

A Probabilistic Approach to Robust Optimal Experiment Design with Chance Constraints

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Abstract: Accurate estimation of parameters is paramount in developing high-fidelity models for complex dynamical systems. Model-based optimal experiment design (OED) approaches enable systematic design of experiments to generate input-output data sets with high information content for parameter estimation. Standard OED approaches however face two challenges: (i) experiment design under incomplete system information due to unknown true parameters, which usually requires many iterations of OED; and (ii) incapability of systematically accounting for the inherent uncertainties of complex systems, which can lead to diminished effectiveness of the designed optimal excitation signal as well as violation of system constraints. This paper presents a robust OED approach for nonlinear systems with arbitrarily-shaped time-invariant probabilistic uncertainties. Polynomial chaos is used for efficient uncertainty propagation. The distinct feature of the robust OED approach is the inclusion of chance constraints to ensure constraint satisfaction in a stochastic setting. The presented approach is demonstrated by optimal experimental design for the JAK-STAT5 signaling pathway, which regulates various cellular processes in a biological cell.

1. INTRODUCTION

The prediction capability of first-principles models of complex dynamical systems largely relies on the accuracy of model parameters. Parameter estimation for complex systems is often a challenging task due to nonlinear nature of system dynamics as well as system uncertainties and disturbances that are ubiquitous in real-world applications. Hence, dynamic experiments that provide as much information as possible about the system dynamics in the face of system nonlinearities and uncertainties are crucial for obtaining accurate estimates of model parameters. This consideration has led to the development of model-based optimal experiment design approaches (e.g., see [Pronzato, 2008] and the references therein) that facilitate systematic design of the excitation inputs to maximize the information content of dynamic experiments. Optimal experiment design (OED) also enables seeking trade-offs between the economic costs and information content of dynamic experiments, which is particularly important when dynamic experiments are economically expensive [Bombois et al., 2006].

The primary challenge in model-based OED approaches arises from the fact that the OED problem depends on the unknown model parameters. Hence, the excitation inputs are designed merely based on the current best estimate of the parameters, which can be largely different from the true parameter values. Designing experiments under

incomplete system information (i.e., unknown true parameters) is likely to diminish the effectiveness of the optimal excitation inputs and, therefore, lead to loss in information content of the designed experiments [Asprey and Macchietto, 2002]. Another difficulty in OED originates from the inherent system uncertainties that can result in violations of (state and/or output) constraints incorporated into the OED problem.

One approach to deal with the inadequate system information and system uncertainties in OED is to adopt sequential experiment design strategies that repeatedly estimate the model parameters and redesign the experiments till parameter estimates with admissible uncertainty are obtained [Asprey and Macchietto, 2002]. Sequential OED can however be economically infeasible for certain applications due to high costs of experiments. Alternatively, robust OED approaches allow for systematically accounting for the effects of uncertainty on the designed experiments by devising the excitation inputs based on a prespecified parameter range around the nominal values. Various robust OED formulations have been proposed in terms of min-max optimization problems, in which uncertainties are typically assumed to be deterministic and bounded [Pronzato and Walter, 1985, Korkel et al., 2004, Flaherty et al., 2006, Goodwin et al., 2007, Welsh and Kong, 2011]. In min-max robust OED approaches, the excitation inputs are designed with respect to worst-case uncertainty realizations, and constraints are satisfied for all admissible values of uncertainties. Such robust OED

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approaches discard the statistical properties of uncertainties, and can be conservative if the worst-case uncertainty realizations have a small probability of occurrence.

This paper considers the problem of robust OED for nonlinear systems with time-invariant probabilistic uncertainties. In the proposed approach, parametric and initial condition uncertainties are described by probability distributions (instead of bounded sets), which can often be readily obtained from a (previous) model identification procedure [Ljung, 1999]. The probabilistic experiment design framework circumvents the conservatism of worst-case OED approaches, as the probability of occurrence of different uncertainty realizations is directly accounted for in design of experiments. More importantly, chance constraints (aka probabilistic constraints) are incorporated into the OED problem to seek a trade-off between the information content of a designed experiment and allowing for prespecified levels of (operational) risks during the experiment. Chance constraints enable satisfaction of constraints with a desired probability level in the presence of system uncertainties (e.g., see [Schwarm and Nikolaou, 1999, Calafiore and Campi, 2006, Oldewurtel et al., 2013, Mesbah et al., 2014a] for the application of chance constraints in stochastic optimal control problems). Recently, Telen et al. [2014] have also used chance constraints for OED of nonlinear systems.

