EXPERIMENTAL COMPARISION OF MODEL PREDICTIVE CONTROL STRATEGIES FOR THE PRODUCTION OF ANTIBIOTICS IN FED-BATCH FERMENTATIONS

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Abstract: The main objective of the presented work is to compare two model predictive control strategies by applying them to an antibiotic production in a fed-batch fermentation process. The reactor is modelled as a nonlinear biological compartment system with 13 states. The well-known nonlinear model predictive control (NMPC) is compared with a control strategy based on online optimization of the full trajectory. The control strategies are applied to real fermentation processes, which are strongly disturbed by a temperature shift. To extend the comparision, two state estimators, the Extended-Kalman-Filter (EKF) and the Constrained-EKF (CEKF), are used.

Keywords: NMPC, EKF, CEKF, nonlinear optimal control, online optimization, fed-batch fermentation, nikkomycin

1. INTRODUCTION

Classical control concepts based on linearized models for nonlinear systems, often yield insufficient results. Therfore, it is necessary to use nonlinear model-based algorithms for process control and monitoring to achieve high productivity. This is of special importance for non-stationary processes with a time dependent set point trajectory.

The basic requirement for model-based control strategies is a process model of high accuracy. Biological processes show complex internal regulation mechanisms and strong nonlinear behavior, which makes it difficult to find an appropriate model structure. In the last years the attempt to describe these internal regulation cycles with structured parametric models increased (Roubos, 2002). These models describe the dynamic interaction of the biological compartments using coupled nonlinear differential equations. For the family of strains considered here, a highly nonlinear compartment model with 13 states was developed (King, 1997).

Using the mathematical description of a system, predictions of future output values, based on assumed future input values, can be made. These predictions can be used to calculate an optimal trajectory. Open-loop control of this optimal trajectory will show that there are differences between the offline calculated prediction and the real fermentation process. Without closed-loop control the result of the process will be suboptimal. But the application of closed-loop control strategies requires the knowledge of the real systems state. In fermentation processes most of the system's states are accessible offline only by ana-

lyzing taken samples in a laboratory. In this case state estimation algorithms, like the Extended-Kalman-Filter (EKF), the Constrained-EKF (CEKF), or the Moving-Horizon-State-Estimation (MHE) can observe the actual state by integrating the few online accessible measurements (Gelb, 1974)(Rao *et al.*, 2003).

A well-known method for nonlinear process control is the Nonlinear Model Predictive Control (NMPC)(Roubos, 2002). NMPC solves an optimization problem by searching for an input sequence, which minimizes the difference between the offline calculated optimal trajectory and the output of the system. It is obvious that if there are strong disturbances or model uncertainties, an optimal route back to the pre-calculated trajectory may not be the optimal choice in general. Because of the system's nonlinearity there may be another new way to achieve optimal productivity in a production process. Here, a control strategy based on online optimization of the complete future trajectory is advantageous.

The paper is organized as follows: After some remarks on the optimal trajectory planning in section 2, section 3 gives a summary of the state estimators used. In section 4 the application of two modell predictive control strategies is shown. The NMPC and the Online Trajectory Planning (OT) are applied to disturbed fed-batch fermentations of *Streptomyces tendae* producing the antibiotic nikkomycin.

2. THE OPTIMAL OFFLINE TRAJECTORY

In fed-batch processes the productivity is affected by the costs of the fermentation, including e.g. feeding components and personal costs, and the gained value of the product. In economy, e.g. the function

$$\Phi = \frac{\text{Gain}}{\text{Costs}} \tag{1}$$

is used to characterize the productivity of a process. Main intention for an optimal trajectory is the maximization of the productivity. Under the assumption that set-up and cleaning are fixed costs, and the costs of the feeding are small compared to the gain of the product, the objective function for optimization of the trajectory can be written as

$$\max_{\underline{x}_0,\underline{u}_1,\ldots,\underline{u}_N,t_{end}} m_{\text{product}}(t_{end}). \tag{2}$$

The product nikkomycin is formed as a so-called secondary metabolite. It's rate of production

$$\mu_{\text{Ni}} = \big(\mu_{max_1}\frac{K_1}{K_1+g_{\text{Aa}}} + \mu_{max_2}\frac{K_2}{K_2+g_{\text{Nu}}}\big)g_{\text{DNA}} \tag{3}$$

depends on intracellular, online unmeasurable states, such as the internal concentrations of amino acids (Aa), nucleotides (Nu), and DNA. That's why it is not easy to find the optimal trajectory by using manual or simple statistical planning methods. A nonlinear optimization algorithm has to be used. In order to apply numerical optimization algorithms, it is necessary to provide a parametric input sequence. In general, it is possible to choose any parametric function. Commonly used are zero- and first-order hold sequences with fixed or variable time increments.

