Moment-based dissipative observer design for cell population balance models ⋆

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Abstract: A dissipativity-based observer design for a class of cell population balance models is presented and evaluated using experimental data. The population balance model is described by a partial integro-differential equation coupled with an ordinary differential equation for a batch bioreactor with biomass measurement via an optical density sensor. The dissipative observer is proven to exponentially converge in the first moment of the cell size distribution and the substrate concentration in the absence of modeling and measurement errors. The theoretical results are evaluated using experimental data from a 2 liter lab-scale reactor for anaerobic yeast fermentation on glucose using nitrogen gas supply, showing a good performance of the dissipativity-based estimation scheme.

Keywords: Cell population balance models, dissipative observer design, Lyapunov's direct method, moments of a distribution

1. INTRODUCTION

Mass-balance based macroscopic models representing the total biomass and substrate in the reactor are typically unsegregated and unstructured [Schügerl and Bellgard 2000]. Models including detailed information about cell-internal metabolism are called structured models, while those providing explicit information about the cell size (or mass) distribution are called segregated models. Cell size population models [Villadsen 1999, Daoutidis and Henson 2002] are thus segregated bioreactor models that offer explicit information about how a cell culture evolves on a microscopic scale by considering explicit cell division rate functions that are experimentally validated using cell size distribution measurements or microscopic image analysis. These models also provide the typical mass-balance information on a macroscopic scale after building the first moments of the distribution [Daoutidis and Henson 2002] and are naturally represented in form of partial integro-differential equations coupled with ordinary differential equations. Process monitoring with explicit cell size distribution information is time and cost intensive due to the need of a particular measurement device, or time consuming and/ or imprecise when using microscopic image analysis. Furthermore, the explicit inclusion of cell size distribution measurement in an existent monitoring system is considerably more involved than using macroscopic data, like the optical density, which is typically measured on–line and is directly correlated with the total biomass in the reactor.

This motivates the question whether it is possible to build a simple extension for a classical optical-density based monitoring system to additionally provide reliable on–line information about the cell size distribution over a batch process. This problem is addressed in this study.

While the observer design problem for unsegregated models has been addressed, e.g., using high-gain observers [Gauthier et al. 1992], asymptotic observers [Dochain et al. 1992, Dochain 2003], dissipativity-based observers [Moreno 2005, Schaum and Moreno 2006] and interval observers [Moisan et al. 2009, Goffaux et al. 2009], only recently the observer design problem for segregated models has attained more focus (see [Schaum and Jerono 2019]). In the mathematically related area of crystal growth models several studies have been reported based on finite-dimensional and moment-based model approximations in combination with Luenberger and high-gain observers [Motz et al. 2008, Bakir et al. 2006] as well as different Kalman Filter concepts [Mesbah et al. 2011]. In contrast to early-lumping, where the resulting convergence properties depend directly on the employed approximation method, late-lumping design approaches enable to exploit the properties of the distributed parameter model directly and yield observation schemes that can be implemented using different kind of numerical approximation algorithms, like the finite-difference, the finite elements or finite volume methods, maintaining the mathematically rigorous convergence properties.

In the present study the late-lumping observer design problem for cell population balance models with biomass measurement (via on–line optical density measurement) is addressed using a dissipativity-based approach. Exponential convergence of the proposed observer in the first moment of the cell size distribution and the substrate concentration is shown for the nominal case, i.e. when no measurement and modeling errors are present. The main

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contribution of the paper consists in (i) extending the dissipative observer design discussed in [Moreno 2004, Schaum and Moreno 2006] to the class of cell population balance models, and (ii) presenting an experimental evaluation of the theoretical findings.

The paper is organized as follows. In Section 2 the problem is stated mathematically. Basic notions from dissipativity theory are summarized in Section 3. The exponential convergence assessment for the dissipative observer is presented in Section 4. The experimental validation of the observer is presented in Section 5. Conclusions and an outlook to future studies are presented in Section 6.

NOTATION

The space of absolutely integrable functions $v : [a, b] \subset \mathbb{R} \to \mathbb{R}$ so that $\int_a^b |v(m)| \mathrm{d}m < \infty$ is denoted by $L^1(a, b)$. The Sobolev space of weakly differentiable functions $v \in L^1(a, b)$ with first derivative in $L^1(a, b)$ is denoted by $H^1(a, b)$. For a vector $\boldsymbol{x} \in \mathbb{R}^n$ its norm is denoted by $\|\boldsymbol{x}\| = \sqrt{\boldsymbol{x}^\intercal \boldsymbol{x}}$, where $\boldsymbol{x}^\intercal$ denotes the transposed of $\boldsymbol{x}$. The set of non-negative real numbers is denoted by $\mathbb{R}_+$.