A nonlinear optimization problem with chance constraints is presented for robust OED (Section 2). The objective function of the OED problem is defined in terms of the weighted sum of the expected value and variance of a scalar metric of the Fisher information matrix (Section 2). Such an OED objective function enables maximizing the information content of the dynamic experiments, while minimizing the variance of the information content with respect to realizations of the probabilistic system uncertainties. Efficient propagation of uncertainties through the nonlinear system dynamics poses a challenge in evaluating the objective function. The generalized polynomial chaos (PC) framework [Wiener, 1938, Xiu and Karniadakis, 2002] is used as a computationally efficient tool for probabilistic uncertainty propagation (Section 3). The PC framework replaces the implicit mappings between the uncertain system variables/parameters and dynamic state variables with a series of orthogonal polynomials, whose statistical moments can be readily computed from the expansion coefficients (e.g., see [Fisher and Bhattacharya, 2011, Fagiano and Khammash, 2012, Mesbah et al., 2014b, Paulson et al., 2014], and references therein for applications of PC expansions). The Cantelli-Chebyshev inequality [Marshall and Olkin, 1979] is used to convert the chance constraints into deterministic expressions and, therefore, obtain a computationally tractable optimization problem (Section 4). The proposed robust OED approach is demonstrated for the JAK-STAT5 signaling pathway [Berridge, 2012] in a biological cell with probabilistic parametric uncertainties (Section 5).

2. PROBLEM FORMULATION

Consider a continuous-time, uncertain nonlinear system

$$\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), \boldsymbol{\theta}), \quad \mathbf{x}(0) = \mathbf{x}_0 \quad (1a)$$

$$\mathbf{y}(t) = \mathbf{h}(\mathbf{x}(t)) + \boldsymbol{\varepsilon}(t), \quad (1b)$$

where $t \in [0, t_f]$ denotes the time; $\mathbf{x} \in \mathbb{R}^{n_x}$, $\mathbf{u} \in \mathbb{R}^{n_u}$, and $\mathbf{y} \in \mathbb{R}^{n_y}$ denote the system states, (excitation) inputs, and outputs, respectively; $\boldsymbol{\theta} \in \mathbb{R}^{n_\theta}$ denotes the time-invariant uncertain system parameters with known probability distribution functions (PDFs) $\{\mathbf{P}_{\theta_i}\}_{i=1}^{n_\theta}$; \mathbf{x}_0 denotes the initial states that are considered to be uncertain with known PDFs $\{\mathbf{P}_{x_{0,i}}\}_{i=1}^{n_x}$; $\mathbf{f} : \mathbb{R}^{n_x} \times \mathbb{R}^{n_u} \times \mathbb{R}^{n_\theta} \rightarrow \mathbb{R}^{n_x}$ and $\mathbf{h} : \mathbb{R}^{n_x} \rightarrow \mathbb{R}^{n_y}$ denote the nonlinear system and (possibly nonlinear) model output functions, respectively, which are typically represented by a set of differential algebraic equations; and $\boldsymbol{\varepsilon} \in \mathbb{R}^{n_y}$ denotes zero-mean additive measurement noise that has a known variance-covariance matrix $\Sigma \in \mathbb{R}^{n_y \times n_y}$. Define a probability space $(\Omega, \mathcal{F}, \mathbf{P})$ on the basis of the sample space Ω , σ -algebra \mathcal{F} , and the probability measure \mathbf{P} on Ω . The time-invariant probabilistic uncertainties $[\mathbf{x}_0^\top \boldsymbol{\theta}^\top]^\top \in \mathbb{R}^{n_\xi}$ (with $n_\xi \leq n_\theta + n_x$) are functions of standard random variables $\boldsymbol{\xi} := [\xi_1, \dots, \xi_{n_\xi}]^\top$ with known independent PDFs $\{\mathbf{P}_{\xi_i}\}_{i=1}^{n_\xi}$ over the common support Ω . Note that $\xi_i \in \mathcal{L}^2(\Omega, \mathcal{F}, \mathbf{P})$, where $\mathcal{L}^2(\Omega, \mathcal{F}, \mathbf{P})$ is the Hilbert space of all random variables with finite variance $\mathbf{E}[\xi_i^2] < \infty$.

