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Optimal experimental design for optimal process design: A trilevel optimization formulation

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Abstract

Typical optimal experimental design (OED) methods aim at minimizing the covariance matrix of the estimated parameters regardless of the intended application of the model that is being estimated. This can unnecessarily increase the experimental costs. Herein, we propose a new OED method, which tailors the designed experiments to the model application. The method is demonstrated for model-based process design and aims at mitigating a worst-case realization of the process design. The proposed formulation results in a min–max–min problem and is based on bounded-error OED. The method is illustrated via an ad hoc solution method using two examples, a simple illustrative example and the van de Vusse reaction, that show the differences between typical and the new tailored OED method: experimental designs can be considered good using the latter method, while the same design would be considered bad with the former methods.

KEYWORDS

bounder-error estimation, min–max, optimal experimental design, process design, worst-case optimization

1 | INTRODUCTION

System models are the backbone of model-based process design and control. To describe the given system, the model equations are fitted to experimental data via estimation methods, for example, regression analysis or set-inversion. During modeling procedures, model uncertainties are unavoidable. These model uncertainties can arise from: (a) structural errors, where the model structure does not accurately represent the reality, (b) parametric errors, that is, the parameter uncertainties arising when fitting the model to the imperfect and/or uninformative experimental data, and (c) regression errors, which occur when suboptimal regression solutions are found. Regression errors can be avoided if global optimization methods are used to fit the system model to the experimental data.[1] In this manuscript we consider only parametric errors and assume that the model is structurally correct and that the regression fit results from a global solution. Therefore, to improve the model accuracy, the parameter uncertainties should be reduced; this can be done by obtaining informative experimental measurements and/or by reducing the measurement errors. Herein, we are concerned with the former.

The improvement of parameter precision with the minimal amount of experimental effort is the aim of optimal experimental design (OED) methodologies.[2-5] Equivalently, this results in the best possible parameter precision for a given experimental effort. Depending on the different hypotheses and assumptions made during the model validation procedure, various OED formulations are used, such as Bayesian and frequentist OED[6-9] or bounded-error OED,[10,11] known also as OED for guaranteed parameter estimation or set-membership estimation. OED methods have been often studied in literature and applied in various research domains, for example, biology,[12,13] medicine,[14,15] enzyme engineering,[16,17] polymerization,[18] reaction kinetics,[19,20] and process systems engineering.[21,22] In most conventional OED problems, the goal of the formulation is to increase the overall precision of the system model parameters, that is, to decrease the confidence region. Often the importance of every model parameter is judged to be equal, since for a very accurate model prediction all parameters have to be estimated with high precision. However, experimental effort puts a cost on increasing the accuracy. This often implies that due to cost constraints as well as experimental feasibility not all model parameters, but rather only a subset can be estimated with high precision. This leads to the following question: if the precision for all the parameters cannot be sufficiently increased, then for which ones should it be? Or rather, should the precision of all the parameters be increased? An intuitive way to answer the above questions is to look at the intended application of the model. It can easily be envisioned that depending on the model application not all the parameters have the same influence on the objective of the application and, therefore, it is reasonable to focus on those parameters with the highest influence.

The idea of tailoring an OED problem to the model's intended end use is established, although not typically applied. Already in the mid-1970s various optimality criteria based on statistical OED were developed. Such design criteria include, among others, the D_s-optimality,[8,23,24] in which the accuracy for only the parameters of interest is increased and the remaining parameters are seen as nuisance parameters. In optimal control the idea of combining model identification and control design also emerged in the 1970s.[25] Various literature exists for OED for linear systems where model identification and optimal control are combined.[26-28] Recently, tailored OED methods were developed for nonlinear dynamic process systems. One example is OED for the improvement of optimal process design variance by introducing a heuristic weight factor into the design matrix, where the weight factor reflects the sensitivity of the process with respect to each of the parameters.[29,30] Another example is the new formulation for the so-called economical OED for optimal control problems, in which the OED problem aims to minimize not the parameter uncertainty but the process optimality gap, which corresponds to the distance between the optimal process and the true process.[31] However, it should be mentioned that OED methods based on the statistical design matrix can run into problems if the design matrix (or a variation of it) is singular.[9] In this manuscript, we look at models that are used for model-based process design optimization.

Conventionally, identification of the system model and conceptual process design optimization, are executed sequentially, that is, first a system model is identified using experimental data and then a process design optimization is performed based on the identified system model. This has the drawback that the region of confidence of the identified model does not necessarily match the relevant operating points of the process. This can, on the one hand, prevent a reliable process design due to model extrapolation, and on the other hand, unnecessarily increase the experimental costs when model components are accurately fitted that are irrelevant to the process design. To avoid these drawbacks, information about the process design should be taken into account in the early stages of model identification. The idea of the proposed approach is to determine a system model such that its parametric errors have a minimal influence on the process design. In other words, the process variation toward the parameter uncertainties is reduced during the model identification procedure via a new OED formulation. Although the presented OED method is developed specifically for process design, it can be easily adapted to other areas, for example, in medical research, where often data is rare and the goal of these studies is to achieve suitable prediction of response curves.[32-35]

In this manuscript we show a new OED formulation, which aims at the improvement of the optimal process design cost and is called hereafter optimal experimental design for optimal process design (OED–OPD). The OED–OPD formulation is a min–max–min (MMM) optimization problem involving nonconvex nonlinear functions. The lower (third) level problem consists of a typical process design optimization, in which a cost function is minimized. The middle (second) level problem is a worst-case formulation for the optimal process design, in which the worst-case realization of the optimal (minimum) cost is determined with respect to the system's model parameters and their uncertainties. Finally, the upper (first) level aims to determine the best experimental conditions that will minimize the worst-case cost function. The MMM problem is a special case of a trilevel optimization problem. In process systems engineering similar trilevel problems arise in the design of flexible chemical processes.[36-39] To the best knowledge of the authors there does not yet exist an algorithm that can guarantee a solution for a nonlinear nonconvex trilevel problem. Solution methods for trilevel problems under restrictive assumptions have been used in literature: for linear problems[40,41] and for convex nonlinear problems[42]; in Reference 42, the trilevel problem is recast as a multi-parametric program where the parameters are the optimization variables from the lower subproblems. While this methodology can in principle be applied to general nonlinear problems, it was illustrated in Reference 42 only using quadratic objectives and linear constraints. For more general problems the scaling of the method may not be favorable. A trilevel problem, however, is an extension of bilevel problem. We, therefore, reduce the MMM problem to a bilevel max–min problem via an ad hoc sampling method. Bilevel problems have been studied extensively in literature with guarantees of a global solution.[43-50] Herein, we adapt the solution method from Djelassi et al,[51] which allows for inequality as well as equality constraints in the subproblems.

Note that throughout the manuscript we only include continuous variables. This is done for simplicity as the considered algorithms for bilevel problems are also applicable to mixed integer problems. Including integer variables is of interest in practice. At the level of process design it would be of interest to consider integer variables, for example, in superstructure formulations or for rigorous modeling of separation units. Similarly, at the level of experimental design, integer variables occur for piecewise constant inputs or if the bounded-error OED formulation from Reference 11 is developed to account for the number of measurement points as optimization variables.

In the following, we will first define a general form for the system model (Section 2), followed by the definition of bounded-error OED (Section 3) which is the basis for the min–max–min OED–OPD formulation, presented in detail in Section 4. A brute-force solution method for the MMM optimization problem is discussed in Section 5 and the new tailored OED problem is illustrated via two examples in Section 6.

