Flatness-Based Design of Experiments for Model Selection

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Abstract: High product standards and cost-efficient robust process designs are key issues in the pharmaceutical industry and require thorough system understanding of the underlying physical phenomena. Model-based approaches have been proven favorable to gain valuable system insights. However, qualitative inferences can be drawn only if the model is adequately derived and validated by – at best – optimally designed experiments. In this paper, we present a new model inversion strategy to solve model-based design of experiments (MBDoE) problems for model selection; i.e., we maximize the difference of competing model candidates by using the differential flatness concept. Differentially flat systems can represent their states and controls analytically by the so-called flat output and its derivatives. By maximizing the difference of the flat outputs of all considered model candidates, we efficiently obtain analytical model-revealing control actions for the MBDoE problem. When these optimized control actions are implemented, the resulting experimental data are expected to invalidate incorrect models more reliably. We demonstrate the effectiveness of the proposed MBDoE concept with potential model candidates that describe different realizations of a mass action reaction system.

Keywords: model selection, differential flatness, design of experiments, optimal control, Akaike information criterion

1. INTRODUCTION

Profit margins in the highly competitive and regulated pharmaceutical industry have been continually declining over the last two decades because of increasing research and development costs (Behr et al., 2004). For instance, during the whole process chain of producing active pharmaceutical ingredients (APIs), thorough system understanding of the underlying physical processes is key to meet the high product standards and to enable cost-efficient drug development and manufacturing. To gain true system insights, the application of first-principles models has been proven beneficial. Process systems engineers, however, often face a plurality of mathematical model candidates which describe the reaction network of the process under study equally well. In addition to the parameter estimation problem, the identification of the most suitable model candidate is crucial for model-based analysis and design. By following the model-based design of experiments (MBDoE) principle, solving a model identification problem for dynamic systems requires optimal control actions. Commonly used collocation and control parameterization techniques result in complex optimization problems that require substantial computational time and efficient solvers (Biral et al., 2016). Alternatively, the differential flatness concept enables effective model selection within the MBDoE framework. In systems theory, differential flatness ensures that the system states and the control functions can be expressed analytically by so-called flat system outputs and their derivatives. Thus, by implementing a differential flatness strategy for MBDoE, we can avoid simplifying assumptions and the need to solve differential equations numerically.

The theory of differential flatness for dynamic systems was derived by Fliess et al. (1992). Since then, flatness-based methods have been widely used in research and industry – primarily in controller design and trajectory planning of electromechanical systems (Franke and Robenack, 2013). Considering MBDoE, strategies based on differential flatness have rarely been considered (Schenkendorf et al., 2012; Schenkendorf and Mangold, 2014) and to our knowledge have not been applied to model selection problems in the literature.

In this paper, we extend the application of the flatness approach within the MBDoE framework to the class of mass action systems because of their fundamental impact on modeling of reaction networks in (bio)chemistry (Voit et al., 2015). We are aiming at falsifying improper models from a set of competing model candidates in two steps. First, we show that the individual models satisfy differential flatness conditions, and second, we solve an optimization problem that uses the flatness property. We efficiently derive analytical optimal control actions for subsequent validation experiments to figure out the most suitable model from a set of potential model candidates describing different realizations of a mass action reaction system.

2. METHODS

Dynamic system behavior is often mathematically described by ordinary differential equations (ODEs) which read in their state-space representation as

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), \boldsymbol{\theta}), \tag{1}$$

where the dynamic of the system is a function of the dynamic states $\mathbf{x}(t) \in \mathbb{R}^n$, the system input $\mathbf{u}(t) \in \mathbb{R}^m$, and the parameter vector $\boldsymbol{\theta} \in \mathbb{R}^p$. The non-linear function $\mathbf{f}$: $\mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^p \to \mathbb{R}^n$ represents the vector field of the dynamic system. The corresponding output equation is

$$\mathbf{y}(t) = \mathbf{h}(\mathbf{x}(t), \mathbf{u}(t), \boldsymbol{\theta}) \tag{2}$$

with outputs $\mathbf{y}(t) \in \mathbb{R}^q$ and $\mathbf{h}$: $\mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^p \to \mathbb{R}^q$ as the (non-)linear output function. For readability reasons, the notion of time dependency and the parameter vector are omitted but are specified when the context demands it.

