Bounds on Reachable Sets Using Ordinary Differential Equations with Linear Programs Embedded ⋆

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Abstract: This work considers the computation of time-varying enclosures of the reachable sets of nonlinear control systems via the solution of an initial value problem in ordinary differential equations (ODEs) with linear programs (LPs) embedded. To ensure the numerical tractability of such a formulation, the properties of the ODEs with LPs embedded are discussed including existence and uniqueness of the solutions of the initial value problem in ODEs with LPs embedded. This formulation is then applied to the computation of rigorous componentwise time-varying bounds on the states of a nonlinear control system. The bounding theory used in this work exploits physical information to yield tight bounds on the states; this work develops a new implementation of this theory. Finally, the tightness of the bounds are demonstrated for a model of a reacting chemical system with uncertain rate parameters.

Keywords: reachable states; invariants; uncertain dynamic systems

1. INTRODUCTION

The problem of interest is the computation of time-varying enclosures of the reachable sets of the initial value problem (IVP)

$$\begin{aligned} \dot{\mathbf{y}}(t, \mathbf{u}, \mathbf{y}_0) &= \mathbf{g}(t, \mathbf{u}(t), \mathbf{y}(t, \mathbf{u}, \mathbf{y}_0)) \\ \mathbf{y}(t_0, \mathbf{u}, \mathbf{y}_0) &= \mathbf{y}_0, \end{aligned} \tag{1}$$

where $\mathbf{u}$ and $\mathbf{y}_0$ take values in some set of permissible controls and initial conditions, respectively. Using a bounding theory recently developed in Scott and Barton [2013], this work demonstrates that tight component-wise upper and lower bounds, called state bounds, can be computed by solving numerically a related IVP depending on parametric linear programs. To this end, this work also analyzes the IVP in ordinary differential equations (ODEs) with parametric linear programs (LPs) "embedded." The fundamental nature of "ODEs with LPs embedded" is an IVP in ODEs, where the vector field depends on the optimal objective values of parametric LPs that are in turn parametrized in the right-hand side of their constraints and/or objective functions by the differential states. The LPs are then said to be "embedded".

Reachability analysis refers to estimating the set of possible states that a dynamic system may achieve for a range of parameter values or controls. This is an important task in state and parameter estimation (Jaulin [2002], Raïssi et al. [2004], Singer et al. [2006]), uncertainty propagation (Harrison [1977]), safety verification and quality assurance (Lin and Stadtherr [2008], Huang et al. [2002]), and as well global dynamic optimization (Singer and Barton [2006b]). This problem traces back as far as the work in Bertsekas and Rhodes [1971], however some of the more recent applicable references are Althoff et al. [2008], Lin and Stadtherr [2007], Mitchell et al. [2005], Singer and Barton [2006a]. Meanwhile, the goal of this work is to introduce a new implementation of the theory developed in Scott and Barton [2013]. This theory relies on differential inequalities, which in essence yields an IVP derived from (1) but involving parametric optimization problems. The implementation in Scott and Barton [2013] uses interval analysis to estimate the solutions of these optimization problems. This work will construct linear programs to estimate the solutions of the necessary optimization problems.

The rest of the article is as follows. Section 2 introduces notation and establishes the formal problem statement concerning the reachable set estimation. Section 3 considers various aspects of ODEs with LPs embedded: Section 3.1 states a Lipschitz continuity result concerning parametric linear programs; Section 3.2 discusses existence and uniqueness of solutions of ODEs with LPs embedded; Section 3.3 considers potential methods for the numerical solution of ODEs with LPs embedded. Section 4 returns to the state bounding problem and demonstrates that estimates of the reachable set can be obtained from the solution of an IVP in ODEs with LPs embedded. Section 5 applies this formulation to calculate state bounds for a reacting chemical system.

2. PRELIMINARIES AND PROBLEM STATEMENT

For vectors $\mathbf{v}, \mathbf{w} \in \mathbb{R}^n$, the notation $\mathbf{v} \leq \mathbf{w}$ means that the inequality holds componentwise. Thus, given $\mathbf{v} \leq \mathbf{w}$, let $[\mathbf{v}, \mathbf{w}] = [v_1, w_1] \times \cdots \times [v_n, w_n]$ be an interval in $\mathbb{R}^n$. A vector of ones and a vector of zeros will be denoted $\mathbf{1}$ and $\mathbf{0}$, respectively. A set-valued mapping S from the set X to the set of subsets of Y is denoted $S : X \rightrightarrows Y$. For

⋆ This work was funded by Novartis Pharmaceuticals as part of the Novartis-MIT Center for Continuous Manufacturing.
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a measurable interval $T \subset \mathbb{R}$, let $L^1(T)$ denote the set of Lebesgue-integrable functions $u : T \to \mathbb{R}$. Let $(L^1(T))^n$ denote the set of vector-valued functions $\mathbf{u} : T \to \mathbb{R}^n$ for which each of the components $u_i \in L^1(T)$.

The formal problem statement is as follows. Given $[t_0, t_f] = T$, compact $U \subset \mathbb{R}^{n_u}$ and compact $Y_0 \subset \mathbb{R}^{n_y}$, one wishes to compute functions $\mathbf{y}^L, \mathbf{y}^U : T \to \mathbb{R}^{n_y}$ such that $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in [\mathbf{y}^L(t), \mathbf{y}^U(t)]$, $\forall (t, \mathbf{u}, \mathbf{y}_0) \in T \times \mathcal{U} \times Y_0$, where $\mathcal{U} = \{\mathbf{u} \in (L^1(T))^{n_u} : \mathbf{u}(t) \in U,\ a.e.\ t \in T\}$ and $\mathbf{y}$ is a solution of

$$\begin{aligned} &\dot{\mathbf{y}}(t, \mathbf{u}, \mathbf{y}_0) = \mathbf{g}(t, \mathbf{u}(t), \mathbf{y}(t, \mathbf{u}, \mathbf{y}_0)) \quad a.e.\ t \in T, \\ &\mathbf{y}(t_0, \mathbf{u}, \mathbf{y}_0) = \mathbf{y}_0. \end{aligned} \tag{2}$$

Such a $\mathbf{y}^L$ and $\mathbf{y}^U$ are called state bounds, as in Scott and Barton [2013]; the intervals $[\mathbf{y}^L(t), \mathbf{y}^U(t)]$ can also be thought of as enclosures of the reachable sets of the ODE system (2).

3. ODES WITH EMBEDDED LPS

To introduce the initial value problem in ODEs with LPs embedded, let $D_t \subset \mathbb{R}$, $D_x \subset \mathbb{R}^{n_x}$ and $D_q \subset \mathbb{R}^{n_q}$ be given nonempty sets. Let $\mathbf{f} : D_t \times D_x \times D_q \to \mathbb{R}^{n_x}$, and for $k \in \{1, \ldots, n_q\}$ let $\mathbf{b}_k : D_x \to \mathbb{R}^{m_k}$, $\mathbf{A}_k \in \mathbb{R}^{m_k \times n_k}$, $I_k = \{1, \ldots, p_k\}$, $\mathbf{c}_k^i : D_t \times D_x \to \mathbb{R}^{n_k}$, and $h_k^i : D_t \times D_x \to \mathbb{R}$ for $i \in I_k$, be given.