2. PROBLEM STATEMENT

Consider the following class of cell population models [Villadsen 1999, Mhaskar et al. 2002, Daoutidis and Henson 2002, Mantzaris and Daoutidis 2004]

$$\partial_t n(m,t) = -Y \partial_m [r(m,s) n(m,t)] - \Gamma(m,s) n(m,t) + 2 \int_m^{m^+} \Gamma(\mu, s) p(\mu, m) n(\mu, t) \mathrm{d}\mu \tag{1a}$$

$$\dot{s}(t) = - \int_0^{m^+} r(m,s) n(m,t) \mathrm{d}m \tag{1b}$$

$$n(m^+, t) = 0 \tag{1c}$$

$$n(m, 0) = n_0(m), \quad s(0) = s_0 \tag{1d}$$

$$y(t) = b(t) = \int_0^{m^+} m\, n(m,t) \mathrm{d}m \tag{1e}$$

with the cell mass $m \in [0, m^+]$, time $t \geq 0$, cell mass distribution $n : [0, m^+] \times [0, \infty) \to \mathbb{R}_+$, yield coefficient Y, substrate concentration $s \in [0, s^+]$, cell growth rate function $r : [0, m^+] \times [0, s^+] \to \mathbb{R}_+$, cell division rate $\Gamma : [0, m^+] \times [0, s^+] \to \mathbb{R}_+$, partition probability density function $p : [0, m^+] \times [0, m^+] \to \mathbb{R}_+$ with $p(\mu, m)$ denoting the probability that by division of a cell of mass μ a cell of m is produced, and the measurement y given by the total biomass b in the reactor which corresponds to the first moment of the distribution n. Note that in virtue of its definition, p has the property that

$$\forall \mu \leq m : \quad p(\mu, m) = 0. \tag{2}$$

In the sequel consider the case of a linear dependency of r on the cell mass m as discussed in [Mantzaris and Daoutidis 2004], i.e.

$$r(m, s) = \rho(s) m, \tag{3}$$

with specific growth rate $\rho : [0, s^+] \to \mathbb{R}_+$ as well as the case that the division rate $\Gamma(m, s)$ is proportional to the cell growth rate in the sense that

$$\Gamma(m, s) = \gamma(m) m \rho(s). \tag{4}$$

The existence, uniqueness and positivity of solutions in $L^1(0, m^+) \times \mathbb{R}_+$ for the equation set (1) has been shown in [Beniich et al. 2018]. Furthermore, for the subsequent analysis the following result provides some useful background.

Lemma 1. The set $[0, s^+]$ is positively invariant for the substrate concentration, i.e., for all $s_0 \in [0, s^+]$ it holds that $s(t) \in [0, s^+]$ for all $t \geq 0$.

Proof: Considering $r(m, s) = \rho(s) m$ with $\rho(0) = 0$, it holds for $s = 0$ that $\dot{s}|_{s=0} = 0$ and for $s = s^+$ that $\dot{s}|_{s=s^+} = -\rho(s^+)\beta \leq 0$ for all real numbers $\beta \in \mathbb{R}_+$. In consequence the vector field at $s \in \{0, s^+\}$ does not point outwards, implying that for any $s_0 \in [0, s^+]$ the associated solution $s(t; s_0)$ is contained in $[0, s^+]$ for all $t \geq 0$. □

For the class of cell population balance models (1) the observability and detectability properties in the first moment have been characterized in [Schaum and Jerono 2019] (cp. also [Schaum et al. 2005] for the unsegregated case), showing that for a monotonic growth rate the reactor in batch operation is observable in the first moment of the distribution and non-observable and non-detectable for non-monotonic growth rates. While in [Schaum and Jerono 2019] an asymptotic-like observer was built for a continuous reactor operation, here the case of a batch operation is considered with a monotonic growth rate, ensuring the reactor observability in the first moment and a dissipativity-based observer with correction scheme in both states is designed. For this purpose some important concepts and results from dissipativity theory are summarized next.

3. RELEVANT NOTIONS AND RESULTS FROM DISSIPATIVITY THEORY

In this section a short review is provided of the relevant notions and results from dissipativity theory that are used later for the design of an exponentially convergent observer for the first moment of the cell size distribution. More detailed discussions of this subject can be seen in the seminal texts [Willems 1972a,b, Hill and Moylan 1980, Brogliato et al. 2007]. In what follows consider a non–linear feedback loop of a non–linear input-output system described in the Euclidean state-space $\mathbb{R}^n$

$$\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x}, \boldsymbol{\nu}), \qquad t > 0, \quad \boldsymbol{x}(0) = \boldsymbol{x}_0 \tag{5a}$$

$$\boldsymbol{\sigma} = H \boldsymbol{x}, \qquad t \geq 0 \tag{5b}$$

$$\boldsymbol{\nu} = \boldsymbol{\psi}(\boldsymbol{\sigma}), \qquad t \geq 0, \tag{5c}$$

with $\boldsymbol{x}(t) \in \mathbb{R}^n$ for $t \geq 0$, $\boldsymbol{f} : \mathbb{R}^n \times \mathbb{R}^p \to \mathbb{R}^n$ a vector field that is continuously differentiable with respect to both arguments, $H \in \mathbb{R}^{q \times n}$ and $\boldsymbol{\psi} : \mathbb{R}^q \to \mathbb{R}^p$. It is assumed that $\boldsymbol{\psi}$ is sufficiently well behaved to ensure existence of a unique solution $\boldsymbol{x} : [0, \infty) \to \mathbb{R}^n$ so that $\boldsymbol{x}(0) = \boldsymbol{x}_0$. For the input-output system (5a),(5b) without the feedback (5c) an input function $\boldsymbol{\nu} : [0, \infty) \to \mathbb{R}^p$ is called admissible, if for all $\boldsymbol{x}_0 \in \mathbb{R}^n$ a unique solution to (5a) exists. Accordingly, for the state at time $t \geq 0$ denote $\boldsymbol{x}(t) = \boldsymbol{x}(t; \boldsymbol{x}_0, \boldsymbol{\nu})$ with $\boldsymbol{x}(0; \boldsymbol{x}_0, \boldsymbol{\nu}) = \boldsymbol{x}_0$. The set of all admissible inputs is called $\mathcal{U}$.

