Available online at www.sciencedirect.com

ScienceDirect

IFAC PapersOnLine 52-1 (2019) 709–714

Multi-mode Model Predictive Control and Estimation for Uncertain Biotechnological Processes

Bruno Morabito * **Achim Kienle** **,*** **Rolf Findeisen** *
Lisa Carius *

* *Laboratory for System Theory and Automatic Control, Otto-von-Guericke University Magdeburg*
** *Laboratory for Automation/Modelling, Otto-von-Guericke University Magdeburg*
*** *Max Plank Institute for Complex Dynamical Systems, Magdeburg*

Abstract: Biotechnological processes are urged to become more flexible and sustainable in order to meet the challenges of modern society. Using renewable feed stocks for the production of value added products is one strategy to achieve sustainability. The challenges arising from the use of renewables are large compared to the commonly used resources. The concentration of nutrients in renewable feed stocks varies between batches and is not optimal in respect to the demands of the cells. The biological system adapts to this situation by changing the metabolic growth modes in dependence of the availability of nutrients in the media. Consequently, the process can run through multiple modes. Each switch of the mode results in a change of the system dynamics which effects the process performance. To overcome the challenges, we propose a model predictive control approach combined with a moving horizon estimator that takes directly the multi-mode nature of the process into account. It ensures optimal performance while guaranteeing that the constraints are met in each phase of the process. The approach is motivated by and applied to a sustainable biopolymer production from juice waste.

© 2019, IFAC (International Federation of Automatic Control) Hosting by Elsevier Ltd. All rights reserved.

Keywords: multi-mode, model predictive control, moving horizon estimation, biotechnology, state estimation, MPC, MHE.

1. INTRODUCTION

Limited resources are a major challenge of modern society. In order to meet the requirements of the increasing world population biotechnological processes have to become more sustainable. Using renewable feed stocks, such as side products and wastes, for the production of value added products has been identified as a promising way to address these challenges (Jain and Tiwari (2015); Patel et al. (2006)). However, the uncertainties and constraints arising from the use of renewable feeds as nutrients sources are large compared to the commonly used designed media with defined amounts of nutrients and pure carbon sources. Waste streams like whey, juice waste, algae biomass, or starch, are natural complex media. Each of these resources contains a unique mixture of nutrients, which concentrations vary between batches and are uncertain. Depending on the availability of all growth influencing nutrients, the biotechnological process eventually runs through different metabolic growth modes. Each metabolic mode corresponds to different system dynamics, and thus is represented by a different model structure, *c.f.*

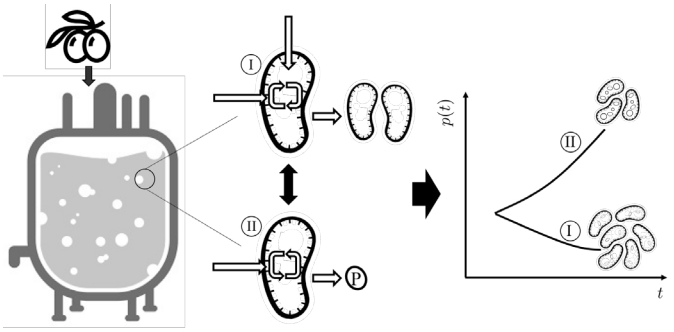

Fig. 1. Depending on the renewable feed composition, different growth modes can be triggered (I = cell division, II = product synthesis), leading to significant changes in the process dynamics.

Fig. 1. These switches can be triggered by many events, *e.g.* the depletion of a growth required nutrients. Due the complex and uncertain composition of the feed and the versatility of the biological system a switch in the mode can not be predicted. Clearly, applying a recipe-based open loop control approach, which is commonly used in biotechnological industry, would very likely result in bad reproducibility, product off-specifications and poor production rates. Here we propose a model-based process control approach which accounts for the switches of the

⋆ {rolf.findeisen,lisa.carius}@ovgu.de.
This work is supported by the EU ERDF program within the state excellence research center for dynamic systems (CDS).
Bruno Morabito is also affiliated to the International Max Planck Research School (IMPRS) for Advanced Methods in Process and Systems Engineering, Magdeburg, Germany.

