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A study of integrated experiment design for NMPC applied to the Droop model

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Abstract

Nonlinear model predictive control (NMPC) has become an important tool for optimization based control of many (bio)chemical systems. A requirement for a well-performing NMPC implementation is obtaining and maintaining an appropriate mathematical process model. To cope with model degradation in view of plant changes and/or system evolution, developments have been made for linear systems to incorporate the information content of future measurements in the closed loop objective. However, formulations for integrated experiment design in nonlinear systems (iED-NMPC) remain scarce. Two different formulations are studied in this paper and applied to a bioprocess, namely, algae growth as described by the Droop model. First, a formulation for the integration of experiment design in linear dynamic systems is extended to nonlinear dynamic systems resulting in an NMPC formulation with integrated experiment design. In a second approach, the notion of economic optimal experiment design is incorporated within the NMPC formulation. Here, an economic loss function related to inaccurate parameter estimates is minimized instead of a measure of the parameter variances, resulting in improved control performance. The advantage of the proposed techniques over a naive experiment design integration approach is illustrated with Monte Carlo simulations.

Keywords: Nonlinear model predictive control, Integrated experiment design, Economic optimal experiment design, Nonlinear matrix inequality, Droop model

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1. Introduction

Cultivation of micro algae has a wide application potential ranging from renewable energy to food and waste water treatment. To improve the exploitation of these micro algae on an industrial scale, advanced control techniques are indispensable for a flexible operation while accounting for operating constraints. This work considers the Droop model (Droop, 1968) for micro algae growth. It describes the ability of micro algae to store nutrients and the decoupling between substrate uptake and biomass growth. A specific challenge for bioprocess models is to remain valid over time as organisms adapt their behavior, and to ensure a continued profitable/desired operation. However, given the inherent variability of biological systems model updates are inevitable.

Model Predictive Control (MPC) has become an industry accepted technology applicable for a wide variety of (bio)chemical (Forbes et al., 2015) systems. The basic idea behind MPC is to repeatedly solve a model-based optimal control problem to control the future behavior of the system (Lee, 2011). The main difference from the more traditional control strategies is that in MPC, the optimal control input is computed iteratively online based on a process model.

Classic (linear) MPC consists of a linear system model, linear constraints and a quadratic (tracking) objective (Lee, 2011). Consequently, the global aim is a smooth tracking of an a priori determined target reference profile while continuously minimizing the effect of disturbances. In the last decades the MPC formulation has been extended to include nonlinear dynamic systems with nonlinear constraints (NMPC) and/or economic objectives (E(N)MPC). For a more detailed description the interested reader is referred to, e.g., Morari and Lee (1999); Rawlings (2000); Diehl et al. (2002); Würth et al. (2009); Diehl et al. (2011).

Before (N)MPC can be applied in practice, one of the main challenges is to obtain and to maintain an accurate process model for the system in consideration. In the literature it has been reported that one of the most expensive parts of MPC commissioning is the modeling effort (Larsson et al., 2013, 2015). However, in a

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real-world operation, bioprocess systems tend to (gradually) change over time, so a model-based controller might not be able guarantee their optimal operation after certain time. The first critical step in the maintenance of model-based controllers is to distinguish between control-relevant plant changes and variations in disturbance characteristics. Following this strategy, Mesbah et al. (2015) recently developed an approach for linear systems.

When it has been determined that the cause is a control-relevant plant change, a dedicated model (re)calibration is required to (re)adjust the model parameters to the observed system's behavior (Larsson et al., 2015; Mesbah et al., 2015). To this extent, the data has to be such that the model parameters can be estimated accurately. To reduce the experimental burden and limit the cost, informative experiments need to be designed. The field of off-line model-based optimal experiment design (OED) for *nonlinear dynamic systems* started with Espie and Macchietto (1989) although many statisticians have addressed the issue earlier for static models (e.g., Fisher (1935); Kiefer and Wolfowitz (1959)) in the previous century. A recent overview of the state-of-the-art for nonlinear dynamic systems is given in Franceschini and Macchietto (2008). More recently, approaches have been developed to design informative experiments where the only parameters considered are the ones relevant for the economic goal of the model (*economic OED*) (Recker et al., 2012; Houska et al., 2015). For linear dynamic systems the first study to address the intended model application in system identification has been Gevers and Ljung (1986). Online experiment design and re-identification approaches in which control is not considered can be found in Zhu and Huang (2011); Galvanin et al. (2012); Barz et al. (2013).

In Espie and Macchietto (1989); Franceschini and Macchietto (2008); Yunfei Chu and Hahn (2013); Houska et al. (2015) experiments are designed and performed in an off-line framework in which systems are excited in contrast with the usual aim of (model predictive) control, i.e., reference tracking objectives and ensuring a smooth operation. Incorporating identification in the control loop results in the so-called *dual control problem* (e.g., Gevers (1993); Hasmet and Michael (1996); Bombois et al. (2006); Gevers et al. (2011); Larsson et al. (2013); Forgione et al. (2015); Larsson et al. (2015). This dual control problem has been studied thoroughly for linear dynamic systems and is still an active field of research (e.g., (Forgione et al., 2015; Larsson et al., 2015; Mesbah et al., 2015; Heirung et al., 2015)), while it remains an open field for nonlinear dynamic systems (Gevers, 2006). One important reason is that the frequency domain identification approaches cannot directly be extended to nonlinear systems. In addition, operating constraints are hard to consider directly in classic frequency domain approaches (Larsson et al., 2013, 2015).

In the current paper, the first contribution is the adaptation of a formulation for linear dynamic systems of Larsson et al. (2013, 2015) to nonlinear MPC, resulting in *NMPC with integrated experiment design* (iED-NMPC). The main challenge in the proposed formulation is that a nonlinear matrix inequality has to be added. However, the nonlinear matrix inequality is reformulated such that these problems can be implemented in standard NMPC packages (Houska et al., 2011; Lucia et al., 2014; Bhonsale et al., 2016) without the need for solving the nonlinear matrix inequality explicitly. A second contribution of this paper is a formulation for joint identification and control based on economic optimal experiment design (Houska et al., 2015). This formulation requires the addition of one scalar constraint. Furthermore, this constraint has, in contrast to the alphabetic OED criteria in optimal experiment design, a straightforward economic interpretation. A third contribution is an extensive case study, for which the proposed techniques are compared with a naive integrated experiment design formulation.

The paper is structured as follows: Section 2 reviews optimal experiment design and how the information content can be quantified with future applications in mind. In Section 3, the integrated experiment design formulations are presented. In Section 4 the employed case study based on the Droop model, is described. The numerical simulation results are discussed in Section 5. Finally, Section 6 summarizes the main conclusions.

2. Optimal experiment design

This section reviews existing methods for optimal experiment design problem formulations for nonlinear dynamic systems. Throughout this paper, the notation

$$\frac{dx}{d\tau}(\tau) = \quad f(x(\tau), u(\tau), p) \ \ \forall \tau \in [t, t + t_{\mathrm{p}}], \tag{1}$$

is used to denote a set of parametric ordinary differential equations. Here, τ denotes time, x the state vector, u input functions that we can choose to control the system, and p a parameter vector, whose exact value is unknown and needs to be (re)estimated. The dynamic system equations are represented by the right-hand side function f. In addition, the function $h(x(t))$ denotes a potentially nonlinear measurement function. The measurements itself, given by

$$\eta(t) = h(x(t)) + v(t),$$

are affected by a zero mean Gaussian measurement noise with variance-covariance matrix $\mathbb{E}\{v(\tau)v(\tau')^\top\} = Q(\tau)\delta(\tau - \tau')$. The functions f and h are assumed to be twice continuously differentiable. Furthermore, in this section, the initial value of the system is considered known, i.e., $x(t) = x_0$.

The focus of Section 2.1 is on how the information content of the measurements η can be quantified. Subsequent sections review both the traditional alphabetic optimal experiment design criteria, as well as modern formulations based on application oriented optimal experiment design and economic optimal experiment design.

2.1. Quantifying information

One way to quantify the information content of the measurements η collected over the time horizon $[t, t+t_p]$ is by computing the Fisher information matrix (Walter and Pronzato, 1997; Franceschini and Macchietto, 2008), which is given by

$$F(t + t_{\mathrm{p}}) = F(t) + \int_t^{t+t_{\mathrm{p}}} \frac{\partial x}{\partial p}(\tau)^\top \frac{\partial h(x(\tau))}{\partial x}^\top Q(\tau)^{-1} \frac{\partial h(x(\tau))}{\partial x} \frac{\partial x}{\partial p}(\tau) d\tau \; . \tag{2}$$

Here, $F(t)$ denotes the Fisher information with respect to the parameters till the time t. As the true values p_0 for the system parameters p are unknown, the Fisher information matrix is evaluated at the current best guess $\hat{p}$, i.e., $F_{\hat{p}}$. For the case that the measurements are only available at discrete time point rather than in continuous time, the Fisher information matrix can be computed similarly by replacing the integral in Equation (2) with a summation (Walter and Pronzato, 1997). Under the assumption of unbiased estimators and uncorrelated Gaussian noise, the inverse of $F(t + t_{\mathrm{p}})$ approximates the lower bound of the parameter estimation variance-covariance matrix, i.e., the Cramér-Rao bound (Ljung, 1999; Walter and Pronzato, 1997). The sensitivities which are needed for the Fisher information matrix, are computed as the solution of the following ordinary differential equations:

$$\frac{d}{d\tau}\frac{\partial x}{\partial p}(\tau) \quad = \quad \frac{\partial f}{\partial x}(\hat{x}(\tau), u(\tau), \hat{p})\frac{\partial x}{\partial p}(\tau) + \frac{\partial f}{\partial p}(\hat{x}(\tau), u(\tau), \hat{p}). \tag{3}$$

Here, $\hat{x}(\tau)$ is the solution of the set of ordinary differential equations:

$$\dot{\hat{x}}(\tau) \quad = \quad f(\hat{x}(\tau), u(\tau), \hat{p}), \tag{4}$$

in which it is assumed that $u(\tau)$ is given. In an experiment design formulation both the Fisher information matrix Equation (2) and the sensitivity Equations (3) have to be added to the dynamic optimization formulation. Thus, the cost of computing the Fisher information matrix is determined by the cost of solving the variational differential equation (Equation (3)) comprising $n_{\mathrm{x}} \cdot n_{\mathrm{p}}$ states, as well as the integral in Equation (2), which can alternatively be computed by solving a (trivial) differential equation with $\frac{n_{\mathrm{p}}(\cdot n_{\mathrm{p}}+1)}{2}$ differential states. An alternative approach for computing the $F(t)$ is based on solving Riccati differential equation, as discussed in Telen et al. (2013).

