Nonlinear Control for Algae Growth Models in the Chemostat

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Abstract This paper deals with output feedback control of phytoplanktonic algae growth models in the chemostat. The considered class of model is of variable yield type, meaning that the ratio between the environmental nutrient absorption rate and the cells' growth rate varies, which is different from classical bioprocesses assumptions. On the basis of weak qualitative hypotheses on the analytical expressions of the involved biological phenomena (which guarantee robustness of the procedure towards modelling uncertainties) we propose a nonlinear controller and prove its ability to globally stabilize such processes. Finally, we illustrate our approach with numerical simulations and show its benefits for biological laboratory experiments, especially for ensuring persistence of the culture facing classical experimental problems.

1 Introduction

The first models describing micro-organisms growth in continuous controlled laboratory devices, so-called chemostats, were proposed by Monod [14]. This class of models are based on the assumption that the micro-organisms growth rate is proportional to their consumption rate of some extracellular limiting nutrient. Thus these models are often referred to as constant yield models [18]. Constant yield models predictions remain good compared to experimental data for micro-organisms like bacteria, but some important differences appear as unicellular photosynthetic algae are considered. This phenomenon was first described by Droop [4]. He therefore proposed a new approach dedicated to phytoplanktonic algae growth, reconsidering the “constant yield” hypothesis. Droop assumed that unicellular algae growth on a limiting nutrient is a two steps phenomenon: first uptake of the nutrient in the cell and then use of the intracellular nutrient to support cell’s growth. As a result, the ratio between cells growth rate and nutrient consumption rate is no more constant. Hence, these kind of models are called variable yield models [18].

In previous works, we exhibited new nonlinear feedback controls for constant yield models, coming from the more general theoretical framework proposed in [9, 10]. A crucial point of these works is that the control procedure requires only qualitative hypotheses on the micro-organisms’ growth rates, what is important for the robustness towards modelling uncertainties that are common in biological models [11, 12]. Here we propose to extend these results to variable yield models.

This paper is organized as follows: first we state the general variable yield model for unicellular algae growth in chemostats and we make some qualitative hypotheses about the algae’s substrate uptake and growth rates. Then we propose the nonlinear controller and prove the global asymptotic stability of the closed loop resulting system. Finally some numerical simulations, assuming various experimental operating conditions or failures, illustrate our approach.

2 The Variable Yield Model

A chemostat is a laboratory apparatus consisting of a vessel enclosing the liquid culture medium. The micro-organisms population grows in this medium consuming a nutrient (i.e. substrate). A liquid flow \( F \) passes through the vessel; the inflow feeds the chemostat with the substrate at concentration \( s_i \), while the outflow is composed by the same compounds than inside the chemostat. The volume of the culture medium \( V \) remains
constant since the inflow and the outflow are equal. Let us define the dilution rate \( D = \frac{C}{V} \).

### 2.1 The Model

The model variables are the extracellular limiting nutrient concentration (denoted \( s \)), the intra-cellular nutrient per unit of biomass (called cell quota and denoted \( q \)) and the biomass concentration (denoted \( x \)). Have a look at the nomenclature in appendix A for the variables units. All the concentrations are supposed to be homogeneous. The function \( \rho(.) \), depending on the substrate concentration \( s \), is the substrate uptake rate while the function \( \mu(.) \), depending on the cell quota \( q \), is the growth rate of the algae. According to [4,18], we obtain the following variable yield model:

\[
\begin{align*}
\dot{s} &= D(s_{in} - s) - \rho(s)x \\
\dot{q} &= \rho(s) - \mu(q)q \\
\dot{x} &= \mu(q)x - Dx
\end{align*}
\]

(1)

It is well known in biology that the most crucial problem in modelling the considered phenomenon is to propose some realistic analytical expressions for the biological functions \( \rho(.) \) and \( \mu(.) \). As in [16], in order to bypass these modelling difficulties, we only suppose qualitative hypotheses about \( \rho(.) \) and \( \mu(.) \).

