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Modeling microalgae cell mass distributions using the Fokker–Planck equation

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Abstract: The modeling of the cell mass distribution for microalgae growth processes is addressed using the Fokker–Planck equation for a stochastic logistic growth model of a single cell. Relations between the proposed model and the classical Droop model used for mass–balance based modeling of the algae growth are established. The proposed model is evaluated using experimentally obtained cell mass distribution data for the microalgae *Chlamydomonas reinhardtti* showing a good correspondence between measurements and model predictions. The obtained model is considerably simpler in comparison to cell mass population balance models used so far to describe the temporal behavior of the cell mass distribution.

Keywords: System identification, cell–mass distribution modeling, microalgae growth, Fokker–Planck PDE.

1. INTRODUCTION

The modeling of particle size distributions is a key in understanding, monitoring and controlling the outcome of many particulate processes in chemical, bioprocess and pharmaceutical engineering [Ramkrishna 2000, Mesbah et al. 2012, Geyyer et al. 2015, Palis and Kienle 2014, Otto et al. 2022]. Many different approaches have been proposed for this purpose depending on the particular application scenario, ranging from crystallization, spray drying to fermentation and microalgae growth. The present paper focusses on the latter, in particular within batch process setups. Microalgae growth can be considerably well described on a (mascroscopic) mass–balance level using, e.g., the Droop model [Droop 1968, Bernard et al. 1999, Mairet and Bernard 2016]. The cell mass distribution (and thus the cell size distribution) can be modeled, e.g., using cell population balance equations, accounting explicitly for cell growth and division [Villadsen 1999]. The cell population balance approach has recently been reported for microalgae in [Atzori et al. 2021] showing a rather good correspondence with measurement data for extracelular substrate (i.e., nitrate) concentration, biomass concentration and cell size distribution. Inspite its usefullness for describing the associated growth phenomena and the ability of parameter identification outlined in [Atzori et al. 2021] (i) the identification is associated to a high experimental and analytic effort, (ii) the model analysis is rather complex, and (iii) it can be computation time–consuming to employ the resulting model for online monitoring and control.

A different approach that has been employed for modeling particle size distribution, in particular in crystallization processes is based on the Fokker–Planck equation [Cogoni et al. 2011, Grosso et al. 2011, Cogoni et al. 2012, 2014] (see also the general purpose discussion of the Fokker–Planck framework, e.g., in [Risken and Frank 1996, Gardiner 2009, Jazwinski 1970]). In these studies quite simple basic crystal growth models, motivated, e.g., by the logistic equation where employed and the parameters identified using experimental data. The results of numerical simulations show a rather convincing correspondence with the measurements and the approach has already been employed in control design studies with experimental validation. A particularly clear advantage of the Fokker–Planck based approach is that the associated equations enable to (i) draw analytic solutions for the stationary state probability density function (PDF), (ii) analyze transients on multiple time scales (deterministic, diffusion and escape time scales, with the latter only applying for multimodal distributions), and (iii) bear the potential for simple, real–time capable monitoring and control implementations.

In spite its usefullness in crystallization processes the Fokker–Planck approach has not been employed for describing cell size distributions in bioreactors so far. The reported studies on the use of this framework for bioreactors have focussed mainly on the mass–balance models [Stephanopoulos et al. 1979] and [Baratti et al. 2021, Schaum et al. 2021] for which the deterministic multiplicity and bifurcation behavior were analytically related to the stochastic multimodality, metastability, fragility and the transient behavior on the associated deterministic, diffusion and escape time scales. The studies in [Baratti et al. 2021, Schaum et al. 2021] extended previous ones on the dynamics and robustness of one– and two–state chemical reactors subject to additive and multiplicative noise disturbances [Tronci et al. 2011, Baratti et al. 2016, 2018, Alvarez et al. 2018].

Having the above mentioned studies as points of departure, the present one addresses the modeling of the time evolution of the cell mass distribution of microalgae in a batch reactor following the Fokker–Planck based approach

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proposed in [Cogoni et al. 2011, Grosso et al. 2011, Cogoni et al. 2012, 2014]. For this purpose a stochastic logistic model approximation for a single cell is derived in Section 2 based on the Droop model [Droop 1968, Bernard et al. 1999], and successively employed to develop a model for the time–evolution of the cell–mass distribution using the Fokker–Planck equation in Section 3. A specific approach for parameter identification based on sampled (in time and space) measurements of the cell–mass distribution and the total biomass in the reactor (sampled in time) is presented in Section 4. The employed numerical solution approach is explained in Section 5 together with the presentation of the comparison between measurements and simulations. The discussions and outlook are presented in Section 6.