Definition 1. The input-output system (5a),(5b) is called dissipative with respect to the supply rate $\omega : \mathbb{R}^p \times \mathbb{R}^q \to \mathbb{R}$, if there exists a positive semi-definite storage function $\mathcal{S} : \mathbb{R}^n \to \mathbb{R}$ so that for all $\boldsymbol{x}_0 \in \mathbb{R}^n$ and admissible inputs $\boldsymbol{\nu} \in \mathcal{U}$ it holds that

$$\mathcal{S}(\boldsymbol{x}(t;\boldsymbol{x}_0,\boldsymbol{\nu})) - \mathcal{S}(\boldsymbol{x}_0) \leq \int_0^t \omega(\boldsymbol{\nu}(\tau),\boldsymbol{\sigma}(\tau))\mathrm{d}\tau. \quad (6)$$

If $\mathcal{S} \in \mathcal{C}^1(\mathbb{R}^n,\mathbb{R})$, then this can equivalently be written as

$$\partial_{\boldsymbol{x}}\mathcal{S}(\boldsymbol{x})\boldsymbol{f}(\boldsymbol{x},\boldsymbol{\nu}) \leq \omega(\boldsymbol{\nu},\boldsymbol{\sigma}). \quad (7)$$

In the following only the case of differentiable storage functions is considered.

Definition 2. For a given triplet (Q,S,R) with $Q \in \mathbb{R}^{n\times n}, Q = Q^\intercal, S \in \mathbb{R}^{n\times p}, R \in \mathbb{R}^{p\times p}, R = R^\intercal$ the input-output system (5a),(5b) is called (Q,S,R)-dissipative, if it is dissipative with respect to the quadratic supply rate

$$\omega(\boldsymbol{\nu},\boldsymbol{\sigma}) = \begin{bmatrix}\boldsymbol{\nu}\\ \boldsymbol{\sigma}\end{bmatrix}^\intercal \begin{bmatrix} Q & S\\ S^\intercal & R\end{bmatrix}\begin{bmatrix}\boldsymbol{\nu}\\ \boldsymbol{\sigma}\end{bmatrix}. \quad (8)$$

It is called (Q,S,R)-strictly state dissipative, if there exists a constant $\kappa > 0$ so that

$$\partial_{\boldsymbol{x}}\mathcal{S}(\boldsymbol{x})\boldsymbol{f}(\boldsymbol{x},\boldsymbol{\nu}) \leq \omega(\boldsymbol{\nu},\boldsymbol{\sigma}) - \kappa\|\boldsymbol{x}\|^2 \quad (9)$$

with ω given by (8).

For the static map (5c) the following definition is useful.

Definition 3. A static map $\boldsymbol{\psi} : \mathbb{R}^q \to \mathbb{R}^p$ is called (Q,S,R)-dissipative, if $\omega(\boldsymbol{\sigma},\boldsymbol{\psi}(\boldsymbol{\sigma})) \geq 0$ for all $\boldsymbol{\sigma} \in \mathbb{R}^q$.

Particular examples of static dissipative maps are given by scalar sector non–linearities $\varphi : \mathbb{R} \to \mathbb{R}$ with $\varphi \in [k_1,k_2]$ (see e.g. [Khalil 1996]), meaning that

$$(k_2\sigma - \varphi(\sigma))(\varphi(\sigma) - k_1\sigma) \geq 0, \quad \forall\,\sigma \in \mathbb{R}, \quad (10)$$

given that the preceding inequality can be rewritten as

$$-\varphi^2(\sigma) + (k_1+k_2)\varphi(\sigma)\sigma - k_1k_2\sigma^2 \geq 0.$$

This implies that the map φ is $(-1,(k_1+k_2)/2,-k_1k_2)$ dissipative.

Using these concepts, the following stability results are obtained (see, e.g., [Willems 1972b, Hill and Moylan 1980, Brogliato et al. 2007]) ensuring the asymptotic and exponential stability of the equilibrium solution $\boldsymbol{x} = \boldsymbol{0}$ for (5). For completeness the short proof is provided here.

Lemma 2. Consider the feedback system (5). Let the map $\boldsymbol{\psi}$ be (Q,S,R) dissipative. If the input-output system (5a), (5b) is $(-R,-S^\intercal,-Q)$ strictly state dissipative with positive definite storage function $\mathcal{S} : \mathbb{R}^n \to \mathbb{R}$ then the solution $\boldsymbol{x} = \boldsymbol{0}$ is asymptotically stable.

