Automatic design of robust model predictive control of a bioreactor via Bayesian optimization ⋆

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Abstract: Model predictive control (MPC) is an advanced control strategy that can deal with general nonlinear systems and constraints but relies on accurate predictions given by a dynamic model. To satisfy constraints and improve performance despite imperfect models, robust MPC methods can be formulated. Multi-stage MPC is a robust MPC method based on the formulation of scenario trees. The resulting optimization problems can be large, as the number of scenarios considered in the tree results from the combinations of all possible uncertainties. For systems with many uncertainties, as it is the case in bioprocesses, the optimization problems become rapidly intractable. To solve this issue, heuristics are typically used to select the most relevant uncertain parameters and their range of uncertainty. In this paper, we propose a two-step approach to obtain a systematic design of multi-stage MPC controllers: First, the key uncertain parameters are extracted based on the parametric sensitivities. Second, Bayesian optimization is employed for tuning of the range of uncertainties. The approach is applied to a bioreactor simulation study. The proposed approach can avoid constraint violations that are otherwise obtained by standard MPC while being less conservative than a manually-tuned robust controller.

Keywords: Model predictive and optimization-based control, Bayesian methods, Robust control, Constrained control, estimation and control in biological systems.

1. INTRODUCTION

Bioprocesses are preferred over chemical production in some situations because of their high selectivity and sustainability. Due to their complexity, bioprocess models consist of numerous model parameters. Optimization-based algorithms like model predictive control (MPC) enhance bioprocess performance but can lead to significant constraint violations when the model is imperfect. Bioprocess models exhibit a high degree of uncertainty due to the simplifications necessary for model development of such complex processes. In addition, the experimental data available for parameter estimation is very limited due to the cost and run time of experiments.

Robust control approaches such as tube-based MPC (Rawlings et al., 2017) and multi-stage MPC (Lucia et al., 2013) are able to account for the uncertainties of a system model. While tube-based MPC is difficult to design for nonlinear systems, multi-stage MPC uses scenario trees to handle nonlinear systems effectively. However, the size of the optimization problem in multi-stage MPC increases exponentially with the number of uncertainties. Consequently, these approaches are inappropriate for bioprocesses with numerous uncertainties.

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Alternatives like sensitivity-assisted multi-stage MPC reduce computational complexity by focusing on worst-case parameter realizations most likely to cause constraint violations (Thombre et al., 2021). Similar approaches by Yu and Biegler (2020) and Puschke and Mitsos (2018) consider only critical scenarios based on parametric sensitivities but investigate just two uncertainties in case studies.

In this paper we focus on systems with numerous uncertainties. We propose a sensitivity-based method with soft constraints that identifies key uncertain parameters affecting both constraints and performance objectives, unlike prior work focusing solely on constraint sensitivities. Our approach reduces model complexity by considering only the uncertain key parameters so that multi-stage MPC becomes tractable. Our main contribution includes automatically tuning the uncertainty ranges of these key parameters via Bayesian optimization (Paulson and Mesbah, 2021), enabling compensation for neglected uncertain parameters while optimizing closed-loop performance.

This paper is structured as follows. In Section 2 the mathematical preliminaries are introduced. Then, the details of the proposed approach are presented in Section 3. In the following, the results for the developed approach applied to a bioreactor model are presented in Section 4 and the paper is concluded in Section 5.

2. PRELIMINARIES

2.1 Nominal model predictive control

We investigate a nonlinear, discrete-time dynamic system given by

$$\boldsymbol{x}_{k+1} = f_{\text{sys}}(\boldsymbol{x}_k, \boldsymbol{u}_k, \boldsymbol{\Theta}), \tag{1}$$

with the states $\boldsymbol{x} \in \mathbb{R}^{n_x}$ and inputs $\boldsymbol{u} \in \mathbb{R}^{n_u}$ at discrete time step k and the time-invariant model parameters $\boldsymbol{\Theta} \in \mathbb{R}^{n_\Theta}$. The optimization problem that is solved in order to control the system (1) via MPC is introduced as:

$$\begin{aligned}
\min_{\boldsymbol{u}_k} \quad & J_{\text{MPC}} = \sum_{k=0}^{N-1} \ell(\boldsymbol{x}_k, \boldsymbol{u}_k) + V_f(\boldsymbol{x}_N), && \text{(2a)}\\
\text{s.t.} \quad & \boldsymbol{x}_0 = \boldsymbol{x}_{\text{init}}, && \text{(2b)}\\
& \boldsymbol{x}_{k+1} = \hat{f}_{\text{sys}}(\boldsymbol{x}_k, \boldsymbol{u}_k, \tilde{\boldsymbol{\Theta}}), \quad k = 0, \dots, N-1, && \text{(2c)}\\
& \boldsymbol{g}_k(\boldsymbol{x}_k, \boldsymbol{u}_k) \leq 0, \quad k = 0, \dots, N-1, && \text{(2d)}\\
& \boldsymbol{g}_N(\boldsymbol{x}_N) \leq 0, && \text{(2e)}
\end{aligned}$$

where N denotes the horizon and the objective function J_{MPC} consists of a stage cost $\ell(\boldsymbol{x}_k, \boldsymbol{u}_k)$ and a terminal cost $V_f(\boldsymbol{x}_N)$. Constraints include the initial state $\boldsymbol{x}_{\text{init}}$, system dynamics modeled by $\hat{f}_{\text{sys}}$ with the controller model parameters $\tilde{\boldsymbol{\Theta}}$. Furthermore, additional arbitrary stage $\boldsymbol{g}_k$ and terminal $\boldsymbol{g}_N$ inequality constraints are set.
Soft constraints allow penalized violations within the cost function when necessary. This involves introducing a slack variable $\boldsymbol{\epsilon}_k$ that is added to the cost function with a penalty term $K_{\boldsymbol{\epsilon}}$, described as:

$$\begin{aligned}
\boldsymbol{g}_k(\boldsymbol{x}_k, \boldsymbol{u}_k) - \boldsymbol{\epsilon}_k \leq 0, \quad k = 0, \dots, N-1, && \text{(3a)}\\
\ell_\epsilon(\boldsymbol{\epsilon}_k) = \boldsymbol{\epsilon}_k \cdot K_{\boldsymbol{\epsilon}}. && \text{(3b)}
\end{aligned}$$

2.2 Robust multi-stage model predictive control

Multi-stage MPC uses a scenario-tree to account for uncertainties in a system. A scenario tree branches over a robust horizon N_r, with n_b uncertainty realizations per parameter representing possible state evolutions. For a prediction horizon beyond N_r, constant uncertainties are assumed. The constraints for all the scenarios are explicitly included in the optimization problem, ensuring constraint satisfaction while consideration of future feedback in the tree structure mitigates overly conservative behavior (Lucia et al., 2013).
Commonly, three possible realizations of the uncertainty are considered (n_b=3). Based on the nominal values $\tilde{\boldsymbol{\Theta}}_{\text{nom}}$ and the uncertainty range $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}$, the model parameters of the controller are $\tilde{\boldsymbol{\Theta}} = \left\{\tilde{\boldsymbol{\Theta}}_{\text{nom}} - \boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}, \tilde{\boldsymbol{\Theta}}_{\text{nom}}, \tilde{\boldsymbol{\Theta}}_{\text{nom}} + \boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}\right\}$.
As a result of the tree structure that considers the combinations of all the uncertain parameters, the number of scenarios n_S grows rapidly with the number of realizations of the uncertainty n_b and exponentially with N_r and with the number of uncertain considered parameters $n_{\tilde{\Theta}}$:

$$n_S = n_b^{N_r \cdot n_{\tilde{\Theta}}}. \tag{4}$$

This results in large optimization problems for a long robust horizon or a large number of uncertainties. To mitigate these issues, in practice N_r is commonly set to 1, which still very often results in a good performance due to the iterative nature of the MPC approach (Lucia et al., 2013). To further reduce the number of scenarios, we propose to consider only the uncertainty of a subset of the model parameters $\tilde{\boldsymbol{\Theta}}_d \in \mathbb{R}^{n_{\tilde{\Theta},d}}$ and to assume for the other model parameters $\tilde{\boldsymbol{\Theta}}_c \in \mathbb{R}^{n_{\tilde{\Theta},c}}$ nominal values ($\tilde{\boldsymbol{\Theta}} = \tilde{\boldsymbol{\Theta}}_c \cup \tilde{\boldsymbol{\Theta}}_d$).
In the event that only a limited number of parameters are considered uncertain, it is not evident which of these should be selected, nor is it clear how an appropriate value for $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}$ should be determined. The primary objective of this paper is to solve these issues.

