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Approximate Robust Optimal Experiment Design In Dynamic Bioprocess Models

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Abstract— **In dynamic bioprocess models parameters often appear in a nonlinear way. When designing optimal experiments to calibrate these models, the Fisher Information Matrix explicitly depends on the current parameter estimates. Hence, it is advisable to take this parametric uncertainty into account in the design procedure in order to obtain an experiment which is robust with respect to changes in the parameters. The current paper applies computationally efficient approximate robustifcation strategies based on a worst case scenario. Both methods exploit linearisation techniques to avoid the hard to solve max-min optimisation problems. The methods will be illustrated on a predictive microbiology case study.**

I. INTRODUCTION

Nonlinear differential equation models are valuable tools for the analysis, design, optimisation and control of nonlinear dynamic processes. Before these models can be used in practice, they often need to be calibrated [1], [2]. More precisely, model parameters have to be estimated such that the model predicts experimental data as accurately as possible. As experiments are often cost and/or labour intensive, Optimal Experiment Design techniques can help to systematically select a limited set of experiments which contain the most information and from which the parameters can be estimated with a high accuracy [3]. Applications in (bio)chemical engineering have been presented in, e.g., [4], [5], [6], [7].

When a parameter appears nonlinearly in the model, it is well-known that an optimally designed experiment depends on its current value. In addition, in real experiments process noise can not be avoided. Both aspects introduce uncertainty in the optimisation problem and, hence, require a robust optimisation approach [8], [9], [10]. In robust optimisation, a so-called robust counterpart formulation has to be solved, i.e., a worst-case scenario needs to be optimized. These kinds of formulations typically yield a hard to solve min-max problem. In this paper two methods to approximate the solution to these challenging optimisation problems are discussed. The method developed by Körkel et al. [8] requires second-order sensitivity information in the objective function. In order to solve the resulting optimisation problem, a strategy to obtain this information, together with the necessary third and fourth order derivatives using the ACADO-tookit [11], is presented.

Finally, it has to be noted that the amount of uncertainty assumed in the process or the emphasis put on obtaining robust solutions induces a trade-off with respect to the original Optimal Experiment Design objective. Such trade-offs can systematically be explored and evaluated using multi-objective optimization techniques [10], [12].

The paper is divided into two parts. Section II-A describes the mathematical formulation of OED. The employed robust formulations are discussed in Section II-B. Section II is concluded with a short description of the used software environment (Section II-C). Section III is dedicated to the results. First, the case study is introduced (Section III-A) and subsequently the obtained results are presented in Section III-B. The conclusion is summarised in Section IV.

II. MATHEMATICAL FORMULATION

A. Optimal Experiment Design

Optimal Experiment Design for nonlinear dynamic systems can be seen as a particular class of optimal control problems. An optimal control problem is in general formulated as follows:

$$\min_{\mathbf{x}(t),\mathbf{u}(t),t_\mathrm{f}} J(\mathbf{x}(t),\mathbf{u}(t),\mathbf{p},t_\mathrm{f}) \tag{1}$$

subject to:

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}(t),\mathbf{u}(t),\mathbf{p},t) \quad t\in[0,t_\mathrm{f}] \tag{2}$$

$$\mathbf{x}(0) = \mathbf{x}_0 \tag{3}$$

$$\mathbf{0} \geq \mathbf{c}_p(\mathbf{x}(t),\mathbf{u}(t),\mathbf{p},t) \tag{4}$$

where $\mathbf{x}$ are the state variables, $\mathbf{u}$ the time-varying control inputs and for some $\mathbf{p}$ the model parameters. The vector $\mathbf{f}$ represents the dynamic system equations (on the interval $t\in[0,t_\mathrm{f}]$) with initial conditions given by the vector $\mathbf{x}_0$. The vector $\mathbf{c}_p$ indicates path inequality constraints on the states and controls. Furthermore, the vector $\mathbf{y}$ contains the measured outputs which are usually a subset of the state variables $\mathbf{x}$. Note that $\mathbf{p}$ is considered known and not a degree of freedom. For the convenience of notation, the optimisation variables can be grouped together as $\mathbf{z} = [\mathbf{x}(t),\mathbf{u}(t),t_f]$. The set of feasible solutions S is formed by all vectors $\mathbf{z}$ that satisfy Equations (2) to (4).