Proof: Let the assumption of the lemma hold true and denote by $s(t) = \mathcal{S}(\boldsymbol{x}(t))$ the value of the storage function $\mathcal{S}$ at time $t \geq 0$ with $\boldsymbol{x}(t)$ being the solution of (5) evaluated at time t. It holds true that for all $t > 0$

$$\begin{aligned}\dot{s}(t) &= \partial_{\boldsymbol{x}}\mathcal{S}(\boldsymbol{x}(t))\boldsymbol{f}(\boldsymbol{x}(t),\boldsymbol{\nu}(t))\\ &\leq \omega(\boldsymbol{\nu}(t),\boldsymbol{\sigma}(t)) - \kappa\|\boldsymbol{x}(t)\|^2\\ &= \omega(\boldsymbol{\psi}(\boldsymbol{\sigma}(t)),\boldsymbol{\sigma}(t)) - \kappa\|\boldsymbol{x}(t)\|^2.\end{aligned}$$

By assumption it holds true that

$$\begin{aligned}\omega(\boldsymbol{\psi}(\boldsymbol{\sigma}),\boldsymbol{\sigma}) &= \begin{bmatrix}\boldsymbol{\psi}(\boldsymbol{\sigma})\\ \boldsymbol{\sigma}\end{bmatrix}^\intercal \begin{bmatrix}-R & -S^\intercal\\ -S & -Q\end{bmatrix}\begin{bmatrix}\boldsymbol{\psi}(\boldsymbol{\sigma})\\ \boldsymbol{\sigma}\end{bmatrix}\\ &= -\begin{bmatrix}\boldsymbol{\sigma}\\ \boldsymbol{\psi}(\boldsymbol{\sigma})\end{bmatrix}^\intercal \begin{bmatrix}Q & S\\ S^\intercal & R\end{bmatrix}\begin{bmatrix}\boldsymbol{\sigma}\\ \boldsymbol{\psi}(\boldsymbol{\sigma})\end{bmatrix} \leq 0,\end{aligned}$$

given that $\boldsymbol{\psi}$ is (Q,S,R)-dissipative. In consequence, for all $t \geq 0$ one has

$$\dot{s}(t) = \partial_{\boldsymbol{x}}\mathcal{S}(\boldsymbol{x}(t))\boldsymbol{f}(\boldsymbol{x}(t),\boldsymbol{\nu}(t)) \leq -\kappa\|\boldsymbol{x}(t)\|^2 < 0,$$

implying that $\mathcal{S}$ is a Lyapunov function and thus the asymptotic stability of $\boldsymbol{x} = \boldsymbol{0}$ follows in virtue of Lyapunov's direct method. □

In addition to this result, the following one gives explicit conditions for exponential stability by restricting the class of storage functions (see also, e.g., [Moreno 2004, 2005]).

Corollary 1. Let the assumptions of Lemma 2 hold true, and let $\mathcal{S}$ be such that there are constants $0 < \alpha_1, \alpha_2 \in \mathbb{R}$ so that

$$\alpha_1\|\boldsymbol{x}\|^2 \leq \mathcal{S}(\boldsymbol{x}) \leq \alpha_2\|\boldsymbol{x}\|^2 \quad (11)$$

holds true for all $\boldsymbol{x} \in \mathbb{R}^n$. Then the solution $\boldsymbol{x} = \boldsymbol{0}$ is globally exponentially stable and it holds that

$$\|\boldsymbol{x}(t)\|^2 \leq \sqrt{\frac{\alpha_2}{\alpha_1}}e^{\frac{-\kappa}{2\alpha_2}t}\|\boldsymbol{x}_0\|^2, \quad \forall\,t \geq 0.$$

Proof: Let $s(t) = \mathcal{S}(\boldsymbol{x}(t))$ for $t \geq 0$ as in the proof of Lemma 2. From the assumptions of the corollary it follows that for all $t > 0$

$$\begin{aligned}\dot{s}(t) &= \partial_{\boldsymbol{x}}\mathcal{S}(\boldsymbol{x}(t))\boldsymbol{f}(\boldsymbol{x}(t),\boldsymbol{\nu}(t))\\ &\leq -\kappa\|\boldsymbol{x}(t)\|^2 \leq -\frac{\kappa}{\alpha_2}\mathcal{S}(\boldsymbol{x}(t)) = -\frac{\kappa}{\alpha_2}s(t)\end{aligned}$$

with $s(0) = \mathcal{S}(\boldsymbol{x}_0)$. It follows from the comparison principle [Khalil 1996, Lemma3.4] that $s(t) \leq s(0)e^{-\frac{\kappa}{\alpha_2}t}$ for all $t \geq 0$. This in turn implies that

$$\|\boldsymbol{x}(t)\|^2 \leq \frac{1}{\alpha_1}\mathcal{S}(\boldsymbol{x}(t)) \leq \frac{1}{\alpha_1}\mathcal{S}(\boldsymbol{x}_0)e^{-\frac{\kappa}{\alpha_2}t} \leq \frac{\alpha_2}{\alpha_1}\|\boldsymbol{x}_0\|^2e^{-\frac{\kappa}{\alpha_2}t}$$

holds true for all $t \geq 0$. The result follows by taking square roots on both sides of the inequality. □

Considering quadratic storage functions, i.e., $\mathcal{S}(\boldsymbol{x}) = \boldsymbol{x}^\intercal P\boldsymbol{x}$ with $P = P^\intercal \succ 0$ the preceding results can be further specified as shown, e.g., in [Moreno 2004, 2005, Schaum and Moreno 2006] and exploited in the following section for the design of an exponentially convergent observer.