2 | SYSTEM MODEL

For the simulation and optimization of real-life systems, the underlying physical-chemical phenomena are often described via a mathematical model. Herein, this type of model is referred to as a *system model*. Such models often consist of a system of ordinary differential (ODE) or differential-algebraic (DAE) equations. Herein, it is assumed that the model structure is correct and identifiable. In the following we consider systems for which the input–output relationship of the system model can be written as:

$$\boldsymbol{y} = \boldsymbol{g}(\boldsymbol{v}, \boldsymbol{p}), \tag{1}$$

where $\boldsymbol{y}$ are the system's outputs of dimension n_y, $\boldsymbol{p}$ are the model parameters of dimension n_p, $\boldsymbol{v}$ are the system's manipulated variables of dimension n_v consisting of the discretized control inputs $\boldsymbol{u}$ and/or initial values of the system's states. For simplicity the time dependency as well as the dependency on initial values has been omitted in Equation (1). This is possible for outputs $\boldsymbol{y}$ that are evaluated at discrete time points and for each time point a new output can be defined. The system outputs can be given explicitly or calculated using the ODE or DAE models. Herein, we assume that the outputs are given explicitly for two reasons: first of all, it is easier to demonstrate and understand the proposed MMM formulation for an explicit output Equation (1), and second of all, available global dynamic optimization methods for ODE and DAE systems still need development.[52,53]

Predicting the system outputs necessitates some sort of insight into the system model parameters. Usually the parameters are determined by fitting the system model to experimental data via estimation methods,[54-56] for example, weighted maximum-likelihood or set-membership estimation. The experimental data is known only up to a certain precision, that is, the data has measurement errors, which are usually bounded between $\boldsymbol{e}^{\min}$ and $\boldsymbol{e}^{\max}$. From a statistical point of view, these error bounds are expressed via probability moments. The experimental errors are propagated to the model parameters during the estimation procedure, thus resulting in parameter uncertainties. Depending on the estimation method, the parameter uncertainties can be characterized in various ways, for example, confidence regions or feasible sets.[8,57] Various formulations for quantifying the parameter uncertainties can be used in the following trilevel OED problem. In this manuscript we consider parameter uncertainties that are expressed via a feasible parameter set as defined below.

In set-membership estimation, instead of estimating a single value of the parameter vector that best fits to the experimental data, a set is determined that contains all parameter values that are consistent with the experimental data and their measurement errors (see Figure 1). In other words the residual, $e_k(\boldsymbol{p})$, between the measured

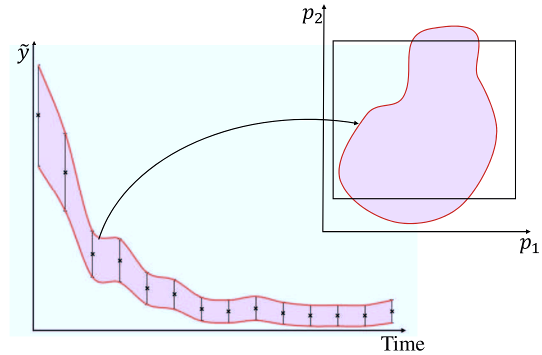

FIGURE 1 Illustration of a feasible parameter set resulting from measurements and their bounded errors. On the left: measured output data $\tilde{y}$ at discrete time points and their errors, resulting in a trajectory space of feasible predictions (red area on the left). The time discrete measurements and their errors are represented via the black crosses and the error bars, respectively. The trajectory space is mapped to a feasible parameter set $\tilde{\mathbb{P}}$ (red area on the right) in the parameter space $\{p_1 \times p_2\}$ during bounded-error parameter estimation. The black box represents the initial parameter host set P [Color figure can be viewed at wileyonlinelibrary.com]

output, $\tilde{y}_k$, and the predicted output, $y_k = g_k(\boldsymbol{v}, \boldsymbol{p})$, has to lie within the measurement error bounds $e_k^{\min}$, and $e_k^{\max}$.[58] The feasible parameter set $\tilde{\mathbb{P}}$, therefore, consists of all values of $\boldsymbol{p}$ in some host set P such that the residual error is admissible and can be expressed using the model outputs as follows:

$$\tilde{\mathbb{P}} := \{\boldsymbol{p} \in P \mid e_k^{\min} \le g_k(\boldsymbol{v}, \boldsymbol{p}) - \tilde{y}_k \le e_k^{\max}\}, \ \forall \ k \in 1, \ldots, n_y. \tag{2}$$

The outputs are defined via the system model $y_k = g_k(\boldsymbol{v}, \boldsymbol{p})$. In bounded-error estimation, also known as set-membership estimation or guaranteed parameter estimation, a parameter set is calculated such that Equation (2) is satisfied.[55,59] It should be noted that the feasible parameter set $\tilde{\mathbb{P}}$ may be empty if the model structure and/or hypotheses on the error bounds are erroneous.[58]

Assuming that the model is structurally correct and identifiable, the accuracy of the output predictions $\boldsymbol{y}$ increases with the precision of the model parameters $\boldsymbol{p}$. The parameter precision can be increased by reducing the measurement errors and/or by obtaining more informative experimental data. Obtaining informative data with minimal experimental effort is the domain of OED for parameter precision.[9]

3 | OED FOR BOUNDED-ERROR MEASUREMENTS

OED for parameter precision is an optimization problem that aims at finding the experimental conditions, that is, values for the manipulated variables $\boldsymbol{v}$, for which the parameter uncertainties are as small as possible.[2,3,8,9] Depending on how the parameter uncertainties are characterized, various formulations for OED exist. If the parameter uncertainties are described using Gaussian probability distributions, then typically statistical frequentist OED is used, in which a measure of an information matrix, often referred to as the Fisher information matrix (FIM), is maximized.[8,9] If the parameter uncertainties are described using a feasible parameter set $\tilde{\mathbb{P}}$, then bounded-error OED can be used,[58] in which the parameter uncertainty is usually related to the size of the feasible parameter set. Typically, in bounded-error OED an over-approximation of the feasible parameter set is minimized.[11]

The novel tailored OED formulation presented in Section 4 is based on the bounded-error OED problem from Reference 11. For the new OED formulation we extend the min–max OED problem in Reference 11 to a MMM problem in order to reduce the overall variation of the process design toward the parametric errors of the system model.

The OED formulation proposed in Gottu Mukkula et al[11] is a general and rigorous bounded-error OED method that is neither restricted to linear models as in Reference 60 nor to discrete sets of experimental conditions as in References 61 and 62. The OED problem in Reference 11 is a worst-case formulation written as a bilevel (min–max) program that determines the smallest feasible parameter set that is consistent with the measurement errors, $\boldsymbol{e}^{\min}$ and $\boldsymbol{e}^{\max}$. The solution method proposed in Reference 11 is based on a reformulation of the lower-level problem using KKT optimality conditions. However, this reformulation cannot guarantee a global solution of the lower level and, therefore, cannot guarantee a feasible solution in the upper level. The same bilevel OED formulation was used in Reference 63, however, using a generalized semi-infinite program (GSIP) to solve the problem. The method proposed in Reference 63 can guarantee a global solution for the upper-level and lower-level problems. In Reference 63 it was shown that even if the upper level cannot be solved globally, a global upper bound is still obtained, as long as the lower level is solved to global optimality. Herein, we adapt the formulation and solution method from Walz et al.[63]

$$\mathcal{F}^* = \mathcal{F}(\boldsymbol{v}^*, \boldsymbol{p}^*) = \min_{v \in V} \max_{\substack{\boldsymbol{p}^{L,i} \in P \\ \boldsymbol{p}^{U,i} \in P}} \sum_{i=1}^{n_p} \left(p_i^{U,i} - p_i^{L,i}\right) \tag{3}$$

st.