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In Optimal Experiment Design for parameter estimation, some scalar function Φ of the Fisher Information Matrix is used as the objective function. This matrix is defined as:

$$\mathbf{F}(\mathbf{p}) = \int_0^{t_f} \left(\frac{\partial \mathbf{y}(\mathbf{p},t)}{\partial \mathbf{p}}\right)^T \Big|_{\mathbf{p}=\mathbf{p}^*} \mathbf{Q} \left(\frac{\partial \mathbf{y}(\mathbf{p},t)}{\partial \mathbf{p}}\right) \Big|_{\mathbf{p}=\mathbf{p}^*} dt \tag{5}$$

The true values $\mathbf{p}^*$ are unknown so the Fisher depends on the current best estimate. Two parts constitute the Fisher information matrix: the inverse of the measurement error variance-covariance matrix, $\mathbf{Q}$, and the sensitivities of the output model to small variations in the model parameters, $\frac{\partial \mathbf{y}(\mathbf{p},t)}{\partial \mathbf{p}}$. The latter can be found as the solution to:

$$\frac{d}{dt}\frac{\partial \mathbf{y}(\mathbf{p},t)}{\partial \mathbf{p}} = \frac{\partial \mathbf{f}}{\partial \mathbf{y}}\frac{\partial \mathbf{y}(\mathbf{p},t)}{\partial \mathbf{p}} + \frac{\partial \mathbf{f}}{\partial \mathbf{p}} \tag{6}$$

with initial condition $\frac{\partial \mathbf{y}(\mathbf{p},t)}{\partial \mathbf{p}} = 0$. Under the assumption of unbiased estimators and uncorrelated Gaussian noise, the inverse of $\mathbf{F}$ exhibits an interesting property, i.e., it approximates the lower bound of the parameter estimation variance-covariance matrix, which is the Cramér-Rao lower bound. The most widely used scalar functions are [2], [3]:

A-criterion: min[trace($\mathbf{F^{-1}}$)] A-optimal designs minimise the mean of the parameter estimation errors. The geometrical interpretation is the minimisation of the enclosing frame around the joint confidence region. In order to decrease the computational effort, the problem is often reformulated as maximising the trace of $\mathbf{F}$.

D-criterion: max[det(F)] D-optimal designs minimise the geometric mean. Geometrically, this is minimising the volume of the joint confidence region.

E-criterion: max[$\lambda_{min}(\mathbf{F})$] E-optimal designs aim at minimising the largest parameter error. Uncertainty regarding other parameters is thus neglected. This corresponds to minimising the length of the largest uncertainty axis of the joint confidence region.

Modified E-criterion: min$\left[\frac{\lambda_{max}(\mathbf{F})}{\lambda_{min}(\mathbf{F})}\right]$ The modified E-criterion (ME-criterion) minimises the condition number of the Fisher information matrix. A priori the optimal value of one is known. This corresponds to circular joint confidence regions in a two dimensional case.

B. Robust Optimal Experiment Design

In nonlinear dynamic models the elements of the Fisher matrix depend on the current estimate of the parameters. It is however possible that there is a large uncertainty with respect to these parameter values. This explains the need for *robust Optimal Experiment Design*. This means that the information content depends less on the current estimate of the parameters. However the price to pay is usually a decrease in information content.

1) Method I: This method is first described by Körkel in [8]. In this method, parameters are assumed to be normally distributed:

$$\mathbf{p} \sim N(\mathbf{p_0}, \Sigma) \tag{7}$$

where $\mathbf{p_0}$ is the mean value and Σ the variance. The formulation used as robust Optimal Experiment Design in [8] is a min-max optimisation problem of the following form:

$$\min_{\mathbf{x}(t),\mathbf{u}(t),t_f} \max_{||p-p_0||_{2,\Sigma^{-1}} \leq \gamma} \Phi(\mathbf{F}(\mathbf{p})) \tag{8}$$

where γ is a confidence quantile and the norm as defined in [8]. In [8], this problem is solved by applying a Taylor expansion with respect to the parameters of the objective function, which leads to the following robust experimental design optimisation problem:

$$\min_{\mathbf{x}(t),\mathbf{u}(t),t_f} \Phi(\mathbf{F}(\mathbf{p})) + \gamma \left|\left| \frac{d}{d\mathbf{p}} \Phi(\mathbf{F}(\mathbf{p})) \right|\right|_{2,\Sigma} \tag{9}$$

