_4 > 0$  to  $\xi_n > 0$  can be chosen to obtain an arbitrary (and fixed) sign for  $z_3$  to  $z_{n-1}$ . Now we have to choose a  $\xi_1 > 0$  such that  $z_1 < 0$  and  $z_n > 0$ . This is possible if we take:

$$\xi_1 < \min\left(-\frac{m_{1,2}^q}{m_{1,1}^q}\xi_2, -\frac{m_{n,n}^q}{m_{n,1}^q}\xi_n\right)$$

This result can clearly be extended to all the situations where there exists an index  $k$  such that  $z_k z_{k+1} < 0$ .

Let us prove that to find  $\xi$  such that  $z$  is positive, it is necessary to have  $\det(\mathcal{M}^q) > 0$ . Indeed, to have  $z_p > 0$  for every  $p$ , there must exists a positive  $\xi$  such that the following conditions hold for every  $p$ :

$$\xi_{p+1} < \frac{m_{p,p}^q}{-m_{p,p+1}^q}\xi_p \quad (6)$$

it follows that:

$$\xi_n < \prod_{j=1}^{n-1} \frac{m_{j,j}^q}{-m_{j,j+1}^q}\xi_1 < \prod_{j=1}^n \frac{m_{j,j}^q}{-m_{j,j+1}^q}\xi_n \quad (7)$$

Condition (7) imposes:

$$\lambda^q \stackrel{\text{def}}{=} \prod_{j=1}^n m_{j,j}^q + (-1)^{n+1} \prod_{j=1}^n m_{j,j+1}^q > 0 \quad (8)$$

It is noteworthy that, for the loop structured system  $(\Sigma)$ ,  $\lambda^q$  is nothing but the determinant of matrix  $\mathcal{M}^q$ :

$$\lambda^q = \det(\mathcal{M}^q) = \det(Df(x^*)) \prod_{j=1}^n \sigma_j^q$$

Reciprocally, let us show that if  $\lambda^q$  is positive, it is possible to find a positive  $\xi$  such that  $z$  is positive.

First, we choose an arbitrary  $\xi_1$ . We compute  $\xi_2$  to  $\xi_n$  by the following induction formulae for  $1 \leq p \leq n-1$ :

$$\xi_{p+1} = \epsilon \frac{m_{p,p}^q}{-m_{p,p+1}^q}\xi_p \quad (9)$$

with:

$$\epsilon \stackrel{\text{def}}{=} \left( \prod_{j=1}^n \frac{-m_{j,j+1}^q}{m_{j,j}^q} \right)^{\frac{1}{n}}$$

while  $\lambda^q$  is positive, it implies  $\epsilon < 1$ , and thus condition (6) holds for  $1 \leq p \leq n - 1$ . We have now to prove that it also holds for  $p = n$ . If we compute  $\xi_n$  we get:

$$\xi_n = \epsilon^{n-1} \prod_{j=1}^{n-1} \frac{m_{j,j}^q}{-m_{j,j+1}^q} \xi_1$$

and then

$$\epsilon \frac{m_{n,n}^q}{-m_{n,1}^q} \xi_n = \xi_1 < \frac{m_{n,n}^q}{-m_{n,1}^q} \xi_n$$

We have then found a positive  $\xi$  ensuring  $z > 0$ .

2. The proof has now to be achieved by symmetry for a general  $D^q$ : the problematic cases correspond to  $\text{sign}(z) = D^q$ . The problem is then equivalent to find  $\xi > 0$  such that  $\text{sign}(\text{diag}(D^q)z) = \sigma^1$ , it consists therefore in considering matrix  $\text{diag}(D^q)\mathcal{M}^q$ , which determinant is  $\det[Df(x^*)] \prod_{j=1}^n \sigma_j^q s_{j,j}^q$ .

### 3.2 Global approach

In order to determine the set of possible signs for  $f(x)$ , we will rewrite the system  $(\Sigma)$  into another form. Using the fact that  $\mathcal{L}^q \subset \mathcal{F}^q$ , we will determine the different cases for which this inclusion is strict.

**Lemma 3** *If  $x^*$  is an equilibrium point, the system  $(\Sigma)$  can be rewritten*

$$\overline{\dot{x} - x^*} = A(x, x^*) \cdot (x - x^*)$$

*If  $(\Sigma)$  has monotonous interactions, then matrix  $A(x, x^*)$  has the same off-diagonal signs as the Jacobian matrix  $Df(x^*)$  of  $(\Sigma)$ . If moreover  $(\Sigma)$  is diagonally  $x^*$ -monotonous, the diagonal terms of  $A(x, x^*)$  are of fixed signs in the different  $W_{\sigma^q}(x^*)$ . The signs of these elements corresponding to these of the same elements in  $Df(x^*)$  if these elements are non zero.*

**Proof:** This is an application of the generalized first order Taylor formula [7]:

$$f(x_1) = f(x_2) + \left[ \int_0^1 Df(\alpha x_1 + (1 - \alpha)x_2) d\alpha \right] (x_1 - x_2)$$

so that

$$A(x, x^*) = \int_0^1 Df(\alpha x + (1 - \alpha)x^*) d\alpha$$

where the Jacobian matrix  $Df$  is of fixed sign on  $\Omega$ . The results follow easily from the convexity of  $\Omega$ .

We will use the same notations for  $A(x, x^*)$  than for  $Df(x^*)$ , *i.e.* we will denote  $\mathcal{M}^q(x) = A(x, x^*)\text{diag}(\sigma^q)$ , and  $t_{kl}^q$  the (fixed) sign of its elements  $m_{kl}^q(x)$ .

We first consider the simple case where the diagonal elements of the Jacobian matrix are non zero (and therefore matrix  $A(x, x^*)$  and  $Df(x^*)$  are of the same sign (*cf.* lemma 3)), therefore the simple framework of lemma 1 is satisfied:

**Lemma 4** *Consider a diagonally  $x^*$ -monotonous loop system  $(\Sigma)$  where  $x^*$  is an equilibrium point. If the following two conditions hold in  $W_{\sigma^q}$ :*

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$$1. \forall k, t_{k,k}^q = s_{k,k}^q \neq 0$$

$$2. \exists k, t_{k,k}^q = t_{k,k+1}^q$$

then we have  $\mathcal{F}^q = \mathcal{L}^q$ .

**Proof:** It is straightforward that  $\mathcal{F}^q \subset \{l^q; l_j^q \in \{t_{j,j}^q \vee t_{j,j+1}^q\}\}$ , for the same reasons as in the local case, when considering  $z_k = m_{k,k}^q(x)\xi_k + m_{k,k+1}^q(x)\xi_{k+1}$ .

