A Physiologically Structured Equation to Consider Quota Heterogeneity in the Droop Model

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Abstract: The Droop model allows to represent microalgae growth limited by a nutrient, using a cell quota (also referred to as variable-yield) approach. Single-cell measurements have revealed quota heterogeneity in phytoplankton collected from field studies. Such heterogeneity can be due, among other factors, to spatial structure (e.g. in biogeochemical cycles in the ocean, or for photobioreactors connected in series). Nonetheless, quota heterogeneity is generally omitted in modelling studies, using an average quota approach, or included in size-structured or individual-based models. Here, we propose a distributed Droop equation to tackle this problem, considering subpopulation growth -in line with Droop macroscopic view- rather than cell division dynamics. We provide analytical solutions for two case studies. First, we consider a constant substrate concentration without biomass input, which leads to a monomorphic population. The second case, considering a biomass input without substrate, leads to quota heterogeneity. Simulations are then carried out for the two case studies (showing good agreements with the analytical solutions) and for a more general case. Finally, we show that the error induced by the average quota approach increases considerably with microalgae plasticity (i.e. the maximal over minimal quota ratio), which points out the benefit of considering quota heterogeneity in these cases.

Keywords: Population Balance Model; Variable-yield model; Cell Quota; Phytoplankton; Microalgae.

1. INTRODUCTION

From the comprehension of ecosystems to the design and optimization of biotechnological processes, modelling microorganism growth is a key issue. Here, we will focus on photosynthetic microorganims (also called microalgae or phytoplankton), which present a great potential for industrial production (feed, cosmetics...) and play a key role in the ocean. Due to their important plasticity, constant-yield approach is not adequate to model microalgae growth limited by a nutrient(Flynn, 2010). By decoupling substrate uptake and biomass growth, the Droop model (Droop, 1973) allows to represent the variable stoechiometry of microalgae. The main assumption is that the specific growth rate depends on the intracellular nutrient over biomass ratio - the so-called quota - of the limiting nutrient. This model has been widely used and adapted to describe nutrient-limited algal growth (see e.g. Mairet et al. (2011); Bougaran et al. (2010)).

On top of that, phenotypic heterogeneity appears to play a key role in several phenomena, such as bacterial persistance (Ackermann, 2015; Heins and Weuster-Botz, 2018). Cellular heterogeneity has therefore been widely studied, both experimentaly and theoretically, from early works (von Foerster, 1959; Fredrickson et al., 1967) to more recent studies, in particular in bioprocesses (Morchain et al., 2013; Ramkrishna and Singh, 2014; Waldherr, 2018). For

microalgae, heterogeneity can appear in terms of elemental composition (quota), as it has been observed using X-ray microanalysis (Sigee and Holland, 1997; Segura-Noguera et al., 2016). Despite some recent promising works, the causes of algal quota heterogeneity and its impact on cellular growth has been relatively unexplored. Quota heterogeneity can results naturally from spatial heterogeneity. The question then is how to apply Droop model in such case? Can we assume average behavior? For example, when two populations with distinct quotas are mixed, can we take the average quota of the whole population to compute growth? Theoretically, the answer is no, due to the non-linearity in the response, but is this approximation reasonable in some situations?

These questions have arisen concomitantly in different fields. In biogeochemical models (such as used for climate change predictions), phytoplankton is now sometimes represented with variable stoichiometry (e.g. in the models REcoM2 (Hauck et al., 2013) or PISCES-v2 (Aumont et al., 2015)), improving model capacity to represent observations in comparison with the classical constant yield approach (Ayata et al., 2013). This is done considering the transport of each particulate elements and using average quotas. Such tacit assumption -neglecting cellular heterogeneity- induces a bias, which should be estimated. The same problematic also arises in mathematical ecology (with the objective of understanding the quota effect on
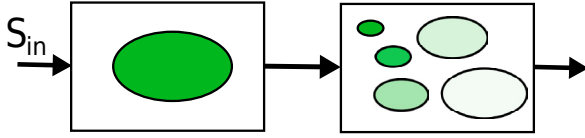
Fig. 1. Scheme of two photobioreactors in series. Ellipse size depicts subpopulation density with a quota represented by the shades of green. Almost all the limiting nutrient is uptaken in the first reactor. Microalgae enters continuously in the second reactor with a high quota. Their quotas then decrease due to growth, leading to quota heterogeneity. Can we estimate the growth rate of the population by its average quota?

species growth and competition in a water column)(Hsu et al., 2010; Mei et al., 2016) or in bioprocess engineering (when coupling photobioreactor in series (Diehl et al., 2018), see Fig. 1). These studies are also based on the average quota approach.