2. MICROALGAE GROWTH MODEL

2.1 The Droop model revisited

The Droop model [Droop 1968, Bernard et al. 1999, Mairet and Bernard 2016] for microalgae growth in a batch reactor is given by

$$\dot{b} = \mu(q)b, \qquad t > 0, \quad b(0) = b_0 \tag{1a}$$
$$\dot{q} = \rho(s) - \mu(q)q, \qquad t > 0, \quad q(0) = q_0 \tag{1b}$$
$$\dot{s} = \rho(s)b, \qquad t > 0, \quad s(0) = s_0 \tag{1c}$$

where b, q, s are the dimensionless state variables representing the biomass concentration $b = B/B_r$ with reference value B_r, internal nutrient quota q, i.e. the intracellular nutrient concentration per biomass unit and extracellular nutrient concentration $s = S/S_r$ with reference concentration S_r. The specific biomass growth rate is denoted by $\mu(q)$ which is a smooth function depending on q (and on the light intensity). The substrate uptake rate is denoted by $\rho(s)$, which is a smooth function of s.

2.2 A logistic model approximation

Considering that the internal nitrogen quota remains constant over time, i.e.

$$q(t) = \text{const.} = q_0 > 0 \quad \Leftrightarrow \quad \mu(q)q = \rho(s) \tag{2}$$

one can simplify the Droop model (1) to the simple two–state bioreactor model

$$\dot{b} = q^{-1}\rho(s)b \tag{3a}$$
$$\dot{s} = -\rho(s)b \tag{3b}$$

with the associated reaction invariant [Aris 1969, Feinberg 1977, Bastin and Dochain 1990]

$$m = qb + s, \quad m(t) = \text{const.} = m_0 = b_0 + s_0. \tag{4}$$

Accordingly, for all $t \geq 0$ one has that

$$s(t) = m_0 - qb(t) \tag{5}$$

implying that

$$\dot{b} = q^{-1}\rho(m_0 - qb)b.$$

Considering the monotonically increasing Monod uptake (and growth) rate function

$$\rho(s) = \frac{k_0 s}{K_s + s} \tag{6}$$

with the maximum growth rate k_0 and half–saturation constant K_s yields the biomass dynamics

$$\dot{b} = \frac{k_0(m_0 - qb)}{q(K_s + s)}b$$

that can be recast into the form of the logistic growth model [Bacaër 2011]

$$\dot{b} = r(s)b\left(1 - \frac{b}{K}\right) \tag{7a}$$

with

$$r(s) = \frac{k_0 m_0}{q(K_s + s)} > 0, \quad K = \frac{m_0}{q} \tag{7b}$$

and the two equilibrium solutions

$$b = 0 \text{ (repulsor) and } b = K \text{ (attractor).} \tag{7c}$$

It should be noted that for a monotonic Monod growth rate (6) with half–saturation constant $K_s \sim 1$ (considering $s \in [0, 1]$) the value of $r(s)$ will be almost constant (cp. Figure 1). Accordingly, for $K_s \sim 1$ it is reasonable

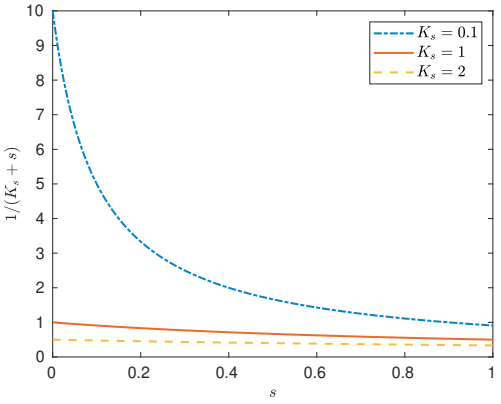

Fig. 1. Behavior of the growth rate parameter $r(s) = \frac{1}{K_s+s}$ (i.e., considering $k_0 m_0 = 1$) with $K_s = 0.1, 1, 2$.

to approximate the logistic model (7a) with a constant growth factor $r > 0$.

Remark 1. It should be noted that one could also write the growth factor $r(s)$ in the model (7a) in the form $r(s) = r(m_0 - qb)$ as substrate and biomass are strictly related through the total mass according to (4). Here the dependency on the substrate is used to motivate the consideration of a constant growth rate coefficient to maximally simplify the model.