But  $\mathcal{L}^q = \{l^q; l_j^q \in \{s_{j,j}^q \vee s_{j,j+1}^q\}\} \subset \mathcal{F}^q$ , and because the  $s^q$  equal the  $t^q$  we have  $\mathcal{F}^q = \mathcal{L}^q$ .

**Remark 1:** If  $s_{k,k}^q = 0$  and  $t_{k,k}^q \neq 0$ , no conclusion can be drawn in the general case on the possible signs of the  $k^{\text{th}}$  component  $z_k$  and one has to consider the analytical formulation of the model. Consider for example the following differential system defined on  $\mathbf{R}^2$ :

$$\begin{cases} \dot{x}_1 = x_2 - x_1^2 \\ \dot{x}_2 = x_1 - x_2^2 \end{cases} \quad (10)$$

For the equilibrium point  $x^* = {}^t(0, 0)$ , the Jacobian matrix has the following signs:

$$\begin{pmatrix} 0 & + \\ + & 0 \end{pmatrix} \quad (11)$$

so that for  $x$  in  $\mathbf{R}^{+*}$ ,  $\mathcal{L}^q = \{\sigma^1\}$ . Nevertheless the matrix  $A(x, x^*)$  has the following signs:

$$\begin{pmatrix} - & + \\ + & - \end{pmatrix} \quad (12)$$

and it is clear from (10) that  $\mathcal{F}^q = \mathcal{S}_2$ .

We will now consider the other case corresponding to that treated in Lemma 2.

**Lemma 5** Consider a diagonally  $x^*$ -monotonous loop system  $(\Sigma)$  where  $x^*$  is an equilibrium point. Suppose that for all we have  $t_{k,k}^q = -t_{k,k+1}^q$ .

If  $\det(A(x, x^*))$  cancels and changes its sign on  $W_{\sigma^q}(x^*)$ , then the set  $\mathcal{F}^q$  covers all the possible orthants:

$$\mathcal{F}^q = \mathcal{S}_n \quad (13)$$

in the other cases, then

$$\mathcal{F}^q = \mathcal{S}_n - \mathcal{C}^q \quad (14)$$

where  $\mathcal{C}^q = \{-\text{sign}(\det[A(x^\dagger, x^*)]) \prod_{j=1}^n \sigma_j^q s_{j,j}^q D^q\}$  and  $D^q = {}^t(t_{1,1}^q, t_{2,2}^q, \dots, t_{n,n}^q)$ ,  $x^\dagger \in W_{\sigma^q}(x^*)$  being a point where the determinant of  $A(x^\dagger, x^*)$  does not cancel.

**Proof:** We have  $\mathcal{L}^q \subset \mathcal{F}^q \subset \mathcal{S}_n$ . From Lemma 2, we know that  $\mathcal{L}^q$  corresponds to  $\mathcal{S}_n$  except one or two elements. The question is to know if these elements can nevertheless be in  $\mathcal{F}^q$ . To answer this question, the same reasoning can be made as for proof of lemma (2), but with  $z_k = m_{k,k}^q(x)\xi_k + m_{k,k+1}^q(x)\xi_{k+1}$ . This reasoning will give rise to a constraint on the sign of the determinant of  $A(x, x^*)$ .

If the determinant can change its sign on  $W_{\sigma^q}(x^*)$ , then on each of the part of  $W_{\sigma^q}(x^*)$  the determinant has a fixed sign and therefore  $D^q$  or  $-D^q$  is possible.

**Remark.** Let us remark that if there exists another equilibrium point  $x^\dagger \in W_{\sigma^q}(x^*)$ , then  $A(x^\dagger, x^*)(x^\dagger - x^*) = 0$  and therefore  $\det(A(x^\dagger, x^*)) = 0$ .

### 3.3 Partition of the state space: possible regions

**Definition 4** For  $\sigma^p \in \mathcal{F}_q$  let us define the following open set:

$$\Omega_{\sigma^q \sigma^p}(x^*) \stackrel{\text{def}}{=} W_{\sigma^q}(x^*) \cap Z_{\sigma^p} = \{x \in W_{\sigma^q}(x^*); \text{diag}(\sigma^p)f(x) > 0\} \quad (15)$$

Note that some  $\Omega_{\sigma^q \sigma^p}(x^*)$  are empty. The non empty remaining  $\Omega_{\sigma^q \sigma^p}(x^*)$  represents therefore the qualitative situations allowed by the model and will be called the possible regions. Remark also that they does not intersect the nullclines  $U_i$  and the hyperplane  $V_i(x^*)$ .

We can now consider the following partition of the state space  $\Omega$ :

$$\Omega = \left( \bigcup_{q \in \{1, \dots, 2^n\}, p \in \mathcal{F}^q} \Omega_{\sigma^q \sigma^p}(x^*) \right) \cup V(x^*) \cup U \quad (16)$$

## 4 The restricted phase space

In this chapter, we will remove from  $\Omega$  some manifolds for which trajectories may have undesirable behaviors (with respect to our goals): we will show that this set of trajectories is of measure zero, under some technical assumptions. The final phase space will be named  $\tilde{\Omega}$ .

In fact, we want to remove a set of trajectories issued from some  $(n-2)$ -dimensional manifold  $M$ , typically the intersection between two isoclines. It is clear that, in finite time, such a set of trajectories is  $(n-1)$ -dimensional, but the limit set (in positive time) can be, in some (rather intricate) case, of non-empty interior. This case is undesirable, because if we remove this set, it can be that we remove the trajectories that are experimentally observed. We will therefore suppose that the differential system is such that the limit set of any manifold  $M$  of dimension  $(n-2)$  is of measure zero (Property P). There are many cases where such a property is verified, and many ways to check it. Let us list some sufficient conditions:

- if the system admits a Lyapunov function for the equilibrium  $x^*$ , then it is globally stable. The limit set of any manifold is  $x^*$  itself.
- if the system admits a function  $V(x)$  decreasing along the trajectories, then the Lasalle's theorem ([8]) gives us that the limit sets of any bounded trajectories are contained into the set  $\{x; \overline{V(x)} = 0\}$ . If this set is of measure zero (if it is contained in an  $(n-1)$ -manifold for example), then the property is verified.
- if there exists an application  $h : \mathbf{R}^n \longrightarrow \mathbf{R}^p$ , with  $p < n$  of class  $C^1$ , regular at every point, such that

$$\overline{\dot{h}(x)} = g(h(x))$$

along the trajectories of the system  $\Sigma$ , and if the limit sets of the new differential system in  $\mathbf{R}^p$

$$(\Sigma_1) \left\{ \begin{array}{l} \dot{h} = g(h) \end{array} \right.$$

verify the property P, then the system  $\Sigma$  verifies the property P (indeed, because of the regularity of  $h$ , the preimage of a set of measure zero is of measure zero). For example, if

we know that the limit sets of  $\Sigma^1$  are a finite number of points (it is the case in dimension one), then the property stands for  $\Sigma^1$ , and therefore for  $\Sigma$ .