2.1 Differentially flat systems

A non-linear dynamic system {(1),(2)} is called differentially flat or shortly flat if there exists an output vector

$$\mathbf{y}^{\mathrm{flat}} = \mathbf{h}^{\mathrm{flat}}(\mathbf{x}, \mathbf{u}, \dot{\mathbf{u}}, \ldots, \mathbf{u}^{(s)}), \tag{3}$$

with a finite value $s \in \mathbb{N}$, referred to as a flat output which fulfills the following conditions:

(1) The states and the controls can be described as a function of the flat output and its derivatives:

$$\mathbf{x} = \boldsymbol{\Psi}_x(\mathbf{y}^{\mathrm{flat}}, \dot{\mathbf{y}}^{\mathrm{flat}}, \ldots, \mathbf{y}^{\mathrm{flat}\,(r)}), \tag{4}$$

$$\mathbf{u} = \boldsymbol{\Psi}_u(\mathbf{y}^{\mathrm{flat}}, \dot{\mathbf{y}}^{\mathrm{flat}}, \ldots, \mathbf{y}^{\mathrm{flat}\,(r+1)}). \tag{5}$$

(2) The dimensions of the control and the flat output vector are equal:

$$\dim \mathbf{y}^{\mathrm{flat}} = \dim \mathbf{u}. \tag{6}$$

In general, $r \in \mathbb{N}$ is not known a priori, except for single-input and single-output (SISO) systems, where $r = n - 1$ (Adamy, 2014). There is an infinite number of flat outputs, and often, they are a function of the states only (Adamy, 2014), where valuable information about the flat output design can be extracted from graph theory (Wey, 2002; Richard et al., 2002). Flat outputs might be fictitious or real, i.e., the flat outputs have no physical meaning, or they might be equal to measurable quantities. In the latter case, the controls are also referred to as flat inputs (Waldherr and Zeitz, 2008). Flatness-based methods are also being researched and used for partial differential equations (PDEs); see Wagner and Meurer (2018) and references therein.

In practice, there is no general method for either determining if a system is flat or constructing a flat output. Several exceptions exist: Systems that are linearizable by static feedback control are flat systems by definition. In the case of linear systems, differential flatness is equal to the system being controllable and vice versa (Rigatos, 2015). The construction of flat inputs was shown for SISO systems and a limited set of multi-input and multi-output (MIMO) cases (Waldherr and Zeitz, 2010). Further methods of determining flat outputs are currently being researched (Kolar et al., 2016; Franke and Robenack, 2013; Victor et al., 2014). In practice, an expert guessing strategy to identify flat outputs (3) followed by a subsequent validation step in the form of equations (4), (5), and (6) has proven favorable. This trial-and-error approach is supported by the fact that many technical systems are flat systems, and that often, informative flat outputs have physical meaning, similar to Lyapunov functions (Adamy, 2014).

2.2 Design of experiments for model selection

In the literature one can distinguish between statistical and model-based design of experiments, where methods of the former, e.g., response surface methods, are popular and widely used because of their simplicity but are not able to properly cope with complex dynamic systems for the same reason (Franceschini and Macchietto, 2008). A generic scheme of the proposed MBDoE strategy for model selection is given in Fig. 1. Typically, MBDoE results in a dynamic optimization problem of the form

$$\begin{aligned} \max_{\boldsymbol{\Phi} \in \boldsymbol{\Phi}} \quad & \mathcal{J}(\boldsymbol{\Phi}) \\ \text{s.t.} \quad & \mathbf{g}_{\mathrm{eq}}(\boldsymbol{\Phi}) = 0, \\ & \mathbf{g}_{\mathrm{ineq}}(\boldsymbol{\Phi}) \leq 0. \end{aligned} \tag{7}$$

Here, $\mathcal{J}$ is a scalar objective function, and $\boldsymbol{\Phi}(\mathbf{u}, \mathbf{x}_0)$ is the design vector within the design space $\boldsymbol{\Phi}$ specified by the control $\mathbf{u}$ and the initial states $\mathbf{x}_0 = \mathbf{x}(t = 0)$. The optimization problem is subject to equality constraints $\mathbf{g}_{\mathrm{eq}}$ and inequality constraints $\mathbf{g}_{\mathrm{ineq}}$ which, for instance, might be introduced to limit the concentration of a species or to ensure positive values of the system states. Various scalar objective functions for MBDoE have been proposed in the literature; an overview can be found in Verheijen (2003). Thus, an optimal control problem is given, where the continuous time-dependent control inputs $\mathbf{u}(t)$ are parameterized by solving the underlying ODE system (1) numerically while aiming to maximize some distance measure between the competing model candidates.