Recently, some studies have tried to go behind the averaging approach. Thus, models with size structured (Perthame, 2006; Metz and Diekmann, 2014) have been proposed to analyze quota heterogeneity (Grover et al., 2012), assuming that the nutrient content is proportional to cell size. These models, in our opinion, misinterpret Droop approach. Actually, Droop model is based on biomass (in g DW [1] or g C) or biovolume quota, although generally referred to as cell quota. Cell basis should be avoided, unless cell biovolume remains constant (Droop, 1979). Thus, models including cell division, in addition to adding unnecessary complexity, does not seem adequate to describe Droop quota heterogeneity. Quota heterogeneity has also been tackled using individual-based models (also called Lagrangian approach in the biogeochemical community). These studies have shown that in some cases, quota heterogeneity can lead to significantly different responses in comparison with an estimation based on the average approach (Bucci et al., 2012; Baudry et al., 2018). Nonetheless, these results are only based on simulations (making generalizations difficult), and this approach can become too costly for large-scale system.

Here, we provide a mathematically tractable framework which allows to better tackle quota heterogeneity. After recalling the Droop model, we introduce a structured equation to consider quota heterogeneity. Analytical solutions are derived for two case studies and then compared with numerical simulations. Finally, we contrast our model with the average approach.

2. THE DROOP MODEL

Contrary to the classical Monod model, substrate uptake and biomass growth are decoupled in the Droop model. In a chemostat, the dynamics of the biomass (X), the quota (Q), and the limiting substrate (S) are given by

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[1] DW: dry weight

$$\begin{cases} \dfrac{dX}{dt} = (\mu(Q) - D)X \\[2mm] \dfrac{dQ}{dt} = \rho(S) - \mu(Q)Q \\[2mm] \dfrac{dS}{dt} = D(S_{in} - S) - \rho(S)X \end{cases} \tag{1}$$

where D and S_{in} are respectively the dilution rate and the input substrate concentration. The specific growth rate $\mu(Q)$ and the substrate uptake rate $\rho(S)$ are generally taken as:

$$\mu(Q) = \bar{\mu}\left(1 - \frac{Q_0}{Q}\right) \tag{2}$$

and

$$\rho(S) = \rho_m \frac{S}{K_S + S} \tag{3}$$

where $\bar{\mu}$, Q_0, $\bar{\rho}_m$, and K_S are respectively the hypothetical maximum growth rate (for an infinite quota), the minimum quota, the maximum uptake rate, and the half-saturation constant for substrate uptake.

The quota dynamics in Eq.(1) comes from mass balance: the quota increases with nutrient uptake, and decreases with biomass growth (intracellular dilution). The Droop model has been analyzed mathematically by, among others, Lange and Oyarzun (1992) and Bernard and Gouzé (1995). If $D < \bar{\mu}$ and $\rho(S_{in}) > D\mu^{-1}(D)$, then System (1) admits a unique positive equilibrium, which is globally asymptotically stable . Additionally, it can be shown that the quota stays between the minimum quota Q_0 and the maximum quota Q_m defined by:

$$Q_m = \frac{\rho_m}{\bar{\mu}} + Q_0.$$

3. MODEL DEVELOPMENT

Our objective is to include quota heterogeneity in the Droop model. The idea is to describe subpopulation of different quotas, rather than including cell division dynamics as it has been done in Grover et al. (2012). To do so, we consider the biomass density $x(t, q)$ which have the quota q at time t, with $q \in \Omega := (Q_0, +\infty)$. From mass balance, we obtain

$$\frac{\partial x(t,q)}{\partial t} + \frac{\partial}{\partial q}\left(\rho(s) - q\mu(q)\right)x(t,q) = (\mu(q) - D)x(t,q) + Dx_{in}(q) \tag{4}$$

with $x_{in}(q)$ a biomass input, and initial condition $x(0, q) = x_0(q)$.