2.3 Bayesian optimization

Bayesian optimization is a global optimization method for expensive black-box functions, where the target function f_{BO} lacks a closed-form expression and is costly to evaluate (Greenhill et al., 2020). It approximates the target function f_{BO} by a probabilistic surrogate model $\hat{f}_{\text{BO}}$, built from n observations $\mathcal{D}_n = \{\vartheta_{1:n}, f_{\text{BO}}(\vartheta_{1:n})\}$ of $\vartheta_{1:n} = \{\vartheta_1, \dots, \vartheta_n\}$ samples. The posterior $P(\vartheta \mid \mathcal{D}_n)$ is computed via Bayes' rule from the prior $P(\vartheta)$, the likelihood $P(\mathcal{D}_n \mid \vartheta)$ and the marginal likelihood $P(\mathcal{D}_n)$:

$$P(\vartheta \mid \mathcal{D}_n) = \frac{P(\mathcal{D}_n \mid \vartheta) P(\vartheta)}{P(\mathcal{D}_n)}. \tag{5}$$

The obtained posterior captures the updated beliefs about the unknown target function (Brochu et al., 2010). An acquisition function α is used to determine the next sampling point ϑ_{n+1}. The target function is then evaluated at ϑ_{n+1}, the new observation is added to the dataset $\mathcal{D}_{n+1} = \mathcal{D}_n \cup \{\vartheta_{n+1}, f_{\text{BO}}(\vartheta_{n+1})\}$ and the surrogate model is updated. After an initialization phase, this process is repeated for n_{iter} iterations, refining the surrogate model.
A common surrogate model is a Gaussian process $\mathcal{GP}$, which is completely specified by its mean function $\mu(\vartheta)$ and covariance function $k(\vartheta, \vartheta')$:

$$\hat{f}_{\text{BO}} \sim \mathcal{GP}\left(\mu(\vartheta), k(\vartheta, \vartheta')\right). \tag{6}$$

The radial basis function k_{RBF} with the length-scale parameter l is commonly employed as the covariance function

$$k_{\text{RBF}}(\vartheta, \vartheta') = \exp\left(-\frac{(\vartheta - \vartheta')^T (\vartheta - \vartheta')}{2l^2}\right). \tag{7}$$

An acquisition function α balances exploration and exploitation to compute the next sampling point. A common choice is the upper confidence bound α_{UCB}, which represents an upper bound of a confidence interval based on mean μ, standard deviation σ, and a z-score z:

$$\alpha_{\text{UCB}}(\vartheta) = \mu(\vartheta) + z \cdot \sigma(\vartheta). \tag{8}$$

The z-score adjusts exploration-exploitation trade-offs.

3. PROPOSED APPROACH

3.1 Choosing the most important uncertain parameters

System models often involve numerous uncertainties that must be addressed for robust control. However, multi-stage MPC becomes intractable when handling multiple uncertainties due to the exponential growth of the optimization problem. Limiting the considered uncertainties to a subset raises the question of how to select which ones should be explicitly included in the scenario tree.
This section introduces a systematic method to identify

influential model parameters. For simplicity, all parameters $\boldsymbol{\Theta}$ are assumed uncertain. To simulate the system, the model parameters $\boldsymbol{\Theta}$ are considered by a simulator, while in the controller the parameters $\tilde{\boldsymbol{\Theta}}$ are assumed. Not all uncertainties significantly affect the system dynamics or control behavior. Parameter uncertainties with minimal impact on constraints or control behavior might be disregarded, reducing problem complexity. By employing soft constraints, special emphasis is placed on the consideration of constraints in the cost function J_{MPC}.
To identify the most important key parameters, the parametric sensitivity of J_{MPC} with respect to $\tilde{\boldsymbol{\Theta}}$ is evaluated:

$$s = \frac{\partial J_{\mathrm{MPC}}}{\partial \tilde{\boldsymbol{\Theta}}} \cdot \tilde{\boldsymbol{\Theta}}, \tag{9}$$

where s represents the scaled sensitivity, focusing on relative rather than absolute parameter impacts. Sorting the absolute values of s reveals which uncertain parameters have the larges impact on the control behavior (constraint satisfaction and process performance). Uncertainties of parameters with low sensitivity may be ignored. Since it is challenging to compute the parametric sensitivities of a multi-stage MPC controller with many scenarios, all model parameters are assumed to be nominal ($\tilde{\boldsymbol{\Theta}} = \tilde{\boldsymbol{\Theta}}_c$) for the computation of the sensitivities.