2.3 Logistic cell mass dynamics

Based on the preceding considerations it is reasonable to assume that each cell satisfies a logistic growth equation and is subject to noise. Denoting in the following with $m \geq 0$ the cell mass of an individual cell, this leads to

$$\dot{m} = rm\left(1 - \frac{m}{K}\right) + w_m, \quad m(0) = m_0 \tag{8}$$

with the white noise variable w_m with variance assumed in the following as depending on the cell mass

$$w_m \sim \mathcal{N}(0, q_n m^2), \quad q_n > 0. \tag{9}$$

The model (8) can be equivalently written as

$$\dot{m} = f(m) + g(m)w \tag{10}$$

with

$$f(m) = rm\left(1 - \frac{m}{K}\right), \quad g(m) = \sqrt{q_n}m, \quad w \sim (0, 1). \tag{11}$$

Remark 2. Note that the analysis of the behavior of the stochastic differential equation (10) can be addressed with different methods, including Monte Carlo simulations [Chen and Zhang 2013, Zhang et al. 2014, Meng et al. 2016, Wang et al. 2017, Sun et al. 2017] or the Fokker–Planck equation approach [Risken and Frank 1996, Gardiner 2009, Jazwinski 1970]. Here the latter approach is followed going in line with studies on crystallization processes [Cogoni et al. 2011, Grosso et al. 2011, Cogoni et al. 2012, 2014].

3. CELL MASS PROBABILITY DENSITY FUNCTION

Following the Fokker–Planck equation based approach employed in [Cogoni et al. 2011, Grosso et al. 2011, Cogoni et al. 2012, 2014] for the modeling and control of crystal size distributions in this section the stochastic logistic model approximation (10) for microalgae growth introduced in the preceeding section is employed to describe the time–evolution of the cell mass distribution.

The Fokker–Planck equation (in Stratonovich form) associated to (10) is given by

$$\partial_t \psi = \partial_m \left(\frac{1}{2} g^2 \partial_m \psi - [f(m) - \frac{1}{2} g \partial_m g] \psi \right) \tag{12a}$$

$$= \partial_m \left(\frac{q m^2}{2} \partial_m \psi - \left[r m \left(1 - \frac{m}{K} \right) - \frac{q_n m}{2} \right] \psi \right) \tag{12b}$$

for $t > 0, m \in (0,1)$ with $\psi : [0,\infty) \times [0,1] \to \mathbb{R}_+$ satisfying the boundary conditions

$$\frac{q_n m^2}{2} \partial_m \psi(\cdot, m) - \left[r m \left(1 - \frac{m}{K} \right) - \frac{q_n m}{2} \right] \psi(\cdot, m) = 0, \tag{12c}$$

for $t > 0, m \in \{0,1\}$. The coefficient of the convective term in (12) can be rewritten as

$$r m \left(1 - \frac{m}{K} \right) - \frac{q_n m}{2} = \bar{r} m \left(1 - \frac{m}{\bar{K}} \right) \tag{13}$$

with

$$\bar{r} = r - \frac{q_n}{2}, \quad \bar{K} = K \frac{\bar{r}}{r}. \tag{14}$$

The stationary solution of (12) satisfies

$$0 = \partial_m \left(\frac{q_n m^2}{2} \partial_m \bar{\psi} - \left[\bar{r} m \left(1 - \frac{m}{\bar{K}} \right) \right] \bar{\psi} \right)$$

what after integration from 0 to m and substitution of the left boundary conditions yields

$$0 = \frac{q_n m^2}{2} \partial_m \bar{\psi} - \left[\bar{r} m \left(1 - \frac{m}{\bar{K}} \right) \right] \bar{\psi}$$

and thus

$$\bar{\psi}(m) = C \exp \left(\int_0^m \frac{2\bar{r} \left(1 - \frac{m'}{\bar{K}} \right)}{q m'} \mathrm{d}m' \right) \tag{15}$$

with the integration constant $C > 0$ chosen so that the integral of $\bar{\psi}$ over the domain is equal to 1. The unique maximum of $\bar{\psi}$ satisfies

$$\partial_m \bar{\psi}(m) = \frac{2\bar{r}}{q_n m} \left(1 - \frac{m}{\bar{K}} \right) = 0$$

$$\Leftrightarrow \quad m^* = \bar{K} = \frac{r - \frac{q_n}{2}}{r} K, \quad \partial_m^2 \bar{\psi}(m^*) = -\frac{2\bar{r}}{q_n \bar{K}^2} < 0.$$

Note that in correspondence the mode of the pdf is not located at the deterministic equilibrium point $\bar{m} = K$ but shifted toward $m^* = \bar{K}$ with a difference that increases with the noise intensity $q_n < 2r$.