$$2e_k^{\min} \leq g_k(\boldsymbol{v}, \hat{\boldsymbol{p}}) - g_k(\boldsymbol{v}, \boldsymbol{p}^{j,i}) \leq 2e_k^{\max} \quad \begin{matrix} \forall j \in \{U, L\}, i \in \{1, \ldots, n_p\}, \\ \forall k \in \{1, \ldots, n_y\} \end{matrix} \tag{4}$$

with $\boldsymbol{p}^{L,i} = \left(p_1^{L,i}, \ldots, p_{n_p}^{L,i}\right)^T$ and $\boldsymbol{p}^{U,i} = \left(p_1^{U,i}, \ldots, p_{n_p}^{U,i}\right)^T$ for $i = 1 \ldots n_p$. P and V are a subset of real numbers of dimension n_p and n_v, respectively. The functions $\boldsymbol{g}$ correspond to the system outputs (see Equation (1)), whereas, $\boldsymbol{g}(\boldsymbol{v}, \hat{\boldsymbol{p}})$ corresponds to nominal output values $\hat{\boldsymbol{y}}$ calculated using nominal parameters $\hat{\boldsymbol{p}}$, which are known (or estimated) a priori. Assuming that the system model is correct (the input–output Equations (1) describe the reality) and that the model is fitted to the experimental data without any regression errors, then the estimated parameter values $\hat{\boldsymbol{p}}$ are close to the true (real) parameter values. In real life applications, this assumption does not necessarily hold, which can result in nonoptimal experimental conditions and uninformative data that does not necessarily reduce the parameter uncertainty. Therefore, often generation of new experimental data, parameter estimation, and OED are conducted sequentially in order to estimate parameter values, $\hat{\boldsymbol{p}}$, close to the true parameter values.[8] The nonoptimal experimental conditions are enhanced in frequentist OED methods based on the FIM due to the linearization of the equations of the system model. The above bounded-error OED and the proposed trilevel OED are not based on linearizing the system model and, therefore, nonoptimal solutions due to system simplification are avoided. One can also extend the above OED formulation into a so called robust (min–max) OED problem[64-66] by replacing (4) by a semi-infinite constraint. This would, however, increase the problem complexity and the computational time needed to solve the problem.

In the above formulation, the feasible parameter set $\mathbb{P}$, described via constraint (4), is over-approximated by an aligned minimum-perimeter bounding box (orthotope), and the optimization problem results in an enclosing box with the smallest possible perimeter, $2 \cdot \mathcal{F}^*$. The enclosing box is constructed using $p_i^{U,i}$ and $p_i^{L,i}$, which correspond to the outermost points of the feasible parameter set $\mathbb{P}$. In this formulation, a special case of the so-called global over-approximation of the realization of the measurement errors[11] is used, in which the absolute values of the lower and upper bounds of the errors are equal: $|\boldsymbol{e}^{\min}| = |\boldsymbol{e}^{\max}|$. It should be noted that the global over-approximation is defined by Gottu Mukkula and Paulen[11] as an envelope of all possible results of bounded-error estimation under each possible realization of the measurement error. In other words the feasible parameter set is defined via the constraints $e_k^{\min} - e_k^{\max} \leq g_k(\boldsymbol{v}, \hat{\boldsymbol{p}}) - g_k(\boldsymbol{v}, \boldsymbol{p}^{j,i})$ and $g_k(\boldsymbol{v}, \hat{\boldsymbol{p}}) - g_k(\boldsymbol{v}, \boldsymbol{p}^{j,i}) \leq e_k^{\max} - e_k^{\min}$. Consequently, the approximated parameter set should be consistent with the experimental data within twice the measurement errors. Various formulations can be defined for the approximation of the parameter set (Equation (4)), for example, using confidence regions for normal distributed measurements, as well as for the measurement errors $e_k^{\min}$ and $e_k^{\max}$.[56,67]

In comparison to bounded-error estimation, in bounded-error OED the feasible parameter set is described using a representative output $\hat{\boldsymbol{y}}$ of the measurements and not the measurements themselves. This is necessary since the measured outputs are directly correlated to the manipulated variables $\boldsymbol{v}$. As a consequence, in the OED formulation the estimated parameter set $\mathbb{P}$ is never empty, independent of the hypotheses on the model structure or the error bounds. In the limiting case, the parameter set is equal to a trivial solution $\boldsymbol{p}^{j,i} = \hat{\boldsymbol{p}}$, which always satisfies the inequality constraints (4).

As seen in the above bounded-error OED formulation (Equation (3)), the precision of each model parameter is judged to be equal (no weight factor is present in the objective). However, as mentioned in the introduction, depending on the intended application of the model, not all parameters should necessarily be judged equally. Due to the generality of the bilevel bounded-error OED formulation,[11] a weight factor can easily be added to the objective (3). However, in this case, the question of how to define the weight factor arises. For example nuisance parameters can be defined (analogously to D_S-optimality[8,23,24]) with a weight factor of zero. However, in the case of model-based process design it is not easy to decide a priori which parameters can be defined as a nuisance parameters. In this case a heuristic similar to References 29 and 30 can be applied to calculate the weight factor. However, a more intuitive approach is to define a new objective in Equation (3) that directly optimizes a metric that describes how good the final optimal process is.

4 | OPTIMAL EXPERIMENTAL DESIGN FOR OPTIMAL PROCESS DESIGN

Conceptual model-based process design consists of defining a cost function Φ that is minimized with respect to the process design variables $\boldsymbol{d}$ (optimization degrees of freedom) subject to constraints. The process design constraints contain model equations, which are determined by fitting experimental data. This means that the uncertainties in the model parameters result in uncertainties in conceptual model-based process design, such as the uncertainties in the process design variables $\boldsymbol{d}$ or the uncertainties in the cost function Φ. Thus, the process design is parametric in the uncertain parameters. For each parameter realization there exists an optimal cost function, $\Phi^*(\boldsymbol{p}) = \min_{\boldsymbol{d} \in D}\Phi(\boldsymbol{p}, \boldsymbol{d})$.

In the context of set-membership estimation, the bounded errors in the measurements result in a feasible parameter set (see Section 3). This in turn will result in a variation in the process design, for example, in the design variables and the cost function. Herein, we are concerned with the variation in the process design cost function. For a feasible parameter set defined via Equation (4), by definition, the set is constructed around a nominal parameter $\hat{\boldsymbol{p}}$; hence, the cost function will also vary around the optimal nominal cost $\Phi^*(\hat{\boldsymbol{p}})$. It is easy to see that for a continuous cost function and compact host sets, the optimal nominal cost is bounded: $\Phi_L^* \le \Phi^*(\hat{\boldsymbol{p}}) \le \Phi_U^*$, where Φ_L^* and Φ_U^* are defined as follows:

$$\Phi_L^* = \min_{\boldsymbol{p}\in\mathbb{P}}\min_{\boldsymbol{d}\in D}\ \Phi(\boldsymbol{p},\boldsymbol{d}) \tag{5}$$

$$\Phi_U^* = \max_{\boldsymbol{p}\in\mathbb{P}}\min_{\boldsymbol{d}\in D}\ \Phi(\boldsymbol{p},\boldsymbol{d}). \tag{6}$$

For a more reliable process design, the process uncertainties of interest have to be reduced, that is, the uncertainties in the process objective cost function Φ. For the proposed trilevel OED method we opt for a conservative formulation by mitigating the worst-case realization of the process cost function, Φ_U^*. The idea behind the presented OED–OPD is, therefore, to plan new experiments that not just minimize the model parameter uncertainties, but minimize the worst-case process cost realization (see Figure 2). The OED–OPD formulation is, therefore, a MMM optimization problem, a special case of a trilevel problem. As a result, the system model is made more precise in such a way that bad process designs are avoided.