**Hypothesis 1 (H1)**

\( \rho(0) = 0 \) and \( \rho(.) \) is \( C^1 \), increasing and bounded \( \mu(\cdot) \) is \( C^1 \), non-negative, increasing and bounded there exists \( q_m > 0 \) such that \( \mu(q_m) = 0 \)

These hypotheses mean that: if substrate \( s \) is available then the cell uptakes it. The more substrate is available, the highest the uptake rate is. Boundness of both \( \rho(.) \) and \( \mu(.) \) comes from biological evidences. The parameter \( q_m \) stands for the minimum cell quota: when \( q \) drops below \( q_m \) there is insufficient internal nutrient for the cell to grow, and the more internal quota \( q \) is available, the more the cell grows.

Hence we do not consider neither the possibility of inhibition of substrate that is modeled by non-monotone functions (e.g. Haldane model). However this phenomenon may also be addressed with a quite similar procedure (see [12,11]).

Throughout the paper we only consider initial conditions for the state variables belonging to the open biological meaningful cone \( \Omega = \{ s > 0, q > q_m, x > 0 \} \). Observe that the closure of \( \Omega \) is invariant by system (1). In order to exhibit a better form of system (1), we use the change of coordinates \( z = s + qx \). \( z \) represents the total amount of intra-cellular and extracellular nutrient in the chemostat. Then we obtain the following system, which is easier to deal with, especially due to the autonomous and almost linear \( z \) dynamics:

\[
\begin{align*}
\dot{z} &= D(s_{in} - z) \\
\dot{x} &= D(s_{in} - s) - \rho(s)x \\
\dot{x} &= \mu(\frac{z}{x})x - Dx
\end{align*}
\]

(2)

### 2.2 Behavior of the Open Loop Model

The asymptotic behavior of system (1) has been thoroughly studied in [2,18,7]; results are of two different types depending on the value of \( D \) compared to \( s_{in} \): either there exists a positive equilibrium point and each forward positive orbit initiated in \( \Omega \) goes towards it, either not and every forward orbit goes to the washout point corresponding to the disappearance of the algae from the chemostat \( x = 0 \).

It is clear that washout of the culture must not happen. Here, via the control of the model, we aim at preventing the disappearance of the positive equilibrium, i.e. at preventing biomass washout. In other words we intend to impose the convergence of the state towards a positive equilibrium point. Specifically, we want to drive and keep biomass concentration towards a chosen positive value. Moreover, uncertainty in feeding substrate concentration \( s_{in} \) may sometimes destabilize the system leading to biomass washout. Another point important to be addressed is the possible algae stress (unpredicted fall of cells growth rate) that may as well lead to biomass washout. Then it is crucial to guarantee that the biomass goes towards its chosen positive value, independently from \( s_{in} \) variations and / or potential algae stress.

### 3 Nonlinear Control Design

#### 3.1 Statement of the Control Framework

Applied control of biological systems generally differs from the classical framework of control where it is usually assumed that the model is perfectly known [15]. To control biological systems, we have to take into account that the model may be only qualitatively known and that the outputs may be some unknown nonlinear functions of the state variables. Moreover, inputs are considered unconstrained in classical control theory, whereas they usually fulfill some constraints (e.g. positivity) in biological systems.

Due to the high variability of biological phenomena, we consider here a qualitatively known model, qualitative outputs and constrained input. Therefore we can not apply classical linearisation techniques requiring a detailed analytical expression of the model (see e.g. [5]).
However, we still have to define the manipulated variable (input), and the online measured variable (output). In chemostat-like systems, it is well known that the (non-negative) dilution rate $D$ is easy to manipulate, thus we use it as the (constrained) input of the system. Now we define the output; here we suppose that our chemostat is instrumented with sensors that can measure, either the uptaked carbon or the produced oxygen due to the algae photosynthesis. Note that both quantities are proportional to the cells growth. Hence we assume that the output $y = \mu(q)x$, namely the cells population growth velocity, is available online from the plant. Let us summarize these assumptions in the following hypothesis.

Hypothesis 2 (H2)

$D \geq 0$ is the constrained input of system (1) and $y = \mu(q)x$ is an output of system (1).

3.2 Nonlinear Control Design

Now we state and prove our main result, using the notation $\xi$ for the state vector.

Proposition 1

Under assumptions (H1) and (H2), the nonlinear output feedback control law:

$$D(\cdot) = \gamma y = \gamma \mu(q)x \quad \text{with} \quad \gamma > \frac{q_m}{s_m} \quad \text{(3)}$$

globally stabilizes system (1) towards the single positive equilibrium $\xi^*$, determined by the value of $\gamma$.