This paper considers the problem of robust OED for parameter estimation.¹ The information content of experiments can be quantified in terms of some scalar metric of the Fisher information (FI) matrix $F(t_f)$ defined by [Bard, 1974]

$$F(t_f) = \int_0^{t_f} \left(\frac{\partial \mathbf{h}}{\partial \mathbf{x}} \frac{\partial \mathbf{x}(t)}{\partial \boldsymbol{\theta}} \right)^\top \Sigma^{-1} \left(\frac{\partial \mathbf{h}}{\partial \mathbf{x}} \frac{\partial \mathbf{x}(t)}{\partial \boldsymbol{\theta}} \right) dt, \quad (2)$$

where sensitivities $\frac{\partial \mathbf{x}(t)}{\partial \boldsymbol{\theta}}$ are obtained through integrating

$$\frac{d}{dt} \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}}(t) = \frac{\partial \mathbf{f}}{\partial \mathbf{x}} \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}}(t) + \frac{\partial \mathbf{f}}{\partial \boldsymbol{\theta}}, \quad \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}}(0) = \frac{\partial \mathbf{x}_0}{\partial \boldsymbol{\theta}}.$$

The FI matrix describes the amount of information that system outputs \mathbf{y} provide on the unknown parameters $\boldsymbol{\theta}$. The FI matrix accounts for the effects of measurement noise $\boldsymbol{\varepsilon}(t)$ and sensitivities of the system states to variations in the model parameters (i.e., $\frac{\partial \mathbf{x}(t)}{\partial \boldsymbol{\theta}}$). Under the assumption of unbiased parameter estimates and uncorrelated measurement noise, the inverse of the Fisher information matrix $F(t_f)$ provides an approximation of the Cramér-Rao lower bound [Bard, 1974], which is closely related to the lower bound of variance-covariance matrix of the estimated parameters.

The E-optimality criterion [Pronzato, 2008] is used as a scalar metric of the FI matrix to formulate the OED problem.² The E-optimality criterion aims to maximize the minimum eigenvalue of the Fisher information matrix, i.e.,

$$\Phi(F(t_f)) := \max [\lambda_{\min}(F(t_f))].$$

Hence, E-optimal designs in effect minimize the length of the largest uncertainty axis of the joint confidence region of parameters that corresponds to the largest parameter errors.

The primary challenge in performing OED results from the fact that the optimality criterion depends on the current

¹ The problem of robust OED for model discrimination *without* chance constraints is addressed in [Streif et al., 2014].

² The proposed robust OED approach can be straightforwardly adapted for other optimality criteria such as A- and D-optimal designs.

estimates of the to-be-estimated parameters (required to evaluate the FI matrix (2)). The uncertainty in initial estimates of the to-be-estimated parameters can render the OED in practice largely ineffective, as the excitation inputs are designed on the basis of an inadequate description of the system dynamics. In addition, plant-model mismatch due to initial condition and parametric uncertainties is likely to further diminish the effectiveness of the designed excitation inputs.

This paper proposes the following robust OED formulation for the nonlinear system (1) to systematically incorporate the knowledge of time-invariant probabilistic uncertainties into the OED problem.

Problem 1 (Robust optimal experiment design with chance constraints): The optimal excitation inputs \mathbf{u}^* to system (1) (over the horizon $[0, t_f]$) that maximize the information content of a dynamic experiment, while being robust to the probabilistic uncertainties in $[\mathbf{x}_0^\top \boldsymbol{\theta}^\top]^\top$, are defined by

$$\mathbf{u}^* := \arg \min_{\mathbf{u}} \mathbf{E}[\Phi(F(t_f))] + w \mathbf{Var}[\Phi(F(t_f))]$$

subject to :