For example, for biological, ecological or chemical models, it is often the case that some mass balance or mass conservation relation holds, giving easily a scalar differential equation; the property is therefore verified.

Now we examine each set of initial conditions of the trajectories we want to remove. It is roughly the set of the intersection between the  $V_i(x^*)$  and  $U_j$ , because there is two signs that change simultaneously. In all the following, **we suppose that the above property P holds.**

We recall first that it is not possible to stay on an isocline.

#### 4.1 Remaining in a nullcline or in an equilibrium hyperplane

**Property 1** *A trajectory cannot remain in a  $V_i(x^*)$  set or in a  $U_i$  set, unless it is the equilibrium point  $x^*$ .*

The proof is in [1].

#### 4.2 Intersecting nullclines and equilibrium hyperplanes

**Property 2** *For loop structured systems with monotonous interactions, the set of trajectories intersecting simultaneously two (different)  $V_i(x^*)$  is of measure zero.*

Indeed, the intersection of the two hyperplanes  $x_i = x_i^*$  and  $x_j = x_j^*$  is a  $(n - 2)$ -dimensional plane. Because of property P, the trajectories are of measure zero.

**Property 3** *For loop structured systems with monotonous interactions, the set of trajectories intersecting simultaneously two (different)  $U_i$  is of measure zero.*

The intersection is defined by  $f_i(x) = f_j(x) = 0$ . The derivative of this application is of full rank two because the interactions are monotonous. Therefore the preimage of 0 is a manifold of dimension  $(n - 2)$ , and property P applies.

**Property 4** *For loop structured systems with monotonous interactions, the set of trajectories intersecting simultaneously  $U_i$  and  $V_j(x^*)$  ( $j \neq i - 1$ ) is of measure zero. The set of trajectories intersecting simultaneously  $U_i$  and  $V_{i-1}(x^*)$  is of measure zero except in the case (let us call it case E) where the system  $(\Sigma)$  is such that the two surfaces coincide on an open set.*

In the first case, the intersection is defined by  $x_i = x_i^*$ ,  $f_j(x_j, x_{j-1}) = 0$ , and the same reasoning as above applies. If  $j = i - 1$ , then the intersection  $\{x \in \Omega, f_{i-1}(x_{i-1}), x_i^* = 0\}$  can be of dimension  $(n - 1)$ : take for example the Lotka-Volterra system:

$$\begin{cases} \dot{x}_1 = x_1(1 - x_2) \\ \dot{x}_2 = x_2(x_1 - 1) \end{cases}$$

then the equilibrium hyperplane  $x_2 = 1$  is included in the nullcline  $\dot{x}_1 = 0$ .

Now we are able to define the open set  $\tilde{\Omega}$ , which is  $\Omega$  minus these sets of measure zero (in finite number) from the three above properties; in the last particular case E, we do not remove

the corresponding set. From now on, everything will take place in this restricted space  $\tilde{\Omega}$ . For a possible region  $\Omega_{\sigma^q \sigma^p}(x^*)$  (see section 3), we define the non-empty sets:

$$\tilde{\Omega}_{\sigma^q \sigma^p}(x^*) \stackrel{\text{def}}{=} \Omega_{\sigma^q \sigma^p}(x^*) \cap \tilde{\Omega}$$

and the neighbors in  $\tilde{\Omega}$ : two regions of the phase space are neighbors if they differ only by one sign (of a deviation or a velocity). It is to be remarked that we have suppressed (by restricting  $\Omega$ ) the possibility of going from one region  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  to another if they differ by more than one sign (except in the last case E which is a bit degenerate, but will happen in the example of section 6).

**Definition 5** *Two domains  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  and  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$  are called:*

- *strict U-neighbors if  $\sigma^{q_1} = \sigma^{q_2}$ , and there exists a unique  $k \in \{1, \dots, n\}$  such that  $\sigma_k^{p_1} = -\sigma_k^{p_2}$ .*
- *strict V-neighbors if  $\sigma^{p_1} = \sigma^{p_2}$ , and there exists a unique  $k \in \{1, \dots, n\}$  such that  $\sigma_k^{q_1} = -\sigma_k^{q_2}$ .*

**Definition 6** *In the case E, we say that  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  and  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$  are strict UV-neighbors if for all  $i \neq k$ ,  $\sigma_i^{p_1} = \sigma_i^{p_2}$ ,  $\sigma_{i+1}^{q_1} = \sigma_{i+1}^{q_2}$  and  $\sigma_k^{p_1} = -\sigma_k^{p_2}$ ,  $\sigma_{k+1}^{q_1} = -\sigma_{k+1}^{q_2}$ .*

## 5 Transition between the domains $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$

We can now consider the restricted space  $\Omega$  partitioned in open domains  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$ . We will then show that the transition between these domains obey some rules determined by the extradiagonal terms of the Jacobian matrix.

### 5.1 Transition theorem

**Theorem 1 [Transitions between regions]** *Consider a loop system  $(\Sigma)$  with monotonous interactions and an equilibrium point  $x^*$ . Suppose that  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  and  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$  are two strict neighbors. We recall that  $t_{k,k+1}$  is the sign of the  $(k, k+1)$  element of the Jacobian matrix.*

- *Crossing of an  $U_k$ :*

*Assume they are strict U (or UV)-neighbors. If  $t_{k,k+1} \sigma_{k+1}^{p_1} = \sigma_k^{p_1}$  [resp.  $-\sigma_k^{p_1}$ ], then the crossing of  $U_k$  is possible only from  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$  to  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  [resp.  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  to  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$ ], and it corresponds to a minimum [resp. a maximum] of variable  $x_k$ .*

- *Crossing of a  $V_i$ :*

*Assume they are strict V (or UV)-neighbors. If  $t_{k,k+1} \sigma_{k+1}^{q_1} = \sigma_k^{q_1}$  [resp.  $-\sigma_k^{q_1}$ ], then the crossing of  $V_k(x^*)$  is possible only from  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$  to  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  [resp.  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  to  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$ ], and it corresponds for  $x_k$  to a crossing bottom-up [resp top-down] of its equilibrium  $x_k^*$ .*

*We say that  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  [resp  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$ ] is accessible from  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*)$  [resp  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$ ].*

The proofs of these theorems are very similar and can be founded in [1, 2].