The proposed flatness-based approach for MBDoE performs differently. It operates in an inverse manner. The difference between the model outputs is maximized by optimized flat output curves; i.e., the corresponding controls $\mathbf{u}$ and the initial states $\mathbf{x}_0$ are recalculated and have to be equal for all considered model candidates and their optimized flat outputs. Assuming M model candidates and taking the Euclidean metric as distance measure, the optimization problem (7) reads as

$$\begin{aligned} \max_{\mathbf{y}^{\mathrm{flat}}} \quad & \int_{t_0}^{t_\mathrm{f}} \sum_{i=1}^{M-1} \sum_{j=i+1}^{M} \Big[\mathbf{y}^i(\mathbf{y}^{\mathrm{flat},i}, \dot{\mathbf{y}}^{\mathrm{flat},i}, \ldots, \mathbf{y}^{\mathrm{flat},i\,(r)}) \\ & \qquad - \mathbf{y}^j(\mathbf{y}^{\mathrm{flat},j}, \dot{\mathbf{y}}^{\mathrm{flat},j}, \ldots, \mathbf{y}^{\mathrm{flat},j\,(r)}) \Big]^2 \, \mathrm{d}t \\ \text{s.t.} \quad & \Delta\mathbf{u}(\mathbf{y}^{\mathrm{flat}}) = 0, \\ & \Delta\mathbf{x}_0(\mathbf{y}^{\mathrm{flat}}) = 0, \\ & \mathbf{g}_{\mathrm{eq}}(\mathbf{y}^{\mathrm{flat}}) = 0, \\ & \mathbf{g}_{\mathrm{ineq}}(\mathbf{y}^{\mathrm{flat}}) \leq 0. \end{aligned} \tag{8}$$

The inputs and outputs are expressed according to equations (2), (4), and (5). The Delta function $\Delta(\cdot)$ measures the differences between the recalculated inputs and the initial states for all M model candidates. The flat outputs themselves are specified by time-dependent empirical

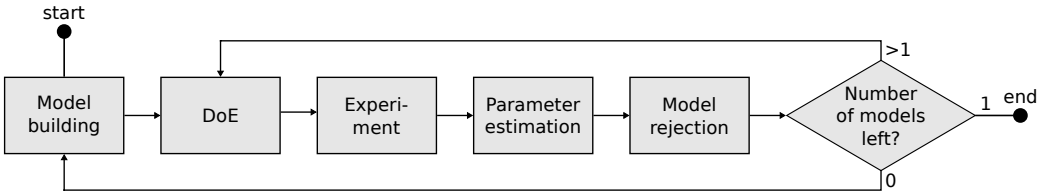

Fig. 1. MBDoE work-flow for model selection

basis functions $\mathbf{y}^{\text{flat},i} = \mathbf{y}^{\text{flat},i}(\boldsymbol{\theta}^{\star,i}, t) \ \forall i \in \{1, ..., M\}$ and their meta-parameters $\boldsymbol{\theta}^{\star,i}$. As the inputs and the outputs are available in closed form, the optimal control problem given in (7) is transformed in an algebraic nonlinear optimization problem. The gained optimal control profiles and the initial conditions are subsequently used to run a new experiment which is expected to provide more informative data in terms of model falsification.

After the experiment is run and the parameters estimated, model invalidation is performed. Here, we can distinguish between several approaches for model selection: testing strategies, goodness-of-fit measures, cross-validation, and criteria based on information theory (Burnham et al., 2002). A well-accepted metric based on information theory is the corrected Akaike information criterion (AIC)

$$\text{AIC}_\text{c} = -2 \log \mathcal{L}(\boldsymbol{\theta}) + 2K + \frac{2K(K+1)}{N-K-1}, \tag{9}$$

where K is the total number of estimated regression parameters, N is the number of data sample points, and $\mathcal{L}$ is the likelihood function, which measures the mismatch between simulation results and the measurement data. Please note, that the use of the corrected AIC is recommended for values N/K below 40 (Burnham et al., 2002).