$$\begin{aligned} \dot{\mathbf{x}}(t) &= \mathbf{f}(\mathbf{x}(t), \mathbf{u}(t), \boldsymbol{\theta}), & \forall t \in [0, t_f] \\ \frac{d}{dt} \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}}(t) &= \frac{\partial \mathbf{f}}{\partial \mathbf{x}} \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}}(t) + \frac{\partial \mathbf{f}}{\partial \boldsymbol{\theta}}, & \forall t \in [0, t_f] \\ \frac{d}{dt} F(t) &= \left(\frac{\partial \mathbf{h}}{\partial \mathbf{x}} \frac{\partial \mathbf{x}(t)}{\partial \boldsymbol{\theta}} \right)^\top \Sigma^{-1} \left(\frac{\partial \mathbf{h}}{\partial \mathbf{x}} \frac{\partial \mathbf{x}(t)}{\partial \boldsymbol{\theta}} \right), & \forall t \in [0, t_f] \\ \mathbf{Pr}[b_i x_i(t) \geq x_i^{\max}] &\leq \beta_i, \quad \forall i \in \mathcal{I}, & \forall t \in [0, t_f] \\ \mathbf{u}(t) &\in \mathbb{U}, & \forall t \in [0, t_f] \\ F(0) &= 0 \\ \frac{\partial \mathbf{x}}{\partial \boldsymbol{\theta}}(0) &= \frac{\partial \mathbf{x}_0}{\partial \boldsymbol{\theta}} \\ x_i(0) &\sim \mathcal{P}_{x_{0,i}}, & i = 1, \dots, n_x \\ \theta_i &\sim \mathcal{P}_{\theta_i}, & i = 1, \dots, n_\theta, \end{aligned} \quad (3)$$

where $\mathbf{E}[\cdot]$ and $\mathbf{Var}[\cdot]$ denote the expected value and variance of a stochastic variable; w denotes a scalar weight; \mathbf{Pr} denotes probability; the scalar values $b_i \in \mathbb{R}$ and $x_i^{\max} \in \mathbb{R}$ define the state constraints; $\beta_i \in (0, 1) \subset \mathbb{R}$ denotes an upper bound for the probability that each state constraint can be violated due to system uncertainties; $\mathcal{I} \subseteq \{1, \dots, n_x\}$ denotes a subset of states for which the chance constraints are defined; and \mathbb{U} denotes the convex compact set of input constraints. Note that the initial conditions $\{x_i(0)\}_{i=1}^{n_x}$ and parameters $\{\theta_i\}_{i=1}^{n_\theta}$ have probability distributions $\mathcal{P}_{x_{0,i}}$ and \mathcal{P}_{θ_i} , respectively.

The robust OED problem (3) can effectively account for the uncertainty in the initial parameter estimates and the inherent system uncertainties. This is due to (i) defining the objective function in terms of the statistical moments of the metric $\Phi(F(t_f))$ that are evaluated with respect to the probabilistic system uncertainties³, and (ii) including chance constraints to seek trade-offs between maximizing the information content of experiments and constraint satisfaction (typically associated with operational risks) in a stochastic setting. The variance term in the objective

function of (3) allows for minimizing variations in the information content of the experiments due to probabilistic uncertainties.

The key challenges in solving Problem 1 are to efficiently propagate the probabilistic uncertainties through the nonlinear system dynamics (1) and to obtain a computationally tractable surrogate for the chance constraints in (3). To this end, polynomial chaos is introduced, which provides a computationally efficient means to evaluate statistical moments of a stochastic variable.

3. POLYNOMIAL CHAOS FOR UNCERTAINTY PROPAGATION

This work uses the generalized polynomial chaos framework [Wiener, 1938, Xiu and Karniadakis, 2002] to efficiently propagate the time-invariant probabilistic uncertainties $[\mathbf{x}_0^\top \boldsymbol{\theta}^\top]^\top$ through the nonlinear system (1). In the PC framework, a second-order stochastic variable $\psi(\boldsymbol{\xi}) \in \mathcal{L}^2(\Omega, \mathcal{F}, \mathcal{P})$ is defined in terms of an expansion of orthogonal polynomial basis functions

$$\psi(\boldsymbol{\xi}) = \sum_{k=0}^{\infty} a_k \Phi_k(\boldsymbol{\xi}), \quad (4)$$

