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to appear in: Computer Aided Chemical Engineering, Vol 37, pp. 905–910, 2015

ZIB Report 15-03 (April 2015)

Herausgegeben vom
Konrad-Zuse-Zentrum für Informationstechnik Berlin
Takustraße 7
D-14195 Berlin-Dahlem

Telefon: 030-84185-0
Telefax: 030-84185-125

e-mail: `bibliothek@zib.de`
URL: `http://www.zib.de`

ZIB-Report (Print) ISSN 1438-0064
ZIB-Report (Internet) ISSN 2192-7782

A robust minimax Semidefinite Programming formulation for optimal design of experiments for model parametrization

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Abstract

Model-based optimal design of experiments (M-bODE) is a crucial step in model parametrization since it encloses a framework that maximizes the amount of information extracted from a battery of lab experiments. We address the design of M-bODE for dynamic models considering a continuous representation of the design. We use Semidefinite Programming (SDP) to derive robust minmax formulations for nonlinear models, and extend the formulations to other criteria. The approaches are demonstrated for a CSTR where a two-step reaction occurs.

Keywords Optimal design of experiments, Semidefinite Programming, Robust minmax designs

1 Introduction

M-bODE is a classic problem with substantial interest nowadays, particularly in pharmacokinetics, pharmacodynamics, drugs trials design, and on general model parametrization, a challenge shared by various disciplines such as Chem. Eng. (Goos and Jones, 2011). Kiefer (1959) proposed to relax the original combinatorial experiment design problem to obtain a tractable convex optimization representation. This alternative is designated as *the approximate optimal design problem*, and consists in determining a probability measure over the design space (rather than the exact number of trials for each point of the design space). Many authors have proposed algorithms to compute optimal designs in a systematic way, starting with the exchange-based method of Wynn (1972) for local designs (see also Chaloner and Larntz (1989) for Bayesian optimal designs). Within the same framework Duarte and Wong (2014a) proposed a systematic algorithm for finding minmax optimal designs employing a reformulation to convert the original problem into a semi-infinite program. The criterion to maximize is a concave operator of the Fisher Information Matrix (FIM), which in turn is linear with respect to the design measure. Convex analysis can thus be used to establish the optimality conditions of a design, also known as *equivalence theorems*, see Pukelsheim (1993). This theoretical framework enabled to derive

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convex programming formulations for the M-bODE problem, although the regressor domain needs to be discretized (see Atkinson et al. (2007, Chap. 12) for discretized designs). Exploiting this route, among others Vandenberghe and Boyd (1999) proposed SDP formulations for $D-$, $A-$, and $E-$optimal designs for linear models, Sagnol (2011) derived Second Order Conic Programming formulations, and recently Duarte and Wong (2014b) extended the SDP formulations to nonlinear models employing the Bayesian paradigm. Here we derive SDP formulations for robust minmax optimal designs for nonlinear models in the spirit of Wong (1992) employing discretization techniques to convert the original semi-infinite program into a convex optimization problem.

2 Mathematical formulation

2.1 Preliminaries

We consider dynamic models represented by Differential-Algebraic Equations of the following form, the regressor being $t \in T \equiv [0, t^{\max}]$

$$\frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = f(\mathbf{x}, \boldsymbol{\theta}), \quad \mathbf{x}(0) = \mathbf{x}_0 \tag{1a}$$

$$\mathbf{y} = g(\mathbf{x}), \tag{1b}$$

where f and g are continuously differentiable functions, the process states are $\mathbf{x}(t) \in \mathbb{X} \subset \mathbb{R}^{\mathrm{m}}$, measurements at time t are $\mathbf{y}(t) \in \mathbb{Y} \subset \mathbb{R}^{\mathrm{n}}$, and $\boldsymbol{\theta} \in \Theta \subset \mathbb{R}^{\mathrm{p}}$ is an unknown parameter. The domain Θ is a cartesian box $\times_{j=1}^{\mathrm{p}} [\theta_j^{\mathrm{LO}}, \theta_j^{\mathrm{UP}}]$. For the sake of simplicity we consider $n = 1$, so measurements are scalar, but it is straightforward to extend our approach to larger values of n. The goal of the M-bODE problem is to find a *design* –i.e., a selection of measurements– that enables to estimate $\boldsymbol{\theta}$ with the best possible accuracy.