By “positive” equilibrium point we refer to a point whose elements are all positive. For instance the washout point that corresponds to the disappearance of algae from the chemostat ($x = 0$) is an equilibrium point of (1), but not a positive one. Moreover, note that with expression (3), the input $D(\cdot)$ remains non-negative and therefore fulfills its positivity constraint (see (H2)).

The control law (3) leads to the following closed loop system:

$$\begin{align*}
\dot{z} &= D(\cdot)(s_m - z) \\
\dot{x} &= D(\cdot)(\frac{1}{\gamma} - x) \\
\dot{s} &= D(\cdot)(s_m - s) - \rho(s)x
\end{align*} \quad \text{(4)}$$

We first want to show that for the closed loop system (4), both variables $z$ and $x$ converge (asymptotically) to $s_m$ and $\frac{1}{\gamma}$, respectively. Let us integrate the equations $\dot{z}$ and $\dot{x}$ of system (4), we have:

$$\begin{align*}
z(t) &= s_m + (z(0) - s_m)e^{-\int_0^t D(\cdot) d\tau} \\
x(t) &= \frac{1}{\gamma} + (x(0) - \frac{1}{\gamma})e^{-\int_0^t D(\cdot) d\tau}
\end{align*} \quad \text{(5)}$$

Thus, we have to prove that the quantity $\int_0^t D(\cdot) d\tau$ diverges towards infinity as time tends to infinity to show the convergence of $z$ and $x$ towards $s_m$ and $\frac{1}{\gamma}$.

Therefore, before proving Proposition 1, we show the following:

Lemma 1

Under hypotheses (H1) and (H2) and with the control procedure (3) applied to model (1), we have:

$$\lim_{t \to +\infty} \int_0^t D(\cdot) d\tau = +\infty$$

Proof

Since $D(\cdot)$ is non-negative, it is straightforward that:

$$e^{-\int_0^t D(\cdot) d\tau} \in [0, 1].$$

Then, we have:

$$\forall t \geq 0 \left\{ \begin{array}{ll} \max(s_m, z(0)) \geq z(t) \geq \min(s_m, z(0)) > 0 \\ \max(\frac{1}{\gamma}, x(0)) \geq x(t) \geq \min(\frac{1}{\gamma}, x(0)) > 0 \end{array} \right. \quad \text{(6)}$$

Let us suppose that $\lim_{t \to +\infty} \int_0^t D(\cdot) d\tau$ is bounded. Thus, since $D(\cdot) \geq 0$, a necessary condition is that:

$$\lim_{t \to +\infty} D(t) = 0$$

From (6) and (3), since $\gamma$ is positive and $x$ lower bounded by a positive constant, it implies at least that:

$$\lim_{t \to +\infty} \mu(q(t)) = 0 \implies \lim_{t \to +\infty} q(t) = q_m$$

Since $q(t)$ is a time-Lipschitz function ($\dot{q}$ is bounded), it is uniformly continuous in time. Then, using Barbalat’s lemma (see Appendix B), we show that:

$$\lim_{t \to +\infty} \dot{q}(t) = 0$$

that leads to (see (1)): $\lim_{t \to +\infty} \rho(s(t)) = 0$ and thus:

$$\lim_{t \to +\infty} s(t) = 0$$

Observe that these points, corresponding to $q = q_m$ and $s = 0$, are equilibria of the system (4) for all values of the variable $x$. Since $x$ is positively lower bounded, they are defined, for all $x \geq \min(\frac{1}{\gamma}, x(0))$, by:

$$\xi_u = (s = 0, q = q_m, x)^T$$

Now we want to show that these equilibria are not reachable from initial conditions belonging to the cone $\Omega$. To achieve this purpose, let us compute the Jacobian matrix at these equilibrium points, in the $(s, q, x)^T$ variables. With $\rho'(0) = \left(\frac{\partial \rho}{\partial s}\right)_{s=0}$ and $\mu'(q_m) = \left(\frac{\partial \mu}{\partial q}\right)_{q=q_m}$, we have:

$$J(\xi_u) = \begin{pmatrix}
-\rho'(0)x & \gamma \mu'(q_m)x & 0 \\
\rho'(0) & -\mu'(q_m)q_m & 0 \\
0 & \gamma \mu'(q_m)x (\frac{1}{\gamma} - x) & 0
\end{pmatrix} \quad \text{(7)}$$
It is straightforward that one of the eigenvalue is zero, with the associated eigenvector \((0,0,1)^T\), which corresponds to the fact that we have a continuum of equilibria along the \(x\) direction.

