Set-based Experiment Design for Model Discrimination Using Bilevel Optimization

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Abstract: Experiment design can be used to discriminate between valid and invalid models. This task is not trivial as models are typically nonlinear and the kinetic parameters and initial conditions are uncertain. In this work, we propose a set-based and bilevel optimization approach to design an input sequence such that nonlinear models with uncertainties can be discriminated with guarantees based on a single measurement. In the outer program of the bilevel optimization program, an input minimizing a given norm and satisfying input constraints is determined. For the determined input sequence, the inner program certifies that the reachable output sets of the models are nonoverlapping at a chosen time-point, thus guaranteeing model discrimination. To be able to provide guarantees despite the nonconvexities of the reachable sets, we convexify the inner program. We demonstrate our approach at the chemostatic signaling system of Dictyostelium discoideum.

Keywords: set-based approach; convex optimization; experiment design; model discrimination; bilevel optimization

1. INTRODUCTION

Mathematical models are used for design and analysis of complex dynamical systems. However, modeling dynamical systems is challenging since many uncertain factors exist. In biological systems, e.g., the interactions of the system components are not fully understood. Furthermore, measurement data are uncertain and model parameters are usually unknown (Bruggeman and Westerhoff, 2007).

These uncertainties typically lead to a large number of competing model candidates. Therefore, methods are desired for the design of experiments that allow discrimination between invalid and valid models. However, the discrimination task is generally difficult due to the uncertainties and the typically nonlinear model equations.

In the past, many experiment design methods for model discrimination were proposed. In Apgar et al. (2008), e.g., a model-based approach is presented which is used for input design to facilitate model discrimination in cell signaling. The approach of Mélykúti et al. (2010) is based on maximizing the distance between the output trajectories of two models. The advantage is that if the output trajectories are far apart, noisy measurements will not have a detrimental influence on the discrimination. In Georgiev et al. (2010) a linear discrimination problem is examined. The goal is to determine an input that is guaranteed to produce different output trajectories for two systems of linear differential equations with parameter uncertainties. Flassig and Sundmacher (2012) introduce an optimal control-based approach in which the sigma-point method is applied to model parameter uncertainties. As a measure for model discrimination, the authors compute the expected model response probability distribution functions. Other noteworthy examples regarding experiment design for model discrimination are, e.g., Skanda and Lebiedz (2010) and Streif et al. (2014). For a short review see also Kreutz and Timmer (2009).

In this work, we address the problem of experiment design for guaranteed discrimination of nonlinear models under consideration of uncertainties. To this end, we use a set-based approach as developed by Rumschinski et al. (2010). In this approach, uncertain initial conditions and parameters as well as the nonlinear model and output equations are combined into a feasibility problem. By applying relaxation methods, the posed feasibility problem can be solved very efficiently allowing guaranteed model (in)validation (Rudolph et al., 2015), parameter estimation (Streif et al., 2013) as well as fault diagnosis and isolation (Savchenko et al., 2012; Paulson et al., 2014).

This paper is structured as follows. In Sec. 2, the problem is formally described. Sec. 3 presents the proposed bilevel optimization-based approach. Sec. 4 illustrates the approach for the chemostatic response in Dictyostelium discoideum, and Sec. 5 summarizes our work.

2. PROBLEM SETUP

2.1 Description of Model Candidates

We consider discrete-time systems of the form
\[c[i] : \begin{cases} x[i](k+1) = f[i](x[i](k), u(k), p[i]) \\ y[i](k) = g[i](x[i](k), u(k), p[i]) \end{cases} \tag{1}\]

where \(f[i] : \mathbb{R}^{n_x} \times \mathbb{R}^{n_u} \times \mathbb{R}^{n_p} \rightarrow \mathbb{R}^{n_x}\) are polynomial or rational functions, \(x[i](k) \in \mathbb{R}^{n_x}\) is the time-variant state vector, \(u(k) \in \mathbb{R}^{n_u}\) the time-variant input vector, and \(p[i] \in \mathbb{R}^{n_p}\) the time-invariant parameter vector. Time is indexed by \(k \in \mathbb{N}^0\). The polynomial output equations are denoted by \(g[i] : \mathbb{R}^{n_x} \times \mathbb{R}^{n_u} \times \mathbb{R}^{n_p} \rightarrow \mathbb{R}^{n_y}\), and \(y[i](k) \in \mathbb{R}^{n_y}\) denotes the time-variant output vector.