2.2. *Alphabetic experiment design criteria*

In a classic optimal experiment design approach a scalar measure of the Fisher information matrix ($\Phi(\cdot)$) is usually optimized, which is often described by the so-called alphabetic design criteria. Some widely used scalar functions are listed below (Pukelsheim, 1993; Walter and Pronzato, 1997; Franceschini and Macchietto, 2008):

- **A-criterion:** $\min[\text{trace}(F^{-1})]$. An A-optimal design minimizes the average of the parameter estimation errors. Geometrically this is the minimization of the enclosing frame of the joint confidence region. A computationally efficient formulation using sequential semidefinite programming can be found in Telen et al. (2014a). This criterion is sometimes heuristically reformulated as maximizing the trace of F.

- **D-criterion:** $\max[\det(F)]$. A D-optimal design minimizes the geometric mean. Geometrically, this is minimizing the volume of the joint confidence region. A distinct advantage of this criterion is that it is scaling invariant.

- **E-criterion:** $\max[\lambda_{\min}(F)]$. E-optimal designs aim at minimizing the largest parameter error, which corresponds to minimizing the length of the largest uncertainty axis of the joint confidence region.

- **Modified E-criterion:** $\min[\frac{\lambda_{\max}(F)}{\lambda_{\min}(F)}]$. The modified E-criterion (ME-criterion) minimizes the condition number of the Fisher information matrix. A priori the theoretical lowest possible value of one is known (though not always achievable). This corresponds to circular joint confidence regions. However, an absolute decrease of the joint confidence region is not guaranteed with this criterion.

A severe drawback of the aforementioned criteria is that there is no direct connection with how efficient the experiment is with respect to the later use of the model. It is entirely possible that too much effort is spent for estimating the parameters which hardly influence the considered operating objectives. In the following two subsections, approaches which consider the model application are discussed.

2.3. Application oriented OED

The technique which is discussed in this section has originally been developed for linear dynamic systems. As discussed previously, it is assumed that there exists a vector p_0 which contains the true system parameters (which have slowly evolved/changed over time after the NMPC development). The Fisher information matrix can subsequently be used to compute an approximation of the parameter confidence ellipsoid:

$$P(\alpha) = \{p : (p - p_0)^\top F_{p_0}(p - p_0) \leq \chi^2_\alpha(n_p)\} , \tag{5}$$

here $\chi^2_\alpha(n_p)$ is the α-percentile of the χ^2-distribution with n_p degrees of freedom (Walter and Pronzato, 1997) and F_{p_0} denotes the Fisher information matrix evaluated with the true system parameters. In Larsson et al. (2013, 2015) this ellipsoid which approximates the set of estimates for a specified confidence level, is called the *identification ellipsoid*.

In system identification the notion of an *application cost* has been introduced (Hjalmarsson, 2009; Larsson et al., 2013, 2015). It is a measure of the performance degradation due to model and plant mismatch. The application cost is denoted by C_{app} in the current paper. The following assumptions are made with respect to the application cost: $C_{\text{app}}(p) \geq 0$ and $C_{\text{app}}(p_0) = 0$. A model is considered acceptable if the degradation is small. A set of acceptable models is described by:

$$\mathcal{S}(\gamma) = \{p : C_{\text{app}}(p) \leq \gamma^{-1}\} , \tag{6}$$

here γ represents an application specific constant governing the model accuracy (note that γ has the inverse units of the application cost). The larger gamma, the more accurate the model and the smaller the performance degradation. A discussion on how to choose γ can be found in Larsson (2011). A convex approximation of the set of acceptable models is obtained by requiring that $C_{\text{app}}(p_0) = 0$ and $\frac{\partial C_{\text{app}}(p_0)}{\partial p} = 0$, so the set of acceptable model parameters is approximated by a second-order Taylor expansion (Larsson et al., 2013, 2015):

$$E(\gamma) = \{p : (p - p_0)^\top C''_{\text{app}}(p_0)(p - p_0) \leq 2\gamma^{-1}\}. \tag{7}$$

Here, C''_{app} denotes the Hessian of the application cost with respect to p.

In Larsson et al. (2013, 2015), this ellipsoid is called the *application ellipsoid*. The goal of application oriented experiment design is to find an input with a high prob-

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ability to result in acceptable parameters while minimizing the cost of the identification experiment. In Hjalmarsson (2009) it is suggested to formulate this aim as $P(\alpha) \subset E(\gamma)$ which means that the identification ellipsoid should be a subset of the application ellipsoid. Mathematically this is equivalent to:

$$F_{p_0} \succ \frac{\gamma \chi^2_\alpha(n_p)}{2} C''_{\mathrm{app}}(p_0) \; . \tag{8}$$

Here, $\succ$ denotes the matrix inequality. So, this approach leads to a lower bound for the Fisher information matrix based on the considered application.

Remark 1. A first important issue of this formulation is that both the computation of the Fisher information matrix as well as $C''_{\mathrm{app}}(p_0)$ depend on p_0, the true system parameters for the theoretical derivation. However, the goal is to design an experiment that yields the estimate p_0. This means that in the formulations the current best guess for the parameters, i.e., $\hat{p}$ has to be used instead of the unknown p_0. As the values $\hat{p}$ are not the true parameter values, the obtained profile has to be *robust* with respect to the information content and with respect to constraint satisfaction. This relates to the field of *robust optimal experiment design/NMPC*. The approaches presented in the literature, i.e., a worst case approach (Körkel et al., 2004) or an expected value approach (Ostrovsky et al., 2013; Li et al., 2008; Galvanin et al., 2010; Telen et al., 2014b; Mesbah and Streif, 2015; Rasoulian and Ricardez-Sandova, 2016), (possibly with chance constraints), can be used to extend and to make the presented approaches more robust.

Remark 2. In Larsson (2011); Ebadat et al. (2014) several application costs have been discussed. In this paper a least squares type of function is employed:

$$C_{\mathrm{app}}(p) = \int_0^{t_{\mathrm{f}}} (x(\tau)_p - x(\tau)_{p_0})^\top S (x(\tau)_p - x(\tau)_{p_0}) d\tau \; , \tag{9}$$

here, S is an user defined weighting matrix while $x(\tau)_{p_0}$ are the state profiles based on parameter p_0. The symbol $x(\tau)_p$ denotes the state profiles based on parameter p. The goal is to minimize the model and plant difference over, e.g., the NMPC tracking profile. An advantage of such a least squares objective function is that the

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Hessian can be consequently computed using a Gauss-Newton approximation. This results in the following:

$$C''_{\mathrm{app}}(p_0) = \int_0^{t_f} \frac{\partial x}{\partial p}(\tau)\Big|_{p_0}^{\top} S \frac{\partial x}{\partial p}(\tau)\Big|_{p_0} d\tau \ . \tag{10}$$

The above formulation which resembles quite closely the Fisher information matrix is subsequently used as lower bound for the Fisher information matrix. In Larsson et al. (2015) a relation between the different types of performance measures and the application cost is discussed.

2.4. Economic experiment design

In this section, the main idea of *economic optimal experiment design* is reviewed. Here, the main assumption is that the ultimate goal is to solve a parametric optimal control problem of the form:

$$\begin{aligned} &\min_{x(\cdot),u(\cdot)} \int_t^{t+t_{\mathrm{p}}} J(x(\tau),u(\tau))d\tau \quad \text{with} \\ J(x(\tau),u(\tau)) =& (x(\tau)-x_{\mathrm{ref}}(\tau))^{\top} W (x(\tau)-x_{\mathrm{ref}}(\tau)) + \\ & (u(\tau)-u_{\mathrm{ref}}(\tau))^{\top} R (u(\tau)-u_{\mathrm{ref}}(\tau)) \end{aligned} \tag{11}$$

subject to:

$$\frac{dx}{d\tau}(\tau) = f(x(\tau),u(\tau),p) \ \ \forall \tau \in [t, t+t_{\mathrm{p}}], \tag{12}$$

$$u(\tau) \in U, \quad x(\tau) \in X, \quad x(t+t_{\mathrm{p}}) \in \ X_{\mathrm{f}}, \tag{13}$$

$$x(t) = \bar{x}_{\mathrm{t}}. \tag{14}$$

The vectors x_{ref} and u_{ref} denote the state and control reference profiles while the matrices R and W are positive semidefinite weighting matrices. Recall that the vector x contains the state variables while X is the set of the state bounds and X_{f} the terminal set. The set U is the set of admissible control values for the controls u. When, an optimal control problem is solved based on the current parameter estimate $\hat{p}$, instead of the true system parameter p_0 an optimality gap is obtained which is mathematically defined in Houska et al. (2015) as:

$$\Delta(p) := J(\xi^*(\hat{p}, p_0), u^*(\hat{p})) - J(\xi^*(p_0, p_0), u^*(p_0)) \ ,$$

where the function $\xi^*(\hat{p}, p_0)$ denotes the solution of the dynamic equations:

$$\dot{\xi}(t) = f(\xi(t), u^*(\hat{p})(t), p_0)$$

in dependence on $\hat{p}$ and p_0. The vector $u^*(p)$ denotes an optimal solution for the control input profile u in dependence on p of the problem (11)-(14). In many experiment design approaches the parameter variance is minimized by optimizing some scalar measure of the Fisher information matrix. Instead, it is proposed in Houska et al. (2015) to determine the parameter p in such a way that this expected loss of optimality, i.e., $\mathbb{E}_p \{\Delta(p)\}$ is minimized. Unfortunately, the exact expectation value $\mathbb{E}_p \{\Delta(p)\}$ is rather difficult to compute, since the evaluation of the function Δ requires to solve a parametric nonlinear programming problem. However, under mild assumptions on the objective function and the constraints, the function Δ can be approximated by a second-order Taylor expansion of the Lagrangian based on the state and control profiles which have been obtained by solving the underlying optimal control problem on the current parameter estimate, see Houska et al. (2015) for more details:

$$\begin{aligned}\mathbb{E}_p \, \Delta(p) \;\approx\; & \frac{1}{2}\mathbb{E}_p \left((p-p_0)^\top V(p_0)(p-p_0)\right) \\ = \; & \frac{1}{2}\mathrm{Tr}\left(V(p_0)\mathbb{E}_p\left\{(p-p_0)(p-p_0)^\top\right\}\right) .\end{aligned}$$

The expression for the second-order expansion of the expected loss of optimality leads to the introduction of a weighted A-criterion of the form:

$$\Phi_{\text{Economic}}(F_{\hat{p}}^{-1}) \;:=\; \frac{1}{2}\,\mathrm{Tr}(V(\hat{p})F_{\hat{p}}^{-1}) \ .$$

Here, matrix V and the Fisher information matrix has to be evaluated at the currently best available estimate $\hat{p}$, since the exact parameter p_0 is unknown. A formula to compute the function $V(\hat{p})$ can be found in Houska et al. (2015). Based on this

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definition, the economic optimal experiment design proceeds in exactly the same way as traditional optimal experiment design formulations with the only difference that a very particular choice for the scalar design criterion, namely the function Φ_{Economic}, is used for solving the optimal experiment design problem. A particular feature of the economic experiment design criterion is that each parameter is directly weighted with the relative importance to the economic objective function.

3. Integrated experiment design model predictive control

The goal of this section is to discuss variants of nonlinear model predictive control (NMPC) Rawlings (2000); Diehl et al. (2002) in order to control the system (1). However, instead of using a standard NMPC formulation, the focus of this paper is on integrated optimal experiment design criteria for NMPC. Such iED-NMPC formulations are needed if the model parameters, which have been obtained in a past NMPC commissioning, are not necessarily able to describe the future system behavior properly. In this situation, the MPC controller has to be used in combination with an estimator, e.g., an extended Kalman filter, or a moving horizon estimator (Robertson et al. (1996); Bagterp Jorgensen et al. (2007); Särkkä (2007)), in order to update the parameter estimates based on the incoming measurements. Now, the actual challenge is that not only the nominal control performance of the NMPC controller, but also the accuracy of future parameter estimates is influenced by the choice of the control input u. Consequently, iED-NMPC objectives intend to find a trade-off between optimizing the economic control performance and the information on future parameter estimates.

Throughout this paper, it is assumed that the model structure itself remains valid (but the parameter estimate may be inaccurate). An approach to distinguish control-relevant system changes from variations in disturbance characteristics for linear systems can be found in Mesbah et al. (2015). In the remainder of the paper it is assumed that the controller has already been diagnosed with a significant control-relevant system change. Consequently, the model output and the actual systems behavior can be attributed to a slow degradation/evolution of natures parameters, as conceptually illustrated in Figure 1.

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In this section, the specifics of an NMPC formulation are discussed first. Subsequently, a naive integration of OED in NMPC is introduced. In the third subsection, the first integrated experiment design formulation is presented while the section concludes with the second integrated experiment design formulation.

3.1. NMPC formulation

The optimal control problem (11)-(14) is solved at every step in the NMPC formulation employed in this paper (Vallerio et al., 2014). It is assumed that $\tau \in [0, t_\mathrm{f}]$ denotes the time and t_f denotes the total length of the simulation/operation window. Note that in this paper a fixed final time for the NMPC is considered which is similar to NMPC formulations for batch processes. This is also motivated by the fact that also in continuous processes a limited experimental window can be allowed. The variable t_p is the prediction horizon in the NMPC algorithm. The vector $\bar{x}_\mathrm{t}$ denotes the state measurements or estimates at time instance t.

3.2. Naive integration of OED in NMPC

A straightforward but naive formulation for integrating experiment design in NMPC is the following:

$$\min_{x(\cdot),u(\cdot)} \int_t^{t+t_\mathrm{p}} J(x(\tau), u(\tau)) d\tau \quad \text{with} \tag{15}$$

$$\begin{aligned} J(x(\tau), u(\tau)) =& (x(\tau) - x_\mathrm{ref}(\tau))^\top W (x(\tau) - x_\mathrm{ref}(\tau)) + \\ & (u(\tau) - u_\mathrm{ref}(\tau))^\top R (u(\tau) - u_\mathrm{ref}(\tau)) \end{aligned}$$

subject to:

Equations (2)-(3) and (12)-(14) and

$$\begin{aligned} \Phi\left(F(t+t_\mathrm{p})\right) \geq& \frac{t+t_\mathrm{p}}{t_\mathrm{f}} \Phi_\mathrm{LB}, \quad \text{if } t_\mathrm{f} \notin [t, t+t_\mathrm{p}], \\ \Phi\left(F(t_\mathrm{f})\right) \geq& \Phi_\mathrm{LB}, \quad \text{if } t_\mathrm{f} \in [t, t+t_\mathrm{p}]. \end{aligned} \tag{16}$$

Equation (16) guarantees the excitation of the system because the above formulation enforces a specific minimum value (Φ_LB) of one of the scalar measures of the

Fisher information matrix at the end of experimental window t_f of the NMPC run.

A potential way to choose Φ_LB could be by first performing an open loop multi-objective optimization for the total simulation time t_f by considering both the maximization of the information content and the objective of the NMPC. Based on the user preferences a compromise can be chosen as, e.g., suggested in Telen et al. (2012). A challenge which remains, is how the information content is related to the future system behavior. The following two formulations tackle the issue of relating information content to the expected system behavior in an integrated experiment design setting.

Note. Besides an estimation or measurement of the actual states, the values of the sensitivity and Fisher information matrix elements need to be acquired. In this paper the exact values of the predictions are employed. In practice, however, an estimation algorithm is required, e.g., an extended/unscented Kalman filter (Särkkä, 2007; Bagterp Jorgensen et al., 2007) to estimate the actual sensitivity equations/Fisher information matrix elements from the noisy measurements of the actual state. For the illustrative purposes of the presented iED-NMPC approaches this aspect is considered out of the scope of the presented paper.

3.3. iED-NMPC Formulation 1: A matrix inequality based integrated experiment design formulation

By using the consideration from Section 2.3, an iED-NMPC formulation based on application oriented OED is obtained:

$$\min_{x(\cdot),u(\cdot)} \int_t^{t+t_\mathrm{p}} J(x(\tau),u(\tau))d\tau \tag{17}$$
$$\begin{aligned} J(x(\tau),u(\tau)) =&(x(\tau)-x_\mathrm{ref}(\tau))^\top W(x(\tau)-x_\mathrm{ref}(\tau))+\\ &(u(\tau)-u_\mathrm{ref}(\tau))^\top R(u(\tau)-u_\mathrm{ref}(\tau))\end{aligned}$$

subject to:

Equations (2)-(3) and (12)-(14) and

$$\begin{aligned} &F(t+t_{\mathrm{p}})_{p_0} \succ \tfrac{t+t_{\mathrm{p}}}{t_{\mathrm{f}}} \tfrac{\gamma\chi^2_\alpha(n_p)}{2} C''_{\mathrm{app}}(p_0), \quad \text{if } t_{\mathrm{f}} \notin [t, t+t_{\mathrm{p}}]\,, \\ &F(t_{\mathrm{f}})_{p_0} \succ \tfrac{\gamma\chi^2_\alpha(n_p)}{2} C''_{\mathrm{app}}(p_0), \quad \text{if } t_{\mathrm{f}} \in [t, t+t_{\mathrm{p}}]. \end{aligned} \tag{18}$$

In the above formulation there is a hard, time-dependent constraint that at t_{f} the Fisher information matrix should satisfy the information constraint (18). This increases linearly as long as the final experimental time is not part of the prediction horizon and is fixed at the minimum required information content value when the final experimental time is part of the prediction horizon. These time-dependent constraints are necessary to ensure that the controller does not postpone the control actions indefinitely required to sufficiently excite the system.