2405-8963 © 2019, IFAC (International Federation of Automatic Control) Hosting by Elsevier Ltd. All rights reserved.
Peer review under responsibility of International Federation of Automatic Control.
10.1016/j.ifacol.2019.06.146

system dynamics. The approach combines moving horizon estimation (MHE), a trust update policy and model and predictive control (MPC). The multi-mode MHE gives an estimate of the current system state using the limited online measurements considering model uncertainties, measurement noise and process constraints. The MPC uses the state estimate to predict future process evolution and to compute the optimal input trajectory (see Fig.2). The trust update policy weights the effect of the different models in both MPC and MHE cost functions, while the constraints for each of the models are enforced. Doing so optimizes the performance for the active mode while guaranteeing robust constraints satisfaction also in the case of an undetected mode switch. In Bethge et al. (2018)

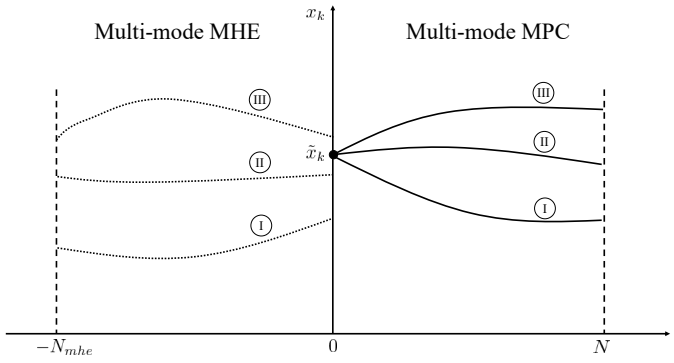

Fig. 2. Illustrative representation of the coupling between MPC and MHE.

we developed a tube-based multi-mode, machine learning supported MPC scheme for linear systems with guaranteed stability. Constraints are enforced for all possible modes, while performance is optimized for one learned model. In this work we expand the work considering the output feedback problem for nonlinear systems and using a multi-mode moving horizon estimator. Various MPC approaches using multiple models have been proposed, spanning from average multiple model based MPC (Kuure-Kinsey and Bequette, 2007; Rao et al., 2003; Ferramosca et al., 2014), fault-tolerant (Camacho et al., 2010; Scott et al., 2014), scenario-based MPC (Bernardini and Bemporad, 2009; Lucia and Engell, 2012), and discrete event based MPC formulations (Lazar et al., 2006; Seatzu et al., 2012), such as max-plus predictive control (De Schutter and Van Den Boom, 2001). In average multi-model based MPC predictions from different models are used to compute a single averaged output prediction and in general no states constraints are considered, while we compute different output predictions and we assume state constraints. Fault-tolerant predictive control (see e.g. Camacho et al. (2010); Scott et al. (2014) and references therein) considers that the system has a nominal (normal) operational mode and a set of known faulty modes, which can occur at any time. Our approach differs from fault-tolerant control as we do not assume to know the currently active mode, the system modes are not necessarily faulty modes, and the controller could take advantage of the modes to improve overall performances. Scenario-based MPC approaches typically focuses on disturbances and parametric uncertainties, not structural changes in the mode, while we allow the different modes to be structurally different. Discrete event based and max-plus predictive control approaches are typically limited to linear system and it is often assumed that the transition rules, switching between the modes are explicitly known. The following notation is used throughout the paper: the system states of model m at time k are represented as $x_k^m \in \mathbb{R}^n$, while the inputs as $u_k \in \mathbb{R}^m$. In some cases, which will be clear from the context, the subscript will be use to indicate specific metabolites or substrates concentration. The notation $a_{i|j}$ refers to the variable a at time j computed at time i while $\{a\}$ is the sequence $\{a_{i|i}, a_{i|i+1}, ..., a_{i|N}\}$ where i and N will be clear from the context. $\|a\|_A^2$ is the weighted norm $a^T A a$ where $a \in \mathbb{R}^n$ and $A \in \mathbb{R}^{n\times n}$. $\tilde{a}$ is the estimated variable while $\hat{a} = \arg\min_a f(a)$.

2. MODELLING MULTI-MODES

As an example process we consider the biotechnological production of poly-β-hydroxybutyrate (PHB), a biodegradable and biocompatible polymer, using the bacteria *Cupriavidus necator* (*C.necator*) in a fed-batch bioreactor. Under the given condition we consider that *C.necator* can operate in three different metabolic modes in dependence on the availability of the two main nutrients, the nitrogen and carbon source: optimal growth (mode I), optimal PHB productivity (mode II), optimal PHB yield (mode III) (see Fig.3). PHB production occurs under an excess of carbon and when nitrogen is depleted. In this conditions, the bacteria starts to store the excess carbon in form of PHB granulas. Thus, for this system switches in the mode are triggered by the availability of nitrogen. Mode III is active when ammonium is depleted, mode I when it is available in large concentrations and mode II in the transition zone of mode I and III, *i.e.* for small concentrations of ammonium. We use an hybrid modelling approach to represent the different growth modes of the system. We do this by combining a simple ODE formulation which describes the mass balances of a bioreactor with constrained-based modeling approach of the cellular metabolism.