2.3 Basis functions

Selecting suitable, preferably analytic basis functions is a non-trivial task because of the complex expressions of the inverse system's states and controls resulting from the nonlinear structure of the underlying system of differential equations. Often, higher-order derivatives appear, where small changes in these derivatives may cause large effects in the states and controls. Additionally, differentiability and the end conditions have to be taken care of, notably the initial conditions of the states, which are not part of the flat output vector. Previously free to choose when the system of differential equations was numerically integrated, the initial conditions are now bounded by the flat output and its derivatives. Further constraints, e.g., lower and upper limits on states and constraints or restrictions on operational characteristics, can be incorporated as well, but have to be considered in parallel when choosing the basis functions. Concerning model selection, where constraints are integrated into the optimization problem, an evolutionary approach starting from simple functions with few meta-parameters as lower order polynomials towards functions, that ensure considerable design freedom like splines, is recommended.

3. CASE STUDY

The studied mass action system forms product E from two reactants A and B while two intermediates, C and D, are produced. To describe this process mathematically, three different potential model candidates are proposed. The candidates were deliberately chosen to integrate typical phenomena that are considered in model selection when dealing with chemical reaction systems like adding/removing of intermediates and inclusion of back reactions. Product E is formed by: 1) reactant B and intermediate D, 2) intermediate D solely, and 3) intermediate D but the reaction is reversible. The described reaction mechanisms are summarized and shown below.

$$\begin{aligned} 5\,\text{A} + 2\,\text{B} &\xrightarrow{\text{k}_1} \text{C} \\ \text{C} &\xrightarrow{\text{k}_2} \text{A} + \text{D} \\ \text{B} + \text{D} &\xrightarrow{\text{k}_3} \text{E} \end{aligned} \qquad \text{Model 1}$$

$$\begin{aligned} 5\,\text{A} + 2\,\text{B} &\xrightarrow{\text{k}_1} \text{C} \\ \text{C} &\xrightarrow{\text{k}_2} \text{A} + \text{D} \\ \text{D} &\xrightarrow{\text{k}_3} \text{E} \end{aligned} \qquad \text{Model 2}$$

$$\begin{aligned} 5\,\text{A} + 2\,\text{B} &\xrightarrow{\text{k}_1} \text{C} \\ \text{C} &\xrightarrow{\text{k}_2} \text{A} + \text{D} \\ \text{D} &\underset{\text{k}_4}{\overset{\text{k}_3}{\rightleftharpoons}} \text{E} \end{aligned} \qquad \text{Model 3}$$

Model 1 is assumed to represent the true model and is used to generate simulated data, i.e., in-silico measurement data with a zero intercept and a constant variance. In principle, however, the reactants and products could be measured in the laboratory, and both reactants might be added independently via pumps and used as control inputs for MBDoE. Thus, for example, the state equations of the dynamic system of Model 1 according to equation (1) are

$$\begin{aligned} \dot{x}_1 &= -k_1 x_1 x_2^{2/5} + k_2 x_3 + u_1 \\ \dot{x}_2 &= -\frac{2}{5} k_1 x_1 x_2^{2/5} - k_3 x_2 x_4 + u_2 \\ \dot{x}_3 &= \frac{1}{5} k_1 x_1 x_2^{2/5} - k_2 x_3 \\ \dot{x}_4 &= k_2 x_3 - k_3 x_2 x_4 \\ \dot{x}_5 &= k_3 x_2 x_4. \end{aligned} \tag{10}$$

The state vector $\mathbf{x}$ comprises the concentrations of the five participating species A to E. Typically, not all quantities are measurable. Thus, we assume $\mathbf{y}^1 = (x_1 \ x_5)^T$ as the output vector for Model 1. Please note that measuring x_1 does not result in a flat output but might be reconstructed by an alternative flat output as shown below. Model 2 and Model 3 can be assembled analogically.

4. RESULTS

4.1 Flat output vector

As x_5 does not appear on the right side of the dynamic equations in (10), it must be included in the flat output vector. A self-evident guess for additional flat outputs with a physical meaning are the concentrations themselves. For instance, a flat output candidate for Model 1 is $\mathbf{y}^{\text{flat},1} = (x_4\ x_5)^T$; i.e., the conditions (4), (5), and (6) are fulfilled. The resulting algebraic terms of the states and controls are not shown here for the lack of space. Two situations occur where the system is not controllable with the specified flat output, i.e., when $x_4 = 0$ or $\dot{x}_5 = 0$. By changing the flat output to

$$\mathbf{y}^{\text{flat},1} = \begin{pmatrix} x_2 \\ x_5 \end{pmatrix}, \tag{11}$$

we circumvent the singularity at $\dot{x}_5 = 0$; this effect is known in the literature as an extrinsic singularity (Kaminski et al., 2018). In either case, the singularities lie on constraint borders of the optimization problem if assumed that the concentrations can be interpreted only when they are positive. Accordingly, it can be shown that the output vector (11) is a flat output for Model 2 and Model 3 alike. Thus, all of the model candidates' dynamic systems are differentially flat.