To achieve maximum productivity, trajectory optimizations using zero-, first- and second-order hold feeding trajectories for three nutrients (ammonia, phosphate, and glucose) were compared. Additionaly, the initial values of these substrates at the start of the fermentation could be changed. Figure 1 shows the results of the optimizations. Although the trajectories of the nutrients show major differences, the product yield (m_{Ni}) is nearly the same for all three predictions. Taking a look at the internal compartments the trends of DNA and nucleotides after $t = 60\,h$, which mainly influence the formation of the product, are nearly the same. That is why the simplest, zero-order hold parametrization of the input trajectory is chosen for the following process control.

For the comparison of the closed-loop controls presented in section 4 the optimal trajectory was recalculated using fixed initial conditions. The new trajectory shows another input sequence but equally the same amount of product.

3. STATE ESTIMATION

During a fermentation process the real state differs from the model prediction due to uncertainties. Thus it is necessary to adjust the state predictions by integrating the online accessible measurements.

A classical state estimation algorithm for nonlinear state space systems is the Extended Kalman-Filter (EKF) (Gelb, 1974). As some of its equations are needed as well for the Constrained-EKF considered next, the well-known EKF equations are given here for completeness.

time-update:

$$\dot{\underline{\hat{x}}}_t = \underline{f}(\underline{\hat{x}}_t, \underline{u}(t), t),\ t_k < t < t_{k+1} \tag{4}$$

$$\underline{\hat{x}}_t(t_k+) = \underline{\hat{x}}_k^{(+)}$$

$$\dot{\mathbf{P}}(t) = \mathbf{F}(\underline{\hat{x}}_t)\mathbf{P}(t) + \mathbf{P}(t)\mathbf{F}^T(\underline{\hat{x}}_t) + \mathbf{Q} \tag{5}$$

$$\mathbf{P}(t_k+) = \mathbf{P}_k^{(+)}$$

$$\mathbf{F}(\underline{\hat{x}}_t) = \left.\frac{\partial \underline{f}}{\partial \underline{x}}\right|_{\underline{x}=\underline{\hat{x}}_t}$$