It is clear that there are two parts in this objective function: the nominal Optimal Experiment Design objective, $\Phi(\mathbf{F}(\mathbf{p}))$ and the robust objective, $||\frac{d}{d\mathbf{p}}\Phi(\mathbf{F}(\mathbf{p}))||_{2,\Sigma}$. The latter objective aims at having a cost surface which is flat with respect to the unknown parameters. An interesting thing about the formulation above is that it can be viewed as a *multi-objective optimisation* problem consisting of two different, conflicting, objectives. Using some value for the quantile boils down to weighing the different objectives. In order to study the trade-off between the two objectives in a systematic way a multi-objective approach can be used.

An important aspect is to obtain an expression for the robust part of the objective function. Applying the chain rule results in the following mathematical expression [13]:

$$\frac{d\Phi}{d\mathbf{p}} = \frac{\partial \Phi}{\partial \mathbf{F}} \frac{\partial \mathbf{F}}{\partial \frac{\partial \mathbf{y}}{\partial \mathbf{p}}} \frac{d\frac{\partial \mathbf{y}}{\partial \mathbf{p}}}{d\mathbf{p}} \tag{10}$$

In order to have an expression for the robust part, an expression is needed for the second-order sensitivities of the system with respect to the parameter: $\mathbf{S}_p = \frac{d\frac{\partial \mathbf{y}}{\partial \mathbf{p}}}{d\mathbf{p}}$. These second-order sensitivities can be found as the solution to the following dynamic equations [14], [15]:

$$\begin{aligned} \frac{d\mathbf{S}_p}{dt} = & \left[\frac{\partial \mathbf{f}}{\partial \mathbf{y}} \otimes \mathbf{I}_p\right]\mathbf{S}_p + \\ & \left[\mathbf{I}_n \otimes \frac{\partial \mathbf{y}}{\partial \mathbf{p}}^T\right]\left[\frac{\partial^2 \mathbf{f}}{\partial \mathbf{y}^2}\frac{\partial \mathbf{y}}{\partial \mathbf{p}} + \frac{\partial^2 \mathbf{f}}{\partial \mathbf{p}\partial \mathbf{y}}\right] + \\ & \frac{\partial^2 \mathbf{f}}{\partial \mathbf{y}\partial \mathbf{p}}\frac{\partial \mathbf{y}}{\partial \mathbf{p}} + \frac{\partial^2 \mathbf{f}}{\partial \mathbf{p}^2} \end{aligned} \tag{11}$$

with the initial conditions $\mathbf{S}_p(0) = 0$. The symbol $\otimes$ is the Kronecker matrix-product operator. The number of additional states is $n \times p \times p$ with n, the number of states and p, the number of parameters. The variational states and variational differential equations have to be added to the optimal control problem (1)-(4).

2) Method II: The second method is based on a linear approximation where disturbances w are taken into account [10]. The basic idea is that the disturbances are small and that the dynamic equations can be split in the nominal dynamics and the approximate linearisation based dynamics of the uncertainty. Based on the approximate linearisation, the hard to solve min-max optimisation problem can be reformulated as a sole minimisation problem. Summarising the result, the underlying optimisation problem becomes:

$$\min_{\mathbf{z}} \Phi(\mathbf{F}(\mathbf{p})) \tag{12}$$

subject to: $\mathbf{z} \in S$, in this the set S is extended to $[\mathbf{x}_{\text{ref}}(.), \mathbf{P}(.), \mathbf{u}(.), t_f]$ which have to satisfy the following equations:

$$\begin{aligned}
\frac{d}{dt}\mathbf{x}_{\text{ref}} &= \mathbf{g}(\mathbf{x}_{\text{ref}}(t), \mathbf{u}(t), \mathbf{p}, t, w = 0) && (13)\\
\frac{d}{dt}\mathbf{P} &= \mathbf{AP} + \mathbf{PA}^T + \mathbf{BB}^T && (14)\\
\mathbf{x}_{\text{ref}}(0) &= \mathbf{x}_0 && (15)\\
\mathbf{P}(0) &= \mathbf{B}_0\mathbf{B}_0^T && (16)\\
\mathbf{0} &\geq \mathbf{c}_p(\mathbf{x}_{\text{ref}}(t), \mathbf{u}(t), \mathbf{p}, t) + \Gamma\sqrt{\mathbf{C}_i\mathbf{P}\mathbf{C}_i^T} && (17)
\end{aligned}$$