Now let us wonder about the two other eigenvalues. These are the same eigenvalues as the matrix \(B\):

\[
B = \begin{pmatrix}
-\rho'(0)x & \gamma \mu'(q_m)x & s_m \\
\rho'(0) & -\mu'(q_m)q_m & 0 \\
0 & 0 & 0
\end{pmatrix}
\]  

(8)

Remind that since (H1) hold, \(\rho'(0)\) and \(\mu'(q_m)\) are positive, then the trace of matrix \(B\) is obviously negative. Now we compute the determinant, we have:

\[
\det B = \rho'(0)x \mu'(q_m)(q_m - \gamma s_m)
\]

This determinant is negative since \(\gamma > \frac{q_m}{\rho'(0)}\), then there exists a positive real eigenvalue and unfortunately a negative real one that generates a stable manifold of the point \(\xi_u\). Now we focus only on the stable manifold, since the equilibrium point \(\xi_u\) can only be reached from this set.

Hence, we want to show that the stable eigenvector, at \(\xi_u\), does not point from the cone \(\Omega\) towards the point \(\xi_u\), which will prove that \(\xi_u\) can not be locally reached from \(\Omega\).

Note that the matrix \(B\) is off-diagonal positive and irreducible. Then we apply a corollary of the Perron-Frobenius theorem (see Appendix C), showing that the positive eigenvectors are only associated with the eigenvalue of largest real part (here the positive one). Then the stable eigenvector of matrix \(B\) is not positive (not all its elements are positive).

From matrix \(B\), since none of its components is zero, straightforward calculus show that the stable eigenvector has no zero component and then, both its components have different signs. Remind that these two components are the first two of the stable eigenvector of \(F\). The converse is true for the point \(\xi_u\) (a translation of \(\mathbb{R}^3\)). Consider the opposite sign of the first two components of the stable eigenvector, it is clear that this vector does not point towards the stable cone \(\mathbb{R}^3_{>0} \) and thus not to \(\Omega\) (a translation of \(\mathbb{R}^3_{>0} \)).

Therefore, the stable eigenvector does not point from \(\Omega\) to \(\xi_u\). Then \(\xi_u\) can not be locally reached from \(\Omega\). From the invariance of the closure of \(\Omega\) by system (4), the stable manifold of \(\xi_u\) can not be reached from \(\Omega\) and no trajectory initiated in \(\Omega\) converges towards \(\xi_u\).

Remember that the convergence towards \(\xi_u\) is a necessary condition for the boundedness of \(\lim_{t \to +\infty} \int_0^t D(\tau) d\tau\), hence it cannot be bounded, and since \(D(.) \geq 0\), we have:

\[
\lim_{t \to +\infty} \int_0^t D(\tau) d\tau = +\infty \quad \square
\]

Now, using Lemma 1, we can prove Proposition 1.

**Proof**

Note that Lemma 1 together with (5) implies that:

\[
\begin{align*}
\lim_{t \to +\infty} z(t) &= s_m \\
\lim_{t \to +\infty} x(t) &= \frac{1}{\gamma}
\end{align*}
\]  

(9)

Then all forward trajectories of system (4), converges towards the set \(E = \{\xi \in \Omega, z = s_m, x = \frac{1}{\gamma}, s < s_m\}\).

Now let us consider the “reduced” system (4), in \(s\), under the constraint \(\xi \in E\), we have:

\[
\dot{s} = (s_m - s)\mu(\gamma(s_m - s)) - \rho(s) \gamma
\]

(10)

which, using a time scale change, is equivalent to (see e.g. [3]):

\[
\dot{s} = (s_m - s)\mu(\gamma(s_m - s)) - \rho(s) \gamma
\]

(11)

From the invariance of the cone \(\Omega\) and since \(\mu(.)\) is an increasing function, it is straightforward that:

\[
g(\gamma, s) = \gamma(s_m - s)\mu(\gamma(s_m - s))
\]

is a decreasing function of \(s\). Furthermore, \(g(\gamma, s)\) is an increasing function of \(\gamma\). This situation corresponds to figure 1, which shows that there exists a single, positive, equilibrium \(s^*\) for (11) which is globally asymptotically stable. Note that \(s^*\) increases as \(\gamma\) increases.