Now, make the following definitions. For $k \in \{1, \ldots, n_q\}$, let

$$\begin{aligned} P_k(\boldsymbol{\beta}) &\equiv \{\mathbf{v} \in \mathbb{R}^{n_k} : \mathbf{A}_k \mathbf{v} = \boldsymbol{\beta}, \mathbf{v} \geq \mathbf{0}\}, \\ F_k &\equiv \{\boldsymbol{\beta} \in \mathbb{R}^{m_k} : P_k(\boldsymbol{\beta}) \neq \varnothing\}, \\ K &\equiv \bigcap_{i=1}^{n_q} \mathbf{b}_k^{-1}(F_k) \subset D_x. \end{aligned}$$

The following assumption simplifies the analysis of the problem and naturally occurs in the application of ODEs with LPs embedded.

Assumption 1. For each $k \in \{1, \ldots, n_q\}$ and $\boldsymbol{\beta} \in F_k$, $P_k(\boldsymbol{\beta})$ is bounded:

$$\sup_{\mathbf{v} \in P_k(\boldsymbol{\beta})} \|\mathbf{v}\| < +\infty, \forall \boldsymbol{\beta} \in F_k.$$

Consequently it is clear that the functions $\widehat{q}_k : F_k \times \mathbb{R}^{p_k n_k} \times \mathbb{R}^{p_k} \to \mathbb{R}$ given by

$$\begin{aligned} \widehat{q}_k(\boldsymbol{\beta}, \boldsymbol{\gamma}_1, \ldots, \boldsymbol{\gamma}_{p_k}, \boldsymbol{\eta}) = \min_{\mathbf{v} \in \mathbb{R}^{n_k}} \max_{i \in I_k} &\left\{\boldsymbol{\gamma}_i^{\mathrm{T}} \mathbf{v} + \eta_i\right\} \\ \text{s.t. } \mathbf{A}_k \mathbf{v} &= \boldsymbol{\beta}, \\ \mathbf{v} &\geq \mathbf{0}, \end{aligned} \tag{3}$$

are well defined for $k \in \{1, \ldots, n_q\}$. Letting

$$\mathbf{c}_k : D_t \times D_x \ni (t, \mathbf{z}) \mapsto (\mathbf{c}_k^1(t, \mathbf{z}), \ldots, \mathbf{c}_k^{p_k}(t, \mathbf{z})) \in \mathbb{R}^{p_k n_k}$$

and

$$\mathbf{h}_k : D_t \times D_x \ni (t, \mathbf{z}) \mapsto (h_k^1(t, \mathbf{z}), \ldots, h_k^{p_k}(t, \mathbf{z})) \in \mathbb{R}^{p_k},$$

one can define $\mathbf{q} : D_t \times K \to \mathbb{R}^{n_q}$ by letting its k^{th} component be given by

$$q_k : (t, \mathbf{z}) \mapsto \widehat{q}_k(\mathbf{b}_k(\mathbf{z}), \mathbf{c}_k(t, \mathbf{z}), \mathbf{h}_k(t, \mathbf{z})).$$

The focus of this section is an initial value problem in ODEs: given a $t_0 \in D_t$ and $\mathbf{x}_0 \in D_x$, we seek an interval $[t_0, t_f] = T \subset D_t$, and continuous function $\mathbf{x} : T \to D_x$ which satisfy

$$\begin{aligned} &\dot{\mathbf{x}}(t) = \mathbf{f}(t, \mathbf{x}(t), \mathbf{q}(t, \mathbf{x}(t))), \quad a.e.\ t \in [t_0, t_f], \\ &\mathbf{x}(t_0) = \mathbf{x}_0. \end{aligned} \tag{4}$$

Such a T and $\mathbf{x}$ will be called a *solution* of (4).

3.1 Parametric Optimization

This section establishes a continuity property of the parametric optimization problem that is essential for proving existence and uniqueness of the solutions of (4).

First, define the distance from a point x to a set Y in a metric space (X, d) by $d(x, Y) \equiv \inf_{y \in Y} d(x, y)$. The Hausdorff distance d_H between two sets Y, Z in the metric space (X, d) is given by

$$d_H(Y, Z) = \max\left\{\sup_{y \in Y} d(y, Z), \sup_{z \in Z} d(z, Y)\right\}.$$

The following lemma concerns a Lipschitz property of polyhedral sets with respect to perturbations of the right-hand side of the constraints. This is a well-established result in the literature (see Mangasarian and Shiau [1987]). In addition, one should note that it applies equally to polyhedra of the form $P(\boldsymbol{\beta}) = \{\mathbf{v} : \mathbf{A}\mathbf{v} \leq \boldsymbol{\beta}\}$.

Lemma 2. Let $\mathbf{A} \in \mathbb{R}^{m \times n}$, $\boldsymbol{\beta} \in \mathbb{R}^m$,

$$P(\boldsymbol{\beta}) = \{\mathbf{v} \in \mathbb{R}^n : \mathbf{A}\mathbf{v} = \boldsymbol{\beta}, \mathbf{v} \geq \mathbf{0}\}, \tag{5}$$

and

$$F = \{\boldsymbol{\beta} \in \mathbb{R}^m : P(\boldsymbol{\beta}) \neq \varnothing\}. \tag{6}$$

Then for any norm $\|\cdot\|$, there exists $L_P \geq 0$ such that

$$d_H(P(\boldsymbol{\beta}_1), P(\boldsymbol{\beta}_2)) \leq L_P \|\boldsymbol{\beta}_1 - \boldsymbol{\beta}_2\|$$

for all $\boldsymbol{\beta}_1, \boldsymbol{\beta}_2 \in F$.

We will also require the following result concerning the local Lipschitz continuity of the functions $\widehat{q}_k$. It can be proved using Lemma 2 above and Lemma 1 in Klatte and Kummer [1985], combined with the local Lipschitz continuity of $f(\mathbf{v}, \boldsymbol{\gamma}, \boldsymbol{\eta}) = \max_{i \in I}\left\{\boldsymbol{\gamma}_i^{\mathrm{T}} \mathbf{v} + \eta_i\right\}$.