## 5.2 Barrier in the state space

**Lemma 6** *Suppose there exists two  $C^1$  mappings*  $\Phi : x \in \Omega \longrightarrow \Phi(x) \in \mathbf{R}$   
 $\Psi : u \in \mathbf{R} \longrightarrow \Psi(u) \in \mathbf{R}$  *verifying:*

$$L_f \Phi = \Psi \circ \Phi$$

*then  $\mathcal{R} \stackrel{\text{def}}{=} \{x \in \Omega; \Psi(\Phi(x)) = 0\}$  separates  $\Omega$  into positively invariant regions,  
 $\mathcal{R}^- \stackrel{\text{def}}{=} \{x \in \Omega; \Psi(\Phi(x)) < 0\}$  and  $\mathcal{R}^+ \stackrel{\text{def}}{=} \{x \in \Omega; \Psi(\Phi(x)) > 0\}$*

$L_f \Phi$  denotes the Lie derivative of  $\Phi$  along the vector field  $f$  :  $L_f \Phi = \sum f_i \frac{\partial \Phi}{\partial x_i}$ .

**Proof:** If we set  $u = \Phi(x)$ ,  $u$  satisfies the first order scalar differential equation:

$$\dot{u} = \psi(u)$$

The zeros of  $\psi$  separates the space into invariant regions where  $\psi$  is always positive or negative.

**Corollary 1** *If there exists a region of the state space  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  such that:  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*) \cap \mathcal{R}^- = \{\emptyset\}$  [resp  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*) \cap \mathcal{R}^+ = \{\emptyset\}$ ], then any trajectory initiated in  $\mathcal{R}^-$  [resp in  $\mathcal{R}^+$ ] will never reach the region  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$ .*

**Corollary 2** *Any trajectory initiated in a region  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*) \in \mathcal{R}^+$  [resp  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*) \in \mathcal{R}^-$ ], will never reach the regions  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*) \in \mathcal{R}^-$  [resp  $\tilde{\Omega}_{\sigma^{q_2} \sigma^{p_2}}(x^*) \in \mathcal{R}^+$ ].*

### Remarks

- Because  $u$  verifies a scalar differential equation, the non-empty limit sets are the equilibria; property P thus holds.
- For bioreactors,  $u$  is linked to mass balance, and  $\Psi$  is linear ([9]).

## 5.3 Main theorem of behavior

The following theorem describes the behavior of the trajectories of a differential system  $(\Sigma)$  with monotonous interactions, loop structured and diagonally-monotonous: the domain  $\Omega$ , restricted to  $\tilde{\Omega}$  (cf. section 4) is partitioned with the possible regions  $\tilde{\Omega}_{\sigma^{q_1} \sigma^{p_1}}(x^*)$  (section 3); the possible transition rules (cf. section 5) between these regions are given by Theorem 1.

**Theorem 2 (Global qualitative behavior)** *Every trajectory of  $(\Sigma)$  in a domain  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  either:*

- *stays in  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  and go to infinity*
- *stays in  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$ , and goes toward an equilibrium  $x^\dagger$  in the closure of  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$*
- *goes to one of the strict neighbors  $\tilde{\Omega}_{\sigma^{q'} \sigma^{p'}}(x^*)$  that are accessible.*

**Proof:** Indeed, if a trajectory remains in a possible  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  (section 3), then the  $\dot{x}_k$  are of fixed signs, therefore the  $x_k$  are monotonous. If they are bounded, they have to converge toward an equilibrium in the closure of  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  or to go towards an accessible neighbor (section 5). Moreover, this neighbor must be a strict neighbor, because we have removed the trajectories going to non-strict neighbors (section 4).

**Remark 2.** Note that the trajectories cannot become unbounded in a domain  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  where for all  $i$ ,  $\sigma_i^q = -\sigma_i^p$ , because that would mean that the state variables are decreasing above their equilibrium, or increasing under their equilibrium. If the state variables are positive (as often in biological modeling), a necessary condition for unboundedness in  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  is that there exists  $i$  for which  $\sigma_i^q = \sigma_i^p = 1$ .

**Remark 3.** The equilibrium  $x^*$  can be reached from a domain  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  if and only if  $\sigma_k^p = -\sigma_k^q$  for all  $k$ . If this condition is not fulfilled for a  $k$ , then variable  $x_k$  is decreasing under its equilibrium  $x_k^*$  or increasing above its equilibrium, it can therefore not converge.

**Remark 4.** A local linear study can also give interesting informations on the possibility of convergence in a given region ([1]).

## 5.4 Graphical representation

We will represent each possible region  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  by a two columns matrix of signs, the first column stands for  $\sigma^q$ , and the second for  $\sigma^p$ . For example, the region  $\{x \in \Omega; x_1 > x_1^*, x_2 < x_2^*, x_3 > x_3^*, \dot{x}_1 < 0, \dot{x}_2 < 0, \dot{x}_3 > 0\}$  is represented by the matrix:

$$\begin{pmatrix} + & - \\ - & - \\ + & + \end{pmatrix}$$

A possible transition between two regions is represented by an oriented arrow between these regions, the arrows are oriented by the conclusions of theorem (1). A letter on the arrow will indicate if the variable  $x_k$  admits a minimum ( $m_k$ ), a maximum ( $M_k$ ), if it crosses its equilibrium  $x_k^*$  top-down ( $t_k$ ) or bottom-up ( $T_k$ ). The set of all  $\tilde{\Omega}_{\sigma^q \sigma^p}(x^*)$  partitioning  $\tilde{\Omega}$  related by the arrows reflecting the transition rules of theorem (1) is called the basic mixed transition graph. The nodes where it is possible to converge to equilibrium (cf remark 3) will be called equilibrium nodes.

Our main theorem has now a “graphical version” (cf. the detailed example below and figures 3 and 4). For the sake of simplicity, we will restrict ourselves to the case where all the trajectories are bounded. We obtain then (cf figures 3 and 4):

**Theorem 3 (Graphical version of the global qualitative theorem)** *On each non equilibrium node, the trajectories follow an arrow of the graph to go toward an accessible node. On each equilibrium node, the trajectories either stay in the node and converge to equilibrium or go toward an accessible node.*

## 5.5 Asymptotic behavior

Some theorems (admitting a simple interpretation in terms of the graph) on the behavior of loop structured systems with monotonous interactions have already been given ([1]). We will just give the following lemma derived from considerations of both deviation from a reference point and tendency of the variables.