The time domain is discretized into s points, denoted by $\mathbb{T} = \{t_1, \ldots, t_s\}$, and $[s] = \{1, \cdots, s\}$. A design ξ with support points in $\mathbb{T}$ can be represented using the notation $\xi = \begin{pmatrix} t_1 & \cdots & t_s \\ w_1 & \cdots & w_s \end{pmatrix}$, where $\mathbf{w} \in [0,1]^s$ is a vector of weights satisfying $\sum_{i=1}^{s} w_i = 1$, and w_i represents the fraction of the total number of measurements N to perform at time t_i. The quantity $N w_i$ should be constrained to take integer values for all i, but this constraint is dropped for approximate designs, and in practical applications of M-bODE we may require to round the optimal approximate design. The set of all design measures supported by $\mathbb{T}$ is denoted by Ξ.

The FIM of a single "observational unit" t_i at $\boldsymbol{\theta} = \boldsymbol{\theta}_0$ is $M(t_i, \boldsymbol{\theta}_0) = \boldsymbol{\eta}(t_i, \boldsymbol{\theta}_0) \boldsymbol{\eta}(t_i, \boldsymbol{\theta}_0)^T$, where $\boldsymbol{\eta}(t_i, \boldsymbol{\theta}_0) = \left.\frac{\partial g(\mathbf{x}(t_i, \boldsymbol{\theta}))}{\partial \boldsymbol{\theta}}\right|_{\boldsymbol{\theta}=\boldsymbol{\theta}_0}$ is the sensitivity of the measurement at t_i with respect to $\boldsymbol{\theta}$. The FIM of an approximate design ξ is obtained by summing the FIM over the individual design points

$$\mathcal{M}(\xi, \boldsymbol{\theta}_0) = \int_T M(t_i, \boldsymbol{\theta}_0) \ \mathrm{d}(\xi) = \sum_{i \in [s]} w_i \, M(t_i, \boldsymbol{\theta}_0) \succeq 0, \tag{2}$$

where $A \succeq 0$ means that A belongs to the space of symmetric positive semidefinite matrices $\mathbf{S}_{+}^{\mathrm{p}}$. Note that for $\boldsymbol{\theta}_0 \in \Theta$, $\mathcal{M}(\xi, \boldsymbol{\theta}_0)$ depends only on the weights w_i of the design, and so we also denote it by $\mathcal{M}(\boldsymbol{w}, \boldsymbol{\theta}_0)$. The quality of a design is measured by a criterion Φ, such as the criterion of $D-$optimality, $\Phi_D(M) = (\det\ M)^{1/p}$, $A-$optimality, $\Phi_A(M) = (\mathrm{trace}\ M^{-1})^{-1}$, or $E-$optimality, $\Phi_E(M) = \lambda_{\min}(M)$. We refer to Pukelsheim (1993) for more details on optimality criteria.

The representation of $\mathcal{M}(\xi, \boldsymbol{\theta})$ for nonlinear models depends on the unknown parameters that we wish to estimate, which is a challenging cyclic problem. In practice there are three approaches to handle it: *(i)* sequential designs which rely on a sequence of local designs, computed at the current best estimate $\hat{\boldsymbol{\theta}}$ of $\boldsymbol{\theta}$; *(ii)* Bayesian designs which are derived to optimize the expectation over Θ of an optimality criterion assuming that a prior distribution for parameters is available; *(iii)* minmax designs which are derived so that we maximize the design efficiency for the worst combination of parameters in Θ. Such a framework is used in this paper, that is, we want to find a design ξ solving the following saddle point optimization problem:

$$\max_{\xi \in \Xi} \min_{\boldsymbol{\theta} \in \Theta} \Phi(\mathcal{M}(\xi, \boldsymbol{\theta})). \tag{3}$$