in which the following short-hands are used:

$$\begin{aligned}
\mathbf{A} &= \frac{\partial \mathbf{g}(\mathbf{x}_{\text{ref}}(t), \mathbf{u}(t), \mathbf{p}, t, w_{\text{ref}})}{\partial \mathbf{x}} && (18)\\
\mathbf{B} &= \frac{\partial \mathbf{g}(\mathbf{x}_{\text{ref}}(t), \mathbf{u}(t), \mathbf{p}, t, w_{\text{ref}})}{\partial w} && (19)\\
\mathbf{C}_i &= \frac{\mathbf{c}_{p,i}(\mathbf{x}_{\text{ref}}(t), \mathbf{u}(t), \mathbf{p}, t, w_{\text{ref}})}{\partial \mathbf{x}} && (20)
\end{aligned}$$

where $i \in 1, ..., n_{\mathbf{c}_p}$. The dynamic system represented by $\mathbf{g}$ is the dynamic system $\mathbf{f}$ but extended with the $n \times p$ sensitivity equations and the $p \times p$ Fisher elements. The number of additional states, however, increases quadratically: $m \times m$, with m the number of states of the system in its extended formulation (sensitivity equations and Fisher elements). But when exploiting the symmetry in $\mathbf{P}$, this can be reduced to $\frac{m\times(m+1)}{2}$. To employ this method in practice, the cost function has to be reformulated into a constraint by introducing a slack variable. When the disturbance w in the dynamic system is Gaussian white noise, then $\mathbf{P}$ is a linear approximation of the variance-covariance matrix of the states $\mathbf{x}$. For a more elaborate discussion on this robust optimisation technique, see [10]. This interpretation allows to compare this robustification method with the previous described method.

C. Software

Both methods require a dedicated software environment in order to easily use them. The aforementioned approximation strategies lead to tractable optimal control problems. On the other hand, both methods require the evaluation of additional partial derivatives of the dynamic equations. In addition when trying to solve these methods, the number of states increases. To solve these highly challenging optimal control problems, the ACADO-tookit [11] is used. The idea behind ACADO is that it is a self-contained C++ code, meaning that it does not require third-party software. It is programmed according to the ideas of object-oriented programming, which allows the user to link it to existing packages and to develop a new functionality as it is distributed under the GNU Lesser General Public Licence. The features of ACADO can be briefly described as follows:

Direct optimal control methods In ACADO both the Single Shooting (e.g., [16]) and the Multiple Shooting (e.g., [17]) approach are available. Both approaches convert the infinite dimensional optimisation problem in a finite nonlinear program.

Integrators Explicit and implicit integration schemes for ordinary differential equations are available in ACADO. The explicit integrators are based on Runge-Kutta45 and Runge-Kutta78 scheme. The implicit one exploits the backward differential formulae. These integrators are equipped with forward and backward automatic differentiation methods. Possible settings for the user are the absolute and relative tolerances.

Optimisation routine The optimisation routine for the NLPs available is a Sequential Quadratic Programming method. The user can choose the way of computing the Hessian (exact, constant or BFGS), the Karush-Kuhn-Tucker (KKT) optimisation tolerance, the Levenberg-Marquardt regularisation parameter and the minimum step size of the line-search globalisation parameter.

The most important feature, specifically for this paper, is that the dynamic systems are implemented symbolically. Besides the availability of the symbolic differentiation tools, also advanced automatic differentiation methods are provided. In practice, this means that the user has to formulate the dynamic equations in the appropriate syntax. To obtain the symbolic formulation, needed for the robust formulation, he/she can use the provided symbolic differentiation tools. Once the problem is formulated, ACADO is able to derive the necessary third and even fourth order derivatives exactly.