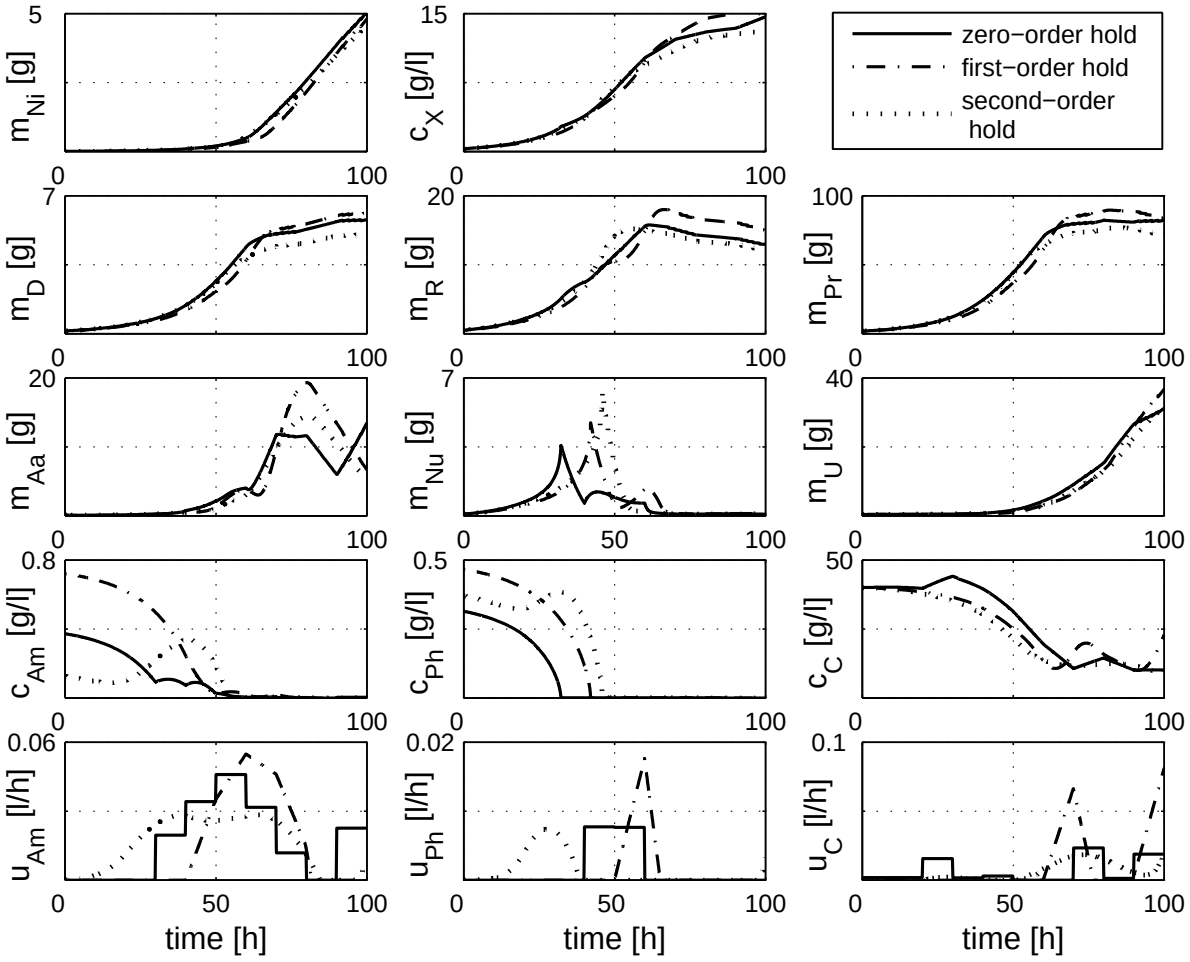

Fig. 1. Comparison of simulated optimal trajectories using different parametrizations of the feedings.
Subscripts: X - dry biomass, Ni - nikkomycin, D - DNA, R - RNA, Pr - proteins, Aa - amino acids, Nu - nucleotides, U - structural elements, Am - ammonium, Ph - phosphate, C - glucose.

measurement-update:

$$\hat{\underline{x}}_k^{(+)} = \hat{\underline{x}}_k^{(-)} + \mathbf{K}_k \left(\underline{y}_k^{\text{measured}} - \underline{h}(\hat{\underline{x}}_k^{(-)}, t_k) \right) \quad (6)$$

$$\mathbf{P}_k^{(+)} = \left[\mathbf{I} - \mathbf{K}_k \mathbf{H}_k^{(-)} \right] \mathbf{P}_k^{(-)} \quad (7)$$

$$\mathbf{K}_k = \mathbf{P}_k^{(-)} \mathbf{H}_k^{(-)^T} \cdot \left(\mathbf{H}_k^{(-)} \mathbf{P}_k^{(-)} \mathbf{H}_k^{(-)^T} + \mathbf{R}_k \right)^{-1}$$

$$\hat{\underline{x}}_k^{(-)} = \hat{\underline{x}}_t(t = t_k -)$$

$$\mathbf{P}_k^{(-)} = \mathbf{P}(t_k -)$$

$$\mathbf{H}_k^{(-)} = \left. \frac{\partial \underline{h}}{\partial \underline{x}} \right|_{\underline{x} = \hat{\underline{x}}_k^{(-)}}$$

As an alternative to the EKF, the optimization-based algorithm named Constrained-EKF (Rao *et al.*, 2003) can be used. Based on the same equations for the time-update (eqn. 4 and 5) the measurement-update is calculated as a maximum a posteriory estimation. The update $\hat{\underline{\xi}}_{k-1} = \hat{\underline{x}}_k^{(+)} - \hat{\underline{x}}_k^{(-)}$ is calculated by the following equations.