2.2 Construction of the FIM

The sensitivity of the measurements with respect to $\boldsymbol{\theta}$ at $\boldsymbol{\theta}_0$ is determined by solving the sensitivity equations (4) simultaneously with Model (1) employing a DAE solver. The sensitivity of state x_i with respect to parameter θ_j is denoted by $\sigma_{i,j}$, yielding:

$$\frac{\mathrm{d}\sigma_{i,j}}{\mathrm{d}t} = \sum_{k=1}^{\mathrm{m}} \frac{\partial f_i(\mathbf{x}, \boldsymbol{\theta}_0)}{\partial x_k} \sigma_{k,j} + \frac{\partial f_i(\mathbf{x}, \boldsymbol{\theta}_0)}{\partial \theta_j}, \qquad i \in [m],\ j \in [p], \tag{4a}$$

$$\boldsymbol{\eta}(t_i, \boldsymbol{\theta}_0) = \sum_{k=1}^{\mathrm{m}} \frac{\partial g(\mathbf{x})}{\partial x_k} \sigma_{k,j}(t, \boldsymbol{\theta}_0), \qquad j \in [p]. \tag{4b}$$

2.3 Robust minmax SDP formulation

We recall that a concave function $f : \mathbb{R}^{n_1} \to \mathbb{R}$ is called semidefinite representable (SDr) if and only if inequalities of the form $u \leq f(\boldsymbol{x})$ are equivalent to a linear matrix inequality (LMI). More precisely, f is SDr if and only if there exists some symmetric matrices $M_0, \ldots, M_{n_1+n_2}$ such that

$$u \leq f(\boldsymbol{x}) \Longleftrightarrow \exists \boldsymbol{y} \in \mathbb{R}^{n_2} :\ u\, M_0 + \sum_{i=1}^{n_1} x_i\, M_i + \sum_{j=1}^{n_2} y_j\, M_{n_1+j} \succeq 0.$$

The criterions of $A-$, $E-$, and $D-$optimality are known to be SDr (Ben-Tal and Nemirovskiĭ, 2001, Chap. 2-3), which gave rise to SDP formulations for the computation of local optimal designs (Boyd and Vandenberghe, 2004, Sec. 7.3). We also point out that Kiefer's Φ_p-criterion is SDr for all rational values of $p \in (-\infty, 1]$ (Sagnol, 2013). Due to space limitations, we give a semidefinite representation for the $D-$criterion only. The inequality $\tau \leq (\det[\mathcal{M}(\xi, \boldsymbol{\theta})])^{1/\mathrm{p}}$ holds if and only if there exists a $p \times p-$lower triangular matrix $\mathcal{C}$ such that

$$\begin{bmatrix} \mathcal{M}(\xi, \theta) & \mathcal{C}^{\mathrm{T}} \\ \mathcal{C} & \mathrm{Diag}(\mathcal{C}) \end{bmatrix} \succeq 0 \quad \text{and} \quad \tau \leq \left(\prod_{j=1}^{\mathrm{p}} \mathcal{C}_{j,j} \right)^{1/\mathrm{p}},$$

where $\mathrm{Diag}(\mathcal{C})$ is the diagonal matrix with same diagonal entries as those of $\mathcal{C}$. The inequality involving the geometric mean of the $\mathcal{C}_{j,j}$ can, in turn, be expressed by a series of 2×2 LMIs, see Ben-Tal and Nemirovskiĭ (2001). It is also straightforward to show that when the concave functions $f_1, \ldots, f_q$ are SDr, then their pointwise minimum $f : \boldsymbol{x} \mapsto \min(f_1(\boldsymbol{x}), \ldots, f_q(\boldsymbol{x}))$ is also concave and SDr. There exists user-friendly interfaces, such as `cvx` (Grant et al., 2012) or Picos (Sagnol, 2012), which automatically transforms constraints of the form $\tau \leq \Phi[\mathcal{M}(\xi, \boldsymbol{\theta})]$ as a series of LMIs, and pass them to SDP solvers such as SeDuMi (Sturm, 1999) or Mosek (Andersen et al., 2009).