4. PARAMETER IDENTIFICATION

In this section the problem of identifying the parameters r, K, q_n in the PDE model (12) for a given microalgae growth process is addressed. For this purpose it is considered that cell size distribution measurements

$$\boldsymbol{y}_d(t_k) = [n_1(t_k) \ \cdots \ n_m(t_k)]^{\mathrm{T}} \tag{16}$$

are at hand at different discrete time instances $0 < t_1, \ldots, t_N$, where $n_i(t_k),\ i = 1, \ldots, n$ denotes the number of cells at time t_k with diameter between d_{k-1} and d_k, where $d_0 = 0$ and $d_m = d^+$, being d^+ the maximum diameter. This means that $\boldsymbol{y}_d$ basically corresponds to a histogram over the diameter of the cell size distribution. Accordingly the total number of cells is given by

$$N(t_k) = \sum_{i=1}^{n} n_i(t_k). \tag{17}$$

Having the total number of cells the mean cell diameter can be directly determined as

$$\langle d \rangle (t_k) = \frac{1}{N(t_k)} \sum_{i=1}^{n} d_i n_i(t_k). \tag{18}$$

In the following it is described how one can derive from this measurement the necessary information about the cell mass probability distribution density function ψ. In the following the cells are considered spherical to simplify the calculations [1]. First of all take into account the relation between the mass $m(d)$ of a cell with diameter d considering a constant (i.e. mass and diameter invariant) density ϱ, given by

$$m(d) = \frac{3\pi}{4} \varrho \left(\frac{d}{2} \right)^3. \tag{19}$$

Equivalently this equation can be solved to describe d in function of m as follows

$$d(m) = 2 \left(\frac{4}{3\pi\varrho} m \right)^{\frac{1}{3}}. \tag{20}$$

A crucial information that is required in the preceding equations is the cell density ϱ. To determine ϱ consider the additional measurement of the biomass at the time instances $t_k,\ k = 1, \ldots, N$, i.e.,

$$y_b(t_k) = b(t_k). \tag{21}$$

With the total biomass measurement and the cell number N from (17) one can directly obtain the mean cell mass

$$\langle m \rangle (t_k) = \frac{b(t_k)}{N(t_k)}. \tag{22}$$

With the mean cell mass $\langle m \rangle$ and the mean cell diameter $\langle d \rangle$ one obtains a value for the cell density for every measurement time t_k by

$$\varrho_k = \frac{\langle m \rangle (t_k)}{\langle v \rangle (t_k)}, \quad k = 1, \ldots, N, \quad \langle v \rangle = \frac{4\pi}{3} \left(\frac{\langle d \rangle}{2} \right)^3$$

from which one can determine the cell density as

$$\varrho = \frac{1}{N} \sum_{k=1}^{N} \varrho_k. \tag{23}$$

To finally get the relation with the cell mass probability distribution density function ψ, denote by ψ_d the cell size

[1] For microalgae this approximation is typically reasonable, at least in most of the cell stages.

probability distribution density function (with respect to the diameter d) defined by

$$\psi_d(t,d) = \psi(t, m(d)) \tag{24}$$

with $m(d)$ defined in (19). Recall the relation (20) between the cell mass m and diameter d so that

$$n_i(t_k) = \int_{d_{i-1}}^{d_i} \psi_d(t_k,\delta)\mathrm{d}\delta = \int_{m_{i-1}}^{m_i} \psi(t_k,\mu)d'(\mu)\mathrm{d}\mu. \tag{25}$$