2.1 State equations

The evolution of the system states (concentration of the carbon source fructose x_{Fr} and the nitrogen source ammonium x_{Am} in [g/l], the total biomass concentration x_{bio} in [g/l] and the PHB content x_{PHB} [g PHB/g bio]) for a fed-batch reactor are described by a continuous-time ODE system of the following form:

$$\dot{x}^m_{\mathrm{Fr}} = Y^m_{\mathrm{Fr/bio}} r^m x^m_{\mathrm{bio}} + F/V(x_{\mathrm{Fr,F}} - x^m_{\mathrm{Fr}}), \tag{1a}$$
$$\dot{x}^m_{\mathrm{Am}} = Y^m_{\mathrm{Am/bio}} r^m x^m_{\mathrm{bio}} + F/V(x_{\mathrm{Am,F}} - x^m_{\mathrm{Am}}), \tag{1b}$$
$$\dot{x}^m_{\mathrm{PHB}} = Y^m_{\mathrm{PHB/bio}} r^m - Y^m_{\mathrm{bio/bio}} r^m x^m_{\mathrm{PHB}}, \tag{1c}$$
$$\dot{x}^m_{\mathrm{bio}} = Y^m_{\mathrm{bio/bio}} r^m x^m_{\mathrm{bio}} - F/V x^m_{\mathrm{bio}} \tag{1d}$$
$$\dot{V} = F. \tag{1e}$$

Here, $Y_{\mathrm{i/j}}$ refers to the yields of component i over component j in [g/g], r^m are the reaction rates in [1/h], F is the feed rate in [l/hr], V is the reactor volume in [l] and $x^m_{sub,F}$ is the substrate composition of the feed. Notice that yield coefficients and reaction rates (4) of the metabolic reactions are different for each mode. In this work we obtain these information by analyzing the

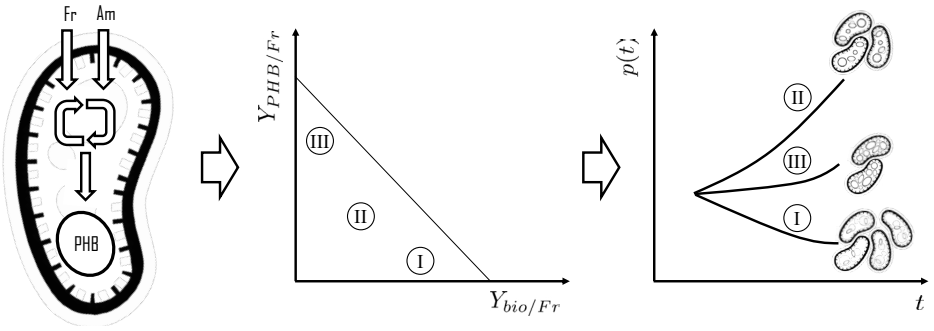

Fig. 3. Schematic representation of multi-mode modelling. Cells use different parts of their metabolism in order to adjust to changes in their environment and thus survive. Here the availability of fructose (Fr) and ammonium (AM) triggers these switches in the growth mode(left). From metabolic network analysis we obtain a finite set of metabolic routes which represent the three different growth modes (I,II,III). These so called active elementary modes shown are shown in the yield space (middle). These modes are reflected in the time domain (right) by models with different parameter and structure. Note that mode II has maximum productivity ($p(t)$) since both biomass growth and PHB production are encouraged.

metabolic network of the organism with constrained-based methods and thus extracting the elementary modes which represent each mode. Metabolic networks are composed of metabolites and metabolic reactions (pathways) which describe the synthesis of biomass and products (outputs) from substrate (inputs). Note that all states of (1) are part of the metabolites of the metabolic network. According to Klamt and Stelling (2006) all metabolites of the network x_{met} (in [g/g bio]) can be represented by the simplified ODE of the following form:

$$\dot{x}_{\text{met}}(t) = Sv. \tag{2}$$

Here, the stoichiometric coefficients, which represent the input-output relation of the metabolic network, are condensed in the stoichiometric matrices $S \in \mathbb{R}^{n_{met} \times n_v}$, and the reaction rates of the metabolic network are condensed in vector v. It is a general assumption in metabolic modelling that the reaction rates of the network are in a quasi-steady state (Stephanopoulos et al. (1998); Carius et al. (2018)). It follows that the metabolic network can be represented by a homogeneous linear algebraic system:

$$\dot{x}_{\text{met}}(t) = Sv = 0. \tag{3}$$

The solutions of (3) are the steady-state rate distributions, and span the infinite solution space of the whole network. To reduce the computational cost, (3) is decomposed into a finite set of unique solutions which can be viewed as a minimal functional sub unit of the network (Song and Ramkrishna (2009)). These so called elementary modes (EMs) describe all possible metabolic growth modes of the system. To select the EMs (metabolic routes) which describe the operation modes of our system we have to analyze all EMs in the 2D yield-space. Here, EMs are represented by the stoichiometry of the net reactions $SZv = 0$. The matrix $Z \in \mathbb{R}^{n_v \times n_{EMs}}$, represents the EMs, where n_{EMs} is the number of EMs. By solving a least-square optimization problem (Franz et al. (2011)) a set of minimal number of EMs can be found, whose non-negative combination represents the operation modes of our system, so called active elementary modes (aEMs). These can be represented in the yield space (*c.f.* Fig.3). Finally, the information contained in the aEMs is combined with the ODE description of the modes. To do so Z_a now represents the aEMs with the dimension of $n_v \times n_{aEMs}$ and the yields

K_{FRU}	K_{AMC}	K_{PHB}	k_r^1	k_r^2	k_r^3
0.06	0.01	0.05	0.8414	0.5211	0.2110

Table 1. Estimated kinematic constants. See Franz (2015); Franz et al. (2011)

of mode m can be obtained from the m-th column of SZ_a that we indicate as $SZ_a[m]$. The structure of the reaction rates r, which states if a certain input contributes to a reaction rate of each mode r^m, is the following

$$r^m = k_r^m \prod_{j \in I(SZ_a[m])} \left(\frac{x_j^m}{K_j + x_j^m} \right). \tag{4}$$

Where $I(SZ_a[m])$ is the set of indices of non-zero elements of $SZ_a[m]$, k_r^m and K_j are parameters that need to be estimated from experimental data. We used the parameters estimated in Franz (2015) which are reported in Tab. 1. Due to (4) the modes have not only different parameters but also different structures, therefore methods considering only parameter uncertainty are not suitable for this system. According to the model (1), model parameters (Tab.1) and experimental data available from Franz (2015) we can approximate the nitrogen concentrations for which the system eventually enters mode II and mode III (see section 4). However, due to the uncertainties in the feed and medium composition, and in the biological system the switching time of the modes remains unknown.

2.2 Measurement Equations

Three online measurements are available. The UV/VIS absorbance of the culture broth at a wavelength $\lambda = 600\,\text{nm}$ (5a) (Franz (2015)), the residual biomass reconstructed from the amount of corrective agent used for pH control (5b) and the volume (5c):

$$y_A = \left(\tilde{k}_1 x_{PHB} + \tilde{k}_2 (1 - x_{PHB}) \right) x_{bio}, \tag{5a}$$

$$y_{res} = x_{res} = (1 - x_{PHB}) x_{bio} = h_2(pH), \tag{5b}$$

$$y_V = V. \tag{5c}$$

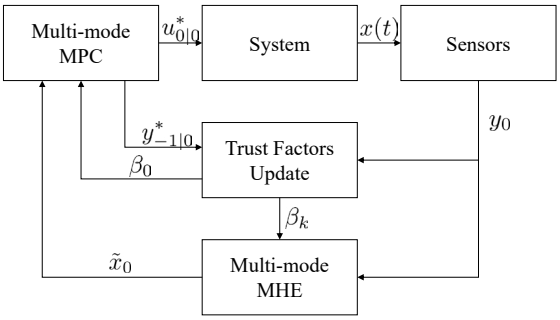

Fig. 4. Schematics of the proposed multi-mode MPC/MHE scheme.

3. MULTI-MODE MPC & MHE

The proposed approach is composed by a multi-mode MPC and a multi-mode MHE, *c.f.* Fig. 2 and 3 . Both use trust factors valuing the contribution of the different modes to the cost function, which are adapted at every time step by an update policy to improve performance. The constraints are enforced simultaneously for all modes. For the remaining of the paper, without loss of generality, we summarize the model (1) and measurement equations (5) in discrete-time form as $x^m_{k+1} = f(x^m_k, u_k)$ and $y_k = h(x_k, u_k)$ respectively, where $x = [x_{Fr}, x_{Am}, x_{PHB}, x_{bio}, V]$ and $u = F$.