In this paper, we consider a sampling mechanism $\mathcal{S}(q)$ that extracts a finite number q of values in Θ, denoted by $\boldsymbol{\theta}_j \in \Theta,\ j \in [q] := \{1, \ldots, q\}$ and we define $\mathbb{P} := \{\boldsymbol{\theta}_1, \ldots, \boldsymbol{\theta}_q\}$. Then, we replace $\min_{\boldsymbol{\theta} \in \Theta}\ \Phi[\mathcal{M}(\xi, \boldsymbol{\theta})]$ by a minimum of finitely many terms, $\min_{j \in [q]}\ \Phi[\mathcal{M}(\xi, \boldsymbol{\theta}_j)]$. As a result, we obtain a SDP formulation that approximates the minmax optimal design problem (3):

$$\max_{\xi \in \Xi} \min_{\boldsymbol{\theta} \in \mathbb{P}} \Phi[\mathcal{M}(\xi, \boldsymbol{\theta})] = \max_{\tau \in \mathbb{R}, \boldsymbol{w} \in \mathbb{R}^s} \quad \tau \tag{5a}$$

$$s.t. \quad \forall j \in [q], \quad \tau \leq \Phi[\mathcal{M}(\boldsymbol{w}, \boldsymbol{\theta}_j)] \tag{5b}$$

$$\forall i \in [s], \quad w_i \geq 0 \tag{5c}$$

$$\sum_{i=1}^{s} w_i = 1, \tag{5d}$$

where –as mentioned above– the constraints (5b) can be rewritten as LMIs if Φ is SDr; however we used this compact formulation for the sake of generality, and because constraints (5b) are accepted *as is* by high-level interfaces.

2.4 Algorithm

To prevent sub-optimal solutions for problem (3), which can be due to the insufficient variability of the sample of parameter combinations $\mathbb{P}$, we use an iterative procedure. Let $\tau^*, \boldsymbol{w}^*$ be a solution returned after solving Problem (5). Then, it is clear that the design associated with the weights $\boldsymbol{w}^*$ solves Problem (3) if and only if τ^* is equal to the optimal value of

$$\min_{\boldsymbol{\theta} \in \Theta} \ \Phi[\mathcal{M}(\boldsymbol{w}^*, \boldsymbol{\theta})]. \tag{6}$$

This justifies the following procedure: at each iteration, we seek a parameter combination $\boldsymbol{\theta}^*$ that solves Problem (6). The procedure stops if $\tau^* \leq \Phi[\mathcal{M}(\boldsymbol{w}^*, \boldsymbol{\theta}^*)] + \epsilon_r$, where ϵ_r is a small tolerance parameter. Otherwise, $\boldsymbol{\theta}^*$ is added in the sample $\mathbb{P}$ and we go to the next iteration. After the convergence is achieved a pruning step deletes support points with $w_i < \epsilon^p$. This procedure is summarized in Algorithm 1.

In practice, the nonlinear optimization problem (6) might be hard to solve. However, since Θ is usually a cathesian box of relatively small dimension, the optimum can be found by using local optimization procedures and multiple restarts. Of course, it is also possible to add several local optima of (6) in the sample $\mathbb{P}$. However, note that (approximate-)optimality of a design can only be assessed when the $\boldsymbol{\theta}^*$ used in the algorithm is a global optimum of (6), which would theoretically require the use of a global NLP solver.