$$\min_{\hat{\underline{\xi}}_{k-1}} \Phi_{\text{CEKF}}(\hat{\underline{\xi}}_{k-1}) \quad (8)$$

$$\Phi_{\text{CEKF}}(\hat{\underline{\xi}}_{k-1}) = \frac{1}{2} \hat{\underline{\xi}}_{k-1}^{\text{T}} \cdot \mathbf{P}_k^{(-)^{-1}} \cdot \hat{\underline{\xi}}_{k-1} + \frac{1}{2} \left(\underline{y}_k^{\text{measured}} - \underline{h}((\hat{\underline{x}}_k^{(-)} + \hat{\underline{\xi}}_{k-1}), t_k) \right)^{\text{T}} \cdot \mathbf{R}_k^{-1} \cdot \left(\underline{y}_k^{\text{measured}} - \underline{h}((\hat{\underline{x}}_k^{(-)} + \hat{\underline{\xi}}_{k-1}), t_k) \right) \quad (9)$$

$$\underline{lo}_{\text{Bound}} \leq \underline{\psi}(\underline{x}, \underline{u}, t_k) \leq \underline{up}_{\text{Bound}}$$

For unconstrained, state space systems with linear measurement equation this measurement-update is equal to the update algorithm of the EKF. The update of the covariance matrix $\mathbf{P}$ can be performed the same way as by the EKF (eqn. 7) or by using the estimated Hessian matrix of an SQP optimization algorithm. The main advantage of the CEKF is the possibility to consider constraints while estimating the state of the system. DNA, for example, must have a value of 2-4% of the dry biomass in the problem considered. As the EKF

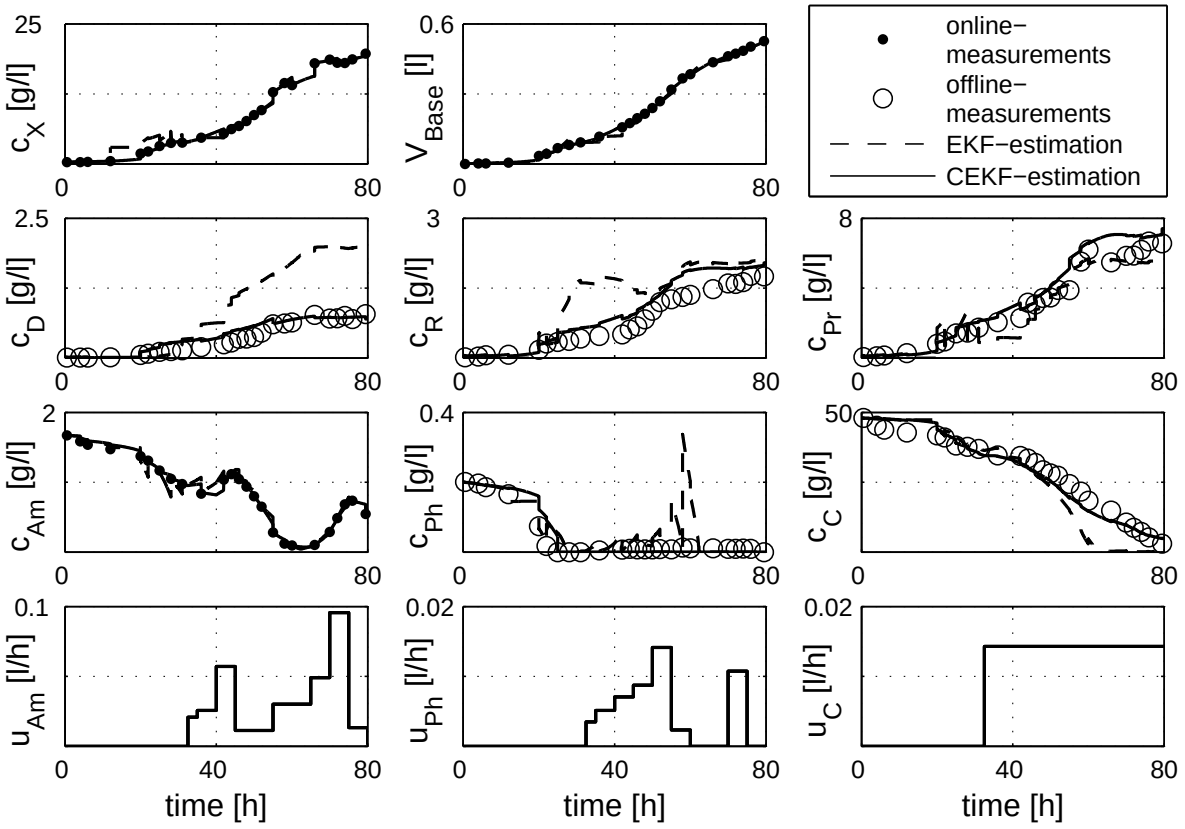

Fig. 2. Comparison of state estimation by a EKF and a CEKF in an experiment. V_{Base} denotes the volume of fed base for pH control. Subscripts see fig. 1.

violates this and other constraints its performance is worse.