**Lemma 7** *If, in the transition graph of a system  $\Sigma$ , there is no cycle containing an extremum of variable  $x_k$ , then for almost every trajectories,  $x_k$  either goes towards an equilibrium in the closure of  $\Omega$  or to infinity.*

**Corollary 3** *If there is no cycle in the transition graph of a system  $\Sigma$ , almost all the trajectories go toward an equilibrium in the closure of  $\Omega$  or diverge.*

## 6 Study of an example: validation of a general class of phytoplanktonic growth models

### 6.1 Presentation of the model

To illustrate the qualitative analysis, we take as an example a class of models describing the behavior of phytoplanktonic cells (whose biomass is  $x_2$ ) growing on a substrate  $x_1$  in a continuous reactor. This process, for dimensionless variables (for a non zero nutrient supply) can be described by the following system:

$$(\Sigma_{PGM}) \begin{cases} \dot{x}_1 = 1 - x_1 - \rho(x_1)x_2 \\ \dot{x}_2 = (\mu(x_3) - 1)x_2 \\ \dot{x}_3 = \rho(x_1) - \mu(x_3)x_3 \end{cases} \quad (17)$$

The variable  $x_3$  is the cell quota *i.e.* the quantity of intracellular nutrient per biomass unit. The functions  $\rho$  and  $\mu$  represents the absorption rate of the substrate and the growth rate. Among the models  $(\Sigma_{PGM})$ , the Droop model ([10, 5]) is largely used in the biological field. For this particular model we have:

$$\rho(x_1) = a_1 \frac{x_1}{a_2 + x_1}; \quad \mu(x_3) = a_3 \left(1 - \frac{a_4}{x_3}\right)$$

In fact, these functions are often unknown or ill-known, and in the following we will do only qualitative hypotheses.

**Hypothesis:** To represent growth of phytoplankton, some hypotheses, corroborated by the experiments, are made in the physical domain considered  $\Omega = \{x \in \mathbf{R}_+^3; x_1 > 0, x_2 > 0, x_3 > 0\}$ .

- **(H1):** The absorption rate  $\rho$  is a non negative bounded function of  $x_1$ . It is strictly increasing and verifies  $\rho(0) = 0$ .
- **(H2):** The growth rate  $\mu$  is a non negative strictly increasing function of  $x_3$ .
- **(H3):** An equilibrium exists in the open domain  $\Omega$ .

The class of models  $(\Sigma_{PGM})$  verifying hypothesis (H1)-(H2)-(H3) is called the class of Phytoplanktonic Growth Models (PGM). It can easily be verified that the Droop model ([10, 5]) is in this class.

## 6.2 The PGM: a non trivial loop structured class of systems with monotonous interactions

**Property 5** *The PGM are loop structured models with monotonous interactions in  $\Omega$ .*

**Proof:** The Jacobian matrix is of the following signs on  $\Omega$  :

$$\begin{pmatrix} -1 & -1 & 0 \\ 0 & t_{22}(x) & +1 \\ +1 & 0 & -1 \end{pmatrix} \quad (18)$$

with

$$t_{22}(x) = \text{sign}(\dot{x}_2) = \mu(x_3) - 1 \quad (19)$$

**Property 6** *The PGM have two equilibria:*

- $x^* \in \Omega$ :

$$x_2^* = \mu^{-1}(1); \quad x_1^* = \rho^{-1}(\mu^{-1}(1)); \quad x_3^* = \frac{1 - \rho^{-1}(\mu^{-1}(1))}{\mu^{-1}(1)}$$

- $x^b$ , unstable equilibrium in the boundary of  $\Omega$ :

$$x_2^b = 0; \quad x_1^b = 1; \quad x_3^b \text{ unique solution of: } \mu(x_3^b)x_3^b = \rho(x_1^b)$$

**Proof:** In concordance with hypothesis (H3), we have  $x^* \in \Omega$  i.e.  $x_2^* > 0$ . Hypotheses (H1) and (H2) ensure the uniqueness of this equilibrium while the applications  $\mu^{-1}$  and  $\rho^{-1} \circ \mu^{-1}$  are strictly increasing. Moreover, it is straightforward from a local study that  $x^b$  is unstable if  $x_2^* > 0$ .

**Property 7** *The PGM are diagonally  $x^*$ -monotonous in the domain  $\Omega$ .*

**Proof:** It can be noticed that  $t_{22}(x) = \text{sign}(x_3 - x_3^*)$ , therefore in each domain  $W_{\sigma^q}(x^*)$ ,  $t_{22}(x) = \sigma_3^q$  is fixed. We have thus  $\text{sign}(\dot{x}_2) = \text{sign}(x_3 - x_3^*) = \sigma_3^q$ .

We are therefore in the case of case E of property 4 (with  $V_3(x^*) \subset U_2$ ), it means that simultaneously when  $x_2$  reaches an extremum,  $x_3$  crosses its equilibrium  $x_3^*$ .

**Property 8** *If  $u$  denotes the total nutrient concentration in the chemostat:*

$$u \stackrel{\text{def}}{=} x_1 + x_2x_3 \quad (20)$$

$u$  satisfies the following differential equation:

$$\dot{u} = 1 - u \quad (21)$$

**Property 9** *The trajectories of the PGM are bounded in the positively invariant domain  $\Omega$ .*

**Proof:** The proof of Property 8 is straightforward from system (17). To show that  $\Omega$  is positively invariant one has to consider the field on the boundaries:

- From (H1), for every  $x$  on the face  $x_1 = 0$  we have:  $\dot{x}_1 = 1 > 0$ ,
- For every  $x$  on the face  $x_2 = 0$  there holds:  $\dot{x}_2 = 0$ ,

- For every  $x$  on the face  $x_3 = 0$ :  $\dot{x}_3 \geq 0$ .

Moreover, to prove the boundedness of the trajectories, we first use Property 8 to show that  $u$  is bounded *i.e.*  $x_1$  and the product  $x_2x_3$  are bounded.

To show that  $x_3$  is bounded, we consider a real  $a$  large enough to ensure that the strictly increasing function  $\mu(a)a$  becomes larger than the upper bound of  $\rho$  (cf. H1). It follows that the field on every hyperplane  $x_3 = b$ , where  $b \geq a$  verifies:  $\dot{x}_3 < 0$ .

The product  $x_2x_3$  is bounded, so that  $x_2$  is also bounded.

## 6.3 Study of the transition graphs

### 6.3.1 The possible qualitative situations

To obtain the set of possible domains allowed by the class of models  $(\Sigma_{PGM})$ , we can now apply results of Lemma 4 and 5 for the 8 orthants  $W_{\sigma^q}(x^*)$ . Note however that the Jacobian matrix (18) at the equilibrium point has a zero on its diagonal ( $s_{22} = 0$ ), therefore (see remark 1) the possible signs for  $\dot{x}_2$  has to be considered directly from the system  $(\Sigma_{PGM})$ . The analysis follows here straightforward from Proposition 7: for  $x \in W_{\sigma^q}(x^*)$ ,  $\text{sign}(\dot{x}_2) = \sigma_3^q$ .