2.5 Extension to find the optimal support points over T

When the criterion Φ is differentiable, it is known that a design ξ is minmax optimal if and only if there exists a probability measure γ supported by $V_\Theta(\xi) :=$

Algorithm 1 Algorithm to find a robust minmax design with support on $\mathbb{T}$

procedure FINDDESIGN($\mathbb{T}, \Theta, \mathcal{S}, q, \epsilon^r, \epsilon^p$)
  Discretize T ▷ Find the grid $\mathbb{T}$
  Generate the initial sample $\mathbb{P} = \mathcal{S}(q)$ ▷ Sample Θ
  $\ell^* \leftarrow -\infty, \tau^* \leftarrow +\infty$
  while $\tau^* > \ell^* + \epsilon_r$ **do**
    Compute $\boldsymbol{\eta}(t_i, \theta_{\mathbf{j}})$ and $M(t_i, \theta_{\mathbf{j}})$ for all $(i, j) \in [s] \times [q]$ ▷ Single point FIMs
    Get a solution $(\tau^*, \boldsymbol{w}^*)$ of the SDP (5) ▷ Get upper bound τ^*
    Get a solution $\boldsymbol{\theta}^*$ of Problem (6), $\ell^* \leftarrow \Phi[\mathcal{M}(\boldsymbol{w}^*, \boldsymbol{\theta}^*)]$ ▷ Get lower bound ℓ^*
    $\ell^* \leftarrow \Phi[\mathcal{M}(\boldsymbol{w}^*, \boldsymbol{\theta}^*)]$, $\mathbb{P} \leftarrow \mathbb{P} \cup \{\boldsymbol{\theta}^*\}$, $q \leftarrow q + 1$ ▷ Update the sample
  end while
  Prune ξ
end procedure

$\arg\min_{\boldsymbol{\theta}\in\Theta} \Phi[\mathcal{M}(\xi, \boldsymbol{\theta})]$ such that

$$\forall t \in T, \quad h_\gamma(t) := \int_{\boldsymbol{\theta}\in V_\Theta(\xi)} \psi(\xi, \boldsymbol{\theta}, t)\ \gamma(\mathrm{d}\boldsymbol{\theta}) \leq 0, \tag{7}$$

with equality attained only at support points of ξ, where $\psi(\xi, \boldsymbol{\theta}, t)$ denotes the directional derivative of Φ at $\mathcal{M}(\xi, \boldsymbol{\theta})$ in the direction of $(M(t, \boldsymbol{\theta}) - \mathcal{M}(\xi, \boldsymbol{\theta}))$, see e.g. Fedorov and Leonov (2013, Theorem 2.5). Let ξ be a solution of Problem (5) and assume without loss of generality that $V_{\mathbb{P}}(\xi) = \{\boldsymbol{\theta}_1, \ldots, \boldsymbol{\theta}_k\}$. By construction, ξ is minmax optimal over the discretized sets $\mathbb{T}$ and $\mathbb{P}$, so there must exist a discrete probability measure $\boldsymbol{\gamma}$ such that Equation (7) holds if we replace T by $\mathbb{T}$ and Θ by $\mathbb{P}$. This measure can be found easily by solving the following linear program (LP):

$$\min_{\boldsymbol{\gamma}\in\mathbb{R}_+^k,\ U\geq 0} U \qquad \text{s.t.} \qquad \sum_{j=1}^k \gamma_j = 1, \qquad \forall i \in [s],\ h_{\boldsymbol{\gamma}}(t_i) := \sum_{j=1}^k \gamma_j\ \psi(\xi, \boldsymbol{\theta}_j, t_i) \leq U.$$

Then, natural candidate support points for the minmax optimal design arise as local maxima of the function $h_{\boldsymbol{\gamma}}(t)$ over T. More precisely, we propose to change the stopping condition of the main loop as "**while** ($\tau^* > \ell^* + \epsilon_r$ and $\max_{t\in T} h_{\boldsymbol{\gamma}}(t) > \epsilon_r$) **do**", and to add the following statements at the end of the **while** loop in Algorithm 1:

$$\text{Compute the dual weights } \boldsymbol{\gamma} \in \mathbb{R}^k, \quad \mathbb{T} \leftarrow \mathbb{T} \cup \arg\max_{t\in T} h_{\boldsymbol{\gamma}}(t), \quad s \leftarrow \mathrm{card}(T).$$