![Fig. 1 Existence, unicity and stability of \(s^*\) for system (11) from the intersection of \(\rho(s)\) and \(g(s, \gamma)\)](image)

Then system (4) has a single, positive, equilibrium denoted \(\xi^* = (z^* = s_m, x^* = \frac{1}{\gamma}, s^*)^T\). Note that the choice of the gain \(\gamma\) allows to choose either the value \(s^*\) either the value \(x^*\).

Now let us come back to system (4) and consider the \(\dot{s}\) equation, injecting the solutions \(z(t)\) and \(x(t)\) initiated
at \( z(0) \) and \( x(0) \) respectively. Then, for each couple of initial conditions \( (z(0), x(0)) \), we obtain the following non-autonomous system:

\[
\dot{s} = D(s, z(t), x(t))(s_{in} - s) - \rho(s)x(t) \tag{12}
\]

Remark that Lemma 1 implies that for each couple of initial conditions \( (z(0), x(0)) \), the non-autonomous system (12) is “asymptotically autonomous” (see Appendix D) with limit equation (10). Applying a theorem on asymptotically autonomous systems from [13, 19] (see Appendix D), we conclude that for each couple of initial conditions \( (z(0), x(0)) \), each forward trajectory of system (12) converges towards the globally asymptotically stable equilibrium point \( s^* \) of the limit autonomous system (10). Thus, for each initial state vector \( \xi(0) \in \Omega \), the forward orbit of system (4) converges asymptotically towards the point \( \xi^* = (z^* = s_{in}, x^* = \frac{1}{\gamma}, s^*)^T \), which is therefore globally attractive on \( \Omega \).

Now let us compute the Jacobian matrix of the closed loop system (4) around the equilibrium point \( \xi^* \) in the \((z, x, s)^T\) coordinates. Remark that this matrix is lower triangular, then we only consider the diagonal terms (\( \bullet \) stands for any possible term). We have:

\[
J^* = \begin{pmatrix}
-D(\xi^*) & 0 & 0 \\
0 & -D(\xi^*) & 0 \\
-\rho(\xi^*) - \frac{\rho'(\xi^*)}{\gamma} & -D(\xi^*) & 0
\end{pmatrix}
\]

Since \( \rho(.) \) is an increasing function, \( \gamma \) is positive and \( D(\xi^*) = \mu(\gamma(s_{in} - s^*)) \) is positive, it is straightforward that \( \xi^* \) is locally stable for system (4). Since \( \xi^* \) is globally attractive too, we conclude that \( \xi^* \) is a positive, globally asymptotically stable equilibrium point for the closed loop system (4). \( \square \)

Remark 1
Remind that the demonstration is not based on any analytical expression for the “biological” functions \( \mu(.) \) and \( \rho(.) \) what is particularly important regarding the difficulty of modelling and identification of these functions.

Remark 2
It is important to note that the asymptotic behavior of biomass concentration \( x \) does not depend on parameter \( s_{in} \). Then, even for a time varying parameter \( s_{in}(t) \), biomass concentration \( x \) will asymptotically converge towards \( \frac{1}{\gamma} \), provided that for all time \( \gamma > \frac{q_m}{s_{in}(t)} \).

Remark 3
Observe that the condition \( \gamma > \frac{q_m}{s_{in}} \) imposes, for a fixed feeding substrate concentration \( s_{in} \), an upper limit on the reachable biomass concentration. This limit is independent from the analytical modelling of the growth rate \( \mu(.) \), and moreover, the uptake rate of extracellular substrate \( \rho(.) \) do not affect at all this limit, which is only determined by the minimum cell quota \( q_m \).

4 Numerical Simulations

We consider as an example the growth of *Dunaliella tertiolecta*, a green micro algae. Then according to [1], the uptake and growth rates are (for all the following simulations):

\[
\rho(s) = \frac{\rho_m s}{k + s} \quad \text{and} \quad \mu(q) = \max \left( 0, \mu_m \left( 1 - \frac{q_m}{q} \right) \right)
\]

Parameters values and units are to be found in the nomenclature (cf. appendix A).