4. DISSIPATIVE OBSERVER DESIGN

Consider the following observer with Luenberger-like simulator-corrector structure

$$\begin{aligned}\partial_t\hat{n} &= -Y\partial_m[r(m,\hat{s})\hat{n}] - \Gamma(m,\hat{s})\hat{n}\\ &\quad + 2\int_m^{m^+}\Gamma(\mu,\hat{s})p\hat{n}\mathrm{d}\mu - l_b(\hat{s})\left(\int_0^{m^+}m\hat{n}\mathrm{d}m - y\right)\end{aligned} \quad (12a)$$

$$\dot{\hat{s}} = -\left(\rho(\hat{s}) + l_s(\hat{s})\right)\int_0^{m^+}m\hat{n}\mathrm{d}m + l_s(\hat{s})y \quad (12b)$$

for $t > 0$, $m \in (0,m^+)$ with initial condition $\hat{n}(\cdot,0) = \hat{n}_0 \in L^1(0,m^+), \hat{s}(0) = \hat{s}_0 \in \mathbb{R}_+$ and boundary condition

$$\hat{n}(m^+,t) = 0, \quad t \geq 0. \quad (12c)$$

In (12) $l_b, l_s : \mathbb{R}_+ \to \mathbb{R}$ denote the observer gains which depend on the estimated substrate concentration $\hat{s}(t) \in \mathbb{R}_+$ at time $t \geq 0$.

Theorem 1. Consider the cell population balance model (1) with a monotonically increasing function $\rho : \mathbb{R}_+ \to \mathbb{R}$ and the observer (12). Assume that $\int_0^{m^+} m n\mathrm{d}m \geq \beta^* > 0$ as well as $s(0) \in [0,s^+]$. Denote by $\tilde{b}(t)$ the first moment of the associated cell size distribution estimation error

$\tilde{n}(\cdot,t) = \hat{n}(\cdot,t) - n(\cdot,t)$ at time $t \geq 0$ and introduce the substrate estimation error $\tilde{s}(t) = \hat{s}(t) - s(t)$. Let

$$k_1 := \min_{s\in[0,s^+]} \partial_s \rho(s), \quad k_2 := \max_{s\in[0,s^+]} \partial_s \rho(s) \tag{13a}$$

so that $0 < k_1 < k_2$, and let $Q = -1, S = (k_1 + k_2)/(2\beta^*), R = -k_1 k_2/\beta^*$. If there exist $p_0, p_2 > 0, p_1 < \sqrt{p_0 p_2}$ and $\lambda_b > 0$ so that for $0 < \kappa < -R$ it holds true that

$$\lambda_b > \frac{1}{2(p_0 p_2 - p_1^2)} \left(\frac{p_2(r+\kappa)(p_0 Y - p_1)^2}{R + \kappa + (S + p_1 Y - p_2)^2} + p_2 \kappa \right), \tag{13b}$$

then $\tilde{\boldsymbol{x}}(t) = [\tilde{b}(t),\ \tilde{s}(t)]^\intercal$ exponentially converges to zero as $t \to \infty$ provided the observer gains are chosen as

$$l_b(\hat{s}) = Y\rho(\hat{s}) + \lambda_b, \quad l_s(\hat{s}) = -\rho(\hat{s}) + \frac{p_1 \lambda_b}{p_2}. \tag{13c}$$

Proof: Consider the observation errors $\tilde{n}(\cdot,t) = \hat{n}(\cdot,t) - n(\cdot,t) \in L^1(0,1), \tilde{s}(t) = \hat{s}(t) - s(t) \in \mathbb{R}$ for $t \geq 0$ and the first moment of the error distribution

$$\tilde{b} = \int_0^{m^+} \mu \tilde{n} \mathrm{d}\mu. \tag{14}$$

According to mass conservation the total mass is not influenced by cell division [Mantzaris and Daoutidis 2004, Schaum and Jerono 2019] so that for $t > 0$

$$\dot{\tilde{b}} = Y\rho(s+\tilde{s})(b+\tilde{b}) - Y\rho(s)b - l_b(\hat{s})\tilde{b}$$
$$\dot{\tilde{s}} = -\Big(\rho(s+\tilde{s})(b+\tilde{b}) - \rho(s)b\Big) - l_s(\hat{s})\tilde{b}$$

and $\tilde{b}(0) = \tilde{b}_0, \tilde{s}(0) = \tilde{s}_0$. Note that

$$\rho(s+\tilde{s})(b+\tilde{b}) - \rho(s)b = \rho(\hat{s})\tilde{b} + (\rho(s+\tilde{s}) - \rho(s))\, b.$$

Introduce for $\tilde{s} \in \mathbb{R}$

$$\varphi(\tilde{s}; s) = \rho(s+\tilde{s}) - \rho(s), \quad \varphi(0; s) = 0, \quad \forall\, s \in \mathbb{R}_+,$$

so that for $t > 0$

$$\dot{\tilde{b}} = (Y\rho(\hat{s}) - l_b(\hat{s}))\, \tilde{b} + Yb\varphi(\tilde{s}; s) \tag{15a}$$
$$\dot{\tilde{s}} = -(\rho(\hat{s}) + l_s(\hat{s}))\, \tilde{b} - b\varphi(\tilde{s}; s). \tag{15b}$$