Using the trapezoidal rule it follows that

$$n_i(t_k) \approx \frac{\psi(t_k,m_i)d'(m_i) + \psi(t_k,m_{i-1})d'(m_{i-1})}{2}\Delta m_i$$

with $\Delta m_i = m_i - m_{i-1},\ i = 1,\dots,n$ with $m_0 = 0$, so that an approximation ψ_a of ψ is given by

$$\psi_a(t_k,m_i) = \frac{\frac{2}{\Delta m_i}n_i(t_k) - \psi_a(t_k,m_{i-1})d'(m_{i-1})}{d'(m_i)}, \quad i \geq 1 \tag{26a}$$

$$\psi_a(t_k,0) = 0. \tag{26b}$$

With the approximated cell mass distribution density function measurement ψ_a and a numerical approximation ψ_n of the solution ψ of the Fokker–Planck equation (12) one can perform a least–squares approximation to identify the parameters with

$$\boldsymbol{p} = \underset{\boldsymbol{p}=[r,K,q_n]}{\operatorname{argmin}} \sum_{k=1}^{N}\sum_{i=1}^{n} \left(\psi_a(t_k,m_i) - \psi_n(t_k,m_i)\right)^2, \tag{27}$$

In the next section this approach is illustrated for a microalgae growth process for *Chlamydomonas reinhardtti* in a lab–scale reactor.

Remark 3. Note that instead of explicitely using the relation (26) to determine the cell mass probability distribution density function one can alternatively use numerical tools, like, e.g., the ones in MATLAB implemented in the STATISTICS AND MACHINE LEARNING TOOLBOX or similar libraries.

5. EXPERIMENTAL VALIDATION

In this section the numerical method employed for solving the Fokker–Planck equation (12) is shortly commented and the results from the parameter identification with experimental data is presented.

5.1 Numerical solution

For the numerical solution of the Fokker–Planck equation the MATLAB standard algorithm `pdepde` was employed. For this purpose (12) is put into the standard form

$$\begin{aligned} \partial_t\psi &= m^{-c}\partial_m\left(m^c F\left(\psi,\partial_m\psi\right) + G(\psi,\partial_m\psi)\right)\\ 0 &= p_l + q_l F(\psi,\partial_m\psi), \quad m = 0\\ 0 &= p_r + q_r F(\psi,\partial_m\psi), \quad m = 1 \end{aligned}$$

with

$$\begin{aligned} c = 0, \quad F = \bar{r}m\left(1 - \frac{m}{\bar{K}}\right), \quad G = 0,\\ p_l = p_r = 0, \quad q_l = q_r = 1 \end{aligned}$$

with $M = 100$ discretization points. The initial condition was set as a lognormal distribution

$$\psi_0 = C_0\frac{1}{\sqrt{2\pi}\sigma_0 m}\exp\left(-\frac{(\ln(m)-\alpha)^2)}{(2\sigma_0^2)}\right)$$

where the parameters σ_0, α are identified using the initial condition from the measurement data.

5.2 Validation with experimental data

Measurements from a microalgae growth experiment were obtained at time instances

$$\begin{aligned} &[t_1,t_2,t_3,t_4,t_5,t_6,t_7,t_8,t_9]\\ &\approx [73,97,121,170,241,265,289,313,338] \text{ (in h)} \end{aligned}$$

and the first measurement used to fit the parameters α, σ_0 in the initial lognormal distribution above for the numerical simulation. Then the MATLAB internal algorithm `fmincon` was used to determine the parameters with lower and upper bounds set as

$$\begin{aligned} K = 0.9480\cdot 10^{-6}\ \text{g}, \quad q_n = 0.0016, \quad r = 0.0063\ \text{h}^{-1}\\ \varrho = 1.11\cdot 10^3\ \text{g/l}, \quad m_0 = -1.1, \quad \sigma_0 = 0.2. \end{aligned}$$

A comparison between the distributions obtained using the numerical solution of the Fokker–Planck equation (12) and the measured ones is shown in Figure 2. It can be seen that a rather good correspondence is achieved, showing the big potential of the proposed method for the prediction of the cell mass distribution.

For further validation the experimentally determined biomass concentration values are compared with the first moment of the cell mass distribution density obtained from the numerical solution of the Fokker–Planck equation multiplied by the measured total number of cells determined in (17). For this purpose the distribution is multiplied with the total number of cells which is obtained at each measurement point from the measurement device yielding the cell mass distribution density function. The biomass value then theoretically corresponds to the mean value (i.e., the first moment) of this density function. Figure 3 shows the comparison at the measurement times, with a considerably good correspondence.

