Parameter Synthesis using Paralleltopic Enclosure

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April 5, 2014

INTRODUCTION

PARAMETER SYNTHESIS FOR BIOLOGICAL MODELS

- Biological models contain interdependent parameters
- Parameters are determined (using nonlinear optimization) so that the model simulates the actual process
- Experimental data: incomplete and subject to measurement errors ⇒ Uncertainty in the parameter
- Our goal:
  - Analyze the behaviors of biological models with uncertain parameters
  - Synthesize parameter values corresponding to expected behaviors

A BIOLOGICAL MODEL

SIR epidemic model

- S susceptible, not sick
- I infected
- R removed
- N = S + I + R

System

- $S(k+1) = S(k) - (\beta S(k) I(k))\, r$
- $I(k+1) = I(k) + (\beta S(k) I(k) - \gamma I(k))\, r$
- $R(k+1) = R(k) + (\gamma I(k))\, r$

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Parameters

- β: contraction rate, $1/\gamma$: mean infection period

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Parameters

- β: contraction rate, $1/\gamma$: mean infection period
- $\beta = 0.34, \gamma \in [0.05, 0.07], S^0 = 80, I^0 = 20, R^0 = 0$

Query: Find the values of γ s.t. $I < 62$?

INTRODUCTION

PROBLEM

- Parametric discrete-time polynomial dynamical system

$$\mathbf{x}(k+1) = f(\mathbf{x}(k), \mathbf{p})$$

- A parameter set P
- An initial set X^0
- An unsafe set $\mathcal{F} = \{\mathbf{x} \mid g(\mathbf{x}) \geq 0\}$
- A time instant $K \in \mathbb{N}$

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Find:

- A subset $P_s \subseteq P$ s.t. from X^0, under P_s, the system does not reach $\mathcal{F}$

INTRODUCTION

ASSUMPTION

$\mathbf{x}(k+1) = f(\mathbf{x}(k), \mathbf{p})$	Vector of polynomials
$f_i(\mathbf{x}(k), \mathbf{p}) : \mathbb{R}^n \times \mathbb{R}^m \rightarrow \mathbb{R}$	Polynomial, non-linear
$g(\mathbf{x})$	Linear
$P \subseteq \mathbb{R}^m$	Polytope
$X \subseteq \mathbb{R}^n$	Parallelotope

BERNSTEIN EXPANSION

Parametric polynomial $\pi : [0,1]^n \times \mathbb{R}^m \to \mathbb{R}^n$

Power basis

$$\pi(\mathbf{x}, \mathbf{p}) = \sum_{\mathbf{i} \le \mathbf{d}} \mathbf{a_i}(\mathbf{p}) \mathbf{x^i}$$

$$\mathbf{x} \in \mathbb{R}^2, \mathbf{i} = (1,2), \mathbf{x^i} = x_1^1 x_2^2$$

Bernstein basis

$$\pi(\mathbf{x}, \mathbf{p}) = \sum_{\mathbf{i} \in I} \mathbf{b_i}(\mathbf{p}) \mathcal{B}_{\mathbf{d},\mathbf{i}}(\mathbf{x})$$

$$\mathcal{B}_{\mathbf{d},\mathbf{i}}(\mathbf{x}) = \mathcal{B}_{\mathbf{d}_1,\mathbf{i}_1}(\mathbf{x}_1) \dots \mathcal{B}_{\mathbf{d}_n,\mathbf{i}_n}(\mathbf{x}_n)$$

$$\mathbf{x} \in \mathbb{R}, \mathcal{B}_{3,1}(y) = \binom{3}{1} y^1 (1-y)^{3-1}$$

$$\mathbf{b_i}(\mathbf{p}) = \sum_{\mathbf{j} \le \mathbf{i}} \frac{\binom{\mathbf{i}}{\mathbf{j}}}{\binom{\mathbf{d}}{\mathbf{j}}} \mathbf{a_i}(\mathbf{p})$$