4.2 Trajectory planning

As mentioned previously, the flatness-based MBDoE strategy benefits from the easiness in system trajectory planning, i.e., for desired system dynamics the related control actions are immediately available. This is in particular true, when the flat output is physically linked to the system. Therefore, in the case study at hand, a target trajectory $\mathbf{y}^*(t) = \mathbf{y}^{\text{flat},*}(t)$ can be designed by choosing basis functions that express the desired time-varying concentration profiles. In a first step before model selection, we aim at transferring the system to a stable operational point, where, for example, Hagenmeyer and Zeitz (2004) used polynomial functions of degree five to realize this transition.

In contrast, in the proposed reaction system the polynomial approach cannot be used due to the mentioned sensitivity effect induced by the used derivatives. In higher-order polynomials, oscillating effects, also known as Runge's phenomenon, occur and may cause difficult-to-implement control actions. In all three models, fourth-order derivatives of the flat output appear in the controls. Simulations have shown that the states and controls are very sensitive to minor changes in these derivatives. At the same time, both model outputs of the flat output vector have to be analyzed in parallel; i.e., the two presumably autonomous design functions cannot be chosen independently if the resulting behavior of the system is restricted to bounds.

In the following, we consider Model 1 and illustrate how to design the desired system trajectory and how it relates to control actions. The concentration of reactant B takes the role of a constant substrate and is therefore expressed as

$$x_2^*(t) = const. \tag{12}$$

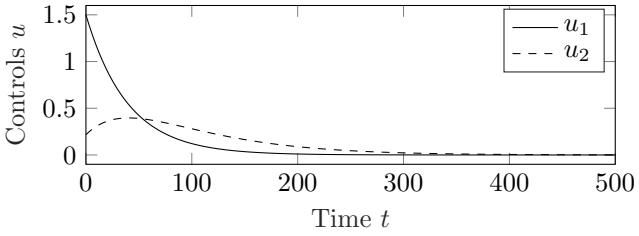

Fig. 2. Control actions needed for the target trajectories

The transient concentration profile of product E is assumed to gradually reach a plateau of desired product concentration, at which, for instance, the product solution could be removed from the reactor. We can realize the desired behavior using exponential functions equal to

$$g(t) = R\left[1 - \frac{T+t}{T}\exp\left(-\frac{t}{T}\right)\right], \tag{13}$$

with constants R and T. From the analytic expressions of the intermediate concentrations $x_3(t)$ and $x_4(t)$ of the inverse system, we obtain that the first and second derivatives of the concentration of product E $x_5(t)$ at the initial point $t_0 = 0$ have to vanish. Otherwise, intermediates C and D have to be available in stock in order to add them to the reactor at the beginning of the reaction. Therefore, we expand the formula in (13) by adding another summand and are left with

$$\begin{aligned} x_5^*(t) = R_1\left[1 - \frac{T_1+t}{T_1}\exp\left(-\frac{t}{T_1}\right)\right] \\ + R_2\left[1 - \frac{T_2+t}{T_2}\exp\left(-\frac{t}{T_2}\right)\right], \end{aligned} \tag{14}$$

and the side condition

$$\frac{R_1}{T_1^2} + \frac{R_2}{T_2^2} = 0. \tag{15}$$

If a substrate concentration of 15 and a product concentration of around 20 is targeted, the constants in equation (14) can be chosen according to the values shown in Table 1. The remaining constant is calculated from the side condition in (15). Results for the controls and states

Table 1. Constants for the target trajectory

Constant	Value
R_1	35
T_1	60
T_2	40

are shown in Fig. 2 and Fig. 3, respectively. The lines represent the solutions obtained from the inverse Model 1, i.e., by applying the differential flatness concept. The solutions of the ODE system, in turn, were numerically integrated using the controls obtained from the inverse system, and are shown as dots in Fig. 3. As expected, the values coincide perfectly.