The set of feasible qualitative domains  $\tilde{\Omega}_{\sigma^q\sigma^p}(x^*)$  follows now from the results of section (3.2) after the computation of the sign of the eight matrices  $\mathcal{M}^q$ . We can remark that none of these matrices presents the case treated in Lemma 5.

**Property 10** *There exists 18 feasible qualitative region  $\tilde{\Omega}_{\sigma^q\sigma^p}(x^*)$  for the class of PGM.*



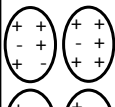

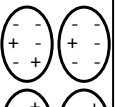




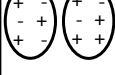

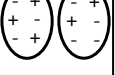



$W_{\sigma^q}(x^*)$	- + +	- - +	+ - +	+ + +	- + -	- - -	+ - -	+ + -
<b>Possible signs for <math>f(x)</math></b>	* + -	+ + -	* + *	- + *	* - *	+ - *	* - +	- - +
<b>Possible regions</b>								
$\Omega_{\sigma^p\sigma^q}$								

Figure 1: The set of feasible domains for the Droop model. The first column contains the sign of deviation toward equilibrium  $x^*$ , the second column the sign of the tendency of the variables. The  $\star$  means either  $+$  or  $-$ .

These qualitative situations are listed in table 1. Remark that *a priori* we have  $2^6 = 64$  possible situations. The consideration of this set of possible domains constitutes therefore a first filter to test the structure of the model. If a qualitative event not belonging to this set can be experimentally observed, it means that the system can not rely on the supposed structure.

### 6.3.2 The basic mixed transition graph

To go further into the description of the qualitative behavior of the model, We can now construct the mixed transition graph by applying Theorem 1 to all the strict neighbors  $\tilde{\Omega}_{\sigma q_1 \sigma p_1}(x^*)$  and  $\tilde{\Omega}_{\sigma q_1 \sigma p_1}(x^*)$  belonging to the set of feasible regions. It can be noticed that  $V_3(x^*) \subset U_2$ , and then from Property 4 (Case E), there exists UV-neighbors.

Finally we obtain the mixed transition graph (fig. 2) associated with the PGM model ( $\Sigma_{PGM}$ ). This graph summarizes the possible succession of extrema or equilibrium crossing from an initial qualitative situation.

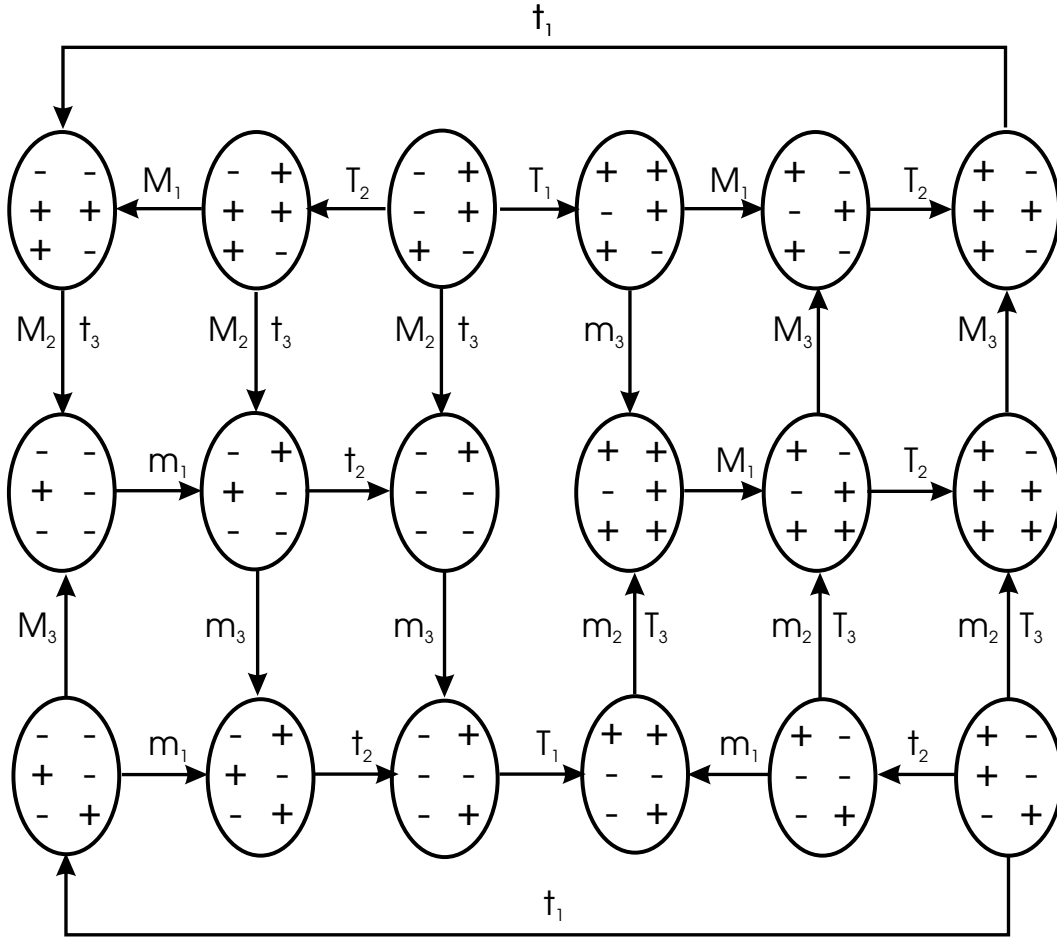


Figure 2: Basic mixed transition graph

It is noteworthy that the construction of this graph relies only on the sign of the Jacobian matrix (the peculiar case of Lemma 5 does not appear here), and not on the precise formulation of the model. The biologist can therefore use these graphs as a second filter to test if the basic structure of his model matches the experiments. He can indeed compare the sequences of maxima and minima or the sequences of equilibrium crossing obtained experimentally with the possible sequences contained in the graph.

### 6.3.3 Simplification of the basic mixed transition graph

The basic mixed transition graph can be simplified by considering the result of Lemma 6.