3 Application and results

To test the algorithm presented in Section 2 we use the example of Atkinson et al. (2007, pag. 270), referring to the model for two consecutive reactions $\mathrm{A} \xrightarrow{\pi_1} \mathrm{B} \xrightarrow{\pi_2} \mathrm{C}$ occurring in a constant volume CSTR, where the concentration C_B of product B is observed, cf. the model in Equations (8).

Table 1: Robust minmax designs obtained for $T = [0, 20]$, $\mathbb{T} = \{0, 0.2, \ldots, 20\}$, and $\Theta \equiv [0.5, 1.0] \times [0.1, 0.5] \times [1.0, 2.0] \times [1.0, 2.0]$. Designs are given using the notation $\xi = \left(\begin{smallmatrix} t_1 & \cdots & t_s \\ w_1 & \cdots & w_s \end{smallmatrix}\right)$.

support	criterion	Optimal design	CPU (s)	iterations
fixed support over $\mathbb{T}$	Φ_D	$\begin{pmatrix} 0.4 & 1.6 & 1.8 & 4.4 & 4.6 & 10.8 & 11 \\ 0.2493 & 0.1517 & 0.0994 & 0.1436 & 0.1057 & 0.0330 & 0.2158 \end{pmatrix}$	11.0	1
	Φ_A	$\begin{pmatrix} 0.2 & 1.6 & 4.6 & 10.8 & 20 \\ 0.3881 & 0.2266 & 0.1595 & 0.1392 & 0.0862 \end{pmatrix}$	7.94	1
	Φ_E	$\begin{pmatrix} 0.2 & 1.6 & 4.6 & 10.8 & 20 \\ 0.3889 & 0.2278 & 0.1565 & 0.1341 & 0.0917 \end{pmatrix}$	11.93	1
optimal support over T	Φ_D	$\begin{pmatrix} 0.44 & 1.66 & 1.7 & 4.0 & 4.49 & 10.77 & 10.8 \\ 0.2498 & 0.0846 & 0.1654 & 0.2448 & 0.0048 & 0.1151 & 0.1338 \end{pmatrix}$	39.19	5
	Φ_A	$\begin{pmatrix} 0.27 & 1.61 & 4.61 & 4.63 & 10.50 & 19.0 \\ 0.3463 & 0.2527 & 0.0670 & 0.1061 & 0.1415 & 0.0851 \end{pmatrix}$	27.46	6

$$\frac{\mathrm{d}C_A}{\mathrm{d}t} = -\pi_1\ C_A^{\lambda_1}, \qquad C_A(0) = 1.0 \tag{8a}$$

$$\frac{\mathrm{d}C_B}{\mathrm{d}t} = \pi_1\ C_A^{\lambda_1} - \pi_2\ C_B^{\lambda_2}, \qquad C_B(0) = 0.0 \tag{8b}$$

$$\frac{\mathrm{d}C_C}{\mathrm{d}t} = \pi_2\ C_B^{\lambda_2}, \qquad C_C(0) = 0.0 \tag{8c}$$

$$y(t) = C_B(t) \tag{8d}$$

The measurements must be selected so as to estimate the vector of parameters $\boldsymbol{\theta} = (\pi_1, \pi_2, \lambda_1, \lambda_2)$ for $\Theta \equiv [0.5, 1.0] \times [0.1, 0.5] \times [1.0, 2.0] \times [1.0, 2.0]$. We considered $T = [0, 20]$, discretized as $\mathbb{T} = \{0, 0.2, 0.4, \ldots, 20\}$ (i.e., $s = 101$). The sampling mechanism $\mathcal{S}$ selects the $2^4 = 16$ corners of Θ, plus 34 vectors drawn from a uniform distribution over Θ (i.e., $q = 50$). We used $\epsilon^p = \epsilon^r = 10^{-3}$, and solved the SDPs with Mosek interfaced by Picos (Grant et al., 2012; Sagnol, 2012).