Proposition 3. Let P and F be defined as in Eqns. (5) and (6), respectively. Assume that $P(\boldsymbol{\beta})$ is bounded for all $\boldsymbol{\beta} \in F$. Let $I = \{1, \ldots, p\}$, and $\boldsymbol{\gamma}_i \in \mathbb{R}^n$ for all $i \in I$. Let $\boldsymbol{\gamma} = (\boldsymbol{\gamma}_1, \ldots, \boldsymbol{\gamma}_p) \in \mathbb{R}^{pn}$ and $\boldsymbol{\eta} = (\eta_1, \ldots, \eta_p) \in \mathbb{R}^p$. Define $\widehat{q} : F \times \mathbb{R}^{pn} \times \mathbb{R}^p \to \mathbb{R}$ by

$$\begin{aligned} \widehat{q}(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\eta}) = \min_{\mathbf{v} \in \mathbb{R}^n} \max_{i \in I} &\{\boldsymbol{\gamma}_i^{\mathrm{T}} \mathbf{v} + \eta_i\} \\ \text{s.t. } \mathbf{A}\mathbf{v} &= \boldsymbol{\beta}, \\ \mathbf{v} &\geq \mathbf{0}. \end{aligned}$$

Then $\widehat{q}$ is locally Lipschitz continuous.

3.2 Existence and Uniqueness

Sufficient conditions for the existence and uniqueness of the solutions of the IVP (4) are given. First, one should note that a solution of the IVP must satisfy $\{\mathbf{x}(t) : t \in T\} \subset K$, since otherwise $\mathbf{q}$ would not be defined. Since K may not be open, an existence result like Carathéodory's cannot be used; results from viability theory must be considered. See Aubin [1991].

An important concept from set-valued analysis that will be used is the Bouligand tangent cone $T_V(\mathbf{z})$ of a set V at $\mathbf{z} \in V$; the following notation is used:

$$\mathbf{v} \in T_V(\mathbf{z}) \iff \liminf_{h \to 0^+} \frac{d(\mathbf{z} + h\mathbf{v}, V)}{h} = 0$$

The following theorem establishes general conditions under which a solution of the IVP (4) exists.

Theorem 4. Let Assumption 1 hold. Assume:

(1) K is locally compact,
(2) D_t is open,
(3) $\mathbf{x}_0 \in K$,
(4) for all $k \in \{1, \ldots, n_q\}$, $\mathbf{b}_k$ is continuous on K and $\mathbf{c}_k$, $\mathbf{h}_k$ are continuous on $D_t \times K$,
(5) $\mathbf{f}$ is continuous,
(6) there exists $t_1 > t_0$ such that $\mathbf{q}(t, K) \subset D_q$ for all $t \in [t_0, t_1]$, and
(7) for all $t \in [t_0, t_1]$, for all $\mathbf{z} \in K$, $\mathbf{f}(t, \mathbf{z}, \mathbf{q}(t, \mathbf{z})) \in T_K(\mathbf{z})$,

then a solution of (4) exists.

Proof. The result follows almost immediately from Theorem I-2 of Haddad [1981]. Since D_t is an open subset of $\mathbb{R}$, it is locally compact, and so $D_t \times K$ is locally compact. By Proposition 3, $\mathbf{q}$ is continuous on $D_t \times K$, thus $\mathbf{f}(\cdot, \cdot, \mathbf{q}(\cdot, \cdot))$ is continuous as well. Applying Theorem I-2 of Haddad [1981], there exists $t_f \in (t_0, t_1]$ and continuous function $\mathbf{x} : [t_0, t_f] \to D_x$ which satisfies Eqn. (4).

Should a solution exist, it is fairly easy to verify its uniqueness, as established in the following theorem. Its proof relies on the construction and application of an appropriate Gronwall-like inequality; see for instance Theorem 1.1 in Ch. III of Hartman [2002].

Theorem 5. Let Assumption 1 hold. Assume a solution $T = [t_0, t_f]$, $\mathbf{x} : T \to D_x$ of IVP (4) exists. Assume for each $k \in \{1, \ldots, n_q\}$ that $\mathbf{b}_k$ is locally Lipschitz continuous on K, and that $\mathbf{c}_k$, $\mathbf{h}_k$ are continuous on $D_t \times K$. Assume for any $(\mathbf{z}, \mathbf{r}) \in K \times D_q$, there exist an open neighborhood $N(\mathbf{z}, \mathbf{r})$ of $(\mathbf{z}, \mathbf{r})$ and $a_1 \in L^1(T)$ such that

$$\|\mathbf{f}(t, \mathbf{z}_1, \mathbf{r}_1) - \mathbf{f}(t, \mathbf{z}_2, \mathbf{r}_2)\|_\infty \leq a_1(t) \|(\mathbf{z}_1, \mathbf{r}_1) - (\mathbf{z}_2, \mathbf{r}_2)\|_\infty,$$

for all $t \in T$, $(\mathbf{z}_1, \mathbf{r}_1)$, $(\mathbf{z}_2, \mathbf{r}_2) \in N(\mathbf{z}, \mathbf{r}) \cap K \times D_q$. Similarly assume for any $\mathbf{z} \in K$, $i \in \{1, 2\}$, and $k \in \{1, \ldots, n_q\}$, there exist open neighborhoods $N_k^i(\mathbf{z})$ and measurable a_k^i, $a_k^i(t) \leq c$, *a.e.* $t \in T$ for some constant c, such that

$$\forall \mathbf{z}_1, \mathbf{z}_2 \in N_k^1(\mathbf{z}) \cap K,$$
$$\|\mathbf{c}_k(t, \mathbf{z}_1) - \mathbf{c}_k(t, \mathbf{z}_2)\|_\infty \leq a_k^1(t) \|\mathbf{z}_1 - \mathbf{z}_2\|_\infty,$$
$$\forall \mathbf{z}_1, \mathbf{z}_2 \in N_k^2(\mathbf{z}) \cap K,$$
$$\|\mathbf{h}_k(t, \mathbf{z}_1) - \mathbf{h}_k(t, \mathbf{z}_2)\|_\infty \leq a_k^2(t) \|\mathbf{z}_1 - \mathbf{z}_2\|_\infty,$$

for all $t \in T$. Then $\mathbf{x}$ is the unique continuous function on T satisfying Eqn. (4).

3.3 Numerical Solution

First, it is shown that the parametric optimization problems (3) can be reformulated as LPs. For $\boldsymbol{\gamma}^k \in \mathbb{R}^{p_k n_k}$, let a partitioning of its components be $\boldsymbol{\gamma}^k = (\boldsymbol{\gamma}_1, \ldots, \boldsymbol{\gamma}_{p_k})$ where each $\boldsymbol{\gamma}_i \in \mathbb{R}^{n_k}$ $(i \in I_k)$. Let

$$\mathbf{M}_k(\boldsymbol{\gamma}^k) = \begin{bmatrix} \mathbf{A}_k & \mathbf{0} \; \mathbf{0} \; \mathbf{0}_{m_k \times p_k} \\ \begin{bmatrix} \boldsymbol{\gamma}_1^{\mathrm{T}} \\ \vdots \\ \boldsymbol{\gamma}_{p_k}^{\mathrm{T}} \end{bmatrix} & -\mathbf{1} \; \mathbf{1} \; \mathbf{I} \end{bmatrix},$$