This approach systematically partitions the model parameters of the controller into two sets: key uncertain parameters explicitly considered $\tilde{\boldsymbol{\Theta}}_d$ and nominally assumed parameters $\tilde{\boldsymbol{\Theta}}_c$. Considering only $n_{\tilde{\Theta},d}$ instead of all n_Θ parameters uncertain, drastically reduces problem size while retaining critical uncertainty representation. For each removed parameter, the number of optimization variables and constraints are roughly divided by n_b.

3.2 Bayesian optimization for tuning of multi-stage MPC

The sensitivity-based selection of uncertain parameters enables the solution of problems with many original uncertainties, but tuning the uncertainty range $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}$ in the multi-stage MPC controller remains challenging. Even if the true uncertainty range is known, adjustments are required because less influential uncertainties are ignored in the scenario tree. Underestimating $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}$ may lead to constraint violations even though multi-stage MPC is employed, while overestimating it results in overly conservative control. Thus, proper tuning of the uncertainty range is essential, and this tuning will additionally help in counteracting the fact that only the most relevant uncertainties are explicitly considered in the tree.
Tuning the uncertainty range requires the selection of $n_{\tilde{\Theta},d}$ variables, and its evaluation involves an MPC controller in closed-loop. As a result, manual tuning is challenging. We propose using Bayesian optimization for systematic tuning of the uncertainty range $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}$. The target function f_{BO} for optimization comprises three components:

$$f_{\mathrm{BO}}(\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}) = f_{\mathrm{CV}}(\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}) + f_{\mathrm{perf}}(\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}) + f_{\Delta_{\tilde{\Theta}}}(\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}}}), \tag{10}$$

where constraint violations (f_{CV}) are severely penalized, while conservative performance (f_{perf}) and large uncertainty ranges ($f_{\Delta_{\tilde{\Theta}}}$) are penalized less. A Gaussian Process with covariance function k_{RBF} (7) serves as the surrogate model. After a grid-based initialization phase using n_{init} points between $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}},\min}$ and $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}},\max}$, the subsequent sampling points are selected by maximizing the acquisition function α_{UCB} (8). For each iteration, the target function is evaluated at the new sample point, the dataset $\mathcal{D}$ updated and the posterior distribution recomputed.

4. USE CASE HYDROXY-L-LYSINE PRODUCTION VIA *PSEUDOMONAS TAIWANENSIS* VLB120

4.1 Bioreactor model

The introduced approach is applied to a fed-batch bioreactor model in a simulation study. The model describes the biotransformation of hydroxy-L-lysine via *Pseudomonas taiwanensis* VLB120 for which more details can be seen in Nerke et al. (2024).

The system consists of one input $\boldsymbol{u}$, nine states $\boldsymbol{x}$ and fourteen model parameters $\boldsymbol{\Theta}$. The two-phase bioreactor model is described by a set of ordinary differential equations (ODEs) for the state variables which are the liquid volume V_L, biomass X, substrates D-xylose S_1 and L-lysine S_2, the intermediates D-xylonolactone A_1 and D-xylonate A_2, the product hydroxy-L-lysine P and the concentration of oxygen in the liquid phase $O_{2,\mathrm{L}}$ as well as in the gas phase of the reactor $O_{2,\mathrm{G}}$. The ODE-system is expressed as

$$\frac{dV_{\mathrm{L}}}{dt} = F_{\mathrm{in}}, \tag{11a}$$

$$\frac{dX}{dt} = -D\ X + X\mu + r_P k_{PX}, \tag{11b}$$

$$\frac{dS_1}{dt} = D\ (S_{1,\mathrm{in}} - S_1) - X\frac{\mu}{Y_S} - r_1 - r_P, \tag{11c}$$

$$\frac{dA_1}{dt} = -D\ A_1 + r_1 - r_2 + r_3, \tag{11d}$$

$$\frac{dA_2}{dt} = -D\ A_2 + r_2 - r_3, \tag{11e}$$

$$\frac{dS_2}{dt} = -D\ S_2 - r_P, \tag{11f}$$

$$\frac{dP}{dt} = -D\ P + r_P, \tag{11g}$$

$$\frac{dO_{2,\mathrm{L}}}{dt} = D(O^*_{2,\mathrm{L}} - O_{2,\mathrm{L}}) - 5X\frac{\mu}{Y_S} - r_P + OTR, \tag{11h}$$

$$\frac{dO_{2,\mathrm{G}}}{dt} = \frac{\dot{V}_{\mathrm{air}}(O_{2,\mathrm{G,in}} - O_{2,\mathrm{G}}) - OTR\ V_{\mathrm{L}}}{V_{\mathrm{R}} - V_{\mathrm{L}}}, \tag{11i}$$