The superscript \([i]\) with \(i \in \mathcal{I} := \{1, \ldots, n_c\}\) is used as an index to the model candidate \(C := \{c[1], c[2], \ldots, c[n_c]\}\). The model candidates are assumed to differ in their functions \(f[i]\) and/or \(g[i]\). Each model has its own set of variables \(x[i](k), y[i](k)\) and \(p[i]\). Note that all model candidates have the same input \(u(k)\).

In this work we assume that initial conditions, parameters and inputs are uncertain-but-bounded, which means they take values from bounded sets. As a consequence and due to the considered model (1), states and outputs are also uncertain-but-bounded. The uncertainty sets are denoted as follows:

\[y[i](k) \in Y[i](k), x[i](k) \in X[i](k), \forall k \in \mathcal{T}, \forall i \in \mathcal{I}\]

\[p[i] \in P[i], \forall i \in \mathcal{I}\]

\[u(k) \in U(k), \forall k \in \mathcal{T}\]  

\[\mathcal{T} := \{0, 1, \ldots, n_t - 1\}\] is the considered finite time horizon.

Please note that we consider only two models for simplicity of notation and presentation in the remainder of this paper. However, the approach can be easily extended to more than two models at once.

2.2 Experiment Design for Model Discrimination

When modeling a dynamical system it sometimes turns out that more than one model candidate is consistent with the available measurement data. In this case, new experiments have to be designed which allow the discrimination between valid and invalid model candidates and consequently further statements on the interaction of the components in the investigated biological system.

Fig. 1 illustrates the general problem as well as the considered solution approach for two competing model candidates: It may happen that the model output sets \(Y[1](k)\) and \(Y[2](k)\) overlap at all time points \(k \in \mathcal{T}\) for the initial input sequence \(\{u(0), \ldots, u(n_t - 1)\}\) (see Fig. 1(a)). In such cases and if the taken measurements fall into the overlapping areas, none of the model candidates can be invalidated with guarantees.

To allow guaranteed invalidation of at least one model candidate, the proposed approach is to design a new input sequence \(\{\tilde{u}(0), \ldots, \tilde{u}(n_t - 1)\}\) such that the output sets do not overlap at least at one time-point \(\tau \in \mathcal{T}\) (see Fig. 1(b)). If a measurement is taken at time-point \(\tau\), it is guaranteed that at least one of the model candidates can be invalidated if the taken measurement does not fall into one of the output sets. Note that it would be too restrictive or even infeasible to demand output set separation for all time-points.

The section proposes a bilevel optimization approach to tackle experiment design as described in Sec. 2. The bilevel optimization problem consists of an outer and an inner program. While the outer program determines a new input sequence, the inner program guarantees that the model output sets are separated.

3. SET-BASED EXPERIMENT DESIGN FOR GUARANTEED MODEL DISCRIMINATION

3.1 Output Set Separation – Inner Program

Let \(\hat{Y}[1](k), \hat{Y}[2](k), k \in \mathcal{T}\) denote the output sets resulting from the input sequence \(\tilde{u} := \{\tilde{u}(0), \ldots, \tilde{u}(n_t - 1)\}\) and uncertainties. To check separation of the output sets at time-point \(\tau\), we determine the distance of the output sets as follows:

\[\hat{\delta} := \min \left(\hat{y}[1](\tau) - \hat{y}[2](\tau)\right)^2\]

s.t. \(\hat{y}[1](\tau) \in \hat{Y}[1](\tau)\)

\(\hat{y}[2](\tau) \in \hat{Y}[2](\tau)\)  

\[\hat{\delta} > 0\] implies output set separation at time-point \(\tau\), as required for guaranteed model discrimination. It is important to point out that for simplicity we do not consider measurement uncertainties. However, including measurement errors is straightforward due to the general formulation of the models (1) and uncertainty description (2). To consider uncertain-but-bounded measurement uncertainties would further require \(\hat{\delta} > \omega\), where \(\omega\) has to be chosen depending on the measurement uncertainty.

Because the output sets \(\hat{Y}[1](k)\) and \(\hat{Y}[2](k)\) are not known explicitly, we reformulate the optimization problem (3) using the model equations (1) and the uncertainty descriptions (2) of both models \(c[1]\) and \(c[2]\) to obtain
\[ \hat{\delta} := \min \left( \hat{y}^{[1]}(\tau) - \hat{y}^{[2]}(\tau) \right)^2 \]

s.t. model equations (1) for \( c^{[1]} \) and \( c^{[2]} \)

uncertainties (2) for \( c^{[1]} \) and \( c^{[2]} \).

To guarantee output set separation, (4) has to be solved globally. However, determining the global optimum of (4) is difficult because the optimization problem is nonlinear and its feasible set is typically nonconvex due to the nonlinear equations (1) and (2). However, as shown in Borchers et al. (2009) and Rumschinski et al. (2010) it is possible to relax the nonlinear optimization problem (4) into a convex semi-definite optimization problem or – if larger problems are considered - into a linear optimization program. The resulting convex optimization problems can be solved efficiently using available solvers for semi-definite or linear solvers.