where a_k denotes the expansion coefficients; and Φ_k denotes polynomial basis functions of maximum degree m with respect to the random variables $\boldsymbol{\xi}$. The basis functions belong to the Askey scheme of polynomials, which entails a set of orthogonal basis functions in the Hilbert space defined on the support of the random variables [Xiu and Karniadakis, 2002]. Hence, $\langle \Phi_i(\boldsymbol{\xi}), \Phi_j(\boldsymbol{\xi}) \rangle = \langle \Phi_i^2(\boldsymbol{\xi}) \rangle \delta_{ij}$, where $\langle h(\boldsymbol{\xi}), g(\boldsymbol{\xi}) \rangle = \int_{\Omega} h(\boldsymbol{\xi}) g(\boldsymbol{\xi}) \mathcal{P}_{\boldsymbol{\xi}} d\boldsymbol{\xi}$ denotes the inner product induced by $\mathcal{P}_{\boldsymbol{\xi}}$, and δ_{ij} denotes the Kronecker delta function. The basis functions Φ_k are chosen in accordance with the PDFs of the uncertain variables $\boldsymbol{\xi}$. The truncated form of (4) used in practice takes the form

$$\hat{\psi}(\boldsymbol{\xi}) := \sum_{k=0}^L a_k \Phi_k(\boldsymbol{\xi}) = \mathbf{a}^\top \boldsymbol{\Phi}(\boldsymbol{\xi}) \quad (5)$$

with $L + 1 = \frac{(n_{\boldsymbol{\xi}} + m)!}{n_{\boldsymbol{\xi}}! m!}$ being the total number of terms in the expansion; $\mathbf{a} := [a_0, \dots, a_L]^\top$; and $\boldsymbol{\Phi}(\boldsymbol{\xi}) := [\Phi_0(\boldsymbol{\xi}), \dots, \Phi_L(\boldsymbol{\xi})]^\top$. Owing to the orthogonality property of the polynomial basis functions, the statistical moments of $\hat{\psi}$ can be computed merely based on the expansion coefficients \mathbf{a} in a computationally efficient manner (e.g., see [Fisher and Bhattacharya, 2011]).

The probabilistic collocation method (see discussion and references in [Nagy and Braatz, 2007]) is used to determine the coefficients \mathbf{a} in (5). The collocation method requires the residuals

$$R(\mathbf{a}, \boldsymbol{\xi}) = \hat{\psi}(\boldsymbol{\xi}) - \psi(\boldsymbol{\xi})$$

be orthogonal to each basis function Φ_k

$$\int_{\Omega} R(\mathbf{a}, \boldsymbol{\xi}) \Phi_k(\boldsymbol{\xi}) d\mathcal{P}_{\boldsymbol{\xi}} = 0, \quad k = 0, \dots, L. \quad (6)$$

Provided that the basis functions are non-zero terms, the coefficients \mathbf{a} can be estimated by computing the residuals $R(\mathbf{a}, \boldsymbol{\xi})$ at n_c samples (i.e., collocation points) of random variables $\boldsymbol{\xi}$ with non-zero probability $\mathcal{P}_{\boldsymbol{\xi}}$ [Tatang et al., 1997]. Alternatively, the expansion coefficients \mathbf{a} in (5) can be determined using the Galerkin-projection method (see [Ghanem and Spanos, 1991]).

³ This is in contrast to classical OED approaches, which evaluate a metric of the FI matrix merely at a given realization of uncertainties.

4. DETERMINISTIC SURROGATE FOR CHANCE CONSTRAINTS

To solve the robust OED Problem 1, the chance constraints in (3) should be replaced with deterministic expressions. The Cantelli-Chebyshev inequality is used to obtain a computationally tractable optimization problem.⁴

Theorem 1 (Cantelli-Chebyshev inequality [Marshall and Olkin, 1979]): Let ψ be a stochastic variable with a finite second-order moment. Then,

$$\Pr[\psi - \mathbf{E}[\psi] \geq \alpha] \leq \frac{\mathbf{Var}[\psi]}{\mathbf{Var}[\psi] + \alpha^2}, \quad \forall \alpha \in \mathbb{R}_0^+. \quad (7)$$

■

Consider the chance constraints

$$\Pr[b_i x_i(t) \geq x_i^{\max}] \leq \beta_i, \quad \forall i \in \mathcal{I} \quad (8)$$

in (3), which are independently defined in terms of state variables $x_i(t)$. Define $\delta x_i \geq 0$ such that

$$b_i \mathbf{E}[x_i(t)] + \delta x_i \leq x_i^{\max}. \quad (9)$$

The chance constraints (8) then satisfy

$$\Pr[b_i x_i(t) \geq x_i^{\max}] \leq \Pr[b_i x_i(t) \geq b_i \mathbf{E}[x_i(t)] + \delta x_i].$$