4.1 Simple Noisy Simulation

We first show in figure 2 a simple noisy numerical simulation of the controlled process. The parameter \( s_{in} \) is assumed to be equal to 20 \( \mu g.L^{-1} \). In addition, we corrupt the output \( y = \rho(q)x \) with a relative white noise of 30% amplitude.

The obtained results agree with the predicted theoretical behavior of the controlled plant (cf. Proposition 1). From the biological point of view, the control law (3) drives the state variables towards the desired equilibrium determined by the value of the feedback gain \( \gamma \) : indeed, since \( \gamma = 0.1 \times 10^{-6} L.c^{-1} \), biomass concentration reaches asymptotically \( x^* = \gamma^{-1} = 10.10^6 c.L^{-1} \). Furthermore, note that despite the high level of noise on the output (30%) perturbations are almost completely filtered and do not really affect the state variables.

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**Fig. 2** Simulation of the closed loop system; constant \( s_{in} \); 30% relative white noise on \( y \).
4.2 Controlled Process Facing Varying $s_{in}$

To illustrate the fact that time variations of influent substrate concentration $s_{in}$ do not change the biomass concentration $x$ behavior, we consider a piecewise constant time-dependent $s_{in}$ that moves from 40µg.L$^{-1}$ to 2.5µg.L$^{-1}$ and back to 40µg.L$^{-1}$ each half day. Results are shown in figure 3. We check that, despite fast and large $s_{in}$ variations, the behavior of the variable $x$ remains almost the same than with fixed $s_{in}$ : it converges towards its equilibrium $x^* = \frac{1}{\gamma}$.

From controllers point of view, note that the only required knowledge for control is the output $y$ and the feedback gain $\gamma$. It ensures (provided that $\gamma > \min_{t}(s_{in}(t))$) a very simple behavior for biomass concentration $x$ that goes asymptotically towards $\frac{1}{\gamma}$ like a first order, independently from $s_{in}(t)$, even for quick and/or large variations. Of course, since model (1) is not controllable in the usual sense [15], some other state variables may change in time as $x$ remains at equilibrium $x^*$ (here $s$ does vary; so does $q$ but its variations remain so small they do not appear on the graph).

![Fig. 3 Simulation of the closed loop system; varying $s_{in}(t)$.](image)

4.3 Controlled Process Facing Periodic Algae Stress

We show in figure 5 a comparison between open and closed loop chemostats facing a periodic “algae stress” that corresponds to a fall of the algae growth rate. This problem is frequently encountered while carrying out chemostat experiments : the medium feeding the vessel (particularly with substrate concentration $s_{in}$ but with a blend of nutrient required for algae growth too) has to be regularly changed (usually each week). Even if one tries to use medias the most similar, there always remains little differences in the composition, the pH or the temperature between the new medium and the previously used one. These differences may cause what is referred to as algae stress.

We choose to model this phenomenon assuming that the cells growth rate is time dependent such that:

$$\mu(.) = \Delta(t)\mu(q)$$

$\mu(q)$ being as previously defined and $\Delta(t)$ following the periodic graph of period 7 days depicted in figure 4. The first 5.5 days, the algae population is in good conditions for growth; at day 5.5, the feeding medium is changed; the differences between this medium and the previous one lead to a sudden fall (from 100% to 10%) of the algae growth rate amplitude that lasts for half a day; this features algae stress; during the last day of the period, the algae population growth goes back to normal as the algae adapt themselves to the new medium. $\Delta(t)$ is defined modulo 7 days.

![Fig. 4 $\Delta(t)$ model for algae stress simulation for the 7 days period.](image)

For the open loop process simulation, we choose the dilution $D = D^*$, the required value so that biomass concentration $x$ would reach $x^* = 10.10^6$ c.L$^{-1}$ if the algae were not stressed, while for the closed loop process the dilution $D(.)$ follows law (3). Results are presented in figure 5.
It is worth noting that the open loop strategy seems dangerous for the culture. Note that in less than three weeks (while experiments usually last for 2 or 3 months), the algae population is almost completely removed from the chemostat, which is from this time of no more use. This leads to the restart of the experiment. On the contrary, the controlled chemostat drives the algae concentration to its desired value $x^*$. Despite the algae stress, biomass concentration dynamics still follows the predicted behavior. Indeed, this interesting property (biomass concentration $x$ can only go closer to $x^*$ as time goes forward) holds due to equation (5) and remains true as long as biomass population growth stays positive, even if it is time varying (cf. [10]).