Remark 4. It should be noted that the measurements of the distributions and the biomass are subject to different sources of errors, given that they involve probe–taking, dilution, device errors, and further filtering for dry biomass determination. The model on the other side is based on a rather simple approximation of the complex cell dynamics which depends on external and internal substrate concentrations and light intensity fluctuations (microalgae grow heterotrophically based on both substrate and light) which are not considered explicitely but implicitly attributed to the white noise perturbation. Having these experimental and model approximation limitations in mind the resulting correspondence between the simulation results and the experiments show the feasibility of the approach. Further improvement could be obtained by considering variations in the substrate. This could be done using the representation pointed out in Remark 1, or introducing the substrate, or quota as in [Mairet and Baron 2019] as additional degree of freedom, implying a two–dimensional spatial dependency in the Fokker–Planck equation.

Remark 5. Note that besides the shown correspondence between model predictions and experimental data for the presented parameter values the stationary solution of the Fokker–Planck equation does not match the final one of the experiment but will have a mode at $\bar{K} \approx 2.85\cdot 10^{-10}$ that is reached along a considerably larger time–scale. Given the monomodality of the distribution no escape–time phenomena will be present. To enable for a good long

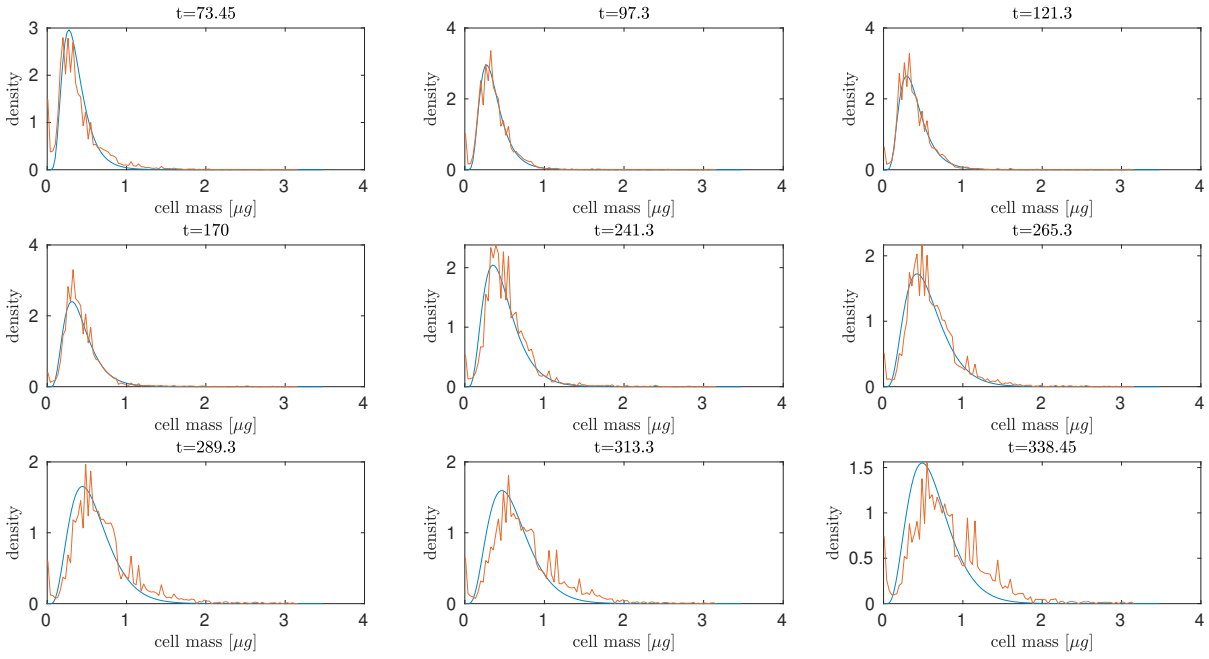

Fig. 2. Comparison of experimental cell mass distribution measurements and the numerical solution of the Fokker–Planck equation.

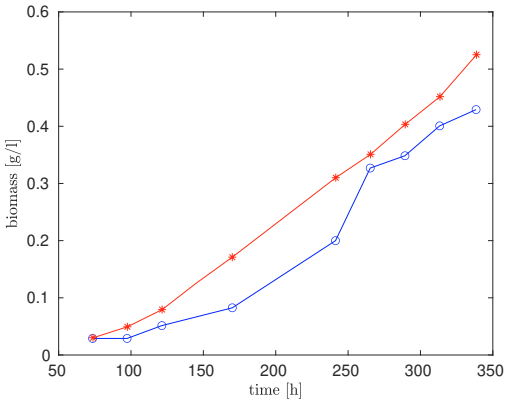

Fig. 3. Comparison of the calculated and experimentally determined biomass concentrations.

term correspondence the possible parameter range would need to be further reduced.