Figure 2 shows a comparision of the state estimation by an EKF and a CEKF. Although the matrix $\mathbf{Q}$ of the EKF was adjusted by a nonlinear optimization of the estimation quality, in this case the EKF fails, because the linearization in the EKF algorithm is invalid if constraints are met. The CEKF meets the constraints and is therefore more reliable than the EKF while working with this highly constrained problem.

Another known optimization-based constrained state estimator is the Moving-Horizon-State-Estimation (MHE). The estimation quality of the MHE is just as good as the estimation quality of the CEKF in this case (Heine, 2004). Compared to the CEKF, the MHE needs much more calculation time (some hours), while the CEKF is nearly as fast as the EKF (some seconds).

4. MODEL PREDICTIVE PROCESS CONTROL

Because of the strong system's nonlinearity and the dynamic setpoint trajectory there is no way using classical linear control strategies for such kind of processes.

Nonlinear Model Predictive Control (NMPC)

NMPC is often the first and a well-known choice for controlling such systems. The main objective of MPC is following an offline planned trajectory by finding an optimal way from the actual process state back to this trajectory. Therefore, an input sequence is calculated which minimizes the difference between the prediction and the offline trajectory (eqn. 10 and 11).

$$\min_{\substack{\underline{u}_{k+N_{comp}},\ldots,\\ \underline{u}_{k+N_{comp}+N_{control}}}} \Phi_{\mathrm{NMPC}}\left(\begin{array}{c}\underline{u}_{k+N_{comp}},\ldots,\\ \underline{u}_{k+N_{comp}+N_{control}}\end{array}\right) \tag{10}$$

$$\Phi_{\mathrm{NMPC}} = \sum_{\substack{i=k\\ +N_{comp}+1}}^{\substack{k+N_{comp}\\ +N_{pred}}} \Big[\big(\underline{x}_{ref}(t_i) - \underline{\hat{x}}(t_i|t_k)\big)^T \cdot \mathbf{W}_i \cdot \big(\underbrace{\underline{x}_{ref}(t_i)}_{\substack{offline\\ trajectory}} - \underbrace{\underline{\hat{x}}(t_i|t_k)}_{\substack{model\\ prediction}}\big)\Big] \tag{11}$$

Only the first part of this new control strategy is realized, because after the next measurement arrives, the optimization is rerun. While optimizing the input sequence, not the whole process is simulated. The system's response is evaluated inside the prediction horizon, only. Changes of