Remark 1. An important issue in the presented approach is whether the lower bound based on the application cost leads to a feasible or infeasible nonlinear matrix inequality in the NMPC formulation. It is possible that for a given case study (with the chosen values for γ and the confidence level α) no Fisher information matrix exists that satisfies the given bound in the given experimental window. The idea is to increase the number of experiments (or the number of independent measurements in a single experiment which is mathematically equivalent but due to, e.g., lack of sensors can be harder to perform in practice) when a single experiment is expected not to be informative enough based on the a priori calculations. The following approach is suggested:

1. Compute $\frac{\gamma\chi^2_\alpha(n_p)}{2} C''_{\mathrm{app}}(\hat{p})$ based on the tracking NMPC profile of past operations, check whether $F(t_{\mathrm{f}})_{\hat{p},\mathrm{NMPCrun}} \succ \frac{\gamma\chi^2_\alpha(n_p)}{2} C''_{\mathrm{app}}(\hat{p})$, if satisfied the NMPC run is already sufficiently informative, re-estimate parameters based on the NMPC data, if not, go to 2.
2. Solve an off-line optimal experiment design optimization problem that optimizes one of alphabetic criteria, set $n_{\mathrm{ex}} = 1$, check whether the $F(t_{\mathrm{f}})_{\hat{p},\mathrm{OED}} \succ \frac{\gamma\chi^2_\alpha(n_p)}{2n_{\mathrm{ex}}} C''_{\mathrm{app}}(\hat{p})$, if this is satisfied go to next step, otherwise $n_{\mathrm{ex}} = n_{\mathrm{ex}} + 1$ and iterate till satisfied considering all n_{ex} experiments.
3. Perform n_{ex} times the NMPC run (or measure each point n_{ex} times) with the information bound $\frac{\gamma\chi^2_\alpha(n_p)}{2n_{\mathrm{ex}}} C''_{\mathrm{app}}(\hat{p})$, collect all measurements and re-estimate

the parameters.

There is always a trade-off between the information content in the experiment and the economic objective. If the user is interested in a thorough numerical trade-off investigation, the following papers are suggested (Telen et al., 2012) on optimal experiment design and (Vallerio et al., 2014) on NMPC and multi-objective optimization under uncertainty (Vallerio et al. (2015)).

NMPC is in general a nonconvex optimization problem. In addition Equation (18) denotes a nonlinear matrix inequality. In a practical setting this nonlinear matrix inequality has to be addressed. A first approach to solve this can be a linearization such that a sequential semidefinite programming approach can be followed (Telen et al., 2014a). A drawback of this approach is that dedicated semidefinite programming solvers are required, which are not always available in standard NMPC packages. Furthermore, due to the linearization, convergence can be slow, especially important in the context of online identification and control. A second approach is to employ Sylvester's criterion (Wicaksono and Marquardt, 2013; Telen et al., 2015).

Sylvester's criterion: a real-symmetric matrix $A \in \mathbb{R}^{n\times n}$ is positive-definite if and only if all of the leading principal minors have a positive determinant.

$$A \succ 0 \iff \det\left(A_{[1:i\times 1:i]}\right) > 0,\ \forall i = 1,\ldots,n\ . \tag{19}$$

When this criterion is applied the following integrated experiment design NMPC (iED-NMPC) formulation for Equation (18) is obtained:

$$\begin{aligned}
&\det\left(\left(F(t+t_\mathrm{p}) - \tfrac{\tau}{t_\mathrm{f}}\tfrac{\gamma\chi^2_\alpha(n_p)}{2}C''_{\mathrm{app}}(p_0)\right)_{[1:i\times 1:i]}\right) && > 0\\
&\text{with}\quad i = 1,\ldots,n_\mathrm{p},\quad \text{if } t_\mathrm{f} \notin [t, t+t_\mathrm{p}]\\
&\det\left(\left(F(t_\mathrm{f}) - \tfrac{\min(\tau,t_\mathrm{f})}{t_\mathrm{f}}\tfrac{\gamma\chi^2_\alpha(n_p)}{2}C''_{\mathrm{app}}(p_0)\right)_{[1:i\times 1:i]}\right) && > 0\\
&\text{with}\quad i = 1,\ldots,n_\mathrm{p},\quad \text{if } t_\mathrm{f} \in [t, t+t_\mathrm{p}].
\end{aligned} \tag{20}$$

The reformulation of the nonlinear matrix inequality into Equation (20) results in a problem formulation with n_p additional nonlinear constraints. The motivation of the presented approach is that *iED-NMPC formulation 1* based on the above formulation can subsequently be implemented in existing NMPC software (Houska et al., 2011; Lucia et al., 2014; Bhonsale et al., 2016) without the need for adaptations of the optimization routines.

3.4. iED-NMPC Formulation 2: Economic integrated experiment design in (N)MPC

Similar to the integrated experiment design approach of the previous paragraph, the following formulation is proposed which includes the economic optimal experiment design notation.

$$\min_{x(\cdot),u(\cdot)} \int_t^{t+t_\mathrm{p}} J(x(\tau),u(\tau))d\tau \tag{21}$$

$$\begin{aligned} J(x(\tau),u(\tau)) = &(x(\tau)-x_\mathrm{ref}(\tau))^\top W(x(\tau)-x_\mathrm{ref}(\tau))+ \\ &(u(\tau)-u_\mathrm{ref}(\tau))^\top R(u(\tau)-u_\mathrm{ref}(\tau)) \end{aligned}$$

subject to:

Equations (2)-(3) and (12)-(14) and

$$\frac{1}{2}\,\mathrm{Tr}(V(\hat{p})F_{\hat{p}}^{-1}(t+t_\mathrm{p})) \le \frac{t_\mathrm{f}}{t+t_\mathrm{p}} E_\mathrm{UB} \quad \text{if } t_\mathrm{f} \notin [t, t+t_\mathrm{p}]\ , \tag{22}$$

$$\frac{1}{2}\,\mathrm{Tr}(V(\hat{p})F_{\hat{p}}^{-1}(t_\mathrm{f})) \le E_\mathrm{UB} \quad \text{if } t_\mathrm{f} \in [t, t+t_\mathrm{p}]\ . \tag{23}$$

The main difference between the proposed formulation of the current section and that of the previous section is the addition of a single scalar information constraint. This leads to a straightforward implementation in standard NMPC tools. A remaining issue is the choice of the upper bound E_UB for the allowed economic optimality gap. The following strategy is proposed:

1. Compute $V(\hat{p})$ and $E_\mathrm{NMPC} := \frac{1}{2}\,\mathrm{Tr}(V(\hat{p})F_{\hat{p}}^{-1})$ based on the computed NMPC profile, assess with the NMPC objective function value if the predicted economic loss is acceptable; if satisfied, perform experiment and re-estimate parameters, else, go to 2.
2. Solve an optimal experiment design optimization problem that minimizes, $E_\mathrm{OED} := \min \frac{1}{2}\,\mathrm{Tr}(V(\hat{p})F_{\hat{p}}^{-1})$, for which $E_\mathrm{OED} \le E_\mathrm{NMPC}$ holds. This provides the minimum achievable optimality loss for the given objective function.

3. Choose $E_{\mathrm{UB}} \in [E_{\mathrm{OED}}, E_{\mathrm{NMPC}}]$, based on preference.
4. Perform the NMPC with the given information bound, collect measurements and re-estimate the parameters.

As in this formulation $\hat{p}$ is used as well, the information content has to be robust in the neighborhood of $\hat{p}$. Potential approaches have been referred to in Remark 2 in Section 3.3. These approaches can be extended to include the formulation of this section.

3.5. A discussion on the two approaches

Both of the presented approaches try to reconcile the control of the system with a sufficient excitation of the system such that the parameters can be estimated accurately. Furthermore, both methods require a previously available function with corresponding state profiles. In iED-NMPC formulation 1, this is the *application cost* while in formulation 2 this is the so-called *economic objective function*. In addition, both methods perform a second-order Taylor approximation with respect to the considered parameters. The first main difference is in how subsequently these matrices are employed. In formulation 1, a matrix inequality is obtained to ensure that the predicted parameter ellipsoid is contained in a lower bound determined by the Taylor expansion. In the second approach this expansion serves as a weighting function with respect to the parameter variance-covariance matrix. When the trace of this matrix is computed, an approximation of the expected economic loss function is obtained. The second main difference is in the way the required information content is added to the optimization formulation. In formulation 1, this is through a nonlinear matrix inequality for which a dedicated treatment is required. In contrast, for the second formulation a single scalar constraint is sufficient which is easier to integrate in existing dynamic optimization software packages.

Remark 3.1. *Notice that even if the nominal objective is a strictly convex (least-squares) tracking term, the proposed iED-NMPC problem formulations lead to economic performance criteria that are in general neither convex nor in a least-squares tracking form anymore. In particular, the additional learning terms in the iED-NMPC formulation might destabilize the controller, if the iED-NMPC excites the system too extremely in order to be able to estimate the parameters. Unfortunately,* *a mathematical stability analysis tailored for existing persistently exciting and iED-NMPC controllers is at the current status of research not available. However, the stability of general economic (N)MPC controllers has been analyzed by many authors (Amrit et al. (2011); Angeli et al. (2012); Diehl et al. (2011); Grune (2011); Houska (2015)). In the sense that the proposed iED-NMPC controllers can be interpreted as economic NMPC controllers, the corresponding stability results can also be applied to analyze (and enforce) the stability of the proposed iED-NMPC controller.*

4. Case study

The case study employed in this paper is the Droop model (Droop, 1968; Bernard, 2011). It describes the growth of micro algae in a photobioreactor under constant temperature and illumination conditions. The model equations are given by:

$$\dot{C}_\mathrm{S} = -\,\rho(C_\mathrm{S})C_\mathrm{X} - D(C_\mathrm{S} - S_\mathrm{in})\ , \tag{24}$$

$$\dot{C}_\mathrm{Q} = \rho(C_\mathrm{S}) - \mu(C_\mathrm{Q})C_\mathrm{Q}\ , \tag{25}$$

$$\dot{C}_\mathrm{X} = \mu(C_\mathrm{Q})C_\mathrm{X} - DC_\mathrm{X}\ . \tag{26}$$