6. CONCLUSIONS

A Fokker–Planck equation based modeling approach for the cell mass distribution of a microalgae growth process of *Chlamydomonas reinhardtti* is employed for describing the temporal behavior of the associated probability density function. The Fokker–Planck equation describes the temporal evolution of the probability density distribution of a stochastic logistic differential equation that is motivated by some assumptions on the behavior of the mircroalgae in terms of their internal nitrogen quota and uptake rates. The comparison of the model predictions with the experimental measurement data shows that this approach can be used for approximating the associated cell mass distribution. It should be noticed that the resulting model is considerably simpler and easier to parameterize than alternative cell population balance equations.

Future studies will focus on the use of this approach for online estimation of substrates and potential applications in the control of the cell size distribution. A further route for future investigations consists in extending the proposed method to consider varying growth rates or additional dependencies through the solution of the Fokker–Planck equation on higher–dimensional spatial domains.

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REFERENCES

Alvarez, J., Baratti, R., Tronci, S., Grosso, M., and Schaum, A. (2018). On the stochastic global-nonlinear dynamics of a class of two-state two-parameter non-isothermal CSTRs. *Journal of Process Control*, 72, 1–16.

Aris, R. (1969). *Introduction to the Analysis of Chemical Reactors*. Prentice-Hall, Englewood Cliffs, N.J.

Atzori, F., Jerono, P., Schaum, A., Baratti, R., Tronci, S., and Meurer, T. (2021). Identification of a cell population model for algae growth processes. *IFAC PapersOnLine*, 54(7), 132–137.

Bacaër, N. (2011). *A Short History of Mathematical Population Dynamics*. Springer Verlag, London.

Baratti, R., Alvarz, J., Tronci, S., Grosso, M., and Schaum, A. (2021). Characterization with fokker–planck theory of the nonlinear stochastic dynamics of a class of two-state continuous bioreactors. *Journal of Process Control*, 102, 66–84. doi:https://doi.org/10.1016/j.jprocont.2021.04.004.

Baratti, R., Tronci, S., Schaum, A., and Alvarez, J. (2016). Dynamics of nonlinear chemical process with multiplicative stochastic noise. In *Proceedings of the 11th IFAC Symposium on Dynamics and Control of Process Systems, including Biosystems*, 869–874.

Baratti, R., Tronci, S., Schaum, A., and Alvarez, J. (2018). Open and closed-loop stochastic dynamics of a class of nonlinear chemical processes with multiplicative noise. *Journal of Process Control*, 66, 108–121.

Bastin, G. and Dochain, D. (1990). *On-line estimation and adaptive control of bioreactors*. Elsevier, Amsterdam.

Bernard, O., Sciandra, A., and Sallet, G. (1999). Use of non linear software sensor to monitor the internal state of a culture of microalgae. *IFAC Proceedings Volumes*, 32 (2), 5806–5811.

Chen, Z. and Zhang, T. (2013). Dynamics of a stochastic model for continuous flow bioreactor with contois growth rate. *J. Math. Chem.*, 51, 1076–1091.

Cogoni, G., Grosso, M., Baratti, R., and Romagnoli, J. (2011). Dynamic evolution of psd modelled using an ornstein-uhlenbeck process approach. *IFAC Proceedings Volumes*, 44(1), 459–464. doi:https://doi.org/10.3182/20110828-6-IT-1002.00853. 18th IFAC World Congress.

Cogoni, G., Widensky, D.J., Grosso, M., Baratti, R., and Romagnoli, J. (2014). A qualitative comparison between population balances and stochastic models for non-isothermal antisolvent crystallization processes. *Computers & Chemical Engineering*, 63, 82–90. doi:https://doi.org/10.1016/j.compchemeng.2014.01.001.

Cogoni, G., Grosso, M., Baratti, R., and Romagnoli, J.A. (2012). Time evolution of the psd in crystallization operations: An analytical solution based on ornstein-uhlenbeck process. *AIChE Journal*, 58(12), 3731–3739. doi:https://doi.org/10.1002/aic.13760.

Droop, M. (1968). Vitamin B12 and marine exology IV: the kinetics of uptake growth and inhibition in monochrisis lutheri. *Journal of the Marine Biological Association*, 48 (3), 689–733.