where the input F_{in} is the feeding flow rate adding D-xylose and oxygen to the system with the respective concentrations of $S_{1,\mathrm{in}}$ and $O^*_{2,\mathrm{L}}$. The dilution rate D is defined as the ratio of the feeding flow rate and the liquid volume

$$D = \frac{F_{\mathrm{in}}}{V_{\mathrm{L}}}. \tag{12}$$

The growth rate of the biomass μ is modeled based on Monod-kinetics

$$\mu = \mu_{\max}\frac{S_1}{K_S + S_1}, \tag{13}$$

with the maximum growth rate $\mu_{\max}$ and affinity constant K_S. The reaction rates r_i are based on Michalis-Menten-kinetics and calculated based on the following expressions:

$$r_1 = X v_{\max,1}\frac{S_1}{K_{M,1} + S_1}, \tag{14a}$$

$$r_2 = v_{\max,2}\left(A_1 - \frac{A_1}{K_2}\right), \tag{14b}$$

$$r_3 = X v_{\max,3} \frac{A_1 - \frac{A_2}{K_2}}{K_{M,2} + A_1 - \frac{A_2}{K_2}}, \tag{14c}$$

$$r_P = X v_{\max,P} \frac{S_1 S_2}{K_{M,3} S_1 + K_{M,4} S_2 + S_1 S_2}, \tag{14d}$$

where $K_{M,i}$ are the respective Michaelis-Menten constants and $v_{\max,i}$ are the respective maximum reaction velocities. Since r_2 and r_3 are reversible, the equilibrium constant K_2 is introduced. While r_2 takes place independent of the biomass, for r_P a multi-substrate Michaelis-Menten kinetic is employed.

The oxygen concentration in the liquid phase $O_{2,\mathrm{L}}$ is computed based on the equilibrium concentration of oxygen in the gas-liquid-boundary interface $O^*_{2,\mathrm{L}}$, the stoichiometric coefficient Y_S and the oxygen transfer rate OTR. The oxygen transfer rate is based on the volumetric mass transfer coefficient kla, $O^*_{2,\mathrm{L}}$ and $O_{2,\mathrm{L}}$:

$$OTR = kla(O^*_{2,\mathrm{L}} - O_{2,\mathrm{L}}), \tag{15}$$

where the concentration at the interface is calculated according to Henry's law based on the pressure p, the molar fraction of oxygen in the gas phase $x_{O_2,\mathrm{G}}$ and the Henry constant H_{O_2}

$$O^*_{2,\mathrm{L}} = \frac{p \cdot x_{O_2,\mathrm{G}}}{H_{O_2}}. \tag{16}$$

The computation of $O_{2,\mathrm{G}}$ relies on the flow rate of the inflowing air $\dot{V}_{\mathrm{air}}$ with an oxygen concentration of $O_{2,\mathrm{G,in}}$ and the volume of the reactor vessel V_R.

In addition to the ODE-system, two auxiliary expressions are introduced: the conversion of L-lysine $\mathcal{X}$ and the dissolved oxygen DO, which are computed as follows

$$\mathcal{X} = 1 - \frac{S_2 \cdot V_{\mathrm{L}}}{S_{2,0} \cdot V_{\mathrm{L},0}}, \tag{17a}$$

$$DO = \frac{O_{2,\mathrm{L}}}{O^*_{2,\mathrm{L}}}. \tag{17b}$$

The system is physically constrained by reactor capacity, pump limits and non-negative concentrations and volumes. In addition to these physical constraints which are implemented as hard constraints, further soft constraints are considered: A minimum level of dissolved oxygen ($DO >$ 30 %) for the strictly aerobic microorganism, and an upper limit on substrate concentration to avoid inhibition (Nerke et al., 2024).

The control objective is the maximization of the product titer P while minimizing the production time t_{batch}. For realization of the product maximization, the following stage cost ℓ and terminal cost V_f are employed

$$\ell(\boldsymbol{x}_k, \boldsymbol{u}_k, \boldsymbol{u}_{k-1}, \boldsymbol{\epsilon}_k) = -100P_k + F_{\mathrm{in},k} + (F_{\mathrm{in},k} - F_{\mathrm{in},k-1})^2 + 10^8(\epsilon_{\mathrm{DO},k} + \epsilon_{S_1,k}), \tag{18a}$$

$$V_f(\boldsymbol{x}_N) = -100P_N, \tag{18b}$$

penalizing any input and input changes while prioritizing product maximization. Each batch is run until 99 % conversion of lysine is obtained ($\mathcal{X}$=0.99).