3.1 Multi-mode MPC

Multi-mode MPC considers all modes in the prediction, solving the following dynamic optimization problem:

$$\min_{\{u\}} \quad L_{mpc}(\{x\},\{u\}) \tag{6a}$$
$$\text{s.t} \quad x^m_{k+1} = f^m(x^m_k, u_k), \tag{6b}$$
$$x^m_0 = \tilde{x}_0, \tag{6c}$$
$$x^m_k \in \mathcal{X}, \quad u_k \in \mathcal{U}. \tag{6d}$$

$\mathcal{X}$ and $\mathcal{U}$ are respectively state and input constraints. $\tilde{x}_0$ represent the state estimate. Notice that the constraints must be satisfied from all modes at all times. It is also important to stress that in general the different modes can have different state dimensions, which is the case if different metabolic pathways are activated or deactivated. The solution of the dynamic optimization will be an optimal control sequence $\{u^*\} = \{u^*_{0|0}, u^*_{0|1}, ..., u^*_{0|N_{mpc}-1}\}$. We define also the optimal state sequence associated with u^* as $\{x^*\} = \{x^{*,m}_{0|0}, x^{*,m}_{0|1}, ..., x^{*,m}_{0|N_{mpc}}\}$ and optimal measurement sequence as $\{y^*\} = \{y^{*,m}_{0|0}, y^{*,m}_{0|1}, ..., y^{*,m}_{0|N_{mpc}-1}\}$. Generally, the problem (6) is solved at every time step and only the first term $u^*_{0|0}$ is applied to the plant, *c.f.* Rawlings and Mayne (2012) for details. The objective function is chosen as

$$L_{mpc}(\cdot) = \sum_{m=1}^{M} \beta^m_0 \left(\sum_{i=0}^{N-1} l(x^m_i, u_i) + e(x^m_N) \right), \tag{7}$$

where $l(x^m_i, u_i)$ and $e(x^m_N)$ are chose as

$$l(x^m_i, u_i) = \|x^m_i - x_r\|^2_Q + \|u_i\|^2_R, \tag{8}$$
$$e(x^m_N) = \|x^m_N - x_r\|^2_E.$$

Where Q, E and R are square matrices and x_r is the reference system state. The cost functions are multiplied by *trust factors* β^m_0. In the case considered, the trust factor of model m is a function of the measured output at the current time y_0 and the *predicted* output $\hat{y}^m_{-1|0}$ *i.e.*:

$$\beta^m_0 = \mathcal{B}(y^{*,m}_{-1|0}, y_0). \tag{9}$$

The $\mathcal{B}(\cdot)$ function is computed as follows: firstly, for each mode, the distance between predicted output and measured output is computed

$$\epsilon^m = d^m_0 \triangleq d(y^{*,m}_{-1|0}, y_0) \tag{10}$$

where d could be any definition of distance. We use the 2-norm $d^m_0 = \|y^{*,m}_{-1|0} - y_0\|$. Secondly, a *score function* $s^m_0 \triangleq s(d^m_0, s^m_{-1})$. This score function rewards one point to the mode which at the previous time step predicted better the measured output and penalizes by one point all the other modes. Finally, the trust factors are computed for each mode using a logistic function and are then normalized

$$\tilde{\beta}^m_0 = \frac{a}{b + e^{-s^m_0}}, \quad \beta^m_0 = \tilde{\beta}^m_0 \frac{1}{\sum_{i=1}^{M} \tilde{\beta}^i_0}, \tag{11}$$

where a, b and c are tuning parameters. The scores s^m_0 are bounded to the an interval $[s_{min}, s_{max}]$ to limit the maximum and minimum value of the trust factors. The smaller the score of the mode, the less its model will be weighted in (6). This will make sure that the optimal control sequence is tailored more towards the mode which is better representing the current system dynamics.

Remark (switching between modes): In the current formulation the prediction and estimation trajectories of MPC and MHE do not branch except at the beginning of the MPC horizon (Fig. 2). In case of slow system dynamics and relatively short horizon length this is a reasonable simplification. This challenge can be overcome considering a scenario tree approach for the estimation and control.

Recursive feasibility Following the idea of Maiworm et al. (2015), feasibility for the MPC can be established by assuming a common control invariant terminal region for every mode. Here only the general idea is given. Assuming that the functions (8) are continuous, and $f^m(0,0) = 0$, $l(0,0) = 0, e(0) = 0 \quad \forall m \in [1, ..., M]$ and assuming $\mathcal{U}$ is compact, $\mathcal{X}$ is closed and both contain the origin. Let Ω_f be a common control invariant region. then the MPC is recursively feasible.