**Fig. 5** Simulation of closed loop and open loop processes facing periodic algae stress; controlled process (—); open loop process with $D = D^*$ (—).

### 5 Conclusions

In this contribution, we have proposed a nonlinear output feedback controller able to globally stabilize variable yield growth models in the chemostat. The hypotheses assumed on the model are of qualitative and of structural type, therefore our approach is suitable for a wide class of variable yield models for micro-organisms growth in continuous bioreactors. Some simulations for *Dunaliella tertiolecta* growth with realistic parameters together with realistic experimental scenarios have been performed and have shown the relevance of our approach. Indeed in each of the considered case (noisy output, time-varying $s_i$ or periodic algae stress) the controller prevents the culture from washout and drives biomass concentration to a chosen steady state value.

### Acknowledgements

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### References


A Nomenclature

Parameters values and units are according to [1] (for all the simulations):

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<th>Symbol</th>
<th>Name</th>
<th>Unit</th>
<th>Value</th>
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</thead>
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<td>c</td>
<td>number of cells</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>µg</td>
<td>10⁻⁶ grams of nitrogen</td>
<td>–</td>
<td>10⁻⁶</td>
</tr>
<tr>
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<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
</tr>
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<td>–</td>
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<td>substrate concentration</td>
<td>µg.L⁻¹</td>
<td>–</td>
</tr>
<tr>
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<td>intracellular quota</td>
<td>µg.c⁻¹</td>
<td>–</td>
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<td>μₘₗ</td>
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<td>feedback gain</td>
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Table 1 Nomenclature

B Barbalat’s Lemma

Lemma 2 (Barbalat, [6])

Let \( \phi : \mathbb{R} \to \mathbb{R} \) be a uniformly continuous function on \([0, \infty)\).

Suppose that \( \lim_{t \to +\infty} \int_0^t \phi(t)dt \) exists and is finite. Then:

\[ \lim_{t \to +\infty} \phi(t) = 0 \]

C Corollary of the Perron Frobenius Theorem

Definition 1 (Metzler matrix, [8])

A is a Metzler matrix iff all its off-diagonal elements are non-negative.

Corollary 1 (Perron Frobenius, [17])

Let \( A \) be an irreducible Metzler matrix. Then, \( \lambda_M \), the eigenvalue of \( A \) of largest real part is real, and the elements of its associated eigenvector \( v_M \) are positive. Moreover, any eigenvector of \( A \) with non-negative elements belongs to \( \text{span}\{v_M\} \).

Remark 4

Actually Smith proves more in his corollary (see [17]), but the remaining results are of no use for our purpose.

D Asymptotically Autonomous Systems

Definition 2 ([13,19])

Consider the systems:

\[
\begin{align*}
\dot{x} &= f(t, x) \\
\dot{y} &= g(y)
\end{align*}
\]

with \( f(x, t) \) and \( g(x) \) continuous in \( x \) and \( t \) and locally Lipschitz in \( x \) on an open set \( \theta \subset \mathbb{R}^n \). System (13) is asymptotically autonomous with limit system (14) if for all compact \( K \subset \theta \):

\[
\lim_{t \to +\infty} f(t, x) = g(x), \quad \forall x \in K
\]

Theorem 1 ([13,19])

Consider the asymptotically autonomous system (13) with limit system (14). Let \( e \) be a locally asymptotically stable equilibrium of (14) and \( \omega \) the \( \omega \)-limit set of a bounded solution \( x(t, x_0) \) of (13). If \( \omega \) contains a point \( y_0 \) such that the forward trajectory \( y(t, y_0) \) of (14) converges to \( e \), then:

\[
\lim_{t \to +\infty} x(t) = e
\]

Remark 5

Observe that in our case, each forward trajectory of the limit system (11) initiated in \( E \) converges towards \( s^* \), and each trajectory of the asymptotically autonomous system (12) converges to \( E \). Then each trajectory of the asymptotically autonomous system (12) converges to \( s^* \).