In accordance with (10), in the target function of the Bayesian optimization the respective production time (linearly interpolated between the discretization points) as well as the magnitude of constraint violations v_{CV} and uncertainty ranges $\Delta_{\tilde{\Theta},i}$ are taken into account

$$f_{\mathrm{BO}} = -\left(1000 v_{\mathrm{CV}} + t_{\mathrm{batch}} + \sum_i^{n_{\tilde{\Theta},d}} \Delta_{\tilde{\Theta},i}\right). \tag{19}$$

Constraint violations are severely penalized and at a lower extent long production times and large uncertainty ranges. Combining different metrics in J_{MPC} and f_{BO} enables the consideration of more complex control goals.

The computations are performed by using do-mpc (Fiedler et al., 2023), CasADi (Andersson et al., 2019) and IPOPT (Wächter and Biegler, 2006). All code to reproduce the results is openly available with details on initial states, constraints and model parameters. [1]

4.2 Modeling the system's uncertainty

Some model parameters are physical constants that are precisely known, but this does not apply to the kinetic parameters. Due to the complexity of coupled reactions in bioreactors, kinetic parameters exhibit uncertainty. A total of n_Θ=14 model parameters are treated as uncertain. Instead of deterministic values ($\boldsymbol{\Theta}$=$\boldsymbol{\Theta}_{\mathrm{nom}}$), these parameters are modeled to be stochastic in the simulation of virtual experiments. In this study, the uncertain model parameters are assumed to be uniformly distributed around their respective nominal value based on the offset $\Delta_{\mathcal{U}}$ according to

$$\boldsymbol{\Theta} = \boldsymbol{\Theta}_{\mathcal{U}} \sim \mathcal{U}(\boldsymbol{\Theta}_{\mathrm{nom}}(1 - \Delta_{\mathcal{U}}), \boldsymbol{\Theta}_{\mathrm{nom}}(1 + \Delta_{\mathcal{U}})). \tag{20}$$

Due to the probabilistic nature of the parameters, several experimental runs have to be performed for evaluation. A number of n_{runs} randomly generated sets of model parameters $\boldsymbol{\Theta}$ are considered and the parameters remain time-invariant during each run but differ across batches according to (20). In the Bayesian optimization, the target function (19) is evaluated for each run individually ($f_{\mathrm{BO,i}}$), and the mean $\overline{f}_{\mathrm{BO}}$ is used for updating the $\mathcal{GP}$

$$\overline{f}_{\mathrm{BO}} = \frac{1}{n_{\mathrm{runs}}} \sum_{i=1}^{n_{\mathrm{runs}}} f_{\mathrm{BO,i}}. \tag{21}$$

4.3 Nominal model predictive control under uncertainty

For optimization of the input trajectory, nominal MPC is employed with a horizon of N=12 h, a step size of 1 h and the cost function introduced in (18). The ODE-system is discretized using orthogonal collocation of finite elements. Under nominal conditions ($\boldsymbol{\Theta}$=$\boldsymbol{\Theta}_{\mathrm{nom}}$), the MPC controller successfully maximizes the product titer, achieving 88.74 mmol l^{-1} after a production time of 41.70 h without constraint violations. As illustrated in Fig. 1 the system is operated directly at the constraint of DO, indicating that this constraint is limiting the performance of the system.

In the presence of stochastic model parameters $\boldsymbol{\Theta}_{\mathcal{U}}$, nominal MPC fails to ensure constraint satisfaction in 87 % of the runs. Since severe constraint violations are present, the control behavior is not acceptable. Thus, consideration of the underlying uncertainties is essential and multi-stage MPC is applied.

[1] https://github.com/MulleBro/2024-BO-msMPC

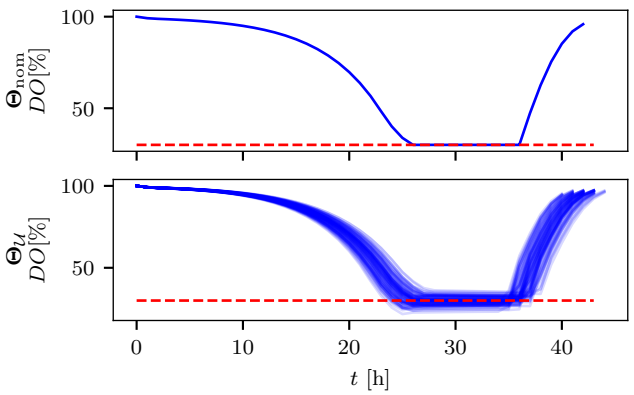

Fig. 1. Nominal MPC under nominal and uniformly distributed model parameters. Trajectories for DO indicated by blue solid line, constraint indicated by dotted red line. $\Delta_{\mathcal{U}}$=5 %, n_{runs}=100.