3.2 Multi-mode MHE

For state (and parameter) estimation we use a optimization based moving horizon estimator considering different modes, c.f. (Rawlings (2013); Findeisen (1997) for a basic introduction to MHE). Compared to other estimation techniques, the MHE has the advantage to easily implement constraints and usually shows better performance, *c.f.* Haseltine and Rawlings (2005); Bavdekar et al. (2013). The multi-mode MHE solves a dynamic optimization spanning over past measurements similar to the multi-mode MPC:

$$\min_{\{w\}} \quad L_{mhe}(\{x\},\{w\}) \tag{12a}$$
$$\text{s.t.} \quad x^m_{k+1} = f^m(x^m_k, u_k) + w^m_k, \tag{12b}$$
$$y_k = h(x^m_k, u_k) + v^m_k, \tag{12c}$$
$$x_k \in \mathcal{X}, \quad w^m_k \in \mathcal{W}. \tag{12d}$$

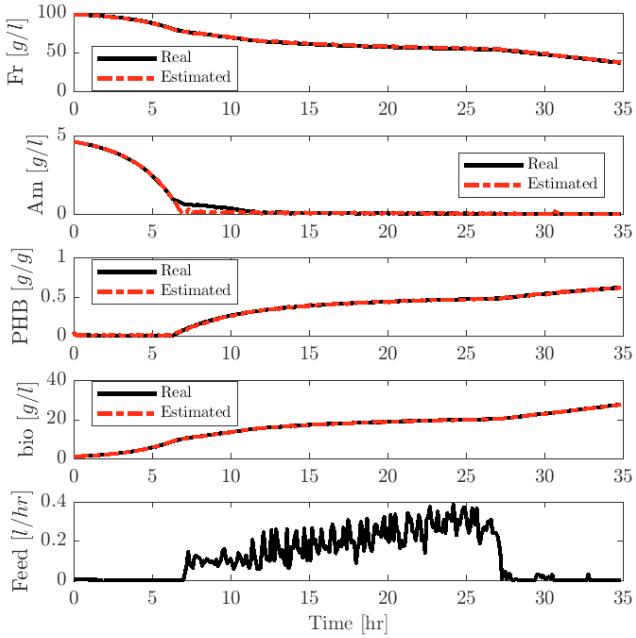

Fig. 5. Simulation results. Fr: fructose, Am: ammonium. PHB content is represented as a fraction of the biomass.

Where N_{mhe} is the horizon length and w_k^m is state noise which lies in a convex set $\mathcal{W}$ containing the origin. This term represents possible model uncertainty and it is often assumed to enter the model linearly. This can be a limitation when the model uncertainty is large. Considering multiple models in the MHE allow us to account for model uncertainties that cannot be represented merely by a additive linear term. The objective function is

$$L_{mhe}(\cdot) = \sum_{m=1}^{M} \beta^m_{-N_{mhe}} p(x^m_{-N_{mhe}}) + \sum_{i=-N_{mhe}}^{0} \sum_{m=1}^{M} \beta_i^m l(\cdot). \tag{13}$$

As in the MPC case, we consider quadratic cost functions:

$$p(x^m_{0|-N_{mhe}}) = \|x_{0|-N_{mhe}} - \tilde{x}_{-N_{mhe}}\|^2_P, \tag{14}$$

$$l(x_i^m, w_i^m) = \|w_i^m\|^2_{Q_{mhe}} + \|y_i - y_i^m\|^2_{R_{mhe}}. \tag{15}$$

Where $\tilde{x}_{-N_{mhe}}$ is the the best guess available of the state at time $-N_{mhe}$ *c.f.* Rawlings and Mayne (2012) for details. As in the multi-mode MPC, in multi-mode MHE the trust factors play a fundamental role. But while in the MPC case the last available value of trust factors is kept constant for the entire prediction horizon (because we have no information on future measurements) the *past* values of the trust factors enter the MHE objective function at the corresponding times. The solution of Problem (12) will be the estimate of the state for each mode at time 0 *i.e.* $\tilde{x}_0^m, \quad \forall m = [1, .., M]$. To obtain the estimate $\tilde{x}_0$ needed by the multi-mode MPC in Problem (6), the estimated weighted mean is used:

$$\tilde{x}_0 = \sum_{i=1}^{M} \beta_0^m \tilde{x}_0^m. \tag{16}$$

This means that at every MPC iteration, all mode predictions start from the same state estimate $\tilde{x}_0$ (Fig.2). In the following we outline the use of the proposed approach for PHB production from fruit waste.