Since the states $\{x_i(t)\}_{i=1}^{i=n_x}$ are stochastic variables due to the probabilistic time-invariant uncertainties in (1), the Cantelli-Chebyshev inequality in Theorem 1 implies that

$$\Pr[b_i x_i(t) \geq b_i \mathbf{E}[x_i(t)] + \delta x_i] \leq \frac{b_i^2 \mathbf{Var}[x_i(t)]}{b_i^2 \mathbf{Var}[x_i(t)] + \delta x_i^2},$$

where the fulfillment of chance constraints (8) requires

$$\frac{b_i^2 \mathbf{Var}[x_i(t)]}{b_i^2 \mathbf{Var}[x_i(t)] + \delta x_i^2} \leq \beta_i. \quad (10)$$

Hence, replacing (10) in (9) for δx_i and rearranging the resulting inequality will lead to a deterministic surrogate for each individual chance constraint in (8)

$$b_i \mathbf{E}[x_i(t)] \leq x_i^{\max} - \sqrt{b_i^2 \mathbf{Var}[x_i(t)]} \sqrt{\frac{1 - \beta_i}{\beta_i}}. \quad (11)$$

In this work, the stochastic state variables $\{x_i(t)\}_{i=1}^{i=n_x}$ and their moments are approximated using polynomial chaos expansions (see (5)). Thus, $x_i(t)$ is replaced with $\hat{x}_i(t)$ in the deterministic constraint (11) and the first- and the second-order moments of $\hat{x}_i(t)$ can be readily computed from the expansion coefficients (e.g., see [Fisher and Bhattacharya, 2011]).

5. ROBUST OPTIMAL EXPERIMENT DESIGN FOR THE JAK-STAT5 CELL-SIGNALING PATHWAY

The dynamics of complex biological systems such as metabolic and cell-signaling pathways in living cells are often described by nonlinear differential equations, which typically have several kinetic parameters. The fidelity of these dynamic models is largely dependent on the quality of the estimated parameters. This work considers the problem of OED in the presence probabilistic uncertainties for the JAK-STAT5 cell-signaling pathway, which is a fast-track signal transduction pathway for transferring

information from cell-surface receptor into the nucleus. Deregulation of the STAT5 signaling pathway is shown to be connected to human cancer [Berridge, 2012].

The STAT5 cell-signaling mechanism entails phosphorylation of the STAT5 molecules, which is governed by the EPO receptor on the cell membrane. The activated STAT5 molecules undergo a dimerization, so that STAT5 dimers can enter the cell nucleus to trigger the transcription of target genes. The STAT5 molecules are then dephosphorylated through separation of dimers, and the single STAT5 molecules re-enter the cytoplasm [Peifer and Timmer, 2007]. Assuming that no concentration gradient occurs in the cell due to fast transport mechanisms from the cell membrane to nucleus, the STAT5 cell-signaling dynamics can be described by [Peifer and Timmer, 2007]

$$\begin{aligned} \dot{x}_1 &= -k_1 x_1 u(t) + k_2 x_3(t - \tau) \\ \dot{x}_2 &= -k_3 x_2^2 + k_1 x_1 u(t) \\ \dot{x}_3 &= -k_2 x_3 + k_3 x_2^2 \\ \dot{x}_4 &= -k_2 x_3(t - \tau) + k_2 x_3. \end{aligned} \quad (12)$$

In (12), x_1 , x_2 , x_3 , and x_4 denote the concentration of the unphosphorylated STAT5, activated STAT5, STAT5 dimer, and STAT5 molecules in the nucleus (mole fractions); u denotes the EPO receptor activity (mole fraction); $k_1 \sim \beta(2, 5, 1.90, 2.34)$, $k_2 \sim \beta(2, 5, 0.094, 0.124)$, and $k_3 = 1.0$ denote rate constants (min^{-1}), with β being the four-parameter beta distribution; and $\tau = 8$ denotes the delay parameter (min). The total amount of activated STAT5 and the total amount of STAT5 in the cytoplasm are defined by

$$\begin{aligned} y_1 &= s_1(x_2 + x_3) \\ y_2 &= s_2(x_1 + x_2 + x_3), \end{aligned}$$

respectively, where $s_1 = 0.33$ and $s_2 = 0.26$ denote scaling constants. The model outputs y_1 and y_2 are assumed to be subject to zero-mean Gaussian noise with a 10% variance. The delay element in (12) is approximated by using a delay chain approach [Peifer and Timmer, 2007].