a $(m_k + p_k)$ by $(n_k + 2 + p_k)$ matrix, where $\mathbf{0}_{m_k \times p_k}$ is a m_k by p_k zero matrix. Then if $\mathbf{e}_{n_k+i} \in \mathbb{R}^{n_k+2+p_k}$ is the $(n_k+i)^{th}$ unit vector for $i \in \{1, 2\}$, let $\widehat{\mathbf{e}}_k = \mathbf{e}_{n_k+1} - \mathbf{e}_{n_k+2}$, and for $\boldsymbol{\beta}_k \in \mathbb{R}^{m_k}$, $\boldsymbol{\eta}_k \in \mathbb{R}^{p_k}$ let

$$\begin{aligned} \widehat{q}_k(\boldsymbol{\beta}_k, \boldsymbol{\gamma}^k, \boldsymbol{\eta}_k) = \min_{\mathbf{v} \in \mathbb{R}^{n_k+2+p_k}} \; & \widehat{\mathbf{e}}_k^{\mathrm{T}} \mathbf{v} \\ \text{s.t. } & \mathbf{M}_k(\boldsymbol{\gamma}^k) \mathbf{v} = \begin{bmatrix} \boldsymbol{\beta}_k \\ -\boldsymbol{\eta}_k \end{bmatrix} = \widehat{\boldsymbol{\beta}}_k, \\ & \mathbf{v} \geq \mathbf{0}. \end{aligned} \quad (7)$$

The so-called matrix case of parametric linear programming results when reformulating the embedded optimization problem as a LP. In general, this kind of parametric dependence is intractable, but considering the origin of the reformulation, one can show that in fact this specific problem can be handled in a fairly efficient way.

First, a basis $B_k \subset \{1, \ldots, n_k + 2 + p_k\}$ is an index set which describes a vertex of the feasible set of a LP. For the LP (7), a basis will have $m_k + p_k$ elements, and so given a matrix $\mathbf{M} \in \mathbb{R}^{(m_k+p_k) \times (n_k+2+p_k)}$, let $\mathbf{M}_{B_k}$ be the square submatrix formed by taking the columns of $\mathbf{M}$ which correspond to elements of B_k, called a basis matrix. Similarly, given a vector $\mathbf{v}$, let $\mathbf{v}_{B_k} \in \mathbb{R}^{m_k+p_k}$ be defined by taking the components of $\mathbf{v}$ which correspond to elements of B_k. Next, under Assumption 1, it follows that the embedded optimization problems always have solutions when they are feasible. Thus, the reformulated problems must also have solutions, and this implies that there exist bases which each describe a vertex which is optimal for the reformulated problems. These bases are called optimal bases. To determine if a basis is optimal, the corresponding basis matrix $\mathbf{M}_{k,B_k}(\boldsymbol{\gamma}^k)$ for (7) must satisfy the algebraic conditions

$$(\mathbf{M}_{k,B_k}(\boldsymbol{\gamma}^k))^{-1} \widehat{\boldsymbol{\beta}}_k \geq \mathbf{0}, \quad (8)$$

$$\widehat{\mathbf{e}}_k^{\mathrm{T}} - \widehat{\mathbf{e}}_{k,B_k}^{\mathrm{T}} (\mathbf{M}_{k,B_k}(\boldsymbol{\gamma}^k))^{-1} \mathbf{M}_k(\boldsymbol{\gamma}^k) \geq \mathbf{0}^{\mathrm{T}}, \quad (9)$$

referred to as primal and dual feasibility, respectively. When solving the LPs with the simplex algorithm, the algorithm can be "warm-started" by providing a basis which is either primal or dual feasible; the algorithm terminates much more quickly than if it was cold-started (if it had to go through Phase I first).

Thus, it is desirable to know, given an optimal basis B_k, whether the left-hand side of the inequality in either of (8) or (9) may be continuous on an open set of $(\boldsymbol{\beta}_k, \boldsymbol{\gamma}^k, \boldsymbol{\eta}_k)$. If this is the case, then in the course of numerical integration of (4), a given optimal basis B that satisfies either (8) and/or (9) with strict inequality will remain primal and/or dual feasible for some finite amount of time (assuming that the functions $\mathbf{c}_k$, $\mathbf{b}_k$, $\mathbf{h}_k$ are continuous). Consequently, for many steps in the integration routine one can warm-start the simplex algorithm to solve the LPs. This will speed up the solution time immensely. The number of steps where a basis is unavailable to warm-start simplex may be small relative to the overall number of steps taken.

So to see this, one can use Cramer's rule; see §4.4 of Strang [2006]. For $\mathbf{M} \in \mathbb{R}^{n\times n}$, $\mathbf{d} \in \mathbb{R}^n$, the vector $\mathbf{v} = \mathbf{M}^{-1}\mathbf{d}$ is given componentwise by

$$v_j = \frac{\det(\mathbf{N}_j)}{\det(\mathbf{M})},$$

where $\mathbf{N}_j$ is the matrix formed by replacing the j^{th} column of $\mathbf{M}$ with $\mathbf{d}$. Since the determinant of a matrix is continuous with respect to the entries of the matrix, it is a simple application of Cramer's rule to see that the left-hand side of the inequalities (8) and (9) are continuous on the set of those $\boldsymbol{\gamma}^k$ such that $\mathbf{M}_{k,B_k}(\boldsymbol{\gamma}^k)$ is invertible. Further, the set of those $\boldsymbol{\gamma}^k$ such that $\mathbf{M}_{k,B_k}(\boldsymbol{\gamma}^k)$ is invertible is an open set noting that it is the preimage of $(-\infty, 0) \cup (0, +\infty)$, an open set, under the continuous mapping $\det(\mathbf{M}_{k,B_k}(\cdot))$. Consequently, the "straightforward" method of solving the IVP (4) numerically by using a LP solver to evaluate the functions $\mathbf{q}$ in the derivative evaluator of a numerical integration routine can be fairly efficient.

4. APPLICATION TO STATE BOUNDING

An application of the IVP (4) is to the computation of state bounds for the control system (2). Sufficient conditions for two absolutely continuous functions to constitute state bounds of (2) are established in Scott and Barton [2013]. That paper also addresses how one can leverage an invariant set to reduce the state bound overestimation. An invariant set $G \subset \mathbb{R}^{n_y}$ is a rough enclosure of the solutions of (2): $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in G$, $\forall (t, \mathbf{u}, \mathbf{y}_0) \in T \times \mathcal{U} \times Y_0$. Depending on the dynamics, this may come from physical arguments, such as conservation of mass. When the ODEs (2) are the dynamics of a chemical kinetics model, one can often determine a convex polyhedral G (Scott and Barton [2010]).