Other formulations are possible, for example, minimizing the width of the uncertainty interval of the process cost $[\Phi_L^*, \Phi_U^*]$ or by using

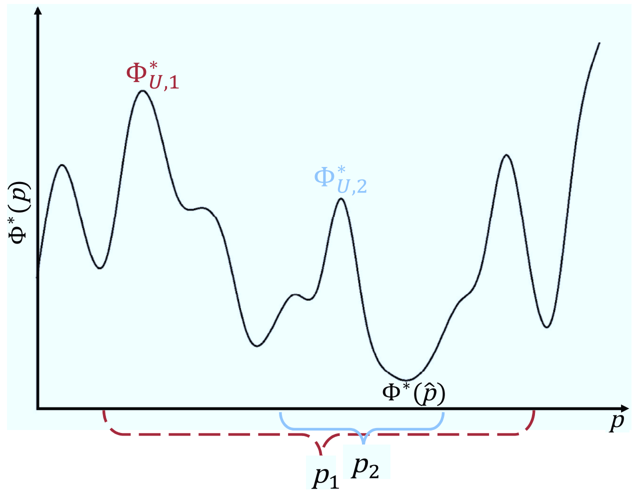

FIGURE 2 Schematical representation of optimal experimental design for optimal process design. The vertical axis corresponds to the optimal process cost, $\Phi^*(\mathbf{p}) = \min_{\mathbf{d} \in D}\Phi$, and the horizontal axis corresponds to the model parameter values. The process design cost is parametric in the parameter uncertainties, represented here via parameter intervals. For one set of experiments, the parameter interval p_1 results in a worst-case realization of the cost function $\Phi^*_{U,1}$ that is greater than the worst-case realization $\Phi^*_{U,2}$ for a new set of experiments that are planned with optimal experimental design. Thus the latter set is preferable. $\Phi^*(\hat{\mathbf{p}})$ corresponds to the optimal nominal cost [Color figure can be viewed at wileyonlinelibrary.com]

statistical likelihood formulations for process design such as in Reference 57. The former formulation can be computationally expensive, since two optimization problems have to be solved in parallel: the best-case (Equation (5)) and the worst-case (Equation (6)) realization of the process cost. The statistical likelihood formulation used in Reference 57 might be a good alternative for the OED–OPD problem since the authors in Reference 57 look at how parametric uncertainties of the system model affect process design optimization, while herein we try to minimize these parametric uncertainties such that in the end the process design is improved, for example, the profit is increased. In the following the three levels will be examined in detail and, finally, combined into a MMM optimization problem. The MMM problem consists of two distinct models: the system model (see Section 2) and the process design model (see Section 4.1).

4.1 | Third-level (lower-level) problem

The third-level problem consists of model-based process design optimization, for which different formulations are possible. Herein, the system of equations used to define the process design optimization problem is referred to as a *process design model*. Here, we formulate the third-level problem as a conventional steady state process design optimization as

$$\Phi^*(\boldsymbol{p}) = \min_{(\boldsymbol{x}_{\mathrm{st}},\boldsymbol{d})\in\mathbb{D}(\boldsymbol{p})}\Phi(\boldsymbol{x}_{\mathrm{st}},\boldsymbol{p},\boldsymbol{d},\boldsymbol{C}). \tag{7}$$

Therein, Φ denotes the process cost and the feasible set is defined as

$$\mathbb{D}(\boldsymbol{p}) = \{(\boldsymbol{x}_{\text{st}},\boldsymbol{d}) \in D \,|\, \boldsymbol{h}(\boldsymbol{x}_{\text{st}},\boldsymbol{p},\boldsymbol{d},\boldsymbol{C}) = \boldsymbol{0} \wedge \boldsymbol{l}(\boldsymbol{x}_{\text{st}},\boldsymbol{p},\boldsymbol{d},\boldsymbol{C}) \geq \boldsymbol{0}\}. \tag{8}$$

$\boldsymbol{p}$ and $\boldsymbol{C}$ are the model and the process specific parameters, respectively, and $\Phi^*(\boldsymbol{p})$ is the optimal (minimum) process cost. $\boldsymbol{d}$ are the design variables of dimension n_{d}, consisting of process design and operational decisions. $\boldsymbol{x}_{\text{st}}$ are the process state variables of dimension $n_{x_{\text{st}}}$ that are not part of the design variables. Note however, that $\boldsymbol{d}$ may include some process states that are of interest for the cost function, such as the amount of product or the reactor temperature. The equality constraints in Equation (8) consist of balance equations (in the above formulation only steady state equations are considered) and design equations, such as closure conditions and constitutive equations. The inequality constraints in Equation (8) are process specifications and physical limits, and depending on the process are sometimes omitted. As can be seen from Equations (7) and (8), the optimal cost is either explicitly or implicitly defined via the state variables dependent on the model parameters, whose uncertainties are further propagated to the cost. In other words $\Phi^*(\boldsymbol{p})$ is parametric in the parameter uncertainties, which are determined in the second-level problem (Section 4.2).

Remark 1 If the set of feasible design variable solutions is empty, then the entire process is infeasible, the third-level problem is infeasible, and the optimal process cost value $\Phi^*(\boldsymbol{p})$ is infinite by convention.

4.2 | Second-level (middle-level) problem

The second-level problem is a worst-case optimization. The optimal process cost is maximized over a set of feasible parameters, for which we choose a similar formulation as the one used in bounded-error OED, see Section 3, Equation (4). The problem is formulated as a max–min problem according to

$$\Phi_U^*(\boldsymbol{v}) = \max_{\boldsymbol{p}\in\mathbb{P}(\boldsymbol{v})} \min_{(\boldsymbol{x}_{\text{st}},\boldsymbol{d})\in\mathbb{D}(\boldsymbol{p})} \Phi(\boldsymbol{x}_{\text{st}},\boldsymbol{p},\boldsymbol{d},\boldsymbol{C}) \tag{9}$$

with the set of feasible parameters being defined as

$$\mathbb{P}(\boldsymbol{v}) = \left\{\boldsymbol{p}\in P \,|\, 2e_k^{\min} \leq g_k(\boldsymbol{v},\boldsymbol{p}) - g_k(\boldsymbol{v},\hat{\boldsymbol{p}}) \leq 2e_k^{\max}, k = 1,\dots,n_y\right\}. \tag{10}$$

$\Phi_U^*(\boldsymbol{v})$ is the worst-case optimal process cost. The model output equations $\boldsymbol{g}$ are either given explicitly or are calculated using the system model ODE or DAE systems. The feasible parameter set $\mathbb{P}(\boldsymbol{v})$ is parametric in the manipulated variables $\boldsymbol{v}$, that is, the size and shape of the feasible parameter set is dependent on the manipulated variables, for example, if the experiment is informative, a smaller feasible set is obtained in comparison to an uninformative experiment. The worst-case realization of the optimal process cost, $\Phi_U^*(\boldsymbol{v})$, is parametric in the uncertainties in the system model parameters, and therefore, is also indirectly parametric in $\boldsymbol{v}$.

Remark 2 In the case that there exists at least one parameter value, for which the third-level feasible set is empty, the worst-optimal process cost value $\Phi_U^*(\boldsymbol{v})$ is infinite (see Remark 1) and the second-level problem is unbounded. Furthermore, since the nominal parameter values $\hat{\boldsymbol{p}}$ are always contained in $\mathbb{P}(\boldsymbol{v})$, the second-level problem is always feasible.