III. RESULTS

A. Case Study

In this case study an optimal experiment for the estimation of the parameters of the Cardinal Temperature Model with Inflection [18] is designed. This secondary model is incorporated in the model of Baranyi and Roberts [19]. The model describes the cell density as a function of time whereas the former incorporates the dependency of the specific growth rate on temperature. The model equations of the Baranyi and Roberts model are:

$$\begin{aligned}
\frac{dn}{dt} &= \frac{Q}{Q+1}\mu_{max}(T(t))[1 - \exp(n - n_{max})] && (21)\\
\frac{dQ}{dt} &= \mu_{max}(T(t))Q && (22)
\end{aligned}$$

in which n [ln(CFU/ml)] is the natural logarithm of the cell density, n_{max} the maximum value for n, μ_{max} the maximum specific growth rate, and Q [-] the physiological state of the cells. In the current Optimal Experiment Design the state Q is omitted [7]. This is because the duration of the microbial adaptation phase, described via the state Q, depends on the actual and previous environmental conditions. As the preceding conditions are unknown, accurate prediction of the adaptation phase and thus of state Q is not possible.

This because the duration of the microbial lag phase determined by the prior and actual experimental conditions, which is modelled through Q, cannot be predicted. The model equations thus reduce to a logistic growth model for the design of the experiments. The temperature dependency described by the Cardinal Temperature Model with Inflection is given by:

$$\mu_{max} \quad = \quad \mu_{opt}\gamma(T) \tag{23}$$

with $\gamma(T)$ as expressed in Table I. In this model four

TABLE I

TEMPERATURE DEPENDENCE AS EXPRESSED IN $\gamma(T)$.

$$\gamma(T) = \frac{(T-T_{min})^2(T-T_{max})}{(T_{opt}-T_{min})[(T_{opt}-T_{min})(T-T_{opt})-(T_{opt}-T_{max})(T_{opt}+T_{min}-2T)]}$$

parameters have to be estimated: T_{min}, T_{opt}, T_{max} and μ_{opt}. The Cardinal Temperature Model with Inflection is illustrated in Figure 1. It depicts the practical interpretation of the four parameters. The values of the parameters for *Escherichia coli K12* are shown in Table II. The initial condition is $n(0) = 7$ ln(CFU/ml). The end time is fixed to 38 h. For model validity reasons the dynamic temperature profiles are constrained to:

$$15°\text{C} \leq \quad T(t) \quad \leq 45°\text{C} \tag{24}$$

$$-5°\text{C/h} \leq \quad \Delta T(t)/\Delta t \quad \leq 5°\text{C/h} \tag{25}$$

Temperatures below T_{min} or above T_{max} result in a maximum specific growth rate (μ_{max}) set to zero. The simplest approach is to estimate the four parameters from one single experiment, but in practice the following approach was followed. From the set of four parameters one can make six possible two-parameter combinations. For each of these combinations an optimal experiment was designed and the four parameters were estimated using the results of the six designed experiments. Each parameter appeared three times in the optimal experiment desing procedure. More details on the case study and the design approach can be found in [6], [7].

TABLE II

PARAMETER VALUES FOR PREDICTIVE GROWTH MODEL.

T_{min}	11.33 °C	T_{opt}	40.85 °C
T_{max}	46.54 °C	μ_{opt}	2.397 1/h
n_{max}	22.55 ln(CFU/mL)	σ_n^2	3.27×10^{-2} ln(CFU/mL)^2

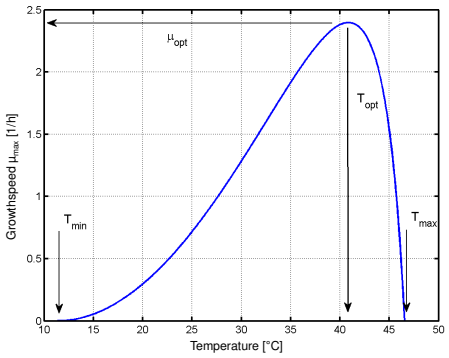

Fig. 1. Cardinal Temperature Model with Inflection.