The main specificity of this equation, in comparison with classical population balance approach, is that biomass growth obviously increases biomass, but also decreases its quota (by intracellular dilution).

The previous equation rewrites:

$$\frac{\partial x}{\partial t} + (\rho(s) - q\mu(q))\frac{\partial x}{\partial q} = (2\mu(q) + q\mu'(q) - D)x(t,q) + Dx_{in}(q) \tag{5}$$

where $\mu'(q) = \frac{d\mu(q)}{dq}$.

In a chemostat, this equation is coupled with the dynamics of the substrate given by:

$$\frac{ds(t)}{dt} = D(s_{in} - s(t)) - \rho(s(t)) \int_{\Omega} x(t,q)dq \quad (6)$$

We conjecture that, in absence of biomass in the input (i.e. $x_{in} = 0$), the trajectories of System (5)-(6) converge towards the equilibrium given by the classical Droop model (1), i.e. if $D < \bar{\mu}$ and $\rho(s_{in}) > D\mu^{-1}(D)$, then $x(t,q)$ concentrates in a Dirac mass

$$x(t,q) \xrightarrow[t \to \infty]{} \bar{x}\delta(q - \bar{q}),$$

with $\bar{q}$ the solution of $\mu(q) = D$. On the other hand, quota heterogeneity appears whenever there is a biomass input (due to spatial structure). Thus, for two photobioreactors connected in series (see Fig. 1), the population could be homogeneous in terms of quota in the first reactor, but heterogeneous in the second one.

4. ANALYTICAL SOLUTIONS

In the following, we will focus only on Eq. (5) (without substrate dynamics), taking ρ constant and using the kinetic expression (2) for the specific growth rate $\mu(q)$, so we finally get:

$$\frac{\partial x}{\partial t} + (\rho - \bar{\mu}(q - Q_0)) \frac{\partial x}{\partial q} = \left[\bar{\mu}\left(2 - \frac{Q_0}{q} \right) - D \right] x(t,q)$$
$$+ Dx_{in}(q)$$
$$(7)$$

Analytical solutions are obtained using the method of characteristics (Evans et al., 2012) for two case studies (which will be used thereafter to validate our simulations). Details are given in Appendix.

For the first case study (Appendix A), we consider Eq. (7) without biomass input (i.e. $x_{in} = 0$). The solution reads:

$$x_A(t,q) = \left[\frac{Q_\rho + (q - Q_\rho)e^{\bar{\mu}t}}{q} \right]^{\frac{Q_0}{Q_\rho}}$$
$$\cdot e^{[\bar{\mu}(2 - Q_0/Q_\rho) - D]t} x_0 \left(Q_\rho + (q - Q_\rho)e^{\bar{\mu}t} \right)$$
$$(8)$$

with $Q_\rho = \frac{\rho}{\bar{\mu}} + Q_0$.

For the second case study (Appendix B), we consider a biomass input $x_{in}(q)$, and we take for sake of simplicity $\rho = 0$ and $D = \bar{\mu}$. The solution of Eq. (7) in this case becomes:

$$x_B(t,q) = \frac{1}{q} \left\{ \left[Q_0 + (q - Q_0)e^{\bar{\mu}t} \right] x_0 \left(Q_0 + (q - Q_0)e^{\bar{\mu}t} \right) \right.$$
$$\left. + g\left(Q_0 + (q - Q_0)e^{\bar{\mu}t} \right) - g(q) \right\}$$
$$(9)$$

with $g(q) = D \int \frac{x_{in}(q)}{\mu(q)} dq$.

5. NUMERICAL SIMULATIONS

Simulations are carried out with the MatMOL toolbox (Logist et al., 2009) in Matlab. It is based on the method of lines, using finite elements. We first test the method on the two case studies, comparing numerical results with the analytical solutions described previously. Parameter

Table 1. Parameter values for simulation, taken from Ducobu et al. (1998).