Here, the states, C_S, C_Q, and C_X denote the substrate concentration (mg N/L), the intracellular quota (mg N/ mg C), and the biomass concentration (mg C/L). All states are assumed to be measurable with the following measurement variances, $\sigma^2_{C_\mathrm{S}} = 1.0$ (mg N/L)^2, $\sigma^2_{C_\mathrm{Q}} = 1.0 \cdot 10^{-5}$ (mg N/ mg C)^2, and $\sigma^2_{C_\mathrm{X}} = 1.0$ (mg C/L)^2, the nondiagonal elements are assumed to be zero. The total simulation time or operation window is $t_\mathrm{f} = 14$ days, while the prediction time is $t_\mathrm{p} = 7$ days in the dynamic optimization problem. The control action is the dilution rate D, while S_in is the fixed, pre-set substrate concentration in the feed. For all optimizations, a single shooting approach is employed, where the control action is discretized in 7 steps (each corresponding to a single day) so $u = (D(0), \ldots, D(t_\mathrm{p}-1))^\top$. All simulations are performed using the ACADO toolkit (Houska et al., 2011). The uptake rate is given by the following equation:

$$\rho(C_\mathrm{S}) = \rho_\mathrm{m}\frac{C_\mathrm{S}}{C_\mathrm{S} + K_\mathrm{s}}\ , \tag{27}$$

while the growth rate is described by:

$$\mu(C_{\mathrm{Q}}) = \mu_{\mathrm{m}} \left(1 - \frac{Q_0}{C_{\mathrm{Q}}}\right) . \tag{28}$$

For this case study the tracking of the biomass concentration at 100 mg C/L is considered as the objective function:

$$J = \int_0^{t+t_{\mathrm{p}}} (C_{\mathrm{X}}(t) - 100)^2 dt . \tag{29}$$

In the model the following three parameters are of interest for the optimal experiment design procedure, i.e., $p = (\mu_{\mathrm{m}}, K_{\mathrm{s}}, \rho_{\mathrm{m}})^\top$. Initially, the parameters have been estimated to be $\hat{p} = (1.6 \text{ day}^{-1}, 7.5 \text{ mg N/L}, 0.10 \text{ mg N/ (mg C . day)})^\top$. The system, however, has evolved as is quite common in biochemical systems and the true system parameters for the simulations are given by:
$p_0 = (1.2 \text{ day}^{-1}, 6.75 \text{ mg N/L}, 0.125 \text{ mg N/ (mg C . day)})^\top$. Bounds on the operating conditions and numerical values for the remaining constants are described in Table 1.

The application cost employed for the given case study is:

$$C_{\mathrm{app}}(p) = \int_0^{t_{\mathrm{f}}} (C_{\mathrm{X}}(\tau)_p - C_{\mathrm{X}}(\tau)_{\mathrm{track},\hat{p}})^\top (C_{\mathrm{X}}(\tau)_p - C_{\mathrm{X}}(\tau)_{\mathrm{track},\hat{p}}) d\tau , \tag{30}$$

while $\gamma = 0.1 \text{ (mg C/L)}^{-2}$ and a 95% confidence level is targeted: Here, $C_{\mathrm{X}}(\tau)_{\mathrm{track},\hat{p}}$ denotes the obtained biomass state profile after a tracking NMPC run using the parameters $\hat{p}$ in the controller and p_0 in the bioprocess plant. To compute the lower bound for the Fisher information matrix, also the parameter sensitivity equations need to be computed from the NMPC run.

5. Simulation results

In this section the obtained numerical results are discussed. The simulation results of the NMPC controller are described in Subsection 5.1. Subsection 5.2 discusses the naive integration approach. In Subsection 5.3, the results for the integrated experiment design formulation 1 are presented while in Subsection 5.4 the results obtained with the integrated experiment design formulation 2 are described.

5.1. NMPC simulations

First, two linearized MPC implementations and a NMPC formulation are performed where the goal for all three is to track the biomass at 100 mg C/L. The corresponding biomass, substrate, internal quota and control profiles are displayed in Figure 2. A distinct difference is observed between the two linearized approaches. Linearized MPC-1 which has the same sampling period and prediction horizon as the NMPC controller has a poor tracking performance and even seems to fail to converge to the desired target of 100 mg C/L. This failure is considered to be caused by the long prediction horizon for which the linearized model results in poor predictions and the lack of timely feedback. For the linearized MPC-2 approach, a higher sampling rate (20 d^{-1}) and a shorter prediction horizon (1 d) is chosen. Note that all control parameters are summarized in Table 2. A significant better control performance is observed for the latter linearized MPC approach with some overshoot and a slight offset in the remainder of the simulation horizon. Furthermore, a significantly more oscillating control reaction with a switching type behavior is observed. Notice that all simulations are performed with the aforementioned model-plant mismatch. Thus, our numerical comparison of linearized MPC and NMPC illustrates that a more accurate nonlinear model can cope with slower sampling rates and a larger prediction horizon. In contrast, linearized MPC approaches for an inherent nonlinear process can possibly lead to an acceptable control performance. The price to pay is however an increased sampling rate. In essence a reduction of the modeling effort is moved to the hardware/sensors. This illustrates the arising dilemma for every practical (N)MPC implementation between on the one hand the modeling/computational effort and the hardware/sampling rate requirement at the other hand.

In addition, both the resulting states of the actual system based on p_0 are depicted as well as the corresponding controller predictions based on $\hat{p}$ for the NMPC controller. It can be observed from Figure 2 that the biomass concentration is slower in reaching the targeted value of 100 mg C/L. Predicted by the controller to reach the target after 2 days while it only arrives in the neighborhood after 6-7 days. If the actual biomass concentration of the plant is investigated in detail, it is noted that the targeted of 100 mg C/L value is never actually reached and an offset is present throughout the simulation. This difference in predicted versus actual behavior is partially managed by the feedback principle but the large difference to reach the targeted value is the motivation the perform an identification experiment.

5.2. A naive integration

A first step in this naive approach is the investigation of the trade-off between the tracking objective J_1 and the maximization of the information content, i.e., $J_2 = \min -\lambda_{\min}(F(t_f))$. So, an E-optimal design has been chosen. The resulting trade-off between these objectives is computed in open loop, i.e., without an NMPC formulation using a multi-objective optimization approach. These simulations are carried out based on $\hat{p}$ as the *true* parameter values are not known. To illustrate the trade-off, a Pareto front of mathematically speaking equivalent points is depicted in Figure 3. These 11 points are computed based on a scalarization technique, i.e., the *enhanced normalized normal constraint* (Sanchis et al., 2008; Logist et al., 2010). Nevertheless, the weights of a classic weighted sum trade-off can be computed using the relations observed in Logist et al. (2012).

A sharp trade-off is observed in the maximization of the information content and the minimization of the tracking error in Figure 3. The corresponding state and control profiles are illustrated in Figure 4. Three profiles are presented, each of the two anchor points, i.e., the optimization of each of the two single objectives and a single compromise/trade-off point (in Figure 3 denoted by the green square). Note the slight difference in the obtained control action between the NMPC and the open loop optimization for the tracking objective (Figure 2 and 5). The difference can be explained by the presence of feedback in the NMPC. The different aims of the different objectives and control actions is clearly visible in Figure 4. The dilution rate starts for the maximization of the information content only at the 5th day leading to a much slower growth of biomass. Furthermore, it reaches a maximum of 140 mg C/L at the 6th day to decrease to 60 mg C/L at the 12th day at which the feed stops. It thus depicts a strong oscillatory reaction to the feeding profile. In contrast, the initial biomass concentration for the tracking objective starts already much higher. The feeding starts much earlier and subsequently decreases as it is targeted at maintaining the concentration at 100 mg C/L. The compromise experiment depicts properties of both extreme aims. It goes much faster to 100 mg C/L than the maximization of the information content profile. Its overshoot is lower and earlier and also its undershoot is not as high.

To illustrate the naive integration, an NMPC run is envisioned in which the minimum eigenvalue (i.e., the E-criterion) has to be greater than 4.0 at the end of the simulation horizon. Mathematically, this is expressed this as $\lambda_{\min}(F(t_{\mathrm{f}})) \geq 4.0$. For the practical implementation the Sylvester's criterion is employed to enforce this minimum eigenvalue (Telen et al., 2015). The obtained state and control profiles are displayed in Figure 5. In Figure 5, e.g., the biomass starts at almost the same concentration as in the NMPC tracking case where in Figure 4 this is notably lower. The biomass increases at the same pace as in the tracking case but overshoots up to 120 mg C/L. Towards 7 days, the biomass concentration decreases to 100 mg C/L after which it increases again to 120 mg C/L at day 9. Subsequently it starts to decrease to 90 mg C/L in day 12 to rise slowly to 100 mg C/L at the final time point.

A difference is observed when comparing Figure 4 and Figure 5 in the expected state evolutions. Two reasons can be envisioned. In NMPC a shorter prediction horizon is used than the open loop dynamic optimization (7 intervals versus 14.). Furthermore, in NMPC there is the aspect of feedback which is totally absent in the a priori open loop simulations. A first numerical simulation is performed by sampling 200 noise realizations for each of the 2 profiles and subsequently performing a parameter estimation procedure. The results are given in Table 3. A decrease in the standard deviation with respect to $\mu_{\max}$ is observed while for the remaining parameter estimates this is more or less in accordance. The main noticeable difference is that the mean parameter estimates of the naive approach are closer to the true system parameters p_0 than the parameter estimates of the tracking profile. However, a significant problem with the naive approach is that an accurate assessment of the future model performance is not directly possible. In the following 2 sections, the 2 presented integrated experiment design approaches are illustrated.