B. Simulation Results

In the following simulation results the A-criterion with respect to the two parameter combination: (T_{min}, T_{max}), is considered as an example to illustrate the outlined approaches. In future work this approach will be extended to the other parameter combinations. In the Optimal Experiment Designs, the following variance-covariance is assumed regarding the current estimate of the parameter values:

$$\Sigma \quad = \quad \begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix} \tag{26}$$

In order to solve the dynamic optimisation problem, the ACADO-tookit is used [11] by applying a Single Shooting approach [16]. The integrator used is Runge-Kutta45. The integrator tolerance and the KKT-tolerance of the SQP-optimiser are both set to 10^{-6}. The Hessian is calculated exactly and does not use any approximation techniques. The decision variables are a dynamic piecewise linear temperature profile split in 19 control intervals. Simulation for both robust methods are performed by introducing an uncertainty quantile of 95% in both methods. In method I this is achieved by selecting $\gamma = 0.95$. To introduce this in method II, similar uncertainty levels are introduced in Γ for the uncertainty of both parameters.

In Figure 2, both the microbial evolution and temperature profiles are displayed. The nominal design consists of a constant temperature at $45°$C with after 2 hours a decrease at almost the maximal admissible rate. The remainder of the experiment consists of a decreasing temperature profile towards $15°$C. The fact that this profile remains at relative high temperatures in the early part of the experiment is also visible in the microbial evolution. At these close to optimal temperatures, the microbial growth is fast. Remark that both robustification methods are initialised using the result of the nominal case. Method I results in a temperature profile which is similar to the nominal case, the constant period at a high temperature is however absent. In method II, a

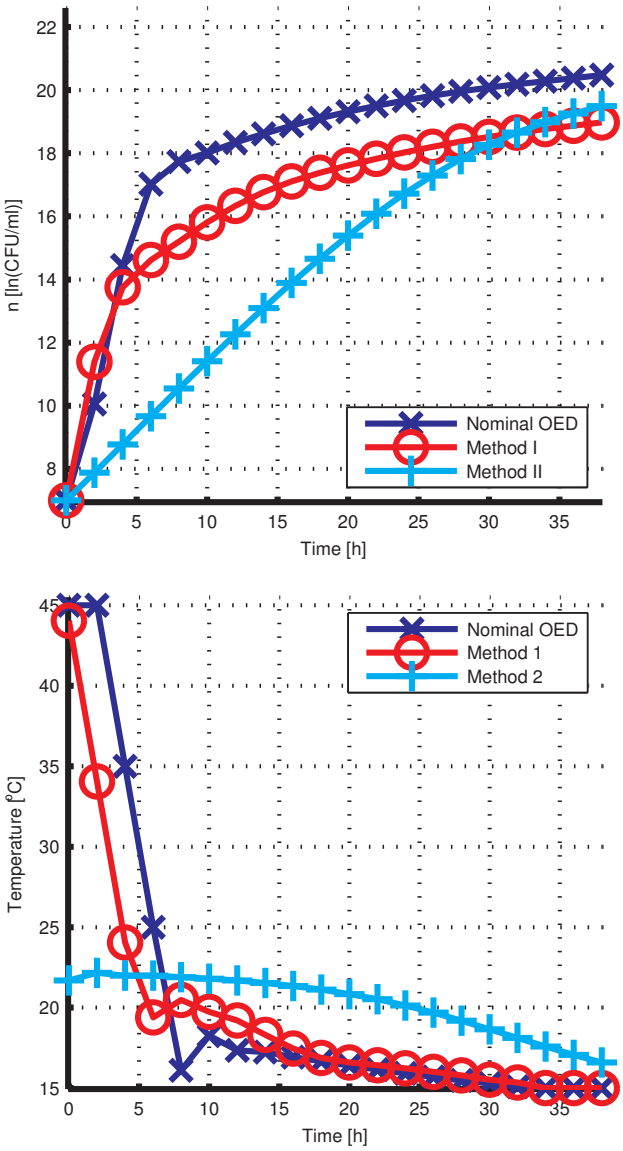

Fig. 2. Corresponding state evolution (top) and temperature profile (bottom) for the nominal case, method I and method II.

different temperature profile is obtained. The profile starts at 21.6°C and decreases almost continuously throughout the experiment without reaching the minimal value. All temperature profiles have in common that the maximum number of cells is not obtained during the experiment. As such, information on the microbial dynamics as a function of temperature remains available up to 38 hours.

In order to investigate the robustness of the designed experiments, Figure 3 is depicted. Herein, the cost surfaces are displayed for the different designed experiments in case the parameters differ from their nominal values. To obtain a *robust design*, a cost surface which is flat with respect to changes in the parameter values is preferred.