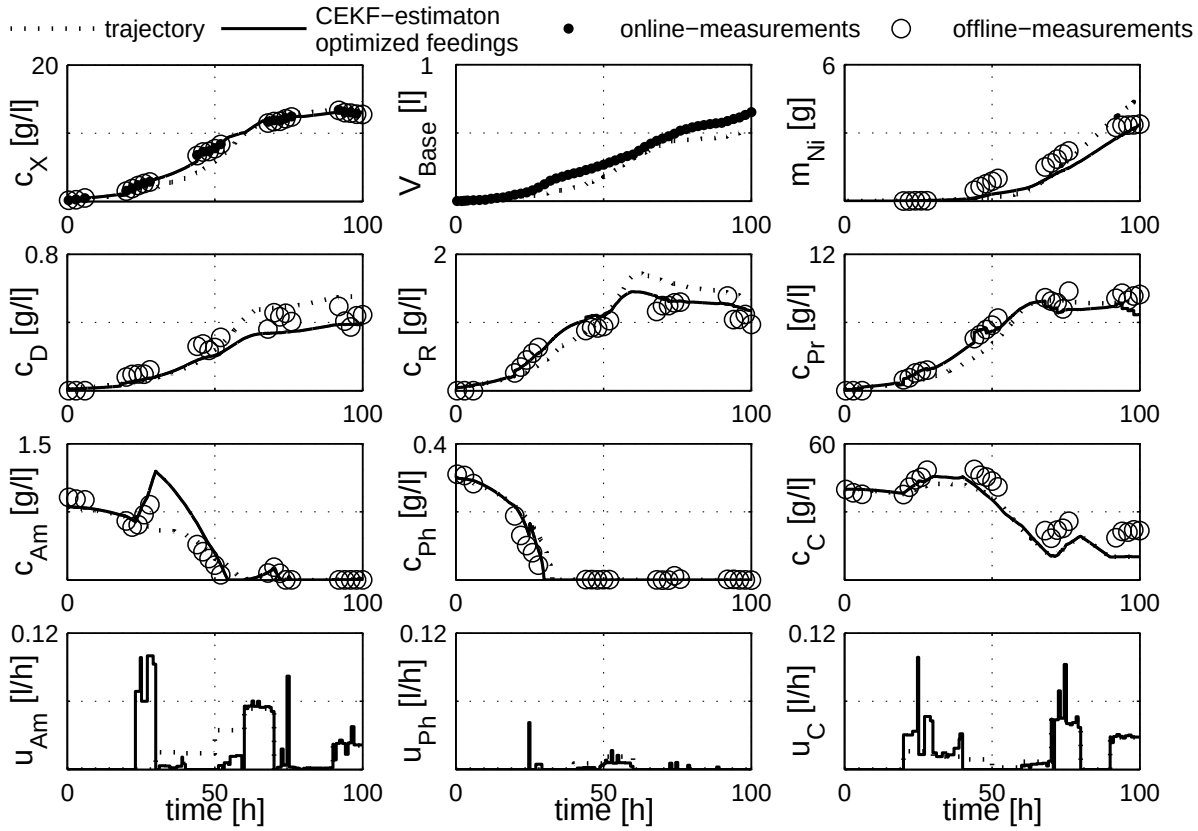

Fig. 3. Application of NMPC to a fed-batch fermentation of *Streptomyces tendae*. Subscripts see fig. 1.

the control trajectory are performed within the control horizon. The only way to find the optimal control for nonlinear constrained processes is given by numerical optimization. Because of the required computing time, the NMPC is only applicable to rather slow systems.

Online Trajectory Planning (OT)

If the system is strongly disturbed, the optimal way back to the offline planned trajectory may not be the way to maximum productivity. It is also not assured, that constraints are met, if not the whole future trajectory is simulated. Therefore, first the lengths of the prediction and the control horizon have to be set up to the end of the fermentation. Due to the fact that the whole future process is simulated, even strong constraints can be met. This is very important, e.g. for the reaction volume. The volume in the experiments performed is limited to ten liter. If the volume reaches this constraint, controllability is lost, because no additional feeding is possible. Second, the objective function (eqn. 11) itself has to be modified. Instead of minimizing the distance between the prediction and the offline trajectory, the maximum productivity itself is the target. In fact, the same cost function is chosen as used for planning the offline trajectory (eqn. 2). Every single control step achieves maximum productivity at the end of the process.

Comparison of NMPC and OT applied to disturbed fermentations

For the comparison of the NMPC and the OT a disturbance scenario was chosen, and both control strategies where applied to control such a defined disturbed fermentation. The disturbance was applied by a temperature shift of $+9\,K$ within the first 20 hours with the consequence of a nearly doubled growth rate. In the model used for state estimation and optimization this temperature shift was not known. As online- or atline-measurements the volume of fed base used for correction of the pH-value and the dry biomass, available 1.5 hours after sampling, are used. The state estimation was performed by a CEKF.