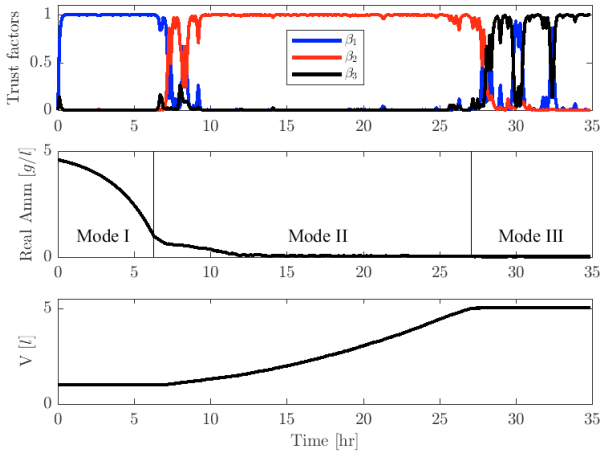

Fig. 6. Upper graph: trust factors, middle graph: real ammonium concentration, lower graph: liquid volume in the reactor.

4. MULTI-MODE PREDICTIVE CONTROL FOR FRUIT WASTE BASED PHB PRODUCTION

In the considered process fruit waste with an uncertain composition is used as feed and medium source, c.f. Section 2 and Fig. 3. Firstly, the concentration of the substrates in the feed is estimated during a short batch phase (with no feed) with an MHE with a single model. This is a reasonable simplification, since estimator converges while nitrogen concentration is still high. Thus, there is no risk of incurring a mode switch (for brevity, results are not shown). After that the composition of the renewable source are estimated we proceed with the fed-batch production phase where the proposed multi-mode approach is used. In a fed-batch process, substrates are fed into a reactor but no product is extracted. The process stops when the volume reaches the maximum reactor capacity. Our objective is maximizing productivity, therefore the goal is to keep the system as long as possible in mode II during the process. From the data of Franz (2015) we know that the system eventually enters PHB production (mode II) for $x_{AM} < 1.0\ g/l$, and reaches the maximum yield (mode III) for $x_{AM} < 0.1\ g/l$. Thus, we used $x_r = 0.5$ as a reference point in (8). By doing so the MPC will compute a control action that leads the system to this concentration regardless of the system's active mode. Notice that, if mode II is active at a different x_{AM} the reference can be adjusted online when more precise information is available. In Fig.5 simulation results show the estimated and simulated concentrations for the entire fed-batch time. A measurement noise of 2% is added to the simulated measurements. We used time steps of 0.1 hours and horizon lengths of $N = N_{mhe} = 10$. In Fig. 6 the trust factors and the real ammonium concentration are shown. The real system switches from mode I to mode II at 6.3 hours when a concentration of ammonium of $1g/l$ is reached, the trust factors of mode II reflects the switch and the objective functions (6) and (12) are adapted to the new estimate. The controller keeps the system in the proximity of the reference point in the region where mode II is active. At time 21.7 hours, the maximum volume is reached. At this point the controller stops feeding. This

terminates the supply of ammonium. Consequently, due to ammonium depletion, the system switches to mode III.

5. CONCLUSIONS

Often models of dynamical systems are effected by structural, state and parametric uncertainties, therefore the design of a model-based robust control system is a challenging task. Examples of such systems are biotechnological processes using renewable feed stocks. In these processes uncertainties can trigger different bacterial growth modes, causing abrupt changes in system dynamics. To maintain optimal process performances, a close loop controller must account for these changes. In this work, we proposed an flexible approach which uses MPC and MHE and considers different growth modes exploiting diffent corresponding models. By doing so we can facilitate constraints satisfaction and rapid adaptation of the controller to new process conditions. By applying the proposed method to a PHB production process, we showed in simulations that, when a switch in the metabolic mode occurs, the controller successfully adapts to new process conditions, and maintains optimal performance.

In the current formulation branching of the state trajectories is considered only at the initial point of the prediction horizon. To increase robustness, the approach can be expand allowing the models to branch in the prediction and estimation horizon in a scenario tree. We furthermore plan to investigate new trust update policies and their performance.

REFERENCES

Bavdekar, V.A., Gopaluni, R.B., and Shah, S.L. (2013). A comparison of moving horizon and bayesian state estimators with an application to a ph process. *IFAC Proceedings Volumes*, 46(32), 160 – 165, 10th IFAC International Symposium on Dynamics and Control of Process Systems.

Bernardini, D. and Bemporad, A. (2009). Scenario-based Model Predictive Control of Stochastic Constrained Linear Systems. *Proc. of the 48h IEEE Conf. on Decision and Control (CDC) jointly with 28th Chinese Control Conf.*, 6333–6338.