When examining Figure 3, it is clear that for the nominal case, there is a high dependency of the A-criterion with respect to changes in the temperature profile. It ranges from order 10^5 to 10^2. From Figure 3, one observes that both robustification methods result in a surface which is more flat than the nominal experiment. Method II is more informative than method I in the sense that it scores systematically higher for all parameter changes. The scores of method I lie all in the range $530 - 870$ whereas the results of method II are in the range $650 - 1660$. Also note that compared to the nominal experiment the dependency in both positive and negative sense are reduced. The lowest values of the nominal experiment are also notably smaller than the robust experiments. In general one obtains a more flat cost surface at the expense of an information decrease with respect to the nominal case.

To evaluate the designed experiments, Table III is presented. For each of the experiments its score for the A-criterion, and the robustness measure of both methods is given. As already indicated in Figure 3, method II has a higher value for the A-criterion than method I. Both method I and II score similar on the robustness measure of method II with method II evidently scoring better. On the criterion of method I, method II scores better than the nominal case but is several orders of magnitude larger than the result obtained by method I. From these results one can conclude that both methods result in a more robust optimal experiment but that how this robustness is obtained differs.

TABLE III

SCORES FOR THE DIFFERENT DESIGNED EXPERIMENTS.

Score for:	A-crit	Method I	Method II
Nominal OED	1518	$2.5\ 10^7$	4040
Method I	797	100	111
Method II	1380	$3.5\ 10^5$	74

IV. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

In this work a robust formulation of Optimal Experiment Design is studied. These robust formulations usually result in hard to solve min-max optimisation problems. Two different methods to approximate the solution are discussed. In this contribution the robust counterpart of the objective function is formulated using second-order sensitivities of the original dynamic system. In order to solve the dynamic optimisation problem, the ACADO-tookit is used. This toolkit has the necessary features like symbolic differentiation and automatic differentiation to obtain the necessary third and fourth order information to solve the dynamic optimisation problem using fast, gradient-based methods. The second method discussed has already been used to obtain robust optimal controls. In this work, this approach is extended to the field of Optimal Experiment Design. Both methods are applied to a case study from the field of predictive microbiology. The case study illustrates that both methods are able to design experiments

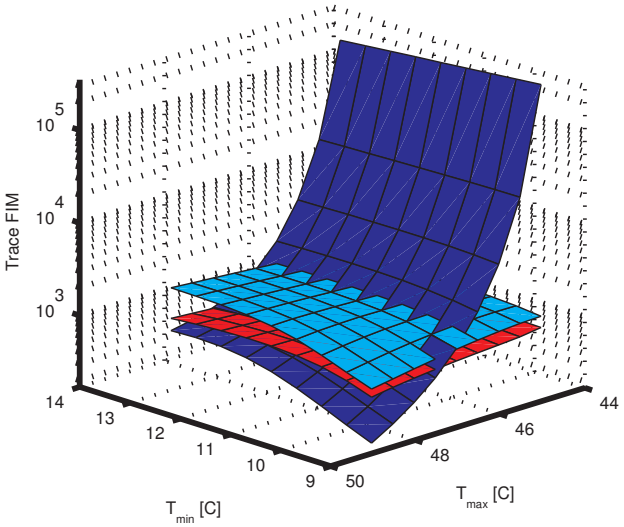

Fig. 3. Optimal Experiment Design cost surface of the three methods in the neighbourhood of the nominal parameter values.

which are robust with respect to small changes in the initial values of the parameters.

B. Future Works

An interesting aspect for future work would be generating the robust formulation for Optimal Experiment Design automatically. Within the ACADO-tookit, the necessary features are available in order to auto-generate the required formulation. An experimenter, not really familiar with mathematics would thus be able to employ these methods in in daily practice. In method II a specific structure is present in the additional dynamic equations. This structure can be exploited by dedicated integrators. This speed-up is necessary due to the large increase in additional states, introduced by this method. Preliminary results regarding work on this integrator look promising. In this work only the robustness aspect with respect to changes in the parameter values have been tackled. For biochemical systems, constraints are present and the robustness with respect to these constraints also need to be taken into account. In the work presented, the robust formulations are solved using approximations, mainly based on linearisations of some sort. In future work, the idea is to provide guarantees on the information content by combining techniques from ellipsoidal calculus [20] and guaranteed state estimation [21].

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