Parameters	Values	Units
Hypothetical max. growth rate $\bar{\mu}$	0.61	d^{-1}
Minimum quota Q_0	1.6	mgP/gDW
Maximum uptake rate ρ_m	67	mgP/(gDW. d)
Half-saturation constant K_S	0.016	mgP/L

values, taken from Ducobu et al. (1998), correspond to the phosphorus-limited growth of *Prochlorothrix hollandica* (see Table 1). For the second case study, we take as biomass input:

$$x_{in}(q) = \begin{cases} \dfrac{q - Q_0}{q} & \text{if } q_1 \leq q \leq q_2, \\ 0 & \text{otherwise,} \end{cases}$$

with $Q_0 < q_1 < q_2$. This allows an easy integration to compute $g(q)$, and we get:

$$g(q) = \begin{cases} 0 & \text{if } q < q_1, \\ q - q_1 & \text{if } q_1 \leq q \leq q_2, \\ q_2 - q_1 & \text{if } q > q_2. \end{cases}$$

In practice, we take q_1 and q_2 close enough to approximate a monomorphic biomass input.

In both cases, the analytical and numerical solutions are very close (see Fig. 2 and 3) [2] . In the first case study (Fig. 2), the population concentrates on the quota $\tilde{q}$, solution of $\rho = q\mu(q)$. With biomass input (Fig. 3), a distribution is observed, starting from the input biomass quota and decreasing with time to the minimum quota with biomass growth. This is what should happen for example in the second reactor in Fig. 1.

6. WHEN DOES QUOTA HETEROGENEITY MATTER?

We have proposed a framework to deal with quota heterogeneity. As discussed in the introduction, another easier option is to use the original Droop model with an average quota. The question is: when is this approximation acceptable? On Fig. 4, we compare in simulation the two approaches for the same conditions, considering a chemostat (Eq. (5)-(6)) with a low-quota initial population and a biomass input with a higher quota, leading to a bi-modal distribution. The growth rate computed from the average quota clearly overestimates the average growth rate of the population, due to model nonlinearity.

To better understand when the approaches differ, we can consider as an extreme case study the mixing of two subpopulations of biomass $1 - \theta$ and θ (with $0 < \theta < 1$), with respectively a quota Q_0 and Q_m. The apparent growth rates of the population for the heterogeneous approach μ_h (that we will consider as the reference) and the average approach μ_a are given by:

$$\mu_h = \theta\mu(Q_m) \quad \text{and} \quad \mu_a = \mu((1 - \theta)Q_0 + \theta Q_m), \quad (10)$$

see also Figure 5. We can express as a function of θ and Q_m/Q_0 the relative error:

$$E_r = \frac{\mu_a - \mu_h}{\mu_h} = (1 - \theta)\frac{\frac{Q_m}{Q_0} - 1}{1 + \theta\left(\frac{Q_m}{Q_0} - 1 \right)} \quad (11)$$

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[2] Some numerical issues appear, in particular when population concentrates, for long-time simulations.
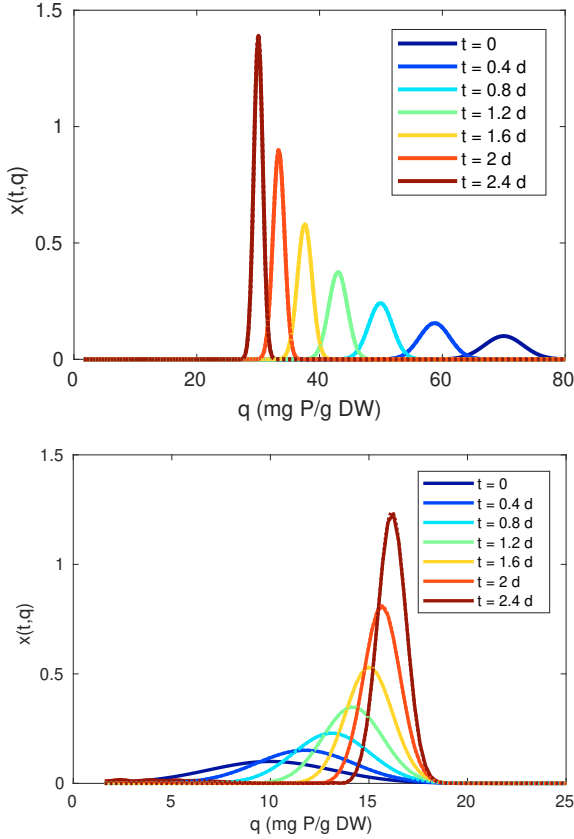
Fig. 2. Time evolution of biomass distribution $x(t,q)$ (in g C. L^{-1}. mg P^{-1}) described by Eq. (7) for the first case study (ρ constant, without biomass input), for two different initial conditions (top and down), with $\rho = 10$ mg P/(g DW. d) and $D = 0.1$ d^{-1}. The analytical (Eq. (8), dotted lines) and numerical (plain lines) solutions are almost indistinguishable. The population concentrates on the quota $\tilde{q} = 18$ mg P/g DW, solution of $\rho = q\mu(q)$.