Note that the solution \( \hat{\delta}_{\text{relax}} \) obtained by solving the relaxed optimization problem satisfies \( \hat{\delta} \geq \hat{\delta}_{\text{relax}} \). Thus, if the output sets \( \hat{Y}^{[1]}(\tau) \) and \( \hat{Y}^{[2]}(\tau) \) do not overlap, i.e. \( \hat{\delta} > 0 \), then the convex relaxation approach guarantees output set separation due to the relations \( \hat{\delta} \geq \hat{\delta}_{\text{relax}} > 0 \).

The formulation of the optimization problem (4) as well as its convex relaxation can be done easily using the freely available MatLab-based toolbox ADMIT (Streif et al., 2012, Analysis, Design and Model Invalidation Toolbox). ADMIT has been used for many applications in the past and provides an useful environment for the design, analysis and (in)validation of model candidates considering different types of uncertainties, e.g. Borchers et al. (2013), Carius et al. (2014), Rausch et al. (2014), Andonov et al. (2015).

3.2 Determining an Input – Outer Program

The outer program is used to determine an input sequence \( \hat{u} \) of minimum norm that satisfies input constraints and for which output set separation can be certified by the relaxed inner program, i.e. \( \hat{\delta}_{\text{relax}} > 0 \). The resulting bilevel optimization problem is given by

\[ \min_{k=0}^{n_{\delta}-1} \| \hat{u}(k) \| \]

s.t. \( \hat{u}(k) \in \mathcal{U}(k), \forall k \in \mathcal{T} \) \( \hat{\delta}_{\text{relax}} > 0 \). (5)

The basic idea is now to solve the (nonconvex) outer program using a deterministic local nonlinear solver. The obtained input sequence \( \hat{u} \) is supplied to the relaxed inner program which can be solved using the ADMIT toolbox. The procedure can be repeated until a (locally) optimal input sequence is obtained.

Note that in general a constant input, i.e. \( \hat{u}(0) = \ldots = \hat{u}(n_{\delta} - 1) \) can be considered. Often, in biological experimental setups, an input is considered to stay constant over time as it is supplied in a large amount compared to e.g. the amount of cell surface receptors that can bind the input.

4. EXAMPLE

To illustrate the proposed approach, we consider the chemostatic response in the amoeba Dictyostelium discoideum. D. discoideum is a species of soil-living amoeba with a relatively short life cycle of about 24 hours (cf. Fig. 2). The simplicity of its lifecycle makes D. discoideum a valuable model organism to study genetic, cellular and biochemical processes (Fey et al. (2007); Devroottes (1989)).

Fig. 2. The 24 hours lifecycle of D. discoideum, adopted from Fey et al. (2007).

4.1 Model Description

Each organism starts its life as a unicellular amoeba. When D. discoideum is starved it secretes cyclic Adenosine monophosphate (cAMP) thus attracting other D. discoideum to aggregate. Aggregation then leads to a multicellular slug and a fruiting body which produces spores (cf. Fig. 2).

Two models exist that can describe adaptation of D. discoideum to chemostatic signals, see Melykít et al. (2010) and Fig. 3. In both models, a chemotaxis response regulator R becomes active forming Rₐ (xₐ) through the action of an activator enzyme A (x₁) when a cAMP stimulus (u) appears. However, the deactivating mechanism determined through the interaction of an inhibiting molecule I (x₂) in the two models can be different.

The reaction mechanisms for Model Candidate 1 (c[1]) is described as follows:

\[
\begin{align*}
\dot{x}^{[1]}_1(k+1) &= x^{[1]}_1(k) + h(-p^{[1]}_0 x^{[1]}_1(k) + p^{[1]}_1 u(k)) \\
\dot{x}^{[1]}_2(k+1) &= x^{[1]}_2(k) + h(-p^{[1]}_0 x^{[1]}_2(k) + p^{[1]}_1 u(k)) \\
\dot{x}^{[1]}_3(k+1) &= x^{[1]}_3(k) + h(-p^{[1]}_0 x^{[1]}_3(k) + p^{[1]}_1 u(k)) \\
&+ p^{[1]}_6 (1 - x^{[1]}_1(k)) x^{[1]}_1(k)
\end{align*}
\]

where \( x^{[1]}_1(k) \) is the model output \( y^{[1]}(k) \in Y^{[1]}(k) \), and \( h \) results from time-discretization and is set to 0.1 hours.