4.3 | First-level (upper-level) problem

In the first-level, the optimal manipulated variables $\boldsymbol{v}$ are determined, for which the worst-case process cost is minimal. The manipulated variables are experimental decision variables, that is, $\boldsymbol{v}$ determine which future experiments, for example, small scale laboratory experiments, should be planned for improving the precision of the system model. The final OED–OPD problem formulation reads as:

$$\Psi^* = \min_{\boldsymbol{v}\in V} \max_{\boldsymbol{p}\in\mathbb{P}(\boldsymbol{v})} \min_{(\boldsymbol{x}_{\text{st}},\boldsymbol{d})\in\mathbb{D}(\boldsymbol{p})} \Phi(\boldsymbol{x}_{\text{st}},\boldsymbol{p},\boldsymbol{d},\boldsymbol{C}), \tag{11}$$

where Ψ^* is the minimal worst-case optimal process cost and $\boldsymbol{v}$ are the manipulated variables of the system model. For simplicity, any constraints on manipulated variables are included in the host set V. Optimal solutions for the three levels of the formulation are denoted by $\boldsymbol{d}^*$, $\boldsymbol{p}^*$, and $\boldsymbol{v}^*$, respectively.

4.4 | Trilevel

The trilevel OED–OPD formulation aims at mitigating the worst-case realization of the process design cost function. The worst-case is calculated using a feasible parameter set defined by the system model, measurement errors, and the manipulated variables $\boldsymbol{v}$ (see Equation (10)). In the OED–OPD formulation it is possible that better process designs (with smaller costs) lie outside the identified feasible parameter set. However, under the assumption that the feasible parameter set is constructed around a nominal parameter $\hat{\boldsymbol{p}}$ value that is close to the true model parameter, these better process designs become unrealistic and should, therefore, be avoided. In other words, the better process designs are superoptimal with respect to the true optimal process. In the context of OED, this means that the OED–OPD formulation aims at finding experimental conditions that minimize the process uncertainty interval around a true, realistic optimal cost $\Phi^*(\hat{\boldsymbol{p}})$ by decreasing the interval's upper bound Φ_U^*.

The OED–OPD problem consists of two distinct constraint sets that correspond to the two different models used in the formulation: the system model (Equation (1)) and the process design model (Equation (8)). This is necessary since often the identification of the system model and process design optimization have different goals and the physical limits, constraints, and level detail that are imposed on the system model or process design vary. Therefore, several important distinctions between variables have to be made: (a) between the system model state variables $\boldsymbol{x}$ and the process state variables $\boldsymbol{x}_{\text{st}}$; while these variables might have the same physical meaning, for example, a reactant concentration, in the optimization they are considered as two different variables. (b) between the system model manipulated variables $\boldsymbol{v}$ and the process inputs, which, depending on the process design, are either part of the design variables $\boldsymbol{d}$ or the process parameters $\boldsymbol{C}$. Again, the manipulated variables and the process inputs can have the same physical meaning, for example, the initial reactant concentration at time $t = 0$, however, they are considered as two different variables in the optimization. (c) between the manipulated variables $\boldsymbol{v}$ and the process design variables $\boldsymbol{d}$. The manipulated variables are decision variables made on the level of the experimental design, while the process variables are operational decision variables made on the level of the process design, and are not equal to each other. As mentioned before, both models can contain integer variables, for example, number of trays in a distillation column or discrete control variables in the system outputs $\boldsymbol{y}$. However, for simplicity we have omitted these in the OED–OPD formulation; the presence of integer variables can make the solution harder since mixed-integer nonlinear solvers have to be used.

In the trilevel formulation, when the set of feasible third-level solutions is empty, that is, no $\boldsymbol{d}$ exists that satisfies the constraints in Equation (8), the minimal worst-case process cost value $\Psi^*(\boldsymbol{v})$ is infinite (see Remarks 1 and 2). In this case, the overall problem is infeasible and the manipulated variables $\mathbf{v}^*$ are also infeasible (since an infeasible process is to be avoided). However, the second-level problem is always feasible (see Remark 2). Essentially, it is possible to find experimental conditions but in a worst-case sense these are not informative enough to ensure a feasible process. This can occur if the constraints of the process model are too restrictive or if the assumptions made in the system model are erroneous. In this case the process design constraints and/or the system model assumptions and constraints, such as the bounds on the measurement errors or the estimated value of the nominal parameters $\hat{\boldsymbol{p}}$, have to be redefined.

The presented trilevel formulation is specifically tailored for the improvement of conceptual model-based process design. However, the methodology itself is much more general and can be applied to different domains. The trilevel formulation can be straightforwardly used for other tailored OED problems by simply changing the objective cost function in Equation (11) and the constraint equations in Equation (8).

5 | BRUTE FORCE SOLUTION METHOD

In process systems engineering, models are typically described using nonlinear functions resulting in nonconvex problems. Algorithms for multilevel optimization problems exist in literature, however, they often rely on some strict assumptions in the problem formulation such as linearity and/or convexity.[42] To the knowledge of the authors no trilevel algorithm exists for general nonlinear nonconvex problems. Hence herein, we opt for a brute force solution method to reduce the problem from a trilevel to a bilevel formulation and the resulting bilevel max–min problem is solved to global optimality using commercially available global solvers in GAMS.[68] This guarantees a feasible solution of the OED–OPD problem through global solution for the third and second level.

For the brute force solution we first perform uniform sampling of the system's manipulated variables $\boldsymbol{v}$ and include the bounds of host set V into the set of random samples. Herein, it is assumed that the host set V of the system's manipulated variables is constrained via a simple hyper box. At each sampling point $\boldsymbol{v}_m$ in the host set V we formulate and then solve the bilevel problem identical to the second-level problem Equations (9) and (10) with the exception that now $\boldsymbol{v}$ comes from a discrete set and is not continuous. The bilevel problem Equations (9) and (10) can be reformulated as a GSIP and solved using the algorithm proposed by Djelassi et al[51] with a specialization of the algorithm to min–max problems as proposed in Reference 63. The smallest worst-case process cost $\Phi_U^*(\boldsymbol{v}_m^*)$ is then chosen as the optimal solution value among all the discrete worst-case realizations.

The GSIP algorithm in Reference 51 requires continuity of all functions and equations and the existence of a Slater point arbitrarily close to a GSIP optimum in the objective. As shown in Reference 63 the assumption of an ε-optimal GSIP Slater point is always satisfied for any feasible GSIP resulting from the reformulation of a min–max program. In Reference 51 it is also assumed that a solution for the equality constraints exists and that it is unique. If this assumption is not satisfied then the process model has to be reformulated such that the solution set is constrained to a unique solution. If the process model does not contain any inequality constraints, then the bilevel max–min problem can be reformulated as a semi-infinite program (SIP).

5.1 | Implementation

The max–min algorithm (see Supporting Information) to solve the OED–OPD problem is implemented in GAMS[68] version 25.0.1 using BARON version 17.10.16. All numerical calculations are run on a 64-bit Intel(R) Xeon(R) E5-2630 v3 CPU with eight cores and hyper threading at 2.40 GHz running Windows Server 2016 Standard. The following algorithm optimization variables are used: optimality tolerance for termination $\epsilon = 10^{-1}$, optimality tolerance for the upper bounding problem and lower-level problem $\epsilon^{LBD} = 10^{-2}$ and $\epsilon^{LBD,\ LLP} = 10^{-2}$, an empty initial set $Y^{UBD,\ 0} = \emptyset$. All GAMS files, the max-min algorithm as well as the case studies models from Section 6 can be found in the Supporting Information.

6 | CASE STUDIES

In the following we present the OED–OPD methodology for model-based process design on two examples. The first example is a simple illustrative example and the other one is a typical chemical processes consisting of an ideal continuous stirred tank reactor (CSTR) and split distillation columns.