The STAT5 cell-signaling mechanism described by (12) comprises a nonlinear system with probabilistic time-invariant parametric uncertainties. To generate input-output data for estimating the kinetic parameters k_1 and k_2 with known PDFs, the robust OED problem (3) is used to design the EPO receptor activity profile (i.e., the excitation input). The polynomial chaos framework with the 4th-order Jacobi polynomial basis functions is used to propagate the beta PDFs of k_1 and k_2 through the nonlinear system (12) (see Section 3). To ensure that the total amount of STAT5 in the cytoplasm (y_2) remains above a desired threshold during the dynamic experiments in the presence of probabilistic uncertainties, the following chance constraint

$$\Pr[y_2(t) \leq 0.038] \leq 0.05 \quad (13)$$

is incorporated into the robust OED problem. The procedure in Section 4 is used to obtain a deterministic

Table 1. Average and maximum relative estimation errors of the model parameters with respect to the true parameter values

	Average Relative Error (%)		Maximum Relative Error (%)	
	k_1	k_2	k_1	k_2
OED	0.02	0.0019	0.07	0.01
Robust OED	0.006	0.0017	0.03	0.009

⁴ The Cantelli-Chebyshev inequality has also been used for converting chance constraints in the context of stochastic predictive control [Farina et al., 2013].

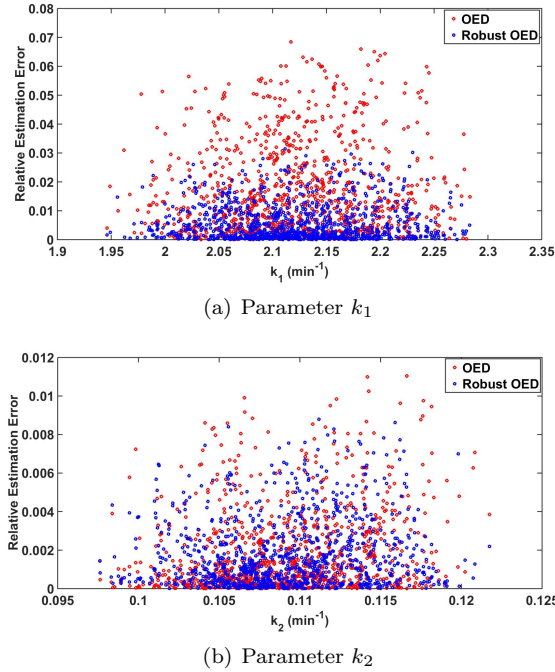


Fig. 1. Relative estimation errors of the model parameters with respect to the true parameter values. The parameter estimates are obtained by exciting the stochastic JAK-STAT5 cell-signaling pathway 1000 times with the excitation inputs designed by the robust and standard OED approaches, and using the generated input-output data sets for parameter estimation.

surrogate (see (11)) for the above chance constraint. In the optimization problem, the excitation input (i.e., $u(t)$) is parameterized in a piecewise-constant manner with five equidistant intervals over the time horizon $[0, t_f]$, where $t_f = 40$ min. The robust OED problem is solved using the MATLAB optimization subroutine *fmincon*.

Monte Carlo simulations are performed to evaluate the performance of the proposed robust OED approach in dealing with the probabilistic system uncertainties. The designed excitation input is applied to the STAT5 cell-signaling mechanism (12) in 1000 runs with different realizations of parametric uncertainties sampled from the known PDFs of k_1 and k_2 . The generated input-output data is subsequently used for obtaining estimates for the parameters k_1 and k_2 using the weighted least-squares estimation method [Bard, 1974]. The same procedure is also performed for an excitation input designed based on a standard OED approach, against which the performance of the robust OED approach is compared. The standard OED approach does not take into account the statistical distributions of the unknown model parameters, and merely assumes some initial estimates for the parameters. Identical realizations of probabilistic uncertainties are used to compare the two OED approaches.