For the non–linearity φ, by virtue of the mean value theorem, it holds true that for all $\tilde{s} \in \mathbb{R}$ there exists $\eta \in (0,1)$ such that

$$\varphi(\tilde{s}; s) = \partial_{\tilde{s}} \rho(s + \eta\tilde{s})\tilde{s}$$

for all $s \in [0, s^+]$. With k_1, k_2 as in the statement of the theorem it follows that for a given $\beta > 0$ the non–linearity $\varphi(\cdot; s)$ satisfies

$$(k_2 \tilde{s} - \varphi(\tilde{s}; \sigma)\beta)\, (\varphi(\tilde{s}; \sigma)\beta - k_1 \tilde{s}) \geq 0 \quad \forall \tilde{s} \in \mathbb{R},$$

for all $\sigma \in [0, s^+]$, implying that $\varphi(\cdot; s)$ is contained in the sector $[k_1/\beta, k_2/\beta]$ (see (10)), uniformly in $\sigma \in \mathbb{R}_+$. In consequence, considering $\beta > \beta^* > 0$ it follows that $\varphi(\cdot; s)$ is (Q,S,R)-dissipative with

$$Q = -1, \quad S = \frac{k_1 + k_2}{2\beta^*} > 0, \quad R = -\frac{k_1 k_2}{\beta^*} < 0 \tag{16}$$

uniformly in $s \in [0, s^+]$. Further note, that for $b(0) \geq \beta^*$ it holds that $b(t; b_0, s) \geq \beta^*$ for all $t \geq 0$ and $s : [0,\infty) \to [0, s^+]$. Introducing $\tilde{\boldsymbol{x}} = [\tilde{b},\ \tilde{s}]^\intercal$, the error dynamics (15) for the first moment can be written in form of the interconnection (5) as

$$\dot{\tilde{\boldsymbol{x}}} = A_L(\hat{s})\tilde{\boldsymbol{x}} + \boldsymbol{g}\nu, \qquad t > 0, \quad \tilde{\boldsymbol{x}}(0) = \tilde{\boldsymbol{x}}_0 \tag{17a}$$
$$\sigma = \boldsymbol{h}^\intercal \tilde{\boldsymbol{x}}, \qquad t \geq 0 \tag{17b}$$
$$\nu = \varphi(\sigma; s)b, \tag{17c}$$

with

$$A_L(\hat{s}) = \begin{bmatrix} Y\rho(\hat{s}) - l_b & 0 \\ -\rho(\hat{s}) - l_s & 0 \end{bmatrix}, \quad \boldsymbol{g} = \begin{bmatrix} Y \\ -1 \end{bmatrix}, \quad \boldsymbol{h} = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

which can be viewed as an interconnection of the linear dynamical subsystem (17a), (17b) parameterized by $\hat{s} : [0,\infty) \to \mathbb{R}$ and the static non–linear feedback map (17c) parameterized by $s : [0,\infty) \to [0, s^+], b : [0,\infty) \to [\beta^*, \infty)$, which is (Q,S,R)-dissipative uniformly in s as discussed above.

In virtue of Corollary 1 it follows that if the linear subsystem is uniformly $(-R,-S,-Q)$-strictly state dissipative with a positive definite storage function $\mathcal{S}$ the exponential stability of $\tilde{\boldsymbol{x}} = \boldsymbol{0}$ follows if there are $0 < \alpha_1 < \alpha_2$ so that (11) holds true. For this purpose consider a quadratic storage function $\mathcal{S} : \mathbb{R}^2 \to \mathbb{R}$ with

$$\mathcal{S}(\tilde{\boldsymbol{x}}) = \tilde{\boldsymbol{x}}^\intercal P \tilde{\boldsymbol{x}}, \quad P = P^\intercal \succ 0 \tag{18}$$

so that α_1, α_2 can be chosen as the minimum and maximum eigenvalues of P, respectively, as long as P has simple eigenvalues. A straight forward calculation, substituting (18) into (7) with $\boldsymbol{f}(\tilde{\boldsymbol{x}}, \nu) = A_L(\hat{s})\tilde{\boldsymbol{x}} + \boldsymbol{g}\nu$, shows that the linear subsystem (17a), (17b) is $(-R,-S,-Q)$-strictly state dissipative with respect to the storage function $\mathcal{S}$ if and only if for all $\zeta \in [0, s^+]$ it holds that

$$\begin{aligned} &\dot{\tilde{\boldsymbol{x}}}^\intercal P \tilde{\boldsymbol{x}} + \tilde{\boldsymbol{x}} P \dot{\tilde{\boldsymbol{x}}} \\ &= (A_L(\zeta)\tilde{\boldsymbol{x}} + \boldsymbol{g}\nu)^\intercal P \tilde{\boldsymbol{x}} + \tilde{\boldsymbol{x}}^\intercal P\, (A_L(\zeta)\tilde{\boldsymbol{x}} + \boldsymbol{g}\nu) \\ &\leq \begin{bmatrix} \sigma \\ \nu \end{bmatrix}^\intercal \begin{bmatrix} -R & -S \\ -S & -Q \end{bmatrix} \begin{bmatrix} \sigma \\ \nu \end{bmatrix} - \kappa \|\tilde{\boldsymbol{x}}\|^2 \\ &= \begin{bmatrix} \tilde{\boldsymbol{x}} \\ \nu \end{bmatrix}^\intercal \begin{bmatrix} -R\boldsymbol{h}\boldsymbol{h}^\intercal - \kappa I & -S\boldsymbol{h} \\ -S\boldsymbol{h}^\intercal & -Q \end{bmatrix} \begin{bmatrix} \tilde{\boldsymbol{x}} \\ \nu \end{bmatrix}, \end{aligned}$$