For the rest of this section assume there is a convex polyhedral set G that is an invariant set for the solutions of (2), and that U is a compact convex polyhedron. Let $\mathbb{KR}_P^{n_y}$ denote the set of nonempty compact convex polyhedra in $\mathbb{R}^{n_y}$. Let $P_i^L, P_i^U : \mathbb{KR}_P^{n_y} \to \mathbb{KR}_P^{n_y}$ be given by

$$P_i^L(\widehat{P}) = \left\{\mathbf{z} \in \widehat{P} : z_i = \min\{\zeta_i : \boldsymbol{\zeta} \in \widehat{P}\}\right\},$$
$$P_i^U(\widehat{P}) = \left\{\mathbf{z} \in \widehat{P} : z_i = \max\{\zeta_i : \boldsymbol{\zeta} \in \widehat{P}\}\right\}.$$

Consider the system of ODEs

$$\begin{aligned} \dot{y}_i^L(t) = \min_{(\mathbf{p},\mathbf{z})} \; & g_i^{cv}(t, \mathbf{p}, \mathbf{z}, \mathbf{y}^L(t), \mathbf{y}^U(t)) \\ \text{s.t. } & \mathbf{p} \in U, \\ & \mathbf{z} \in P_i^L\left([\mathbf{y}^L(t), \mathbf{y}^U(t)] \cap G\right), \\ \dot{y}_i^U(t) = \max_{(\mathbf{p},\mathbf{z})} \; & g_i^{cc}(t, \mathbf{p}, \mathbf{z}, \mathbf{y}^L(t), \mathbf{y}^U(t)) \\ \text{s.t. } & \mathbf{p} \in U, \\ & \mathbf{z} \in P_i^U\left([\mathbf{y}^L(t), \mathbf{y}^U(t)] \cap G\right), \end{aligned} \tag{10}$$

for $i \in \{1, \dots, n_y\}$, with initial condition that satisfies $Y_0 \subset [\mathbf{y}^L(t_0), \mathbf{y}^U(t_0)]$, where $g_i^{cv}(t, \cdot, \cdot, \mathbf{v}, \mathbf{w})$ is a convex piecewise affine underestimator of $g_i(t, \cdot, \cdot)$ on $U \times P_i^L([\mathbf{v}, \mathbf{w}] \cap G)$ and $g_i^{cc}(t, \cdot, \cdot, \mathbf{v}, \mathbf{w})$ is a concave piecewise affine overestimator of $g_i(t, \cdot, \cdot)$ on $U \times P_i^U([\mathbf{v}, \mathbf{w}] \cap G)$. It will now be shown that the solutions (if any) of (10) are state bounds for the system (2).

The result we wish to apply is Theorem 2 of Scott and Barton [2013]. To do so, one needs $D_\Omega \subset \mathbb{R}^{n_y} \times \mathbb{R}^{n_y}$ and for $i \in \{1, \dots, n_y\}$, $\Omega_i^L, \Omega_i^U : D_\Omega \to \mathbb{KR}^{n_y}$ which satisfy certain conditions. For every $i \in \{1, \dots, n_y\}$, assume

(1) For any $(\mathbf{v}, \mathbf{w}) \in \mathbb{R}^{n_y} \times \mathbb{R}^{n_y}$, if there exists $(t, \mathbf{u}, \mathbf{y}_0) \in T \times \mathcal{U} \times Y_0$ satisfying $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in [\mathbf{v}, \mathbf{w}]$ and $y_i(t, \mathbf{u}, \mathbf{y}_0) = v_i$ (respectively $y_i(t, \mathbf{u}, \mathbf{y}_0) = w_i$), then $(\mathbf{v}, \mathbf{w}) \in D_\Omega$ and $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in \Omega_i^L(\mathbf{v}, \mathbf{w})$ (respectively $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in \Omega_i^U(\mathbf{v}, \mathbf{w})$).
(2) For any $(\mathbf{v}, \mathbf{w}) \in D_\Omega$, there exists an open neighborhood $N(\mathbf{v}, \mathbf{w})$ of $(\mathbf{v}, \mathbf{w})$ and $L > 0$ such that
$$d_H(\Omega_i^L(\widehat{\mathbf{v}}, \widehat{\mathbf{w}}), \Omega_i^L(\widetilde{\mathbf{v}}, \widetilde{\mathbf{w}})) \le L(\|\widehat{\mathbf{v}} - \widetilde{\mathbf{v}}\|_\infty + \|\widehat{\mathbf{w}} - \widetilde{\mathbf{w}}\|_\infty)$$
for all $(\widehat{\mathbf{v}}, \widehat{\mathbf{w}})$, $(\widetilde{\mathbf{v}}, \widetilde{\mathbf{w}}) \in N(\mathbf{v}, \mathbf{w}) \cap D_\Omega$, and a similar statement for Ω_i^U also holds.

If one lets

$$\begin{aligned} D_\Omega &= \{(\mathbf{v}, \mathbf{w}) \in \mathbb{R}^{n_y} \times \mathbb{R}^{n_y} : [\mathbf{v}, \mathbf{w}] \cap G \neq \varnothing\}, \\ \Omega_i^L(\mathbf{v}, \mathbf{w}) &= P_i^L([\mathbf{v}, \mathbf{w}] \cap G), \\ \Omega_i^U(\mathbf{v}, \mathbf{w}) &= P_i^U([\mathbf{v}, \mathbf{w}] \cap G), \end{aligned}$$

then these conditions hold.

To see this, choose any $(\mathbf{v}, \mathbf{w}) \in D_\Omega$ and let

$$\begin{aligned} z_i^m(\mathbf{v}, \mathbf{w}) &= \min\{\zeta_i : \boldsymbol{\zeta} \in [\mathbf{v}, \mathbf{w}] \cap G\}, \\ z_i^M(\mathbf{v}, \mathbf{w}) &= \max\{\zeta_i : \boldsymbol{\zeta} \in [\mathbf{v}, \mathbf{w}] \cap G\} \end{aligned}$$

(note that $v_i \le z_i^m(\mathbf{v}, \mathbf{w}) \le z_i^M(\mathbf{v}, \mathbf{w}) \le w_i$). If there exists $(t, \mathbf{u}, \mathbf{y}_0) \in T \times \mathcal{U} \times Y_0$ such that $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in [\mathbf{v}, \mathbf{w}]$, then $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in [\mathbf{v}, \mathbf{w}] \cap G$ by definition of G, so $(\mathbf{v}, \mathbf{w}) \in D_\Omega$. Further, if $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in [\mathbf{v}, \mathbf{w}] \cap G$ and $y_i(t, \mathbf{u}, \mathbf{y}_0) = v_i$, then $z_i^m(\mathbf{v}, \mathbf{w}) \le y_i(t, \mathbf{u}, \mathbf{y}_0) = v_i \le z_i^m(\mathbf{v}, \mathbf{w})$, so it is clear that $\mathbf{y}(t, \mathbf{u}, \mathbf{y}_0) \in P_i^L([\mathbf{v}, \mathbf{w}] \cap G)$. An analogous argument gives the condition for P_i^U.