Bethge, J., Morabito, B., Matschek, J., and Findeisen, R. (2018). Multi-mode learning supported model predictive control with guarantees. *Proc. 6th IFAC Conf. on Nonlinear Model Predictive Control NMPC 2018*, 51(20), 517 – 522.

Camacho, E.F., Alamo, T., and de la Pea, D.M. (2010). Fault-tolerant model predictive control. In *2010 IEEE 15th Conference on Emerging Technologies Factory Automation (ETFA 2010)*, 1–8.

Carius, L., Pohlodek, J., Morabito, B., Franz, A., Mangold, M., Findeisen, R., and Kienle, A. (2018). Model-based state estimation utilizing a hybrid cybernetic model. In *Advanced Control of Chemical Processes (AdChem)*.

De Schutter, B. and Van Den Boom, T. (2001). Model predictive control for max-plus-linear discrete event systems. *Automatica*, 37(7), 1049–1056.

Ferramosca, A., Gonzlez, A., Limon, D., and Odloak, D. (2014). One-layer robust mpc: a multi-model approach. *IFAC Proc. Volumes*, 47(3), 11067 – 11072, 19th IFAC World Congress.

Findeisen, P. (1997). *Moving horizon state estimation of discrete time systems*. Master's thesis, University of Wisconsin–Madison.

Franz, A. (2015). *Nonlinear dynamics of PHB production in Ralstonia eutropha and Rhodospirillum rubrum*. Ph.D. thesis, Otto-von-Guericke-Universität Magdeburg.

Franz, A., Song, H.S., Ramkrishna, D., and Kienle, A. (2011). Experimental and theoretical analysis of Poly(β-hydroxybutyrate) formation and consumption in *Ralstonia eutropha*. *Biochemical Eng. J.*, 55, 49–58.

Haseltine, E.L. and Rawlings, J.B. (2005). Critical evaluation of extended kalman filtering and moving-horizon estimation. *Industrial & Engineering Chemistry Research*, 44(8), 2451–2460.

Jain, R. and Tiwari, A. (2015). Biosynthesis of planet friendly bioplastics using renewable carbon source. *J. of Environmental Health Science and Eng.*, 13(1), 11.

Klamt, S. and Stelling, J. (2006). Stoichiometric and constraint-based modeling. *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts*, 73–96.

Kuure-Kinsey, M. and Bequette, B.W. (2007). Multiple Model Predictive Control: A State Estimation based Approach. *2007 Am. Control Conf.*, 6683(518), 3739–3744.

Lazar, M., Heemels, W., Weiland, S., and Bemporad, A. (2006). Stabilizing model predictive control of hybrid systems. *IEEE Trans. on Automatic Control*, 51(11), 1813–1818.

Lucia, S. and Engell, S. (2012). Multi-stage and two-stage robust nonlinear model predictive control. *IFAC Proc. Volumes*, 45(17), 181 – 186.

Maiworm, M., Bäthge, T., and Findeisen, R. (2015). ScienceDirect Scenario-based Model Predictive Control: Recursive Feasibility and Stability. *IFAC-PapersOnLine*, 48, 50–56.

Patel, M., Crank, M., Dornburg, V., Hermann, B., Roes, A., Huesing, B., Overbeek, L., Terragni, F., and Recchia, E. (2006). Medium and long-term opportunities and risks of the biotechnological production of bulk chemicals from renewable resources.

Rao, R.R., Aufderheide, B., and Bequette, B.W. (2003). Control for automated regulation of hemodynamic variables. *IEEE Trans. Biomed. Eng.*, 50(3), 277–288.

Rawlings, J.B. (2013). Moving horizon estimation. *Encyclopedia of Systems and Control*, 1–7.

Rawlings, J.B. and Mayne, D.Q. (2012). *Model Predictive Control : Theory and Design*. Nob Hill Publishing.

Scott, J.K., Findeisen, R., Braatz, R.D., and Raimondo, D.M. (2014). Input design for guaranteed fault diagnosis using zonotopes. *Automatica*, 50(6), 1580 – 1589.

Seatzu, C., Silva, M., and van Schuppen, J. (2012). Control of discrete-event systems. *Lecture notes in control and information sciences*, 433.

Song, H.S. and Ramkrishna, D. (2009). Reduction of a set of elementary modes using yield analysis. *Biotechnology and Bioengineering*, 102(2), 554–568.

Stephanopoulos, G., Aristidou, A.A., and Nielsen, J. (1998). *Metabolic Engineering: principles and methodologies*. Academic Press.