or equivalently, if the following linear matrix inequality (LMI)

$$\begin{bmatrix} A_L^\intercal(\zeta)P + PA_L(\zeta) + R\boldsymbol{h}\boldsymbol{h}^\intercal + \kappa I & S\boldsymbol{h} + P\boldsymbol{g} \\ S\boldsymbol{h}^\intercal + \boldsymbol{g}^\intercal P & Q \end{bmatrix} \preceq 0 \tag{19}$$

has a feasible solution P for some gain vector $\boldsymbol{l} = [l_b,\ l_s]^\intercal$.

Given the particular structure of (17) and writing the matrix P as

$$P = \begin{bmatrix} p_0 & p_1 \\ p_1 & p_2 \end{bmatrix}, \quad p_0, p_2 > 0, \quad p_0 p_2 > p_1^2,$$

where the last two inequalities ensure the positive definiteness of P, the LMI (19) becomes

$$\begin{bmatrix} 2p_0(Y\rho(\zeta) - l_b) - 2p_1(l_s + \rho(\zeta)) + \kappa & \star & \star \\ p_1(Y\rho(\zeta) - l_b) - p_2(l_s + \rho(\zeta)) & R + \kappa & \star \\ p_0 Y - p_1 & S + p_1 Y - p_2 & Q \end{bmatrix} \preceq 0,$$

where $\star$ represents symmetric entries. Choosing l_b, l_s as in (13c) this LMI further simplifies to

$$\begin{bmatrix} -2\lambda_b \left(p_0 - \dfrac{p_1^2}{p_2}\right) + \kappa & 0 & p_0 Y - p_1 \\ 0 & R + \kappa & S + p_1 Y - p_2 \\ p_0 Y - p_1 & S + p_1 Y - p_2 & Q \end{bmatrix} \preceq 0.$$

With $q = -1$ according to (16), it follows by using the Schur complement [Dym 2007] that the preceding inequality holds true if (13b) is satisfied. □

Remark 1. Note that by choosing λ_b in (13b) sufficiently large, the main condition of Theorem 1 can always be satisfied. Note further that the conditions are potentially conservative. The derivation of less restrictive dissipation inequalities will be addressed in future studies.

5. EXPERIMENTAL VALIDATION

The yeast fermentation was carried out in a 2 liter (l) lab-scale reactor under the following process conditions:

Temperatur $T_p = 25°\mathrm{C}$, aeration $Q_{\mathrm{N}_2} = 0.1\mathrm{vvm}$
pH $= 5.5$, stirrer speed $n_s = 750\mathrm{rpm}$, $s(0) = 8.496\mathrm{g/l}$

Nitrogen gas supply was used to supress aerobic metabolic pathways. Optical Density (OD) measurements were taken on–line at 600 nm wavelength with an identified correlation biomass according to $b = 8.4851$ OD. Glucose and ethanol measurements are evaluated off–line at discrete time instances.

5.1 Cell distribution measurements

The cell size was measured using the Casy TT cell counter and cell analyser from Omni Life Science (OLS). This yields a cell size probability distribution over $N_y = 400$ channels with

$$y_{n,r,i}(t) = \int_{(i-1)\Delta r}^{i\Delta r} n_r(r,t)\mathrm{d}r, \quad \Delta r = \frac{r^+}{N},$$

where n_r is the cell size distribution and r^+ the maximum considered cell radius. Since the cell population model (1) is based on the cell density functions with respect to mass, the raw measurements of the cell analyser have been first transformed to the mass domain leading to measurements $y_{n,m,i}, i = 1,\ldots,N_y$ using a uniform mass density per volume of $44.6801 \cdot 10^4$ g/l, identified on the basis of the first moment of the cell size distribution compared with biomass dry weight measurements. A filtered version $\tilde{y}_n$ of the distribution was then further processed. In order to determine the cell distribution density function with respect to mass, the inverse trapezoidal rule was used to determine the cell density function n at m_{i+1} by

$$n(m_{i+1},t) = \frac{2}{\Delta m}\tilde{y}_{n,m,i}(t) - n(m_i,t), \tag{20}$$

for $i = 1,\ldots,N_y - 1$ with $\Delta m = m^+/N_y$. From this high-resolution distribution over N_y channels a low resolution version y_n was obtained for identification and comparison purposes using standard interpolation in MATLAB.