**Property 11** *Depending on initial conditions some regions of  $\Omega$  are unreachable:*

- if  $u(0) < 1$  then  $\forall t \geq 0$  the regions  $\begin{pmatrix} + & * \\ + & * \end{pmatrix}$  and the regions  $\begin{pmatrix} * & - \\ * & - \end{pmatrix}$  are unreachable
- if  $u(0) > 1$  then  $\forall t \geq 0$  the regions  $\begin{pmatrix} - & * \\ - & * \end{pmatrix}$  and the regions  $\begin{pmatrix} * & + \\ * & + \end{pmatrix}$  are unreachable

The sign  $\star$  means that it can be either  $+$  or  $-$ .

**Proof:** Consider the application  $\phi : x \rightarrow \phi(x) = u = x_1 + x_2x_3$ . From proposition 8 we have that  $L_f\Phi(x) = 1 - \Phi(x)$ .

Lemma 6 say thus that the surface  $x_1 + x_2x_3 = 1$  separates the space into 2 unconnected regions  $\mathcal{R}^+ = \{x \in \Omega; x_1 + x_2x_3 > 1\}$  and  $\mathcal{R}^- = \{x \in \Omega; x_1 + x_2x_3 < 1\}$ .

Indeed, the regions  $\begin{pmatrix} + & * \\ + & * \end{pmatrix}$  are belonging to  $\mathcal{R}^+$ : if  $\forall i x_i > x_i^*$  then  $x_1 + x_2x_3 - 1 > x_1^* + x_2^*x_3^* - 1 = 0$ .

On the same way, the regions  $\begin{pmatrix} * & - \\ * & - \end{pmatrix}$  are belonging to  $\mathcal{R}^+$ : if  $\forall i \dot{x}_i < 0$  then  $\dot{u} = \dot{x}_1 + \dot{x}_2x_3 + x_2\dot{x}_3 < 0$ , and from (21)  $u - 1 = -\dot{u} > 0$ .

The proof is symmetrical for the regions contained in  $\mathcal{R}^-$ .

**Lemma 8** *Almost every trajectory converges toward the equilibrium  $x^*$ .*

**Proof:** If, depending on initial conditions, we remove the infeasible regions (see Lemma 11), then the cycle in graph of fig. (2) disappears. Applying Lemma 7, we conclude that almost every trajectories either go toward an equilibrium in the closure of  $\Omega$  or go to infinity. As these trajectories are bounded (Property 9), the only possibility is to go toward the unique stable equilibrium  $x^* \in \Omega$  (the equilibrium on the boundary of  $\Omega$  is unstable (Property 6)). In fact this equilibrium is globally stable (cf. [2]).

**Property 12** *In the considered domain, if  $u(0) < 1$  [resp  $u(0) > 1$ ], the region  $\begin{pmatrix} - & - \\ + & + \end{pmatrix}$  [resp  $\begin{pmatrix} + & + \\ - & - \end{pmatrix}$ ] is unreachable.*

**Proof:** from Property 8, in the domain  $\Omega$  the PGM have a unique equilibrium globally stable. In the case  $u(0) < 1$ , the qualitative situations mentioned in Property 11 disappeared from the mixed transition graph. It can then be noticed that in this graph, two domains are positively invariant. Among these, the region  $\begin{pmatrix} - & - \\ + & + \end{pmatrix}$  does not satisfy condition of Lemma 5.3, it can therefore not lead to the non trivial equilibrium in the interior of  $\Omega$ .

Properties 12 and 11 can now be used to simplify the mixed transition graph: depending on the initial condition for  $u$  it can then be reduced to two graphs (figure 4 and 3).

**Property 13** *The trajectories of the PGM admit at the most for each of the state variables one minimum, one maximum, one bottom-up equilibrium crossing and one top-down equilibrium crossing.*

**Proof:** This is the consequences of the two graphs (figures 4 and 3) describing the qualitative dynamics of these systems.

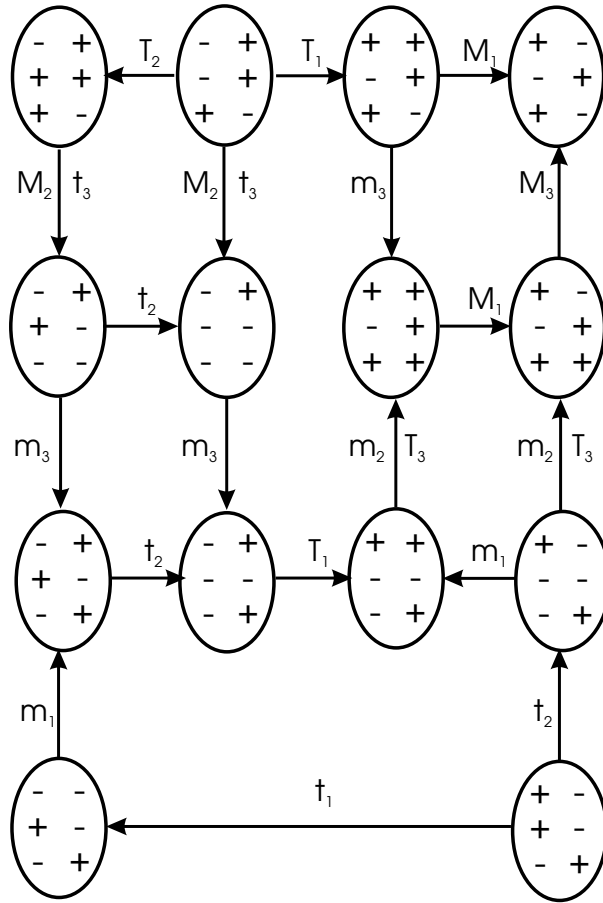


Figure 3: Simplified mixed transition graph for  $u(0) < 1$ .

## 6.4 Qualitative validation

A high number of experiments have been performed with the micro-algae *Dunaliella tertiolecta* in a nitrate depleted environment limiting growth ([11]). The phytoplanktonic biomass has been estimated with different biological indicators: total biovolume, cell concentration (using a particle counter (HIAC/ROYCO with laser sensor HRLD 400)), or carbon concentration (CHN analysis (CHN LECO 900)). Nitrate has been measured by colorimetric methods (Auto-analyzer Technicon). Cell quota is estimated using the conservation law of nitrogen calibrated with measures of particulate nitrogen (see for example [1]). Precise indications on the computer controlled environment controlling the culture so as on the conditions of experiments can be found in [12].

From these experiments, three major deficiencies of the Droop model structure have been pointed out.

- First, a delay has been observed (fig. 5) between extrema of biomass (around time 0.8) and crossing of the quota equilibrium (around time 0.1). From the model, these events should be concomitant. This lag can be explained by the necessary time for inorganic nitrogen to be incorporated into the organic matter. The quota approach, considering cellular nitrogen as an homogeneous whole assumes that nitrogen in the cell is immediately usable for growth. This defect holds however the biomass is measured.