Feinberg, M. (1977). *Chemical Reactor Theory: A review dedicated to Richard H. Wilhelm*, chapter Mathematical aspects of mass action kinetics. Englewood-Cliffs: Prentice Hall.

Gardiner, C. (2009). *Stochastic Methods: A Handbook for the Natural and Social Sciences*. Springer-Verlab Berlin Heidelberg.

Geyyer, R., Kienle, A., and Palis, S. (2015). Robust control of continuous crystallization processes. *IFAC-PapersOnLine*, 48-11, 598–603.

Grosso, M., Cogoni, G., Baratti, R., and Romagnoli, J.A. (2011). Stochastic approach for the prediction of psd in crystallization processes: Formulation and comparative assessment of different stochastic models. *Industrial & Engineering Chemistry Research*, 50(4), 2133–2143. doi:10.1021/ie1010299. URL `https://doi.org/10.1021/ie1010299`.

Jazwinski, A.H. (1970). *Stochastic Processes and Filtering Theory*. Academic Press, New York.

Mairet, F. and Bernard, O. (2016). The photoinhibistat: Operating microalgae culture under photoinhibition for strain selection. *IFAC-PapersOnLine*, 49 (7), 1068–1073.

Mairet, F. and Baron, R. (2019). A physiologically structured equation to consider quota heterogeneity in the droop model. *IFAC-PapersOnLine*, 52(26), 275–280. doi:https://doi.org/10.1016/j.ifacol.2019.12.270. 8th Conference on Foundations of Systems Biology in Engineering FOSBE 2019.

Meng, X., Wang, L., and Zhang, T. (2016). Global dynamics analysis of a nonlinear impulsive stochastic chemostat system in a polluted environment. *J. Appl. Anal. and Comp.*, 6, 865–875.

Mesbah, A., Nagy, Z.K., Huesman, A.E.M., Kramer, H.J.M., and den Hof, P.M.J.V. (2012). Nonlinear model-based control of a semi-industrial batch crystallizer using a population balance modeling framework. *IEEE Transactions on Control Systems Technology*, 20(5), 1188–1201. doi:10.1109/TCST.2011.2160945.

Otto, E., Behrens, J., Palis, S., Dürr, R., and Kienle, A. (2022). Discrepancy-based control of particle processes. *Journal of Process Control*, 110, 99–109. doi:https://doi.org/10.1016/j.jprocont.2021.11.014.

Palis, S. and Kienle, A. (2014). Discrepancy-based control of particulate processes. *J. Proc. Control*, 24, 33–46.

Ramkrishna, D. (2000). *Population Balances: Theory and Applications to Particulate Processes in Engineering*. Academic Press, New York.

Risken, H. and Frank, T. (1996). *The Fokker-Planck equation: Methods of Solution and Applications*. Springer-Verlab Berlin Heidelberg.

Schaum, A., Tronci, S., Baratti, R., and Alvarez, J. (2021). On the dynamics and robustness of the chemostat with multiplicative noise. *IFAC-PapersOnLine*, 54(3), 342–347. doi:https://doi.org/10.1016/j.ifacol.2021.08.265. 16th IFAC Symposium on Advanced Control of Chemical Processes ADCHEM 2021.

Stephanopoulos, G., Aris, B., and Fredrickson, A. (1979). A stochastic analysis of the growth of competing microbial populations in a continuous biochemical reactor. *Math. Biosci*, 45, 99–135.

Sun, S., Sun, Y., Zhang, G., and Liu, X. (2017). Dynamical behavior of a stochastic two-species monod competition chemostat model. *App. Math. and Comp.*, 298, 152–170.

Tronci, S., Grosso, M., Alvarez, J., and Baratti, R. (2011). On the global nonlinear stochastic dynamical behavior of a class of exothermic cstrs. *J. Process Control*, 21 (9), 1250–1264. doi:10.1016/j.jprocont.2011.07.014.

Villadsen, J. (1999). On the use of population balances. *J. Biotechnol.*, 71, 251–253.

Wang, L., Jiang, D., Wolkowicz, G.S.K., and O'Regan, D. (2017). Dynamics of the stochastic chemostat with monod-haldane response function. *Sci. Reports*, 7, 1–16.

Zhang, T., Chen, Z., and Han, M. (2014). Dynamical analysis of a stochastic model for cascaded continuous flow bioreactors. *J. Math. Chem.*, 52, 1441–1459.