Figure 3 shows the realization of a NMPC controlled fed-batch fermentation of *Streptomyces tendae*. The prediction horizon was set to 40 h, the control horizon to 30 h. Despite of the strong disturbance the state estimator works very well, and the controller gets the system nearly back to the offline trajectory. A slightly smaller amount of product was produced then offline predicted. Figure 4 shows as a comparison an OT controlled fermentation. As a result of the control, nearly the same amount of product as for the NMPC controlled fermentation was produced. Taking a look at the trends of the measured nikkomycin, it can be seen that the production slows down when

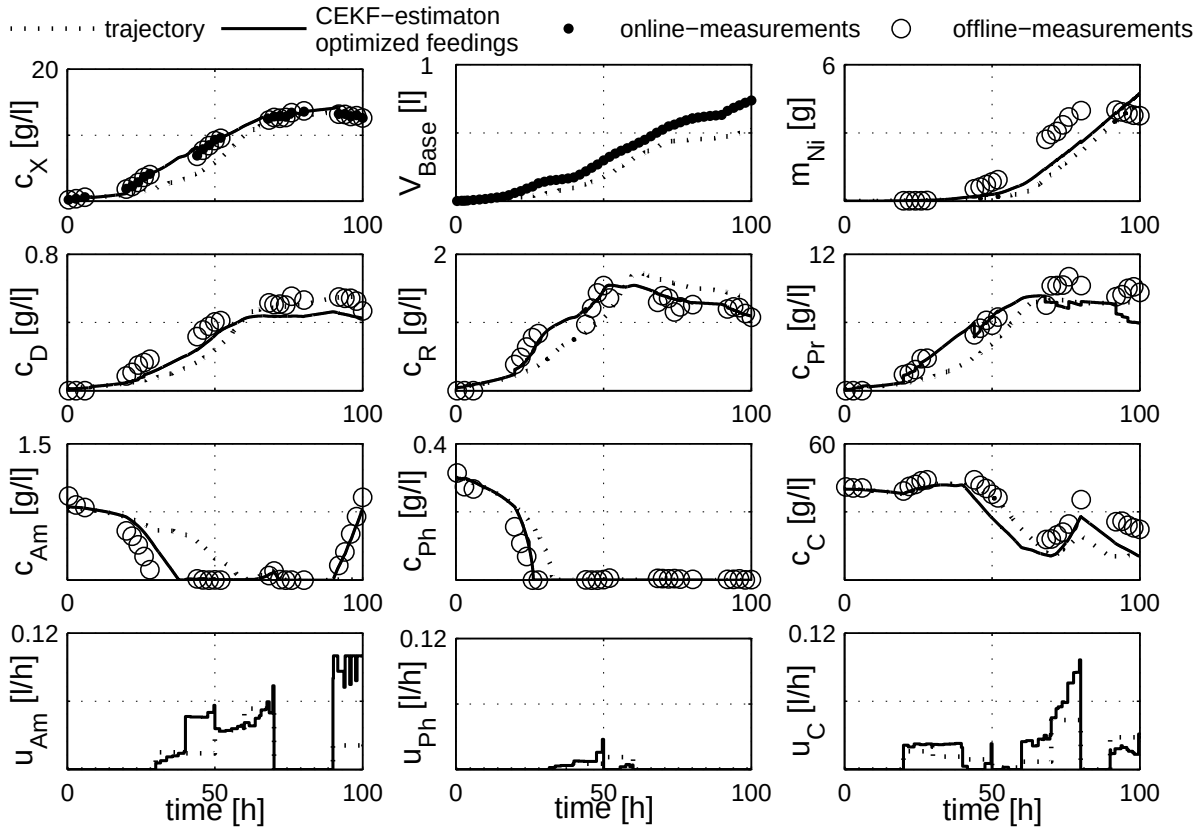

Fig. 4. Application of OT to a fed-batch fermentation of *Streptomyces tendae*. Subscripts see fig. 1.

reaching the end of both fermentations. This effect is not jet modelled. That is why both controllers are not able to prevent the production rate from slowing down. A comparison of the production rates before this unknown effect happens, shows the higher productivity of the OT. Moreover, the largest nikkomycin concentration measurements were obtained in the OT-experiment. The OT uses the higher growth rate at the beginning of the fermentation for an earlier start of the production.

5. CONCLUSIONS

The application of the Nonliner Model Predictive Control (NMPC) and the Online Trajectory Planning (OT) to disturbed fed-batch fermentations of *Streptomyces tendae* is presented here. The OT seems to be able to achieve higher productivity (Heine *et al.*, 2002). But in the presented case it is only as good as the classical NMPC. Although a higher computational burden is obtained compared to the classical NMPC, the OT possesses higher potential with increasing computing power.

Furthermore, an optimization-based estimation algorithm, the Constrained-EKF, is used. For the considered biological compartment model it provides a more accurate and more reliable state estimation compared to the EKF.

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