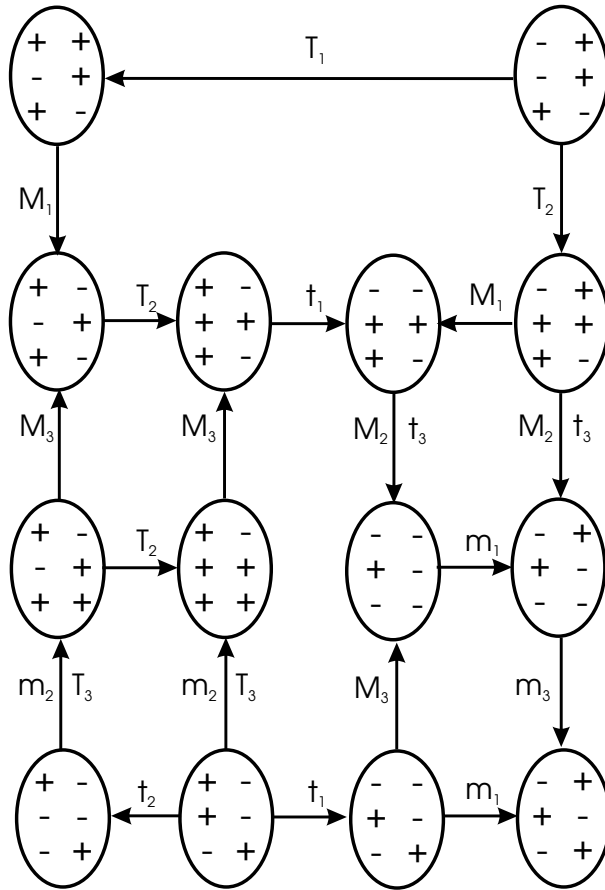


Figure 4: Simplified mixed transition graph for  $u(0) > 1$ .

- Extrema for the substrate have been observed (fig. 5), which are not allowed by the transition graphs. The qualitative state of the system, after time 0 is the following:  $\begin{pmatrix} + & + \\ - & + \end{pmatrix}$ , so that the theoretical possible qualitative events are  $m_2 \& T_3$ ,  $M_1$  and  $M_3$  (the symbol  $\&$  means that the transitions are simultaneous). It can be verified that substrate has (at least) 3 extrema, what is not possible (Property 13). They appear for cells which have been submitted to a high nitrogen starvation (*i.e.* cells with very low internal quota). The observed phenomenon may result from the starvation of algae which affects their uptake potential, so that uptake is no longer an increasing function of substrate ([13]).
- Finally, some extrema not permitted by the graphs have been observed (fig. 6) around equilibrium for biomass. These extrema, which have already been noticed by other authors, may also be the consequence of the lag previously described ([14]).

This example illustrates the main advantages of this dynamical qualitative analysis:

- It does not need to identify parameters, it is therefore well adapted to biological modeling, where parametric uncertainty is very high.
- It enables to compare directly the structure of the model with the data.

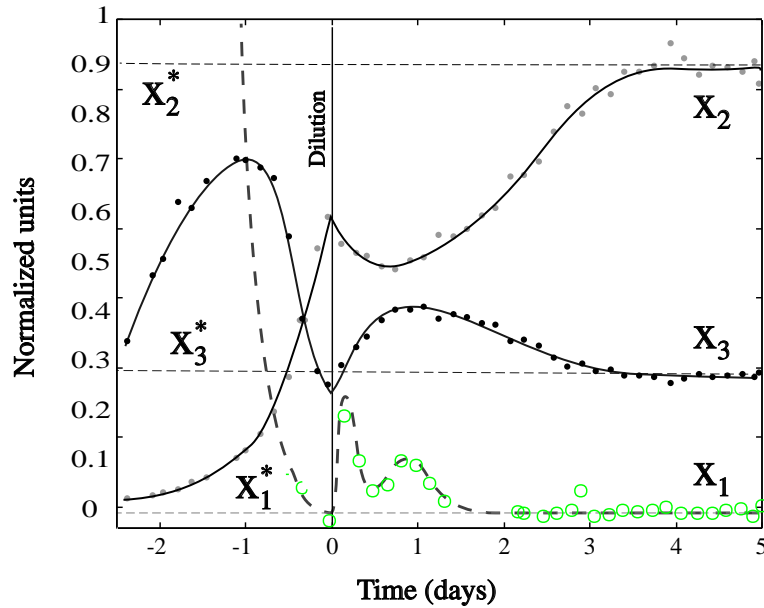


Figure 5: Experiment in chemostat with the green algae *Dunaliella tertiolecta*. The different variables (circles) and their experimentally determined equilibrium (dashed line) are represented. Biomass is measured by biovolume. Units have been normalized, while analysis is independent of scale. For negative time, the culture is in batch (the dilution rate is zero), the dilution is set on at time zero. The total quantity of nitrogen  $u$  verifies  $u(0) < 1$ .

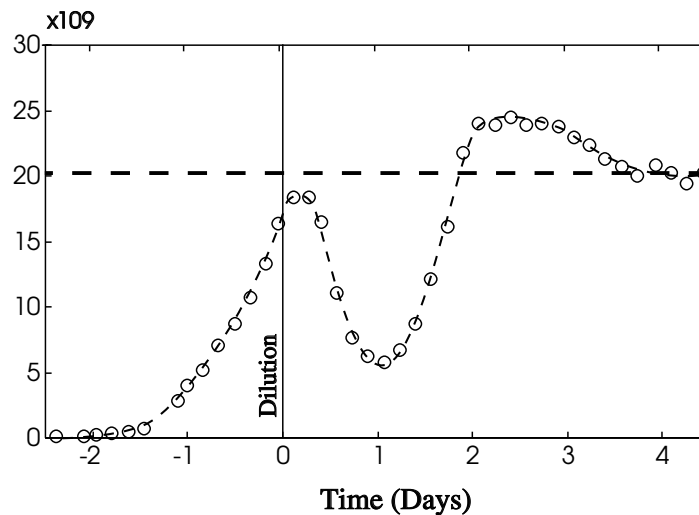


Figure 6: Experiment in chemostat with the green algae *Dunaliella tertiolecta*. Transient for the biomass measured as the total biovolume. The experimentally determined equilibrium (straight lines) are represented. The total quantity of nitrogen  $u$  verifies  $u(0) < 1$ .

- It enables therefore to validate not one model, but a class of model, defined by a general structure.
- It requires only qualitative feature of the data, that can be observed even with noisy data.

- It gives necessary conditions on the qualitative behavior of the states variables, that can be useful for validation even when the whole state is not observed.

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