4.3 Model selection

A translation of the non-linear programming problem (8) into an implementation-related optimization problem results in

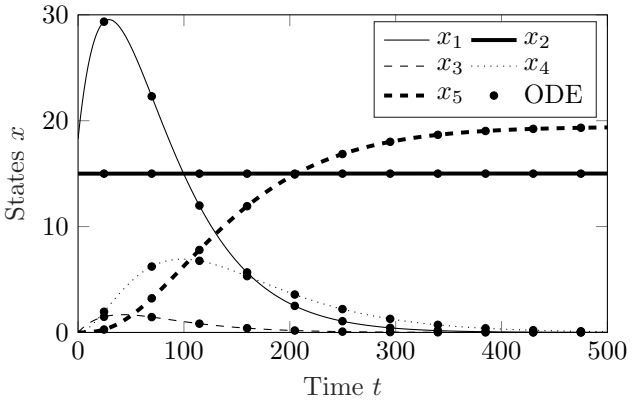

Fig. 3. States of the target trajectory

$$
\begin{aligned}
\max_{\boldsymbol{\theta}} \quad & \sum_{k=0}^{n_t-1} \sum_{i=1}^{M-1} \sum_{j=i+1}^{M} \left[\mathbf{y}^i(\boldsymbol{\theta}^i, t_k) - \mathbf{y}^j(\boldsymbol{\theta}^j, t_k)\right]^2 \\
\text{s.t.} \quad & \sum_{k=0}^{n_t-1} \sum_{i=1}^{M-1} \sum_{j=i+1}^{M} (\mathbf{u}^i(\boldsymbol{\theta}^i, t_k) - \mathbf{u}^j(\boldsymbol{\theta}^j, t_k))^2 = 0 \\
& x_i^j(\boldsymbol{\theta}^j, t_0) = x_i^{j+1}(\boldsymbol{\theta}^{j+1}, t_0),\ i \in \{1,2\}, \\
& \quad j \in \{1, \ldots, M-1\}, \\
& x_i(\boldsymbol{\theta}, t_0) = 0,\ i \in \{3,4,5\}, \\
& x_i(\boldsymbol{\theta}, t_k) \geq 0,\ i \in \{1, \ldots, 5\},\ k \in \{0, \ldots, n_t - 1\}, \\
& x_i(\boldsymbol{\theta}, t_k) \leq 50,\ i \in \{1, \ldots, 5\},\ k \in \{0, \ldots, n_t - 1\}, \\
& u_i(\boldsymbol{\theta}, t_k) \geq 0,\ i \in \{1,2\},\ k \in \{0, \ldots, n_t - 1\},
\end{aligned}
\tag{16}
$$

with $n_t = 30$ the number of data time points. According to the inequality constraints on the concentration states, lower and upper bounds are additionally introduced for the design variables. It was assumed that one experiment was run before the optimization. The model parameters were regressed with the results for the corrected AIC shown in the second column in Table 2. The corresponding results of

Table 2. $\mathrm{AIC_c}$

Model	not optimized	optimized
1	−170.14	−350.76
2	−110.18	+193.31
3	−141.20	+186.51

the model outputs are shown in Fig. 4. As can be observed in the plot, all of the models are able to accurately predict their outputs for the first data set. Model selection is not possible at this stage.

Benchmark case. The basis functions for the flat output vector (11) were taken as first-order polynomials resulting