5.2 Observer evaluation

To illustrate the performance of the dissipative observer a comparison with an open-loop simulation, i.e., without any measurement injection, is carried out for the experimental data and erroneous initial condition. The observer is set up as in (12) with the following functions and parameters. The specific growth rate function is considered as a monotonic Monod kinetics

$$\rho(s) = \frac{k_0 s}{k_s + s}.$$

Following [Mantzaris and Daoutidis 2004], γ and p are defined as

$$\gamma(m) = \min\{\max\{0,\alpha(m-m_0)\},\gamma^+\}$$
$$p(\mu,m) = \frac{1}{B(x,z)}\frac{1}{\mu}\left(\frac{m}{\mu}\right)^{x-1}\left(1-\frac{m}{\mu}\right)^{z-1}$$
$$B(x,z) = \frac{\Gamma_f(x)\Gamma_f(z)}{\Gamma_f(x+z)}$$

where Γ_f is the Gamma-function (i.e. the extension of the factorial on the real numbers). The observer is set with the initial condition

$$\hat{n}_0(m) = \frac{0.225}{(m^+)^2}\sin\left(\pi\frac{m}{m^+}\right)^4, \quad \hat{s}(0) = 10,$$

and implemented by means of a finite-difference approximation with $N = 50$ collocation points, backward differences and a trapezoidal quadrature rule. The remaining parameters read

$$(k_0,k_s) = (2.966\mathrm{h}^{-1}, 0.7\mathrm{g/l}), \quad Y = 0.181, \quad x = z = 5,$$
$$m^+ = 1.5\cdot 10^{-10}\mathrm{g}, \quad \alpha = 1.5011\cdot 10^9, \quad \gamma^+ = 5.4182\cdot 10^{11}$$
$$\lambda_b = (m^+)^{-2}, \quad p_0 = p_2 = 1, \quad p_1 = 8(m^+)^2.$$

The time responses of the first moment, i.e., the total biomass, and substrate together with their estimates are shown in Figure 1 in comparison to an open-loop simulation starting at the same initial condition. It can be seen that the open-loop simulation provides an erroneous estimate that in particular provides a wrong prediction of the harvest time – i.e., the time at which the batch should be ended and the products should be withdrawn – of about 8 h while the dissipative observer adequately converges at about 7 h and can thus be used to obtain a more reliable prediction of the harvest time, which is about 10 h.

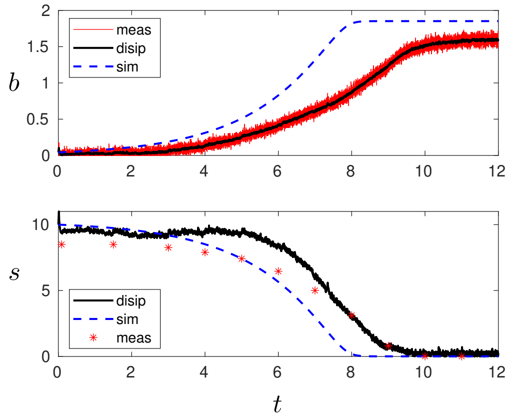

Fig. 1. Top: Measured (red) and estimated (black) total biomass of the distribution. Bottom: actual (stars) and estimated (black line) substrate concentration.

Snapshots of the cell size distribution estimates using the dissipative observer (black continuous line) and open-loop simulations (blue dashed line) are compared with the measurements (red dotted line) at different times in Figure 2. It can be clearly seen how the measurement injection of the first moment corrects the pure prediction model and yields a good convergence behavior within a small uncertainty band in about 7 h in spite of potential modeling and measurement uncertainties.

6. CONCLUSIONS

A dissipative observer for estimating the cell size distribution and substrate concentration in a batch reactor has been designed. Using the on–line measurement of the total biomass via the optical density and adaptive observer correction gains the exponential stability of the observer in the nominal case (i.e., without modeling and measurement errors) has been rigorously established using Lyapunov's

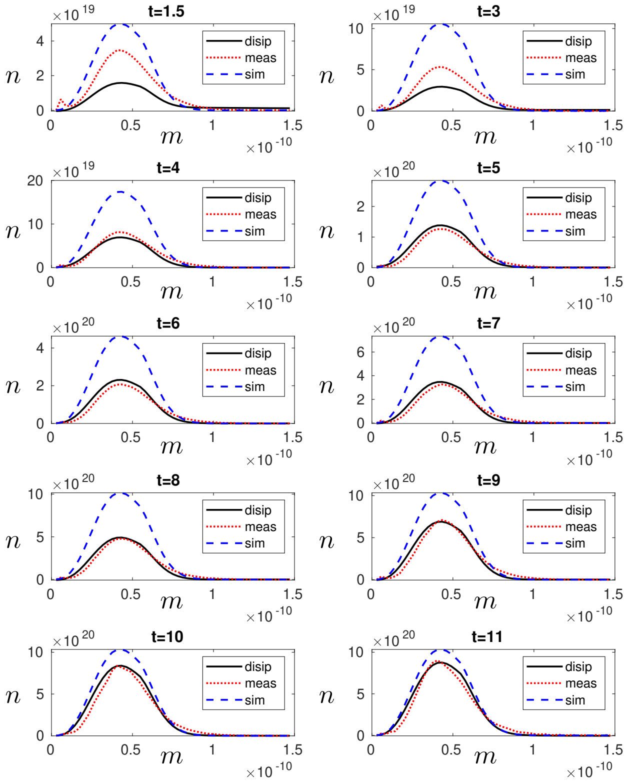

Fig. 2. Snapshots of the cell size distributions: measured (continuous red line), dissipative observer based estimate (continuous black line) and open-loop simulation (dotted blue line).

direct method based on dissipativity theory. The proposed observer performance has been experimentally evaluated in a lab-scale setup showing a good convergence behavior with robustness against potential modeling and measurement uncertainties.

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