BERNSTEIN EXPANSION

PROPERTY

Bernstein basis

$$\pi(\mathbf{x}, \mathbf{p}) = \sum_{\mathbf{i} \in I} \mathbf{b_i}(\mathbf{p}) \mathcal{B}_{\mathbf{d},\mathbf{i}}(\mathbf{x})$$

Important property:

$$\forall \mathbf{p} \in P \, \forall \mathbf{x} \in [0,1]^n : \pi(\mathbf{x}, \mathbf{p}) \in [m^\pi, M^\pi]$$

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Efficient method for computing the Bernstein expansion

BERNSTEIN EXPANSION

GEOMETRIC PROPERTIES

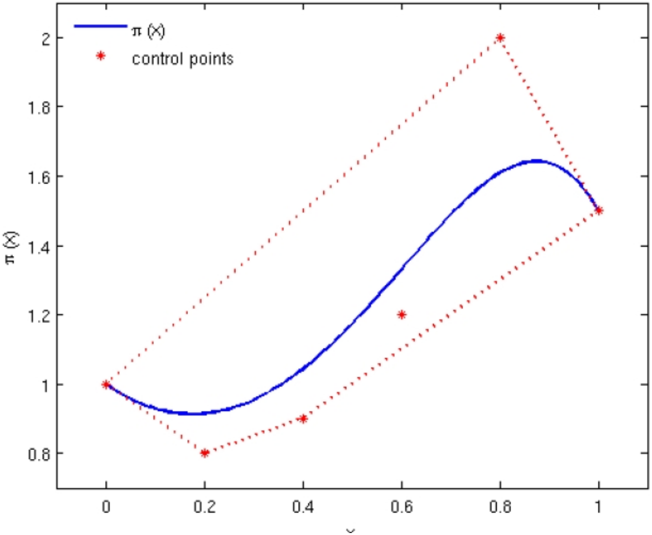

IMAGE COMPUTATION

BOX

How to compute the reach set $X' = f(X, P)$?

Algorithm:

- Map $v : [0, 1]^n \to X$
- Polynomial composition $h \leftarrow f \circ v$
- Computing the Bernstein coefficients B^h
- Computing interval bound for each dimension (m_i^h, M_i^h) for all $i = \{1, \ldots, n\}$
- $X' \leftarrow [m_1^h, M_1^h] \times \ldots \times [m_n^h, M_n^h]$

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Error can be significant

PARALLELOTOPES

- Intuitively, n-dimensional parallelograms
- Representation:

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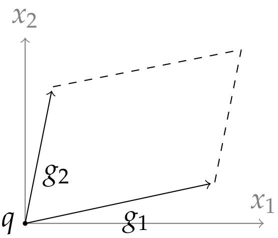
- Representation:

1) Generators

- $G = \{g_1, \ldots, g_n\}$ generators, with $g_i \in \mathbb{R}^n$
- $q \in \mathbb{R}^n$ base vertex

$$P_{gen}(q, G) = \{q + \sum_{j=1}^{n} \alpha_j g_j \mid \alpha \in \mathcal{B}^n \wedge g_j \in G\}$$



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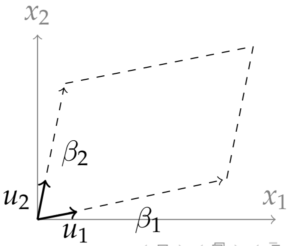
Observation

- $g_i = \beta_i u_i$
- $\beta_i \in \mathbb{R}^n$ Euclidean norm
- $u_i \in [0,1]^n$ Versor



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$$P_{gen}(q, \beta, U) = \{q + \sum_{j=1}^{n} \alpha_j \beta_j u_j \mid \alpha \in \mathcal{B}^n\}$$

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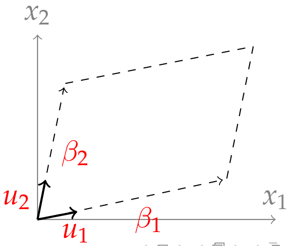