To see that the second condition holds consider the nature of the sets $P_i^L([\mathbf{v}, \mathbf{w}] \cap G)$. Since G is convex polyhedral it can be expressed as $G = \{\mathbf{z} \in \mathbb{R}^{n_y} : \mathbf{A}_G\mathbf{z} \le \mathbf{b}_G\}$ for some $\mathbf{A}_G \in \mathbb{R}^{m_g \times n_y}$ and $\mathbf{b}_G \in \mathbb{R}^{m_g}$. Thus $[\mathbf{v}, \mathbf{w}] \cap G = \{\mathbf{z} : \widetilde{\mathbf{A}}\mathbf{z} \le \widetilde{\mathbf{b}}(\mathbf{v}, \mathbf{w})\}$ where

$$\widetilde{\mathbf{A}} = \begin{bmatrix} \mathbf{A}_G \\ -\mathbf{I} \\ \mathbf{I} \end{bmatrix}, \quad \widetilde{\mathbf{b}}(\mathbf{v}, \mathbf{w}) = \begin{bmatrix} \mathbf{b}_G \\ -\mathbf{v} \\ \mathbf{w} \end{bmatrix}.$$

By Theorem 2.4 of Mangasarian and Shiau [1987], z_i^m is a Lipschitz continuous function on D_Ω with Lipschitz constant L_1. Finally, noting that

$$\Omega_i^L(\mathbf{v}, \mathbf{w}) = P_i^L([\mathbf{v}, \mathbf{w}] \cap G) = \{\mathbf{z} : \widetilde{\mathbf{A}}\mathbf{z} \le \widetilde{\mathbf{b}}(\mathbf{v}, \mathbf{w}), z_i \le z_i^m(\mathbf{v}, \mathbf{w}), z_i \ge z_i^m(\mathbf{v}, \mathbf{w})\},$$

by Lemma 2 there exists $L_2 > 0$ such that

$$\begin{aligned} & d_H\left(\Omega_i^L(\widehat{\mathbf{v}}, \widehat{\mathbf{w}}), \Omega_i^L(\widetilde{\mathbf{v}}, \widetilde{\mathbf{w}})\right) \\ & \le L_2\left(\|\widetilde{\mathbf{b}}(\widehat{\mathbf{v}}, \widehat{\mathbf{w}}) - \widetilde{\mathbf{b}}(\widetilde{\mathbf{v}}, \widetilde{\mathbf{w}})\|_\infty + |z_i^m(\widehat{\mathbf{v}}, \widehat{\mathbf{w}}) - z_i^m(\widetilde{\mathbf{v}}, \widetilde{\mathbf{w}})|\right) \\ & \le L_2\big(\|\widehat{\mathbf{v}} - \widetilde{\mathbf{v}}\|_\infty + \|\widehat{\mathbf{w}} - \widetilde{\mathbf{w}}\|_\infty + \\ & \qquad L_1(\|\widehat{\mathbf{v}} - \widetilde{\mathbf{v}}\|_\infty + \|\widehat{\mathbf{w}} - \widetilde{\mathbf{w}}\|_\infty)\big) \\ & \le L_2(1 + L_1)(\|\widehat{\mathbf{v}} - \widetilde{\mathbf{v}}\|_\infty + \|\widehat{\mathbf{w}} - \widetilde{\mathbf{w}}\|_\infty) \end{aligned}$$

for all $(\widehat{\mathbf{v}}, \widehat{\mathbf{w}}), (\widetilde{\mathbf{v}}, \widetilde{\mathbf{w}}) \in D_\Omega$. Similar reasoning shows that the required Lipschitz condition holds for each Ω_i^U as well, thus by Theorem 2 in Scott and Barton [2013], any solutions of (10) are state bounds.

Next, note that the system (10) has the form of ODEs with LPs embedded, in the same way as the IVP (4). As noted above,

$$P_i^L([\mathbf{y}^L(t), \mathbf{y}^U(t)] \cap G) = \{\mathbf{z} : \mathbf{A}_i^L \mathbf{z} \leq \mathbf{b}_i^L(\mathbf{y}^L(t), \mathbf{y}^U(t))\}$$
$$P_i^U([\mathbf{y}^L(t), \mathbf{y}^U(t)] \cap G) = \{\mathbf{z} : \mathbf{A}_i^U \mathbf{z} \leq \mathbf{b}_i^U(\mathbf{y}^L(t), \mathbf{y}^U(t))\}$$

for some $\mathbf{A}_i^L$, $\mathbf{A}_i^U$, $\mathbf{b}_i^L$, and $\mathbf{b}_i^U$. While the functions $\mathbf{b}_i^L$, $\mathbf{b}_i^U$ are defined by optimization problems themselves, this does not complicate things. First, as was used above, $\mathbf{b}_i^L$ and $\mathbf{b}_i^U$ are Lipschitz functions on D_Ω. Then, since

$$P_i^L([\mathbf{v}, \mathbf{w}] \cap G) \neq \varnothing \iff [\mathbf{v}, \mathbf{w}] \cap G \neq \varnothing$$

for all $i \in \{1, \dots, n_y\}$ (and similarly for $P_i^U([\mathbf{v}, \mathbf{w}] \cap G)$), D_Ω must equal the set K within which the solution points $\{(\mathbf{y}^L(t), \mathbf{y}^U(t)) : t \in T\}$ must remain. Also note that D_Ω is locally compact because it is the preimage of the closed set $\{\mathbf{d} : \exists \mathbf{z} : \widetilde{\mathbf{A}}\mathbf{z} \leq \mathbf{d}\}$ under the continuous mapping $\widetilde{\mathbf{b}}$. Second, the numerical solution method is easily adapted to solve for $z_i^m(\mathbf{w}, \mathbf{w})$ and $z_i^M(\mathbf{v}, \mathbf{w})$, the values of which are used to evaluate $\mathbf{b}_i^L(\mathbf{v}, \mathbf{w})$ and $\mathbf{b}_i^U(\mathbf{v}, \mathbf{w})$, respectively.

Finally, we wish to apply the existence and uniqueness results developed in §3.2 to the problem (10). For $k \in \{1, \dots, 2n_y\}$, let $I_k = \{1, \dots, p_k\}$ and

$$\begin{aligned} &g_k^{cv}(t, \mathbf{p}, \mathbf{z}, \mathbf{v}, \mathbf{w}) = \\ &\quad \max_{i \in I_k} \{(\mathbf{c}_k^i(t, \mathbf{v}, \mathbf{w}))^{\mathrm{T}}(\mathbf{p}, \mathbf{z}) + h_k^i(t, \mathbf{v}, \mathbf{w})\}, \\ &\quad k \in \{1, \dots, n_y\}, \\ &g_{(k-n_y)}^{cc}(t, \mathbf{p}, \mathbf{z}, \mathbf{v}, \mathbf{w}) = \\ &\quad \min_{i \in I_k} \{(\mathbf{c}_k^i(t, \mathbf{v}, \mathbf{w}))^{\mathrm{T}}(\mathbf{p}, \mathbf{z}) + h_k^i(t, \mathbf{v}, \mathbf{w})\}, \\ &\quad k \in \{n_y + 1, \dots, 2n_y\}. \end{aligned}$$