and the absolute error (normalized by the maximum growth rate):

$$E_a = \frac{\mu_a - \mu_h}{\mu(Q_m)} = \theta(1 - \theta)\frac{\frac{Q_m}{Q_0} - 1}{1 + \theta\left(\frac{Q_m}{Q_0} - 1\right)} \tag{12}$$

The average approach always overestimate the growth rate, due to the convexity of the function $\mu(q)$. Additionally, it clearly appears that the errors increase with Q_m/Q_0 (which corresponds to microalgae plasticity), as also illustrated on Fig. 5. The relative error decreases with θ, and

$$\lim_{\theta \to 0^+} E_r = \frac{Q_m}{Q_0} - 1$$

The Q_m/Q_0 ratio is typically 2-3 for nitrogen (Edwards et al., 2015), and much bigger for phosphate (e.g up to 69 for *Prochlorothrix hollandica* (Ducobu et al., 1998)). On Fig. 6, we plot the errors (11)-(12) as a function of θ for two plasticity values (3 and 20, illustrating nitrogen and phosphate limitation respectively). The relative error is very high, in particular for small θ (corresponding to small growth rate), and high Q_m/Q_0. The maximal absolute error corresponds to 20% and 60% of the maximal
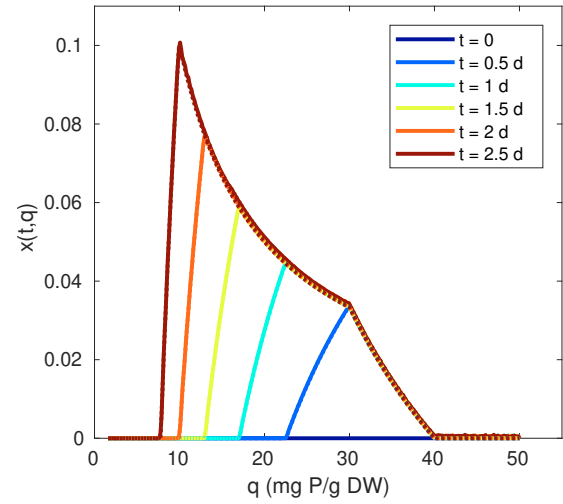

Fig. 3. Time evolution of biomass distribution $x(t,q)$ (in g C. L^{-1}. mg P^{-1}) described by Eq. (7) for the second case study ($\rho = 0$, with biomass input). The analytical (Eq. (9), dotted lines) and numerical (plain lines) solutions are almost indistinguishable. Biomass enters in the reactor with a high quota, and biomass growth lowers the quota.
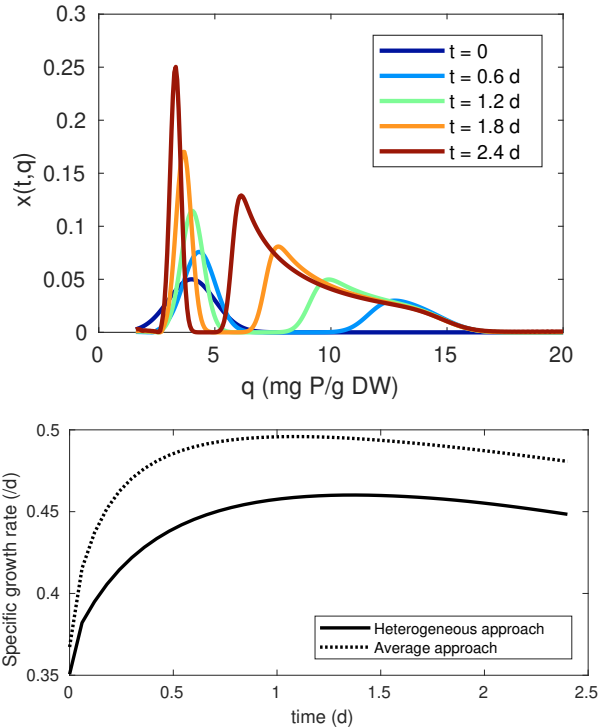