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5.3. iED-NMPC Formulation 1

Based on the obtained profiles of Figure 2, the Hessian of the application cost is computed. Note that as p_0 is not known, this is computed based on $\hat{p}$. The lower bound for the Fisher information matrix is computed where the aim is a 95% confidence region for the set of models which at most deviate 10 (mg C/L)^2 as measured in the application cost, this results in $\gamma = 0.1$ (mg C/L)$^{-2}$. Next, the lower bound of the Fisher information matrix is computed and compared with the Fisher information matrix of the NMPC run. Also an off-line optimization is performed where the minimal eigenvalue of the Fisher information matrix is maximized. Based on these computations a minimum number of 3 experiments is required to estimate the parameters sufficiently accurate, i.e., do 3 NMPC runs with information content constraint/measure 3 times during a single NMPC run. For a relative small process model with 3 states and 3 considered parameters, the computational burden in the NMPC formulation increases already significantly. Besides the 3 states of the process model, 9 sensitivity equations are required in addition to 6 Fisher information matrix elements. So, for a relative small system a total of 18 ordinary differential equations are needed. Given the employed sampling rate, computational time is not a concern for the considered system in this paper, however, for larger systems this may be a point of concern.

The obtained state profiles are displayed in Figure 6. The first two days of the iED-NMPC run, coincide with the NMPC run. After the biomass concentration reaches 90 mg C/L, the feeding rate is kept a 0.5 day^{-1} resulting in a sharp decrease in biomass concentration but resulting in a slight increase in both the internal quota as well as the substrate concentration. It is assumed that this action is performed to increase the information content and to satisfy the information constraint. After seven days the period of feeding stops and the biomass concentration starts to increase again which is in the neighborhood of 100 mg C/L after 9 days. In the remaining part of the experiment the concentration of 100 mg C/L is maintained.

A Monte Carlo simulation is performed to assess both the parameter accuracy as well as the performance with respect to the employed application cost. For each case, the normal NMPC run and the iED-NMPC run, 200 realizations with 3 measurements for each time point are sampled. The resulting mean parameter estimates and the corresponding variances can be found in Table 4. It is observed that both profiles are able to recover the *true* system parameters p_0. In addition, the tracking profile leads to a similar standard deviation for all parameters, except for K_s which is almost 25% larger compared with the iED-NMPC approach.

When the application cost and the number of violations (exceeding the target application cost value) for each approach is computed, a value of 29.5% is obtained for the iED-NMPC approach while the NMPC leads to 63% violations. The a priori determined value of 5% is not reached. Consider that the Fisher information matrix is always an approximation of the true parameter variance-covariance matrix, in particular for nonlinear systems. As the experiment is designed with $\hat{p}$, the robust experiment design approaches must/can be applied to guarantee the information level. However, this is out of scope for the current paper.

The distribution of the application cost is also reported. The distribution is presented as a box plot in Figure 7 (note the logarithmic scale). Mind however that the application cost is skewed, so the quartiles (Q_1, Q_2, and Q_3) are emphasized instead of mean and variance. For Q_1 the iED-NMPC experiments lead to 2.96 while the NMPC run leads to 6.1. For Q_2 this is 5.9 versus 15.6 and for the third quartile, Q_3 this is 12.0 versus 37.2. So, the presented iED-NMPC formulation leads to more informative NMPC runs compared with the tracking NMPC runs. Furthermore, this increased parameter accuracy leads to an enhanced control action in future runs, i.e., less deviations from the tracking biomass profile of p_0.

5.4. iED-NMPC Formulation 2

The obtained biomass, substrate and internal quota profiles for the NMPC tracking objective are also depicted in Figure 8. Based on the obtained profiles and control action the weighting matrix V is computed. The matrix V weighs the variance-covariance matrix such that an approximation of the expected economic loss can be computed. When the expected loss of the tracking profile is computed a value of 100 mg C/L is obtained. Furthermore, an off-line optimal experiment

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design procedure is performed to determine the lowest obtainable economic loss. It is observed that the lowest possible value is 7.25 mg C/L for a single experiment. Based on the value for the objective function, the target of the integrated experiment design is set to 19 mg C/L. The obtained state profiles and control action of the second integrated experiment design formulation are presented in Figure 8. In the integrated experiment design approach, a higher initial concentration of substrate is obtained while the initial biomass concentration is lower than in the NMPC run. The feeding profile results in a biomass increase to 140 mg C/L at day 5. Afterwards the biomass concentration is reduced to 100 mg C/L and maintained at this level for the remainder of the simulation time.

A Monte Carlo simulation is performed to assess both the parameter accuracy as well as the performance with respect to the predicted expected economic loss. So, for each case, the normal NMPC run (note that the normal NMPC run is the same as in Section 6.1) and the iED-NMPC run, 200 realizations of a single experiment are sampled. The resulting mean parameter estimates and the corresponding variance can be found in Table 5. It can be observed that the iED-NMPC experiments are able to recover on average the *true* system parameters p_0 with some uncertainty, in particular when compared to the previous section. Note that as only a single experiment/measurement is taken, the uncertainty is higher than in the previous formulation. The tracking profile parameters deviate more from p_0. Furthermore, it leads to very large confidence regions. When these are compared with the obtained confidence bounds of the previous section, the benefit of repeating measurements multiple times/performing multiple experiments is clearly observed. In addition, it seems that parameter $\mu_{\max}$ benefits the most from the multiple repetitions. Its corresponding confidence region increased by a factor 12 and 5 respectively compared with the confidence region of the previous section. A point of interest while comparing the two formulations is that the smallest confidence regions are obtained for ρ_{m} and μ_{m}. From a biochemical point of view this makes sense as these parameters heavily influence the growth rate and the uptake rate, while it is known that the Michaelis constant has a lesser impact.

Besides the parameter accuracy, the incurred economic loss is investigated. This is done in the simulation because it is known what the *true* system parameters p_0 are. The box plot of both the NMPC and the integrated MPC design are presented in Figure 9 (note again the logarithmic scale). As the economic loss is skewed, the median (Q_2) is reported. For the tracking profile $Q_2 = 555$ whereas for the iED-NMPC formulation $Q_2 = 38$ is obtained. With an objective function value of 1977 this means that in 50% of the parameter estimates a deviation of 2% or less from the objective function is reached. The first and third quartile are for the tracking profile $Q_1 = 85$ and $Q_3 = 1911$ while the iED-NMPC leads to $Q_1 = 9.0$ and $Q_3 = 140$. These quartiles illustrate that the iED-NMPC estimates those parameters accurately which are relevant for the tracking objective and which leads in turn to a model with minimal economic loss.

Remark. In both formulations there is a difference in the predicted economic performance and the observed performance after the re-identification. The difference can be attributed to the following factors: firstly, the predictions are performed using parameter values $\hat{p}$ while the *true* system parameter values are p_0. In an off line setting this difference has been the field of robust optimal experiment design. It is believed that the proposed formulations can benefit by formulating them in these robust experiment design settings. Secondly, the information content is quantified using the Fisher information matrix. This is a linear approximation of the parameter variance-covariance matrix which can sometimes underestimate the actual parameter variance-covariance matrix (Heine et al., 2008).

6. Conclusion

In this paper two practical formulations for the integration of optimal experiment design in NMPC have been proposed with application to the Droop model. The first formulation is an adaptation of a formulation used in linear MPC. For nonlinear system, however, it results in a nonlinear matrix inequality. A solution strategy to reformulate the nonlinear matrix inequality has been presented based on Sylverster's criterion. The second formulation is based on the notion of economic optimal experiment design which aims at reducing the expected economic

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loss. This results in a single inequality that has to be added to the NMPC formulation. A distinct advantage of the suggested approaches is that they can be easily formulated in existing NMPC software packages without the need of tailored optimization tools. Furthermore, in contrast to a naive integration, an assessment of the future model performance is possible. The Droop model has been successfully recalibrated in closed loop by the two presented formulations. Both approaches have been validated using Monte Carlo simulation which illustrates their potential but also reveals the need to include more robust formulations in future work.

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Table 1: Overview of the operating conditions and the remaining constants.

Operating conditions	Constants
$C_S(0) \in [0,\ 15]$ mg N/L	$Q_0 = 0.04$ mg N/ (mg C)
$C_Q(0) \in [0,\ 0.10]$ mg N/ (mg C)	$S_{in} = 4.0$ mg N/L
$C_X(0) \in [0,\ 40]$ mg C/L	
$D \in [0,\ 0.5]$ day^{-1}	

Table 2: Overview of the simulation parameters for the different controllers of Figure 2.

Controller type	Prediction horizon [d]	Sampling period [d]
Linearized MPC-1	7	1
Linearized MPC-2	1	0.05
NMPC	7	1

Table 3: Overview of the true system parameters and the obtained parameter estimates and their corresponding standard deviation (between brackets) for the NMPC tracking profile and the naive approach.

True system parameters	Tracking NMPC	Naive integration
$\mu_{m,0} = 1.2$	$\hat{\mu}_m = 1.59$ (0.52)	$\hat{\mu}_m = 1.24$ (0.055)
$K_{s,0} = 6.75$	$\hat{K}_s = 3.58$ (2.50)	$\hat{K}_s = 6.20$ (2.57)
$\rho_{m,0} = 0.125$	$\hat{\rho}_m = 0.085$ (0.043)	$\hat{\rho}_m = 0.113$ (0.045)

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Table 4: Overview of the obtained parameter estimates and their corresponding standard deviation (between brackets) for three tracking experiments and integrated experiment design formulation 1.