Table 1 compares the optimal designs, obtained for D-, A- and E-criteria, for both the case of fixed support points (Section 2.4) and optimal support points over T (Section 2.5). We observe that the D-optimal design is in good agreement with the local designs presented by Atkinson et al. (2007, pag. 270). The local designs were determined for a singleton Θ employing an exchange algorithm which does not require the discretization of the time domain, and are consistently based on 4 support points. Our designs are based on 7, and 6 support points, respectively, which is consistent with the trend observed by several authors, that minmax and Bayesian designs tend to have more support points than local designs (Chaloner and Larntz, 1989). The increase of the number of support points occurs to handle the larger uncertainty caused by broadening the parameters domain. The sampling instants are similar for all designs, and the $D-$optimality criterion produces a design without the point $t = t^{\max}$ which has low weight for $A-$ and $E-$optimal designs. For the case of fixed support points, the optimal design was found after a single iteration for all three criteria. The reason is that the function $\boldsymbol{\theta} \to \Phi[\mathcal{M}(\boldsymbol{w}^*, \boldsymbol{\theta})]$ seems to exhibit a concave behaviour, so that its minima are at the corners of the region Θ. For example, the *answering set* for minmax $D-$optimality over $\mathbb{T}$ is $V_\Theta(\xi^*) = \{(\frac{1}{2}, \frac{1}{10}, 2, 2), (\frac{1}{2}, \frac{1}{2}, 2, 1), (\frac{1}{2}, \frac{1}{2}, 2, 2)\}$.

Figure 1 displays the evolution of the function $h_{\boldsymbol{\gamma}}(t)$ with the iterations of the modified version of Algorithm 1. We see that as support points are added, the

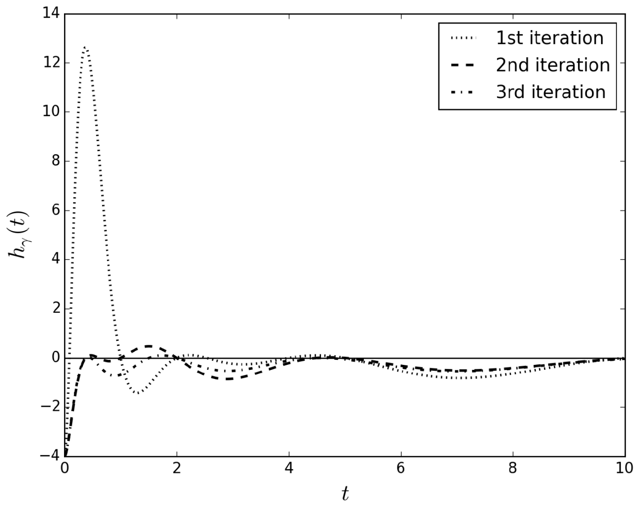

Figure 1: Evolution of $h_{\boldsymbol{\gamma}}(t)$ for $D-$optimality.

upper bound of h_γ is pushed toward 0. Our algorithm was also tested with the logistic model — a nonlinear algebraic model commonly used for benchmark testing — and the results were in agreement with those obtained with other algorithms.

4 Conclusions

We propose a robust minmax SDP formulation for finding the optimal design of experiments for dynamic models. Our approach relies on the discretization of time domain, and subsequent construction of generalized FIM for a sample of parameter combinations. The minmax optimal design problem is solved employing convex optimization techniques. To prevent suboptimal solutions due to the small size of the sample, we iterate to add the worst parameter combinations in the sample, until a convergence condition is satisfied. A small modification of the algorithm allows one to identify the optimal support points of the minmax design. The algorithm is tested for a dynamic model for two consecutive reactions, and the results compare well with earlier references.

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