6.1 | Illustrative example

The first example is a simple system model with a trivial process cost function and is used as a proof of concept. It consists of two distinct models: the system model and the process design model. We start by introducing the system model, which consists of two output equations with two model parameters and two manipulated variables. The system model is as follows:

$$y_1 = v_1 e^{p_1 t} \qquad y_2 = v_2 e^{p_2 t}, \tag{12}$$

where p_1 and p_2 are the system model parameters, v_1 and v_2 are the system's manipulated variables, the model outputs are y_1 and y_2, both of which are measured during an experimental run, and t is time. The manipulated variables v_1 and v_2 correspond to the initial values of the system states $x_1(t = 0)$ and $x_2(t = 0)$, respectively, which are equal to the model outputs $x_1 = y_1$ and $x_2 = y_2$. We want to conduct an experiment that would improve the model predictions, that is, increase the parameter accuracy. With OED formulations, the optimal values for the manipulated variables, for which the parameter uncertainties are decreased, can be determined. However, we want to improve only the parameters with the highest influence on the process design cost function.

For this illustrative example, the process design model consists of one process state equation and a process cost function that is to be minimized. The process model is as follows:

$$x_{1,\mathrm{st}} = u_{\mathrm{proc}} e^{p_1 t_f} \qquad \Phi = \frac{x_{1,\mathrm{st}}}{d}, \tag{13}$$

with Φ being the cost function, x_{st} the process state variable, d the process design variable, t_f is the time point at which the process cost is evaluated, and u_{proc} a constant process input, corresponding to the initial value of the process state variable $x_{1,\,\mathrm{st}}$ at time $t = 0$. As mentioned in Section 4.4, a distinction between the system and process variables has to be made. In this example the state variables y_1 and $x_{1,\,\mathrm{st}}$, and the manipulated variable v_1 and process input u_{proc} have the same "physical" meaning, respectively, but in the OED–OPD formulation they are considered as separate variables. These similarities between the variables of the system and process design model often occur and it is important that these variables are not set to be equal. The process design variable d (operational decision variable) and the system's manipulated variables v_1 and v_2 do not have the same "physical" meaning and are not equivalent to each other.

Using the trilevel OED–OPD problem formulation we want to determine experimental conditions that would mitigate the worst-case realization of the process cost function; in other words, we want to find experimental conditions that would result in the smallest possible upper bound Φ_U^* of the process uncertainty interval. The OED–OPD formulation works as follows: first, knowledge about the nominal parameters $\hat{p}_1$ and $\hat{p}_2$ is acquired, for example, via parameter estimation using an initial set of experimental data. Second, a choice for the manipulated variables v_1 and v_2 is made, for example, via grid sampling of the host set V. Based on these values, the system model and the nominal parameters, a feasible parameter set $\mathbb{P}(\mathbf{v})$ is calculated. Finally, using the determined feasible parameter set, the worst-case realization of the optimal process cost $\Phi_U^*(\mathbf{v})$ is calculated. Using the brute force method, the smallest worst-case realization $\Phi_U^*(\mathbf{v}_m)$ is chosen as the optimal solution.

For the brute force solution, 100 random discrete points from the manipulated variable host set were taken. The exact problem formulation for the illustrative example can be found in the Supporting Information. For each discretization point, an optimal solution was found in two iterations of the SIP max–min algorithm (see Supporting Information) and on average in 30 CPU s.

For this simple example the optimal results can be deduced analytically from the system model and process equations. First of all, the cost function Φ is inversely proportional to the design variable d and thus, Φ is minimal when the design variable is at its upper bound, that is, $d = 10$. Second of all, since the model outputs increase monotonically with the model parameters and the manipulated variables, and absolute error bounds are used in the problem formulation, the size of the feasible parameter set $\mathbb{P}$ decreases for higher values of the manipulated variables; thus, the optimal values for the manipulated variables v_1 and v_2 are at their upper bounds. Third of all, the cost function only depends on model parameter p_1 and therefore, the sensitivity of the cost function depends only on the precision of p_1 and only v_1 influences the optimal cost function solution.

The results of OED–OPD for the illustrative example are as expected. The optimal value for the design variable is found to be $d* = 10$ and the influence of the manipulated variables v_1 and v_2 on the worst-case optimal cost solution $\Phi_U^*(\mathbf{v}_m)$ are shown in Figure 3. As anticipated only v_1 has an influence on the worst-case optimal cost function $\Phi_U^*(\mathbf{v}_m)$: the worst-case cost function decreases with v_1 but

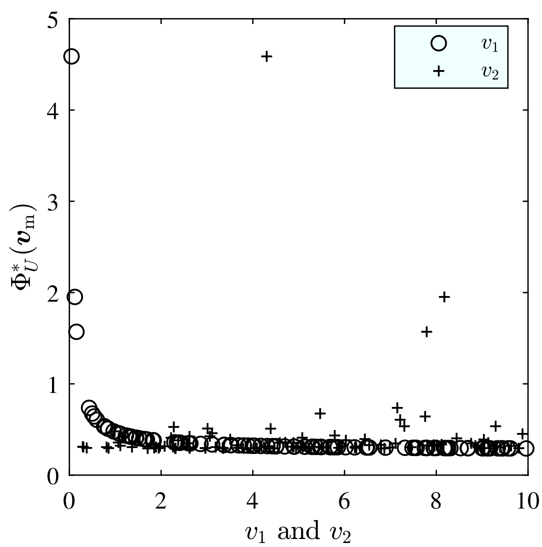

FIGURE 3 Influence of the manipulated variables on the worst-case optimal cost function defined by Equation (9) for the illustrative example (Equations (12) and (13)). Only manipulated variable v_1 (circle) has a direct influence on the cost function. The worst-case optimal cost function decreases with v_1. Manipulated variable v_2 (cross) shows no influence on the cost function: the worst-case optimal cost is arbitrarily scattered with respect to v_2

is arbitrarily scattered with respect to v_2, indicating that v_2 has no influence on the cost. The optimal solution is found to be at the upper bound of v_1, that is, $v_1^* = 10$. Based on the trilevel OED–OPD formulation the optimal experimental conditions are $v_1 = 10$ and $v_2 \in [0,10]$. In this case v_2 can be arbitrarily chosen by the experimenter, for example, $v_2 = 0$. These experimental conditions differ significantly from classical statistical OED formulations,[9] which would give $v_1 = 10$ and $v_2 = 10$ as the optimal experimental conditions since these OED formulations usually target the improvement of all model parameters. Other tailored OED formulations would also give the same optimal experimental conditions. For example, using D_s-optimality p_2 can be defined as a nuisance parameter and since y_1 and y_2 only depend on p_1 and p_2, respectively, the D_s-optimality design then depends only on v_1. Using the heuristic methodology proposed in Reference 29 also results in a weighted FIM matrix that depends only on v_1 since the sensitivity of the process design cost function toward p_2 is equal to zero.

This illustrative example also shows that the system model parameters do not necessarily have to be identifiable for effectively reducing the uncertainty of the process design when using the OED–OPD formulation. If we assume that only the system model output y_1 is measured then the parameter p_2 becomes unidentifiable. This, however, does not influence the above results since the process cost function Φ does not depend on p_2. The OED–OPD formulation, in this case, would work under model unidentifiability.

6.2 | Van de Vusse reaction

For the next example we consider a typical van de Vusse reaction, which consists of one consecutive and one side reaction. The van de Vusse reaction can be written as follows:

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C,$$

$$2A \xrightarrow{k_3} D,$$

where A is the reactant, B is the desired product and C and D are the side-products. We want to determine the optimal experimental conditions that would reduce the parameter uncertainties of the system model that have the highest influence on the process design. In the OED–OPD formulation two distinct models have to be defined, and we start with defining the system model.