Figure 1 shows the relative parameter estimation errors computed with respect to the true parameter values in each Monte Carlo run. The robust OED approach results in smaller estimation errors for the parameter k_1 (see Figure 1a). Table 1 indicates that the average estimation error (computed over the 1000 Monte Carlo runs) for k_1 in

the case of the standard OED approach is almost 3 times larger than that in the case of the robust OED approach. More accurate parameter estimates are also obtained for k_2 (see Figure 1b and Table 1), as the maximum estimation error for k_2 is lower when the system is excited with the input designed by the robust OED approach. Note that the OED problem (3) enables seeking systematic trade-offs between maximizing the information content of the dynamic experiments (through minimizing the expected value of some scalar metric of the FI matrix) and minimizing the variance of the chosen scalar metric of the FI matrix in the presence of probabilistic system uncertainties. In the presented simulation study, the weight function w in (3) is selected to be small in order to generate an input-output data set with high information content, which in turn will lead to more accurate parameter estimates (i.e., small estimation errors in Figure 1).

To demonstrate the ability of the robust OED approach in fulfilling the system constraints in a probabilistic sense (see (13)), the histograms of y_2 at time 40 min are shown in Figure 2. The histograms are obtained based on 1000 simulations of the stochastic JAK-STAT5 cell-signaling pathway when the receptor activity $u(t)$ is excited with the excitation input designed by the robust and standard OED approaches. The histograms of y_2 are shown for time 40 min only, as the total amount of STAT5 in the cytoplasm is closest to its minimum admissible threshold value of 0.038 at $t_f = 40$ min. Figure 2 shows that the constraint

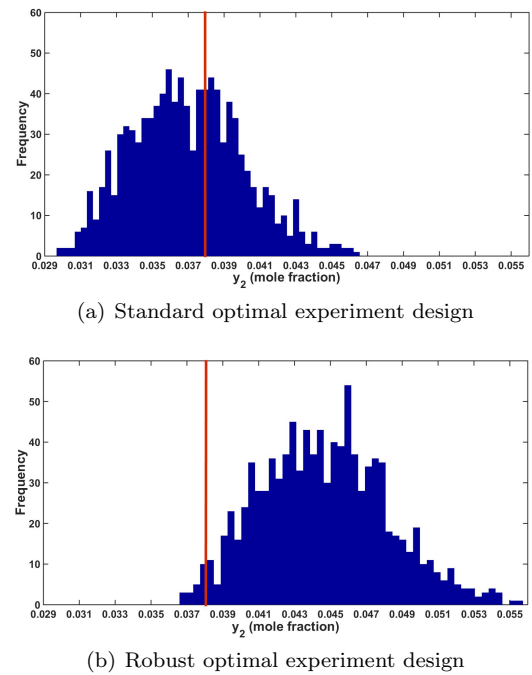


Fig. 2. Histograms of y_2 (the total amount of STAT5 in the cytoplasm) at time 40 min. The red line represents the minimum admissible threshold (i.e., output constraint) for the total amount of STAT5 in the cytoplasm. The robust OED approach ensures constraint satisfaction in nearly 98 % of signaling pathway excitations in the presence of probabilistic uncertainties, whereas the standard OED approach leads to approximately 46 % constraint satisfaction.

on y_2 is satisfied in nearly 98% of the Monte Carlo runs, which is greater than the lower bound (i.e., 95%) of the constraint satisfaction probability in (13). On the other hand, the excitation input designed using the standard OED approach (without the chance constraint) results in merely 46% constraint satisfaction in the presence of probabilistic uncertainties of the system (12). In general, the ability to guarantee state (output) constraint satisfaction in a stochastic setting is paramount in many OED applications to ensure safe, reliable, and high-performance system operation during dynamic experiments.

6. CONCLUSIONS

This paper presents a robust approach for optimal experiment design for nonlinear systems with arbitrarily-shaped probabilistic time-invariant uncertainties. Polynomial chaos is used for efficient uncertainty propagation, and chance constraints are incorporated into the input design problem to ensure constraint satisfaction in a stochastic setting. The simulation results for a cell-signaling pathway demonstrate the capability of the proposed approach in dealing with probabilistic system uncertainties and fulfilling system constraints in a probabilistic sense.

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