The reaction mechanisms for Model Candidate 2 (c[2]) is described as:
Fig. 3. Two competing model candidates of the sensing system of the *D. discoideum*, adopted from Melykuti et al. (2010). While in Model Candidate 1 the inhibitor I is regulated directly by the external cAMP stimulus, in Model Candidate 2, I is regulated via the activator A.

\[
\begin{align*}
\mathbf{c}^{[2]} &= \left\{ \begin{array}{l}
x_3^{[2]}(k+1) = x_3^{[2]}(k) + h(-(p_1^{[2]} x_3^{[2]}(k) + p_2^{[2]} u(k))
\end{array} \right. \\
\mathbf{c}^{[2]} &= \left\{ \begin{array}{l}
x_3^{[2]}(k+1) = x_3^{[2]}(k) + h(-p_3^{[2]} x_3^{[2]}(k) + p_4^{[2]} x_2^{[2]}(k))
\end{array} \right. \\
\mathbf{c}^{[2]} &= \left\{ \begin{array}{l}
x_3^{[2]}(k+1) = x_3^{[2]}(k) + h(-p_5^{[2]} x_3^{[2]}(k) + p_6^{[2]} x_2^{[2]}(k))x_1^{[2]}(k)
\end{array} \right. \\
\mathbf{c}^{[2]} &= \left\{ \begin{array}{l}
x_3^{[2]}(k+1) = x_3^{[2]}(k) + h((1 - x_3^{[2]}(k))x_1^{[2]}(k))
\end{array} \right.
\end{align*}
\]

where \(x_3^{[2]}(k)\) is the model output \(y^{[2]}(k) \in Y^{[2]}(k)\).

Note, in both model candidates we consider the following conserved moiety: \(R_T = R + R_a\) with \(R_T = 1\).

### 4.2 Results for Experiment Design

The presented experiment design approach was performed for the initial input sequence \(u(0) = \cdots = u(n, -1) = 1\). We assumed that the initial input concentration does not saturate the receptor, thus, is not constant over time. Model parameters were considered within the range \(p_i^{[1]} = [0.1, 0.9, 2.1]\). The initial conditions were set to \(x_1^{[1]}(0), x_2^{[1]}(0) \in [0.94, 0.96]\) and \(x_2^{[1]}(0), x_2^{[2]}(0) \in [0.045, 0.055]\), and \(x_3^{[1]}(0), x_3^{[2]}(0) \in [0.045, 0.055]\). We further assumed that values for the input lie within the range \(u \in [0, 1]\) and the time point for which model output set separation is considered, was set to \(\tau = 5\), i.e. 0.5 hours.

For solving the inner and outer program, we used CPLEX (CPL (2007)) and Matlab’s fmincon, respectively.

Fig. 4 shows the result: We performed an outer approximation for the output sets \(Y^{[1]}(\tau)\) and \(Y^{[2]}(\tau)\) for the initial applied input sequence and noticed that these sets do overlap for the considered time-point \(\tau\) (cf. Fig. 4(a)). After applying the proposed framework we could determine a new input sequence such that the resulting output sets \(Y^{[1]}(\tau)\) and \(Y^{[2]}(\tau)\) could be clearly separated. Hence, the models can be discriminated (cf. Fig. 4(b)). While Model Candidate 1 shows an increase of the output \(\hat{y}^{[1]}\), Model Candidate 2 describes a slightly transient behavior of \(\hat{y}^{[2]}\) for the designed input sequence \(\hat{u}\). In Fig. 4(c) the initial and designed input sequences are depicted and compared.

The designed input sequence was determined to around one fifth of the initial input sequence and shows two small steps at \(k = 1\) and \(k = 8\), i.e. 0.1 and 0.8 hours.

### 5. CONCLUSIONS AND OUTLOOK

We presented an experiment design method using bilevel optimization. The approach allows discrimination of valid and invalid models dealing with uncertainties in initial
conditions, parameters, measurement and input data. Furthermore, nonlinearities in the model dynamics leading to nonconvex problems were considered by applying relaxation techniques.

The bilevel problem consists of an outer (nonconvex) optimization problem which supplies an input sequence to the inner program. The inner program is then relaxed and solved for this particular input sequence using freely available state-of-the-art solvers. To check and estimate output set separation, the distance of the output sets were determined with an optimization problem. With that, an input sequence can be determined for which the model output sets are separated and hence, the model candidates can be discriminated with only a single measurement.

In this work we considered only single output sets for which set separation was performed. Future work will focus on multiple output sets. However, the presented method, is computationally very challenging. Hence, the number of considered output sets should be chosen very carefully.

REFERENCES