4.4 Extracting uncertain key parameters

To robustify the control performance against the parameter uncertainties, multi-stage MPC with a robust horizon of N_r=1 is employed. Considering all parameters uncertain ($n_{\tilde{\Theta},d}$=n_{Θ}) leads to 3^{14} scenarios according to (4), which is computationally intractable. Therefore, the methodology introduced in Section 3.1 is utilized for the identification of the key uncertainties. The obtained parametric sensitivities for a nominal open-loop MPC prediction over the full production time (42 h) are shown in Fig. 2.

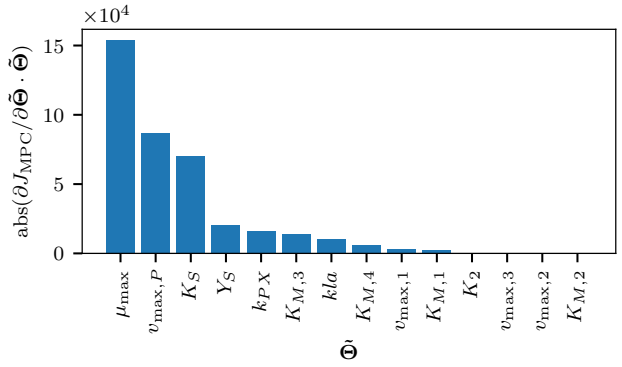

Fig. 2. Key parameters for the uncertainty of the system: Parametric sensitivity of the cost of nominal MPC to the nominal model parameters, open-loop MPC performed for a complete production run (N=42 h).

Most parameters have a minor impact on the system, with $\mu_{\max}$, $v_{\max,P}$ and K_S being the most influential. Given that those three parameters account for the largest impact on the control behavior, the system's uncertainty is approximated by considering only those three parameters uncertain in the controller ($\tilde{\boldsymbol{\Theta}}_d$). Additionally neglecting combinations of nominal parameters and only considering one nominal scenario, the numbers of scenarios is reduced from 3^{14} to 2^3+1=9. This reduction makes multi-stage MPC computationally tractable for the present control problem.

4.5 Tuning of multi-stage MPC

The introduced multi-stage MPC allows for consideration of the present uncertainties but requires careful tuning of the uncertainty range, as only a few key parameters are selected to represent the system's overall uncertainty. Manual tuning is performed via a one-dimensional grid search, assuming the same uncertainty range for all uncertain considered parameters. Table 1 shows the results for manual tuning in terms of percentage of runs with constraint violations r_{CV}, mean magnitude of violations per run $\overline{v}_{\text{CV}}$ and mean batch time $\overline{t}_{\text{batch}}$.

Table 1. Manual tuning of the uncertainty range of multi-stage MPC. $\Delta_{\mathcal{U}}$=5 %, n_{runs}=100.

$\Delta_{\tilde{\Theta},\mu_{\max}}$ [%]	$\Delta_{\tilde{\Theta},v_{\max,P}}$ [%]	$\Delta_{\tilde{\Theta},K_S}$ [%]	r_{CV} [%]	$\overline{v}_{\text{CV}}$ [%]	$\overline{t}_{\text{batch}}$ [h]
0	0	0	87	10.019	41.61
3	3	3	31	1.377	41.93
6	6	6	2	0.064	42.26
7	7	7	1	0.003	42.37
8	8	8	0	0	42.49

With an increasing uncertainty range, the number of runs with constraint violations and mean violations per run are reduced. While at an uncertainty range of 7 % minor violations are present, at a level of 8 % no constraint violations occur. Thus, all constraint violations are successfully mitigated and the multi-stage MPC with $\Delta_{\tilde{\Theta},i}$=8 % is referred to as manually tuned ($\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}},\text{man}}$). However, the mean production time is increased by 0.88 h compared to not considering uncertainties. Since manual tuning is challenging, the introduced control behavior is likely overly conservative. A higher performance might be achieved by considering individual $\Delta_{\tilde{\Theta},i}$ for each uncertainty. A multidimensional grid search would be inefficient due to its inability to incorporate newly obtained knowledge into sampling decisions.