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$$P_{gen}(q, \beta, U) = \{q + \sum_{j=1}^{n} \alpha_j \beta_j u_j \mid \alpha \in \mathcal{B}^n\} \ldots \gamma_U(\alpha, q, \beta)$$

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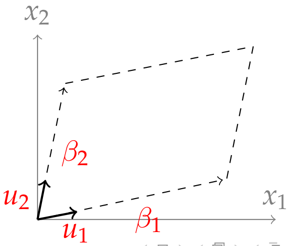

PARALLELOTOPES

- Intuitively, n-dimensional parallelograms
- Representation:

2) Constraints

- Λ directions
- d offsets

$$P_{con}(\Lambda, d) = \{x \mid \Lambda x \leq d\}$$

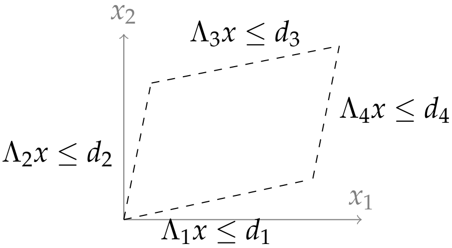

IMAGE COMPUTATION

PARALLEOTOPE

A better approximation of the reach set $X' = f(X, P)$

We fix a parallelotope:

1. $U = \{u_1, \ldots, u_n\}$ (Generator versors)
2. Λ (Template matrix)

IMAGE COMPUTATION

PARALLEOTOPE

A better approximation of the reach set $X' = f(X, P)$

We fix a parallelotope:

1. $U = \{u_1, \ldots, u_n\}$ (Generator versors)
2. Λ (Template matrix)

Algorithm:

- $h_j \leftarrow \Lambda_j f(\gamma_U(\alpha, q, \beta), p)$, for all $j = 1, \ldots, n$
- Computing the Bernstein coefficients B^{h_j}
- Computing j-th offset $d_j = \max B^{h_j}$, for all $j = 1, \ldots, n$
- $X' = \mathcal{P}_{con}(\Lambda, d)$

To iterate:

- Convert X' from constraints to generators

Parameter Synthesis

An iteration

Similarly we synthesize the parameters:

- Actual state set $\gamma_U(\alpha, q, \beta)$
- Compose the polynomial $\pi = g(f(\gamma_U(\alpha, q, \beta), p))$
- Compute $\mathbf{b}^{\pi}_{\mathbf{i}}(\mathbf{p})$
- To assure the safety property: the maximal Bernstein coefficient should be negative (LP solving)

$$\forall \mathbf{p} \in P \, \forall j \leq K \, \forall \mathbf{i} \in I^{\pi} : \mathbf{b}^{\pi}_{\mathbf{i}}(\mathbf{p}) < 0$$

PARAMETER SYNTHESIS

$$\pi_I = \Lambda_j f(\gamma_U(\alpha, q, \beta), p) \qquad \pi_S = g(f(\gamma_U(\alpha, q, \beta), p))$$

To note:

- Domain $\alpha \in [0, 1]^n \Rightarrow$ Bernstein
- Both linear in $p \Rightarrow$ LP
- Control points B^{π_I} and B^{π_S} can be computed symbolically a priori

PARAMETER SYNTHESIS

ANALYSIS

If we get $P_s = \emptyset$,
is the safe parameter set truly empty?

Observation

- Over-approximation error in $\max \mathbf{b}_i^{\pi}(\mathbf{p})$

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Possible solution

- Subdividing X^j

Parameter Synthesis

Analysis

If we get $P_s = \emptyset$,
is the safe parameter set truly empty?