True system parameters	Tracking NMPC	iED-NMPC 1
$\mu_{\mathrm{m},0} = 1.2$	$\hat{\mu}_{\mathrm{m}} = 1.22$ (0.042)	$\hat{\mu}_{\mathrm{m}} = 1.22$ (0.045)
$K_{\mathrm{s},0} = 6.75$	$\hat{K}_{\mathrm{s}} = 6.86$ (2.15)	$\hat{K}_{\mathrm{s}} = 6.65$ (1.76)
$\rho_{\mathrm{m},0} = 0.125$	$\hat{\rho}_{\mathrm{m}} = 0.126$ (0.032)	$\hat{\rho}_{\mathrm{m}} = 0.122$ (0.032)

Table 5: Overview of the obtained parameter estimates and their corresponding standard deviation (between brackets) for a tracking experiment and integrated experiment design formulation 2.

True system parameters	Tracking NMPC	iED-NMPC 2
$\mu_{\mathrm{m},0} = 1.2$	$\hat{\mu}_{\mathrm{m}} = 1.59$ (0.52)	$\hat{\mu}_{\mathrm{m}} = 1.30$ (0.19)
$K_{\mathrm{s},0} = 6.75$	$\hat{K}_{\mathrm{s}} = 3.58$ (2.50)	$\hat{K}_{\mathrm{s}} = 6.07$ (1.04)
$\rho_{\mathrm{m},0} = 0.125$	$\hat{\rho}_{\mathrm{m}} = 0.085$ (0.043)	$\hat{\rho}_{\mathrm{m}} = 0.114$ (0.025)

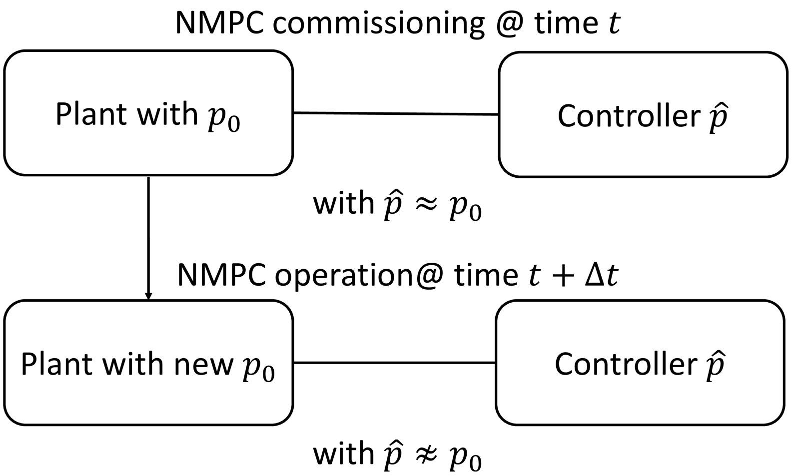

Figure 1: Illustration of the parameter evolution in the plant after a Δt which induces a controller update.

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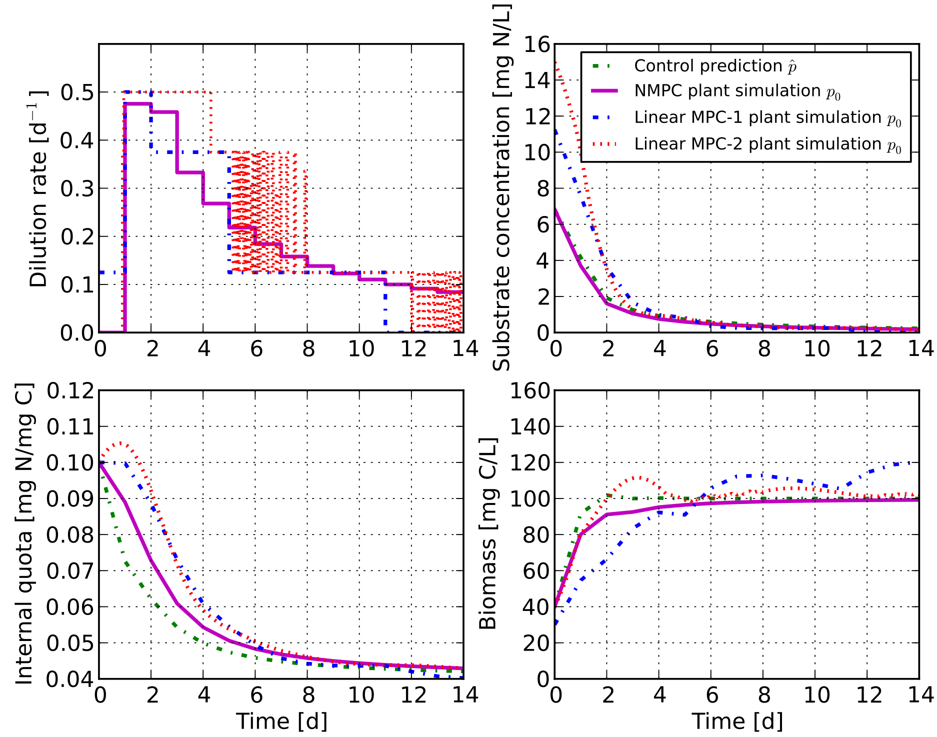

Figure 2: Obtained plant state profiles (by p_0) for two linearized MPC settings, the NMPC approach and the by the controller predicted state behavior (based on $\hat{p}$ for the NMPC approach).

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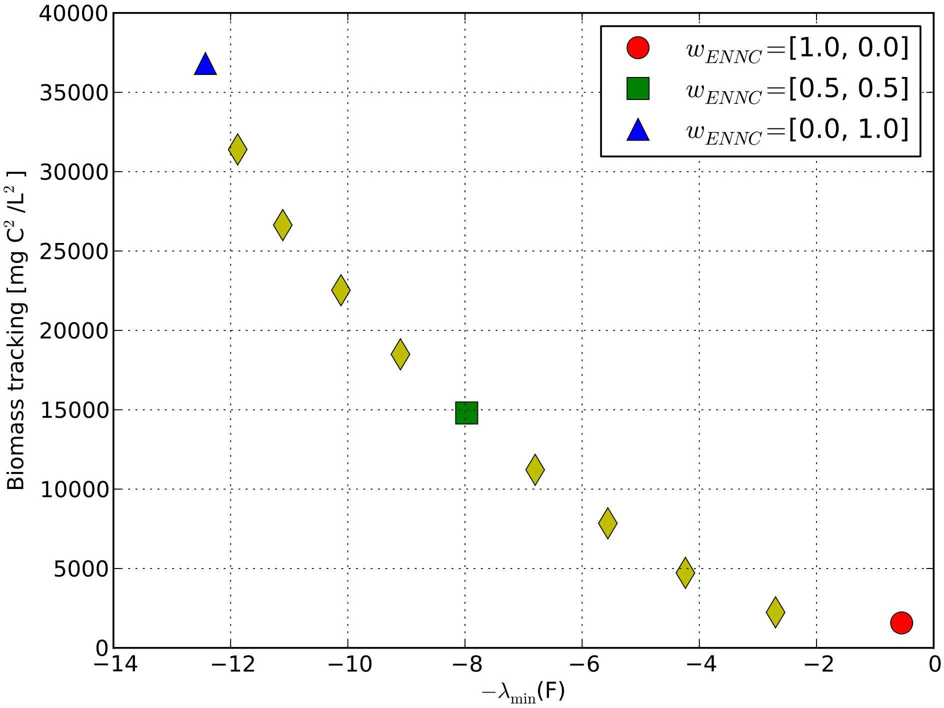

Figure 3: Pareto front illustrating the trade-off between the tracking objective $J_1 = [1.0, 0.0]$ and the maximization E-criterion $J_2 = [0.0, 1.0]$.

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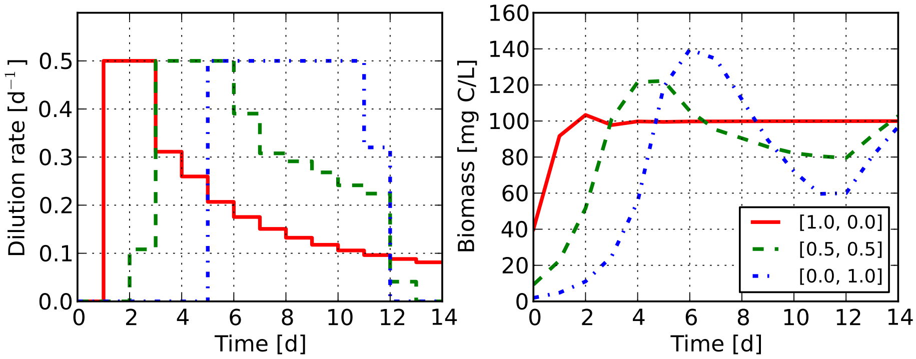

Figure 4: States and control actions for the tracking objective(w_{ENNC} = [1.0, 0.0]), the maximization of the E-criterion (w_{ENNC} = [0.0, 1.0]) and a compromise (w_{ENNC} = [0.5, 0.5]) as denoted in Figure 3.