Fig. 4. Simulation of a chemostat described by Eq. (5)-(6) with a low-quota initial population and a biomass input with a higher quota, leading to a bi-modal distribution. $D = 0.3$ d^{-1}, $s_{in} = 1$ mg P/L. Top: time evolution of biomass distribution $x(t,q)$ (in g C. L^{-1}. mg P^{-1}). Down: specific growth rate as a function of time. The average approach overestimates growth rate in comparison with the heterogeneous approach.
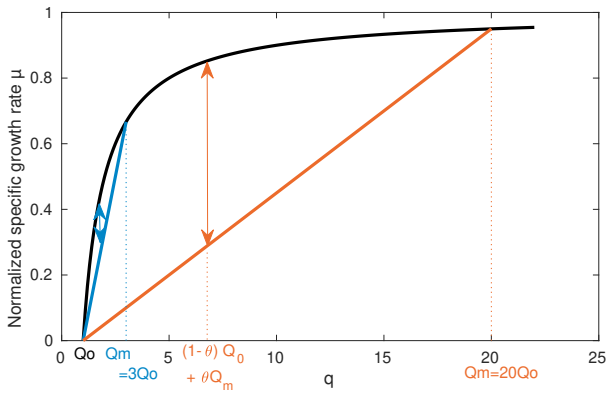
Fig. 5. Specific growth rate μ (black line) as a function of the quota q. The double arrows correspond to the error between the mean growth rate versus the growth rate of the average quota, when mixing two subpopulations of quotas Q_0 and Q_m (see Eq. (10)-(12)), for a low (in blue) and a high (in red) Q_m/Q_0 ratio. The error increases with Q_m/Q_0.
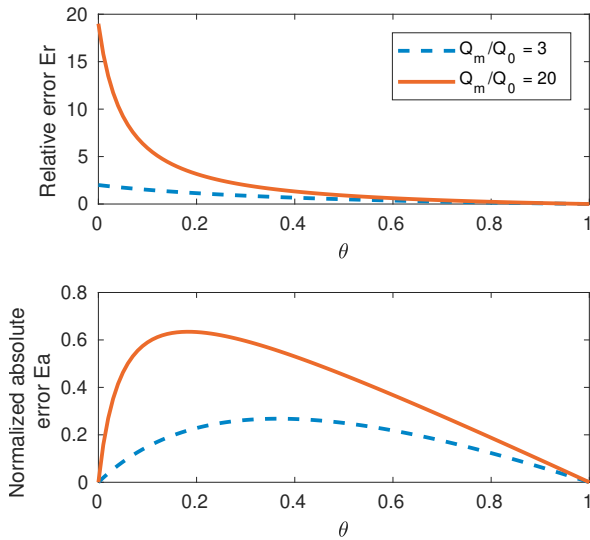

Fig. 6. Relative and (normalized) absolute errors on the specific growth rate using the average approach, as a function of θ (see Eq. (10)-(12)) for a low (blue dashed lines) and a high (red lines) Q_m/Q_0 ratio.

growth rate for respectively the low and high plasticity. Recalling that this case study (by mixing two populations with minimum and maximum quotas) corresponds to the worst case, it appears that the average approach seems reasonable for nitrate limitation (i.e. low Q_m/Q_0), but much more questionable for phosphate (i.e. high Q_m/Q_0).

7. CONCLUSION

Physiologically structured model generally considers the cell cycle, which adds a layer of complexity. This is particularly tricky for photosynthetic microorganism culture where synchronization phenomena may occur. Here, we have proposed an approach to represent quota heterogeneity without age or size structure, focusing on subpopulation growth. We have shown that considering heterogeneity is of the utmost importance for microalgae with a high plasticity (i.e. a high Q_m/Q_0 ratio). Analytical solutions

have been determined for two simple case studies, and a deeper mathematical analysis of the model will deserve further investigations.