For OED–OPD formulation we assume that the reaction takes place in an isothermal batch reactor and that the manipulated variables, that is, experimental conditions, are the initial concentrations of the reactant A and the product B, $v_1 = c_A(t = 0)$ and $v_2 = c_B(t = 0)$. Therefore, the system model for the van de Vusse reaction corresponds to an ODE system that does not have an analytical solution. Hence, for the implementation of the ODE system in GAMS, the midpoint explicit discretization method is used to solve the system model for various time points. We choose the time step such that the discretized reaction equations adequately represent the dynamic behavior of the reaction for the nominal kinetic parameters while still keeping the computation inexpensive. In order to further reduce the computational load, it is assumed that only the concentration of A, B, and C are measured at various time points. Theoretically, the system model is structurally identifiable if three components are measured at various time points.

For the process design model it is assumed that the reaction takes place in an ideal, isothermal CSTR. The reactor is followed by two split distillation columns with 100% recovery. In the first column the reactant is separated from the reaction mixture and recycled back to the reactor and in the second column the product is separated from the side-products. The process design cost is defined as $\Phi = C_{raw} + C_{op} + C_{cap} - C_{prod}$, where C_{raw}, C_{op}, C_{cap}, C_{prod} are the costs for the raw materials, the operating costs, the capital costs and the product cost, respectively. The process design variables, for which the process cost is minimized, are the reactor volume V_R and the product molar flow rate F_B at the end of the process. The exact OED–OPD problem formulation with the various assumptions and variable values made during the optimization can be found in the Supporting Information.

For the brute force solution method 500 random discretization points from the manipulated variable host set V were taken. For each discretization point, a global solution for $\Phi_U^*(\mathbf{v}_m)$ was found in three iterations of the max–min algorithm (see Supporting Information) and on average in 200 CPU s. However, for some discretization points a global optimal solution for max–min problem Equations (9) and (8) was found in about 3,500 CPU seconds.

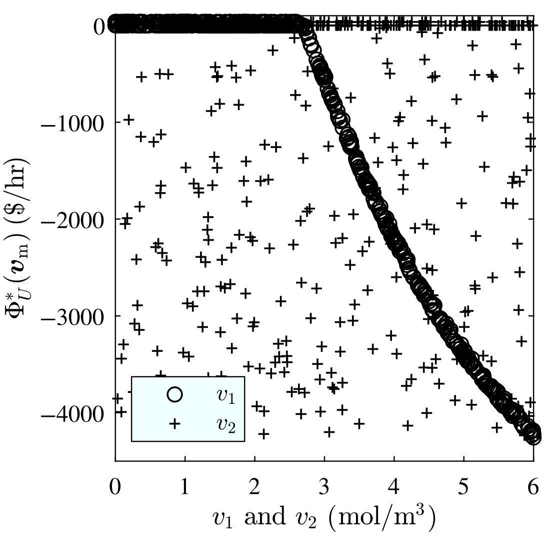

FIGURE 4 The worst-case optimal process cost $\Phi_U^*(\mathbf{v}_m)$ with respect to the manipulated variables v_1 (circles) and v_2 (crosses). The worst-case optimal process cost decreases with variable v_1 and is randomly scattered with respect to v_2. $\Phi_U^*(\mathbf{v}_m)$ becomes economically profitable only when v_1 is greater then 2 mol/m^3; for values below 2.7 mol/m^3 the process is not profitable and $\Phi_U^*(\mathbf{v}_m)$ is, therefore, equal to zero. A slight influence on the worst-case optimal process cost is noticeable with respect to v_2; the variation of $\Phi_U^*(\mathbf{v}_m)$ is around 2% for $v_2 \in [0,6]$ mol/m^3

The worst-case optimal cost, $\Phi_U^*(\boldsymbol{v}_m)$, with respect to the manipulated variables ($v_1 = c_A(t = 0)$ and $v_2 = c_B(t = 0)$) can be seen in Figure 4. The best realization for the worst-case optimal cost is found for the highest possible initial concentration values: $c_A^*(t=0)=6$ mol/m^3 and $c_B^*(t=0)=6$ mol/m^3, and is equal to $\Phi_U^*(\boldsymbol{v}_\mathrm{m}^*)=-4256$ \$/hr. This result is in accordance with classical statistical OED and bounded-error OED,[63] and corresponds to the smallest feasible set obtainable for the given problem assumptions. The optimal solution values for the design variables are found to be $V_\mathrm{R}^*=1$ m^3 and $F_\mathrm{B}^*=23.8$ mol/s.

Depending on the initial concentrations of the reactant and product, the process is found to be either profitable, that is, a negative cost is obtained as the optimal solution, or unprofitable. In the latter case the optimal cost solution is then equal to zero. Interestingly, for the van de Vusse reaction, a similar solution behavior is observed as in the illustrative example: $\Phi_U^*(\boldsymbol{v}_m)$ decreases with v_1 and is arbitrarily scattered with respect to v_2. This indicates that the initial concentration of the reactant *A* influences the process design cost function, and the initial concentration of the product *B* has no or very little influence on the cost function. For a fixed value of v_1 = 6 mol/m^3, the variation of $\Phi_U^*(\boldsymbol{v}_m)$ is found to be only around 2% for a variation of v_2 between 0 and 6 mol/m^3. As can be seen in Figure 4 the process is not economically favorable for all sample points. For the worst-case process to be profitable the initial concentration of reactant *A* has to be greater than 2.7 mol/m^3.

The influence of the manipulated variables on the OED–OPD objective are compared to A-optimality and D-optimality criteria, and to the heuristic method proposed by Recker et al.[29] For the latter comparison, a modified A-optimality is analyzed, since the heuristic method in Reference 29 scales only the diagonal elements of the FIM, and therefore, has little effect on D-optimality. For the calculation of the FIM, the Jacobian of the system model outputs for the measured variables in function of the system model parameters is evaluated for the nominal parameter values and for each discretized grid point from the manipulated variable host set. For the heuristic method in Reference 29, the FIM is weighted using the sensitivities of the process design cost in function of the system model parameters evaluated at the nominal parameter values.

The results of the three mentioned OED optimizations with respect to the manipulated variables are shown in Figures 5 and 6. For the A- and D-optimality both of the manipulated variables influence the OED objective, that is, the trace and the determinant of the FIM, respectively. However, the manipulated variable v_1 has a slightly bigger influence on the classical statistical OED objectives than v_2, since the latter is slightly more scattered along the *y*-axis (Figure 5). For the heuristic method (Figure 6), the influence of variable v_1 is increased while that of v_2 is decreased due to the weighting of the FIM. Nevertheless, the influence of v_2 in is still higher in comparison to the presented OED–OPD method. The influence of the v_2 on the different OED objectives can be determined for a fixed value of v_1 = 6 mol/m^3. For D-optimality the determinant varies around 86% for a variation of $v_2 \in$ [0,6] mol/m^3, for A-optimality the trace of the FIM varies around 53% and for the heuristic method presented in Reference 29 the weighted trace of the FIM varies around 20%.