For a systematic and efficient tuning, we apply the approach based on Bayesian optimization described in Section 3.2 to tune the uncertainty range of the parameters that are considered uncertain in the multi-stage MPC. During initialization, three points per parameter are sampled within $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}},\text{min}} = 0\%$ and $\boldsymbol{\Delta}_{\tilde{\boldsymbol{\Theta}},\text{max}} = 10\%$. The z-score of the acquisition function α_{UCB} (8) is set to 1.96 (95 % confidence interval), and Bayesian optimization is performed for 200 iterations using the Python package bayesopt(Nogueira, 2014). The uncertainty ranges obtained by Bayesian optimization and the resulting controller performance are listed in Table 2.

Table 2. Bayesian optimization of the uncertainty range of multi-stage MPC. $\Delta_{\mathcal{U}}$=5 %, n_{runs}=100.

$\Delta_{\tilde{\Theta},\mu_{\max}}$ [%]	$\Delta_{\tilde{\Theta},v_{\max,P}}$ [%]	$\Delta_{\tilde{\Theta},K_S}$ [%]	r_{CV} [%]	$\overline{v}_{\text{CV}}$ [%]	$\overline{t}_{\text{batch}}$ [h]
8.61	0.03	6.01	0	0	42.37

As expected, the resulting upper bounds are smaller than the initial 10 % at which Bayesian optimization is ini-

tialized. Interestingly $\Delta_{\tilde{\Theta},v_{\max,P}}$ is very small. This may indicate a lower influence of $v_{\max,P}$ regarding constraint violations or a compensation of its influence by the uncertainty in the other key parameters. With these uncertainty ranges, all constraints are respected, leading as expected to an increase in mean production time (42.37 h) when compared to the one obtained by nominal MPC (41.61 h) where 87 % of the runs resulted in constraint violations (cf. Table 1). Manual tuning without any constraint violations resulted in an higher mean production time, illustrating that the performance obtained by our proposed approach could not be easily obtained with manual tuning.
A comparison of the trajectories of the manually and via Bayesian optimization tuned multi-stage MPC is presented in Fig. 3.

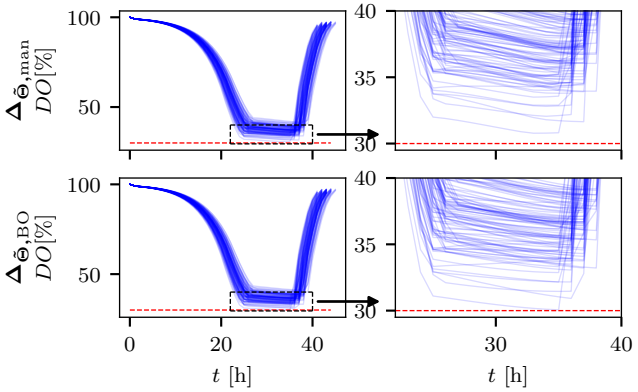

Fig. 3. Trajectories of manually and via Bayesian optimization tuned multi-stage MPC. Trajectories for DO indicated by blue solid line, constraint indicated by dotted red line. $\Delta_{\mathcal{U}}$=5 %, n_{runs}=100.

While by manual tuning, constraint violations are mitigated, the control behavior is conservative since the system does not operate at the constraints. In contrast to that, the via Bayesian optimization tuned multi-stage MPC operates very close to the constraints without violating them, allowing for minimal production times.
All computations were performed on a AMD Ryzen Threadripper 3990X processor with 256 GB of RAM. Employing the MA27-solver from the Harwell Subroutine Library (http://www.hsl.rl.ac.uk) resulted in a mean computation time of 0.146 s for solving a nominal MPC step and 1.191 s for the via Bayesian optimization tuned multi-stage MPC. The computation of the Bayesian optimization, which is performed offline, ran for 11.0 h.

5. CONCLUSION

We proposed an approach to design multi-stage MPC controllers for systems with many uncertainties. In this two-step approach, the uncertain key parameter regarding constraints and performance are determined which is followed by automatic tuning of the uncertainty range via Bayesian optimization. By considering only the uncertainties of the essential key parameters that are determined based on parametric sensitivity, multi-stage MPC became tractable. Manual tuning confirmed the approach's ability to mitigate constraint violations but resulted in conservative control behavior. By employing Bayesian optimization, the challenges of manual tuning were overcome and the uncertainty range was tuned for optimal control performance. Future work will explore grouping uncertain parameters with similar effects based on the monotonicity of model equations with respect to the model parameters.

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