This framework can be used to describe phytoplankton nutrient-limited growth in ecology and oceanography. Spatial dimensions can be added in the model to tackle such problems. The proposed framework can also be used for bioprocess modelling, design and optimization e.g. when a cascade of reactors is used (leading to population heterogeneity). Such configuration allows the continuous production of biomass in unbalanced growth condition, which can be particularly interesting to trigger carbon storage accumulation (e.g. neutral lipid). Given the strong link between nitrogen quota and carbon storage (Mairet et al., 2011), the proposed model can be of great help to optimize system design.

Finally, the model can be adapted to other situations whenever the growth rate is determined by the intracellular content of a key component such as chlorophyll (to describe a heterogeneous photoacclimation dynamics of microalgae), or ribosomes (for bacterial growth). In such cases, ρ becomes the net production of the key component (i.e. synthesis minus degradation), which could depend of the environmental conditions for example.

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Appendix A. ANALYTICAL SOLUTION FOR THE FIRST CASE STUDY

We use the method of characteristics to solve Eq. (7). The characteristic equations are :

$$dt = \frac{dq}{\rho - \bar{\mu}(q - Q_0)} = \frac{dx}{\left[\bar{\mu}\left(2 - \frac{Q_0}{Q}\right) - D\right]x}.$$

We need to find two functions $\phi(t, q, x)$ and $\psi(t, q, x)$ such that $d\phi = d\psi = 0$. Then, the general solution of Eq. (7) is given by $F(\phi, \psi) = 0$, with F an arbitrary function, or similarly $\phi = f(\psi)$ (with f also an arbitrary function).

Using

$$\frac{\left[\bar{\mu}\left(2 - \frac{Q_0}{Q}\right) - D\right]dq}{\rho - \bar{\mu}(q - Q_0)} = \frac{dx}{x}$$

we get

$$\phi = xq^{\frac{\bar{\mu}Q_0}{\rho + \bar{\mu}Q_0}}\left[\rho - \bar{\mu}(q - Q_0)\right]^{2 - \frac{D}{\bar{\mu}} - \frac{\bar{\mu}Q_0}{\rho + \bar{\mu}Q_0}}.$$

Similarly, using $\frac{dq}{\rho - \bar{\mu}(q - Q_0)} = dt$, we get

$$\psi = \left[\rho - \bar{\mu}(q - Q_0)\right]e^{\bar{\mu}t}.$$

The general solution writes:

$$xq^{\frac{\bar{\mu}Q_0}{\rho + \bar{\mu}Q_0}}\left[\rho - \bar{\mu}(q - Q_0)\right]^{2 - \frac{D}{\bar{\mu}} - \frac{\bar{\mu}Q_0}{\rho + \bar{\mu}Q_0}}$$

$$= f(\left[\rho - \bar{\mu}(q - Q_0)\right]e^{\bar{\mu}t}).$$

Using the initial condition $x(0, q) = x_0(q)$, we get the final solution given by Eq. (8).

Appendix B. ANALYTICAL SOLUTION FOR THE SECOND CASE STUDY

Eq. (7) for the second case study is solved using the same method as in Appendix A. The characteristic equations are :

$$dt = \frac{dq}{-q\mu(q)} = \frac{dx}{\mu(q)x + Dx_{in}(q)}.$$

Using

$$\left[x + D\frac{x_{in}(q)}{\mu(q)}\right]dq + qdx = 0$$

we get $\phi = qx + g(q)$, with $g(q) = D\int\frac{x_{in}(q)}{\mu(q)}dq$.

Similarly, using $\frac{dq}{-\bar{\mu}(q - Q_0)} = dt$, we get $\psi = (q - Q_0)e^{\bar{\mu}t}$.

The general solution writes:

$$qx + g(q) = f\left((q - Q_0)e^{\bar{\mu}t}\right).$$

Using the initial condition $x(0, q) = x_0(q)$, we get the final solution given by Eq. (9).