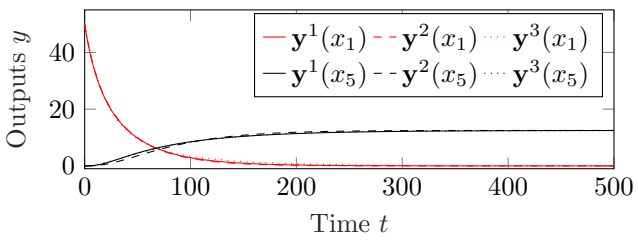

Fig. 4. Results for the three models before optimization

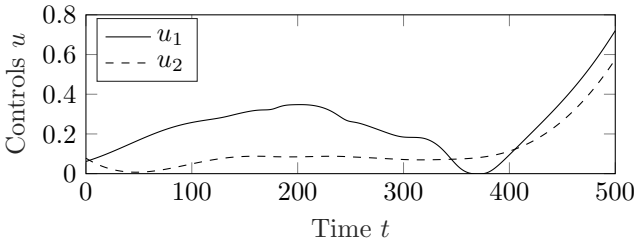

Fig. 5. Optimal experimental conditions

in a 12-dimensional design space. If the initial equality constraints on species C, D, and E are neglected, the solver converges to the objective function value $1.5e5$. It circumvents the dynamics of the underlying systems ending up in a situation where only the flat output is non-zero. Thus, the objective function is maximized when the model output of one model is zero, while the model outputs of the two remaining models are at the objective function's maximum respecting the bound constraints given in (16). In order to ensure an acceptable signal-to-noise ratio, another inequality constraint was introduced:

$$
\sum_{k=0}^{n_t-1} x_i(t_k) \geq n_t \alpha,\ i \in 1, \ldots, 5. \tag{17}
$$

Here, α is a design constant and represents an artificial limit, that depends on the measurement noise of the used measuring device and was set to 5 in the case at hand.

Global optimization using splines. To circumvent difficulties when choosing basis functions, as described in the trajectory planning section, and to omit limitations on the profile of the concentration states, we turn to piecewise functions, because they allow significant freedom when considering the shape of the curves. Commonly used piecewise functions are polynomials within the context of B-splines. Extensive information about B-splines and splines in general is given in the book by de Boor (2001). In the upcoming optimization problem, all of the flat outputs' basis functions were expressed as B-spline curves. The number of control points of the B-spline curves, i.e., the number of meta-parameters, was chosen to be 18, leading to a 54-dimensional design space. The subsequent global optimization was done using a multi-start approach in combination with a gradient-based solver. The resulting optimal control is shown in Fig. 5. Following optimization, new in-silico measurement data were created. Together with the first data set, the outputs of the models were regressed anew. The outcome is illustrated in Fig. 6 and the corrected AIC is given in the third column in Table 2. It clearly can be observed from the plot and the $\mathrm{AIC_c}$ values that both data sets can be accurately reproduced solely by Model 1. Additionally, Model 3 performs slightly better than but qualitatively equal to Model 2, as Model 3 is a super-structure model of Model 2. In conclusion, Model 2 and Model 3 can be rejected after the run of a single additional experiment, and Model 1 is selected as the most promising candidate.

5. CONCLUSION

We have illustrated a novel approach to the model-based design of experiments for model selection using differen-

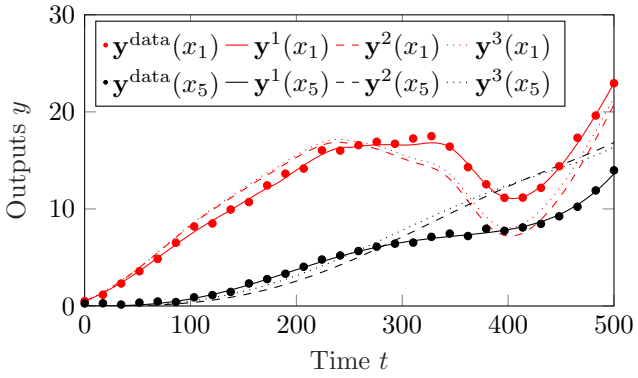

Fig. 6. Model outputs after MBDoE

tially flat methods. Compared to commonly used methods, our approach circumvents the numerical approximations needed for solving the emerging optimal control problem, because in differentially flat systems, the states and controls can be derived analytically without integrating the underlying system of differential equations. Moreover, a supply of analytic gradients to the optimization solver, even for highly non-linear systems, is possible. We successfully applied the strategy to a non-linear mass action system case using B-splines as the parameterization technique, thus obtaining optimal experimental conditions for the subsequent experiment. We successfully falsified improper models and selected the most promising one after a single additional experiment. Furthermore, we showed how the differentially flat methods can be used at the same time to design feedforward control for the desired system trajectory of the study case. Moreover, we also stressed that the determination if a non-linear system is flat and the computation of flat outputs are non-trivial tasks and subject of ongoing research. In future, we plan to apply the proposed flatness-based design of experiments strategy to a reaction system of pharmaceutical relevance and to validate the results with laboratory experiments. Furthermore, we will also focus on systematic ways of finding flat outputs and the subsequent choice of basis function while including noisy observations and uncertainties of initial conditions and model parameters, too.

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