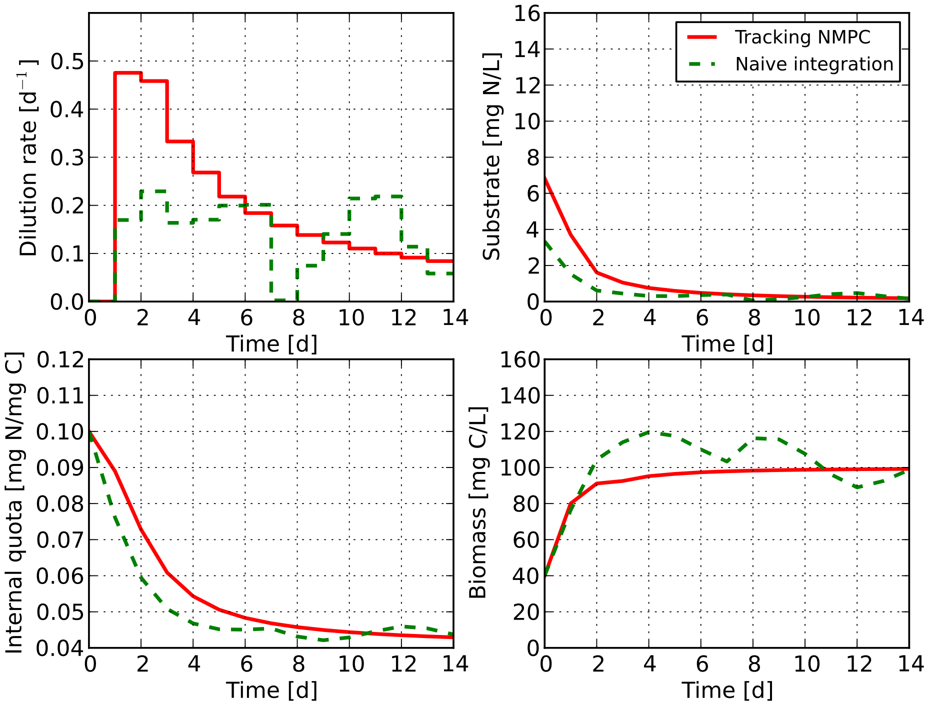

Figure 5: States and control actions for NMPC and a naive integration where $\lambda_{\min}(t_f) \geq 4.0$.

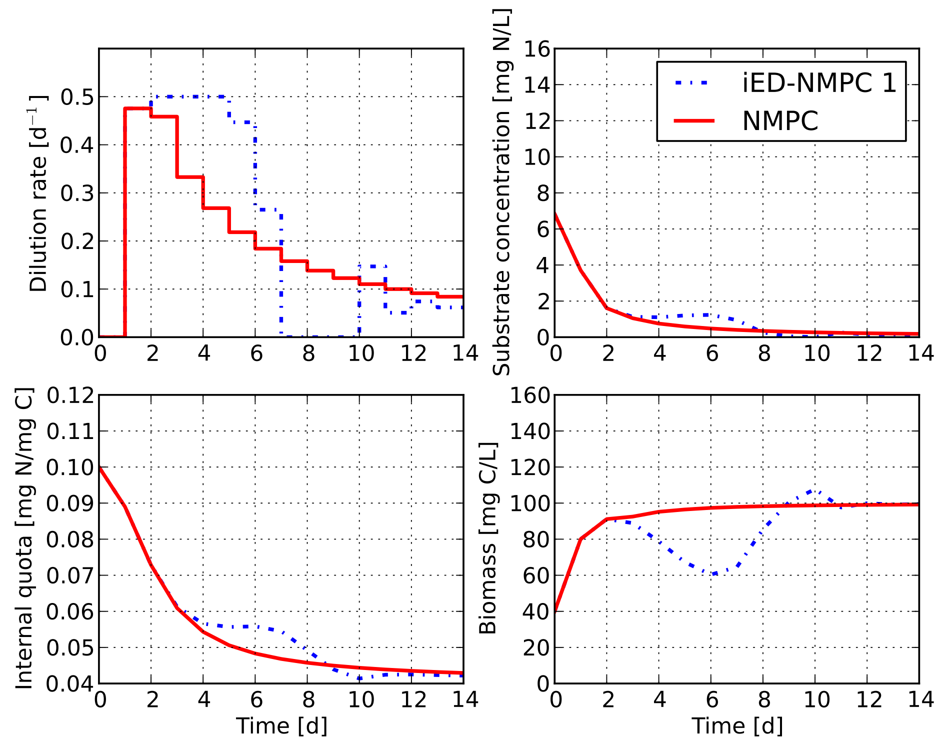

Figure 6: Obtained plant state profiles and applied control action for both the tracking and iED-NMPC formulation 1.

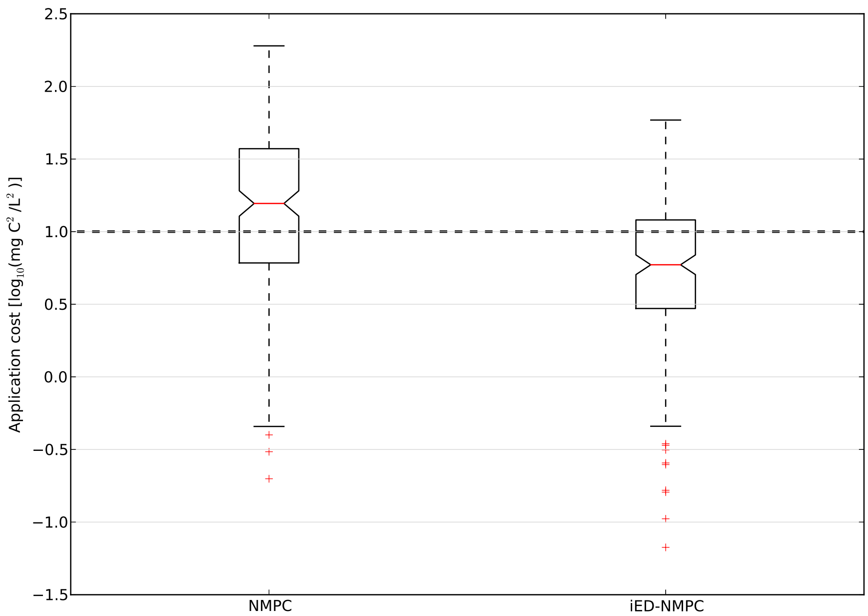

Figure 7: Box plot of the application cost in logarithmic scale for the NMPC and iED-NMPC approach (the targeted application cost value is the dashed line).

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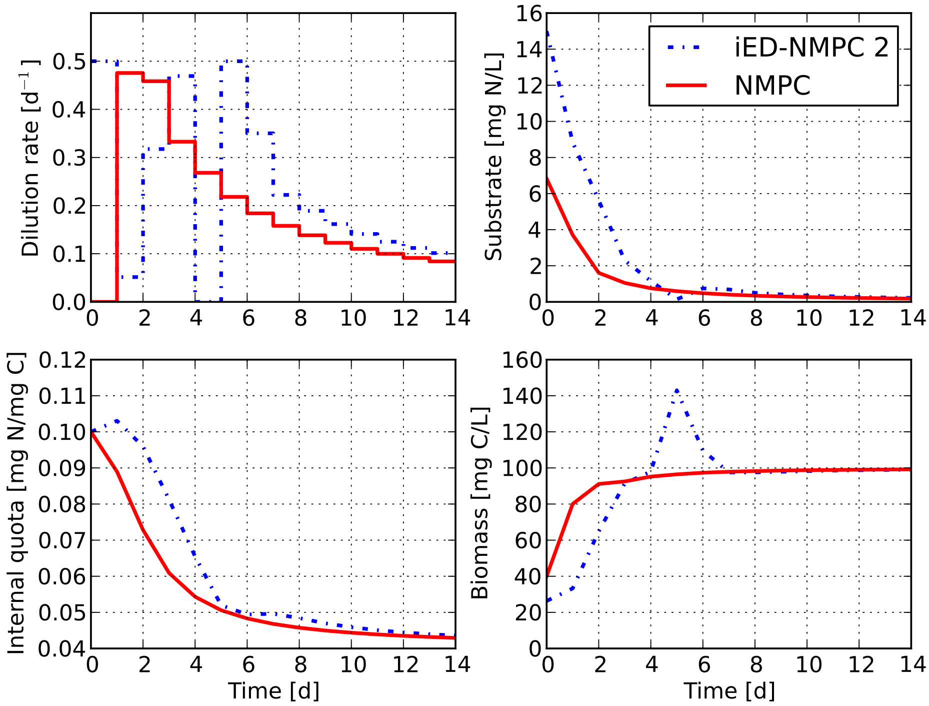

Figure 8: Obtained plant state profiles and applied control action for both the tracking and iED-NMPC formulation 2.

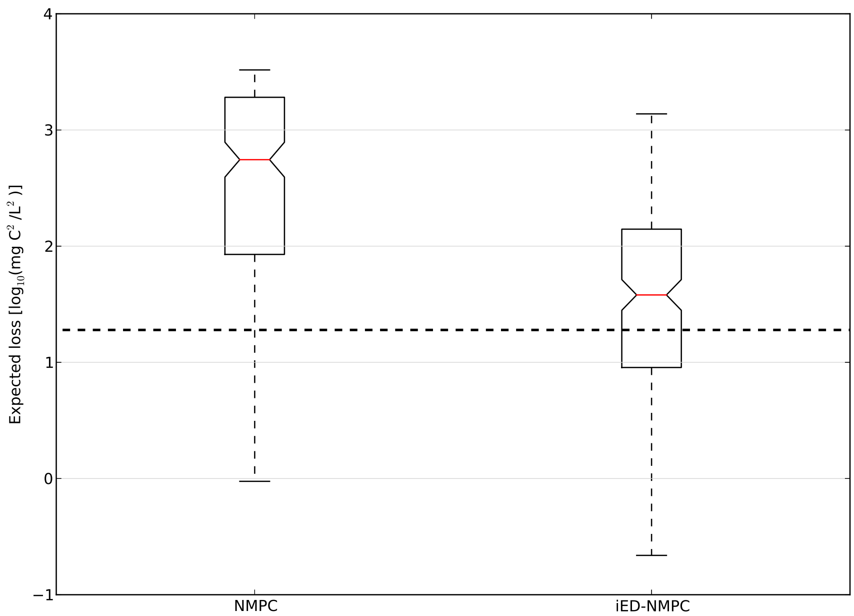

Figure 9: Box plot of the expected economic loss in logarithmic scale for the NMPC and iED-NMPC approach (the targeted expected economic loss is the dashed line).

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