A local Lipschitz continuity condition must hold for the $\mathbf{c}_k^i$ and h_k^i, as required by Thm. 5. For many functions $\mathbf{g}$ (in Eqn. (2)), this can be established by constructing the $\mathbf{c}_k^i$ and h_k^i from subgradients of a convex underestimator of g_k, for $k \in \{1, \dots, n_y\}$, by a modification of the subgradient propagation rules established in Mitsos et al. [2009]. Similarly, $\mathbf{c}_k^i$ and h_k^i can be constructed from subgradients of a concave overestimator of $g_{(k-n_y)}$, for $k \in \{n_y + 1, \dots, 2n_y\}$. However, the specifics of this construction are out of the scope of this article. It is easy to see that the rest of the hypotheses in Thm. 5 hold, letting $D_t = \mathbb{R}$, $D_x = \mathbb{R}^{2n_y}$, $D_q = \mathbb{R}^{2n_y}$,

$$\begin{aligned} q_i(t, \mathbf{v}, \mathbf{w}) = \min_{(\mathbf{p}, \mathbf{z})} \; & g_i^{cv}(t, \mathbf{p}, \mathbf{z}, \mathbf{v}, \mathbf{w}) \\ \text{s.t. } & \mathbf{p} \in U, \\ & \mathbf{z} \in P_i^L([\mathbf{v}, \mathbf{w}] \cap G), \\ q_{(i+n_y)}(t, \mathbf{v}, \mathbf{w}) = \min_{(\mathbf{p}, \mathbf{z})} \; & -g_i^{cc}(t, \mathbf{p}, \mathbf{z}, \mathbf{v}, \mathbf{w}) \\ \text{s.t. } & \mathbf{p} \in U, \\ & \mathbf{z} \in P_i^U([\mathbf{v}, \mathbf{w}] \cap G), \end{aligned}$$

and $\mathbf{f} : (t, \mathbf{v}, \mathbf{w}, \mathbf{q}(t, \mathbf{v}, \mathbf{w})) \mapsto (\mathbf{q}_1(t, \mathbf{v}, \mathbf{w}), -\mathbf{q}_2(t, \mathbf{v}, \mathbf{w}))$, where $\mathbf{q}_1 = (q_1, \dots, q_{n_y})$ and $\mathbf{q}_2 = (q_{n_y+1}, \dots, q_{2n_y})$

Meanwhile, for the IVP (10), the sufficient conditions for the existence of a solution given in Thm. 4 are trivially satisfied with the exception of Hypothesis 7. The following two assumptions, if they hold, imply Hypothesis 7.

Assumption 6. There exists $t_1 > t_0$ such that for each $t \in [t_0, t_1]$ there exists $\mathbf{z} \in [\mathbf{v}, \mathbf{w}] \cap G$ and $\mathbf{p} \in U$ such that $\mathbf{g}(t, \mathbf{p}, \mathbf{z}) \in T_G(\mathbf{z})$.

Assumption 7. If for some $(\mathbf{p}, \mathbf{z}) \in U \times [\mathbf{v}, \mathbf{w}] \cap G$ one has $\mathbf{g}(t, \mathbf{p}, \mathbf{z}) \in T_G(\mathbf{z})$, then $\mathbf{f}(t, \mathbf{v}, \mathbf{w}, \mathbf{q}(t, \mathbf{v}, \mathbf{w})) \in T_{D_\Omega}(\mathbf{v}, \mathbf{w})$.

Whether these assumptions hold for a specific class of problems (i.e. for specific instances of $\mathbf{g}$, U, Y_0, G) is a subject of future research.

5. EXAMPLE

The enzyme reaction network considered in Example 2 of Scott and Barton [2013] is used here to demonstrate the effectiveness of the system (10) in producing tight state bounds for an uncertain dynamic system. The reaction network is

$$\begin{aligned} \mathrm{A} + \mathrm{F} &\rightleftharpoons \mathrm{F:A} \rightarrow \mathrm{F} + \mathrm{A}', \\ \mathrm{A}' + \mathrm{R} &\rightleftharpoons \mathrm{R:A}' \rightarrow \mathrm{R} + \mathrm{A}. \end{aligned}$$

The dynamic equations governing the evolution of the species concentrations $\mathbf{y}(t)$ in a closed system are

$$\begin{aligned} \dot{y}_{\mathrm{F}} &= -k_1 y_{\mathrm{F}} y_{\mathrm{A}} + k_2 y_{\mathrm{F:A}} + k_3 y_{\mathrm{F:A}}, \\ \dot{y}_{\mathrm{A}} &= -k_1 y_{\mathrm{F}} y_{\mathrm{A}} + k_2 y_{\mathrm{F:A}} + k_6 y_{\mathrm{R:A}'}, \\ \dot{y}_{\mathrm{F:A}} &= k_1 y_{\mathrm{F}} y_{\mathrm{A}} - k_2 y_{\mathrm{F:A}} - k_3 y_{\mathrm{F:A}}, \\ \dot{y}_{\mathrm{A}'} &= k_3 y_{\mathrm{F:A}} - k_4 y_{\mathrm{A}'} y_{\mathrm{R}} + k_5 y_{\mathrm{R:A}'}, \\ \dot{y}_{\mathrm{R}} &= -k_4 y_{\mathrm{A}'} y_{\mathrm{R}} + k_5 y_{\mathrm{R:A}'} + k_6 y_{\mathrm{R:A}'}, \\ \dot{y}_{\mathrm{R:A}'} &= k_4 y_{\mathrm{A}'} y_{\mathrm{R}} - k_5 y_{\mathrm{R:A}'} - k_6 y_{\mathrm{R:A}'}. \end{aligned} \tag{11}$$

We wish to estimate the reachable set on $T = [0, 0.04]$ (s), with $Y_0 = \{\mathbf{y}_0 = (24, 30, 0, 0, 16, 0)\}$ (M) and rate parameters

$$\begin{aligned} &\mathbf{k} = (k_1, \dots, k_6) \in \mathcal{U}, \quad \text{with} \\ &U = [\widehat{\mathbf{k}}, 10\widehat{\mathbf{k}}], \\ &\widehat{\mathbf{k}} = (0.1, 0.033, 16, 5, 0.5, 0.3). \end{aligned}$$

A polyhedral invariant G can be determined from considering the stoichiometry of the system and other physical arguments such as mass balance; see Scott and Barton [2010] for more details. For this system, one has

$$\begin{aligned} &G = \{\mathbf{z} \in \mathbb{R}^6 : \mathbf{0} \leq \mathbf{z} \leq \bar{\mathbf{y}}, \mathbf{M}\mathbf{z} = \mathbf{M}\mathbf{y}_0\}, \quad \text{with} \\ &\mathbf{M} = \begin{bmatrix} 0 & -1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & -1 \\ 1 & -1 & 0 & 1 & -1 & 0 \end{bmatrix}, \\ &\bar{\mathbf{y}} = (20, 34, 20, 34, 16, 16). \end{aligned}$$

To get an idea of how the piecewise affine under- and overestimators of the dynamics (11) are constructed, consider the convex envelope of the bilinear term xy on some interval. The convex envelope consists of the maximum of two affine "branches". However, everywhere on the interval, either branch is a valid affine underestimator of the bilinear term, and furthermore the normal vector of the affine subspace defining a branch is Lipschitz continuous with respect to the upper and lower bounds defining the interval (Mitsos et al. [2009]).