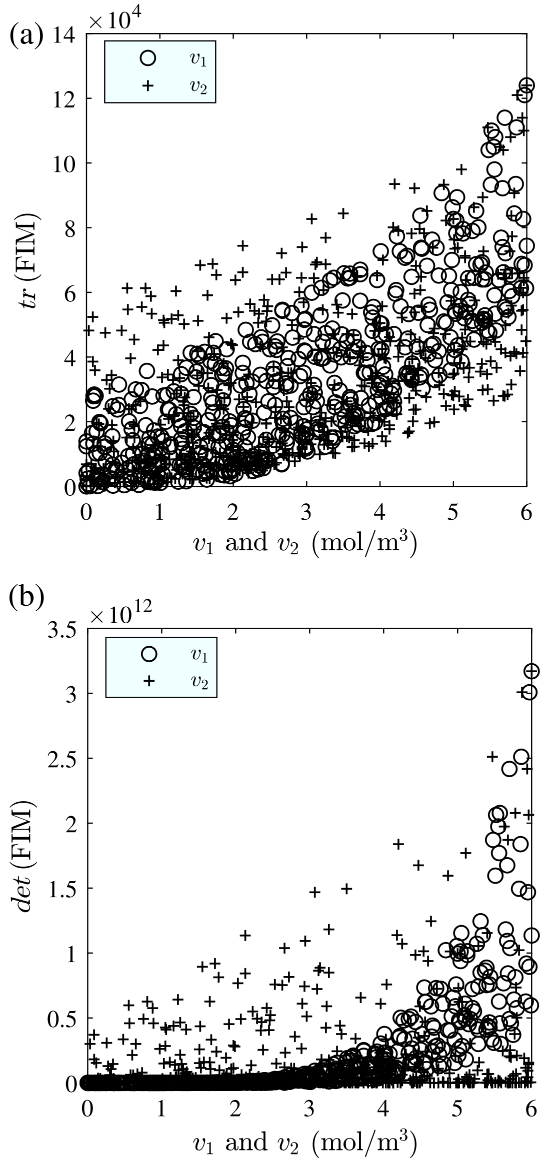

FIGURE 5 The influence of the manipulated variables, v_1 (circles) and v_2 (crosses) on two different optimal experimental design objectives. (a) Classical statistical A-optimality criteria. Both variables v_1 and v_2 influence the objective of A-optimality, that is, the trace of the FIM. The influence of v_2 is a slightly less since it is more scattered among the *y*-axis. The variation of *tr*(FIM) is around 53% for $v_2 \in [0, 6]$mol/m^3. (b) Classical statistical D-optimality criteria. Both variables v_1 and v_2 influence the objective of D-optimality, that is, the determinant of the FIM. The influence of v_2 is a slightly less, since it is more scattered along the *y*-axis. The variation of *det*(FIM) is around 86% for $v_2 \in [0, 6]$ mol/m^3

The optimal experimental conditions for all four cases are found for the highest possible initial concentration values: $c_A^*(t=0)=6$ mol/m^3 and $c_B^*(t=0)=6$ mol/m^3. However, if we compare two different experimental designs: (***a***) v_1 = 6 mol/m^3 and v_2 = 6 mol/m^3, and (***b***) v_1 = 6 mol/m^3 and v_2 = 0 mol/m^3, we see that for the presented

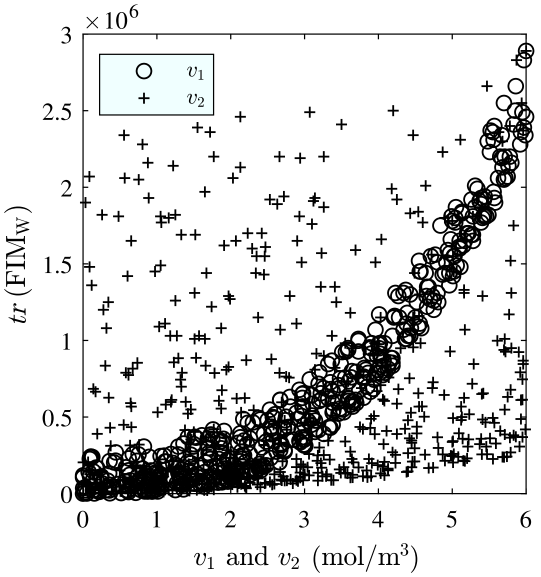

FIGURE 6 The influence of the manipulated variables, v_1 (circles) and v_2 (crosses) on the optimal experimental design objective from Reference 29. The A-optimality criteria is modified by weighting the FIM.[29] Both variables v_1 and v_2 influence the objective of modified A-optimality, that is, the trace of a weighted FIM. The influence of v_2 is a significantly less since it is highly scattered along the y-axis. The variation of $tr(\mathrm{FIM_w})$ is around 20% for $v_2 \in [0, 6]\mathrm{mol/m^3}$

OED–OPD method both experimental conditions lead to very close optimal OED objectives. This is not the case for the classical A- and D-criterion OED and for the heuristic method presented in Reference 29. In the latter cases the experimental conditions of design (***b***) would be most probably judged as unsatisfactory and effort would be applied to conduct experiment (***a***). This of course increases the experimental costs, first of all, due to the additional costs for the raw materials and second of all, this can further increase experimental costs if other problems occur, such as limitations in laboratory equipment or reactant miscibilities issues. In the case of the min–max–min OED formulation both experiments (***a***) and (***b***) led to satisfactory results and, therefore, experiment (***b***) can be conducted instead of (***a***). Additionally, only in the OED–OPD method is it possible to see under which experimental conditions the uncertainty of the system model parameters is reduced sufficiently such that the optimal worst-case process design cost becomes profitable.

7 | CONCLUSION

We present a new OED formulation for parameter precision. The determined optimal experiments are tailored to the intended model application. The presented formulation is a MMM problem resulting in a worst-case formulation, and tailors the OED specifically for model-based process design. The idea of the formulation is to design experiments in such a way that the influence of model parameter uncertainties on the process design is reduced. The three levels—lower, middle, and upper—constitute, respectively, the process design optimization, the calculation of the worst-case process design within a feasible parameter set and the determination of the optimal experimental conditions. Though the methodology is specifically developed for process design, the min–max–min OED formulation can be straightforwardly applied to different application domains by changing the objective function and the constraints of the lower-level, for example, for process control or clinical trials. Since no general global solution method exists for nonlinear, nonconvex MMM problems, herein, we opt for a brute force discretization of the upper-level to reduce the formulation to a bilevel problem. The resulting max–min problem is solved globally using a (G)SIP algorithm with equality constraints. This approach is possible since a global solution is necessary only for the middle- and lower-level. A non-global solution of the first level results only in a suboptimal solution.

By tailoring the experiments to the intended model application, the novel OED–OPD can show how to properly invest experimental effort. The case studies show when experimental costs can be reduced without influencing the end results of process design optimization or when additional experimental effort is needed for improving the results of process design optimization, for example, obtaining an economically profitable process design. The presented numerical case studies are fairly simple and, therefore, the adaption of the above methodology to more complex real-life systems should be further researched. To this end, other formulations can be envisioned. For example formulations for the description of the parameter feasible set based on maximum-likelihood statistics might be more accurate and might lead to quicker computations. A bottle neck of the methodology is the necessity of a global solution for the lower-level problem. If the overall OED–OPD problem can be solved using a local solution for the process design optimization, then the computational effort can be significantly reduced for the trilevel optimization. Likewise, efficient global dynamic solvers would allow to apply the proposed methodology to a wider class of real-life systems. In the future, instead of a brute-force method different solvers, for example, gradient-free or global stochastic solvers, should be applied to generate the upper-level variables that are further propagated to the bilevel max–min problem; thus resulting in better overall better CPU times and in optimal experimental conditions closer to the global solutions.

As with most OED formulations, the OED–OPD problem assumes that the model structure is correct. However, in reality the structural model mismatch will affect the accuracy of the system model and process design. This can yield impractical process designs at the early stages of model development and therefore, can affect the OED–OPD results. The structural mismatch can lead to many iterations between collecting data, model development, and reevaluating the process design. The extent of the affects of model mismatch on the OED–OPD formulation should be further examined.

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SUPPORTING INFORMATION

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