Observation

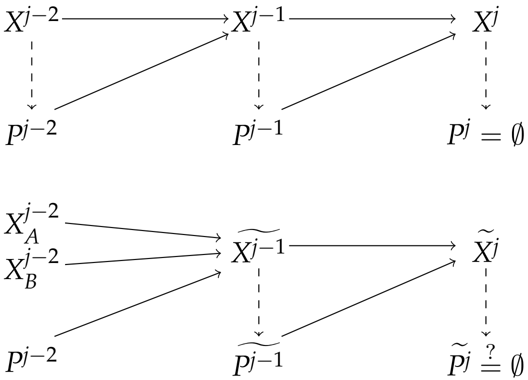
- Over-approximation error in $\max \mathbf{b}_i^{\pi}(\mathbf{p})$

Possible solution

- Subdividing X^j

Other properties: sharpness, monotonicity

PARAMETER SET REFINEMENT



SIR Model: Analysis

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- N = S + I + R
- $\beta = 0.34, \gamma \in [0.05, 0.07]$
- $q = (80, 20, 0)$

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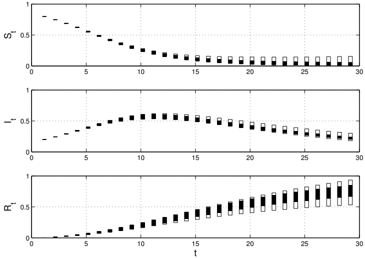
$$u_1 = (0.7, 0.7, 0) \qquad \beta_1 = 0.0014$$
$$u_2 = (-0.7, 0.7, 0) \qquad \beta_2 = 0.0014$$
$$u_3 = (0, 0, 1) \qquad \beta_3 = 0.0010$$

Query: Is there any value of γ s.t. $I < 62$?

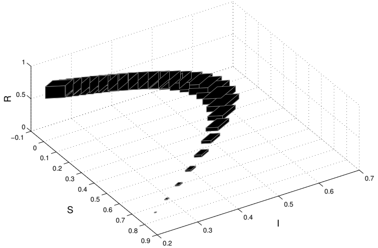
Answer: Yes $P_s = [0.670, 0.700]$

SIR MODEL

SIMULATIONS



Time evolution



Space evolution

$$g(I) = I - 62 < 0 \text{ (Computation time} \approx 40\text{s)}$$

Influenza Model

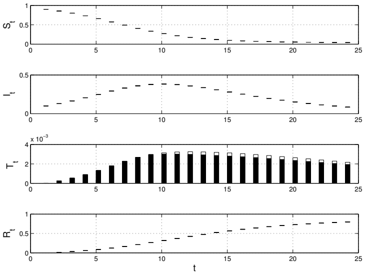
Model

- S susceptible, not sick
- I infected
- T under treatment
- R become immune

- 7 parameters
- Antiviral treatment $\tau \in [0.001, 0.002]$
- Social distancing $d \in [0.005, 0.010]$

INFLUENZA MODEL

SIMULATIONS



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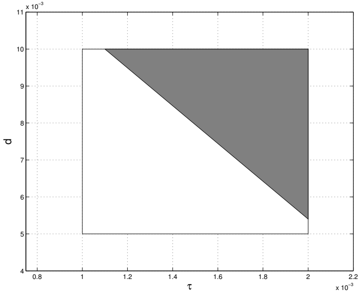

Parameter set

$$g(I) = I - 0.40 < 0 \text{ (Computation time} \approx 304\text{s)}$$

Comparison

Parelleotope VS Box

At each step:

- Parallelotopes do not need $v : [0, 1]^n \to X$
- Boxes do not need the conversion $\mathcal{P}_{gen} \to \mathcal{P}_{con}$

COMPARISON

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Let's represent a box as a parallelotope
with orthogonal generators

Model	Vars	Params	K	Box (sec.)	Paral (sec.)
SIR	3	2	30	45	28 (7)
SARS	6	4	50	2012	907 (14)

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Halved compuations time

CURRENT WORK

- Properties specified by STL
- Study of iron homeostasis in mammalian cells (TIMC, Grenoble)