The state bounds resulting from the solution of (10) and the interval arithmetic-based implementation used in Scott and Barton [2013] are similar; the bounds resulting from the solution of (10) are at least as tight as those in Scott and Barton [2013]. See Fig. 1. However, there are certain states which the previous implementation tended to overestimate. For those states, the system (10) is tighter, but still appears to overestimate the actual reachable set. A comparison of the two implementations for one of these pathological states is in Fig. 2.

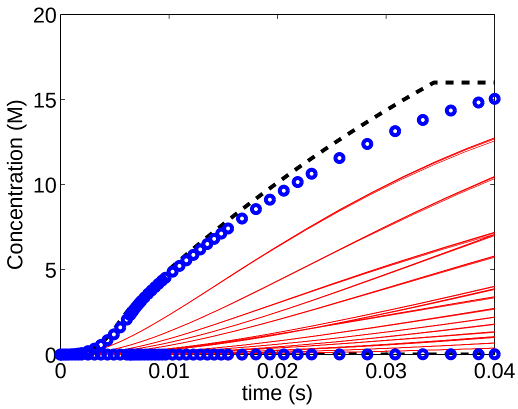

Fig. 1. State bounds for $y_{\mathrm{R:A'}}$ computed from the system of ODE with LPs embedded (10) (blue) and from the implementation in Scott and Barton [2013] (black dashed). Solutions of (11) for constant $\mathbf{k} \in \mathcal{U}$ are in red.

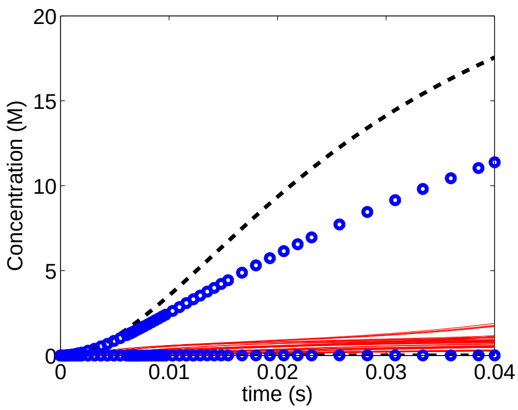

Fig. 2. State bounds for $y_{\mathrm{A'}}$ computed from the system of ODE with LPs embedded (10) (blue) and from the implementation in Scott and Barton [2013] (black dashed). Solutions of (11) for constant $\mathbf{k} \in \mathcal{U}$ are in red.

ACKNOWLEDGEMENTS

The authors wish to thank Novartis Pharmaceuticals for funding this research.

REFERENCES

Matthias Althoff, Olaf Stursberg, and Martin Buss. Reachability analysis of nonlinear systems with uncertain parameters using conservative linearization. *Proceedings of the 47th IEEE Conference on Decision and Control*, pages 4042–4048, 2008.

Jean-Pierre Aubin. *Viability Theory*. Birkhäuser, Boston, 1991.

Dimitri P. Bertsekas and Ian B. Rhodes. Recursive state estimation for a set-membership description of uncertainty. *IEEE Transactions on Automatic Control*, 16(2):117–128, April 1971.

Georges Haddad. Monotone trajectories of differential inclusions and functional differential inclusions with memory. *Israel J. Math.*, 39:83–100, 1981.

G. W. Harrison. Dynamic models with uncertain parameters. In X. J. R. Avula, editor, *Proceedings of the First International Conference on Mathematical Modeling*, volume 1, pages 295–304. University of Missouri, Rolla, 1977.

Philip Hartman. *Ordinary Differential Equations*. SIAM, Philadelphia, second edition, 2002.

H.T. Huang, C.S. Adjiman, and N. Shah. Quantitative framework for reliable safety analysis. *AICHE Journal*, 48(1):78–96, 2002.

L. Jaulin. Nonlinear bounded-error state estimation of continuous-time systems. *Automatica*, 38(6):1079–1082, 2002.

D. Klatte and B. Kummer. Stability properties of infima and optimal solutions of parametric optimization problems. *Lecture Notes in Economics and Mathematical Systems*, 255:190–229, 1985. ISSN 0075-8442.

Youdong Lin and Mark A. Stadtherr. Validated solutions of initial value problems for parametric ODEs. *Appl. Numer. Math.*, 57:1145–1162, 2007.

Youdong Lin and Mark A. Stadtherr. Fault detection in nonlinear continuous-time systems with uncertain parameters. *AIChE Journal*, 54(9):2335–2345, 2008.

O. L. Mangasarian and T. H. Shiau. Lipschitz continuity of solutions of linear inequalities, programs and complementarity problems. *SIAM J. Control Optim.*, 25(3): 583–595, 1987.

I.M. Mitchell, A.M. Bayen, and C.J. Tomlin. A time-dependent Hamilton-Jacobi formulation of reachable sets for continuous dynamic games. *IEEE Trans. Automat. Control*, 50(7):947–957, 2005.

Alexander Mitsos, Benoît Chachuat, and Paul I. Barton. McCormick-based relaxations of algorithms. *SIAM J. Optim.*, 20(2):573–601, 2009.

T. Raïssi, N. Ramdani, and Y. Candau. Set membership state and parameter estimation for systems described by nonlinear differential equations. *Automatica*, 40(10): 1771–1777, 2004.

Joseph K. Scott and Paul I. Barton. Tight, efficient bounds on the solutions of chemical kinetics models. *Computers & Chemical Engineering*, 34(5):717–731, 2010.

Joseph K. Scott and Paul I. Barton. Bounds on the reachable sets of nonlinear control systems. *Automatica*, 49:93–100, 2013.

Adam B. Singer and Paul I. Barton. Bounding the solutions of parameter dependent nonlinear ordinary differential equations. *SIAM J. Sci. Comput.*, 27(6): 2167–2182, 2006a.

Adam B. Singer and Paul I. Barton. Global optimization with nonlinear ordinary differential equations. *J. Global Optim.*, 34:159–190, 2006b.

Adam B. Singer, James W. Taylor, Paul I. Barton, and William H. Green. Global dynamic optimization for parameter estimation in chemical kinetics. *Journal of Physical Chemistry A*, 110(3):971–976, 2006.

Gilbert Strang. *Linear Algebra and its Applications*. Thomson Brooks/Cole, Belmont, CA, fourth edition, 2006.

