Set-based parameter estimation, model falsification and uncertainty analysis using convex optimization

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Institute for Systems Theory and Automatic Control
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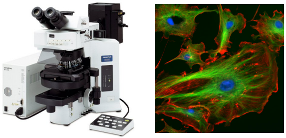
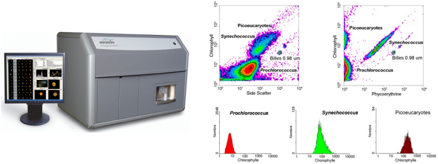
Workshop "Conclusions despite uncertainties"
Linköping, June 2011

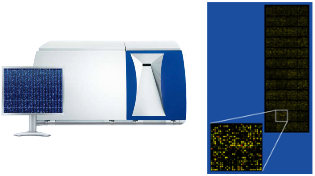
Measurement data



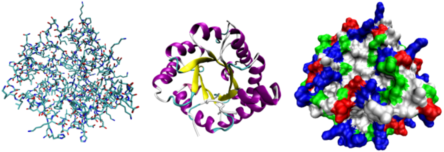
Fluorescence microscopy



Flow cytometry



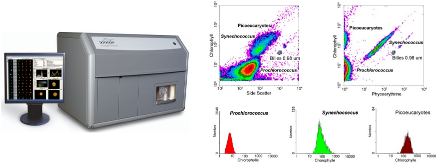
DNA and Protein microarrays
(genomics, proteomics, ...)



X-ray crystallography

Measurement data

Fluorescence microscopy



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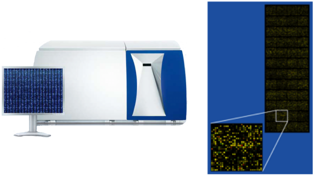

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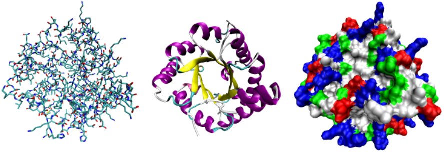


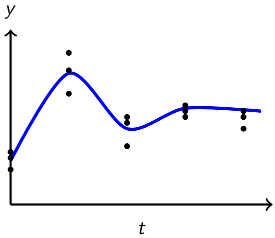
X-ray crystallography

measurement devices improved tremendously

BUT always limited and noise corrupted data!

How can measurement data be used in modeling?

Data + Estimation



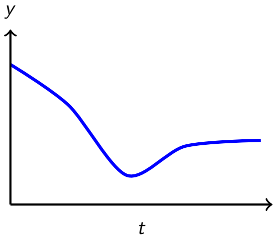
$\Rightarrow$

Model

$$\dot{x} = f(x, p, u)$$
$$y = h(x, p, u)$$

$\Rightarrow$

Prediction



Classical approach

1. Calculation of *optimal* parameter
   (e.g. least-square or maximum-likelihood)

$\Rightarrow$ *optimal* model of the process

2. Model falsification/rejection and prediction using *optimal* model

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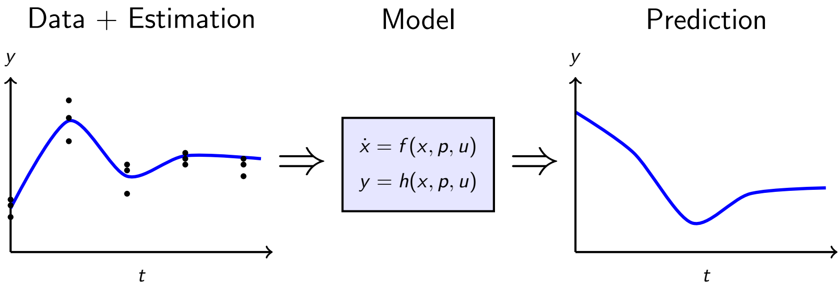

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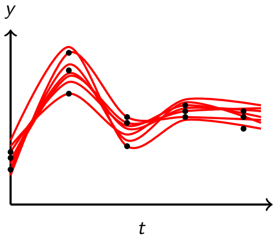
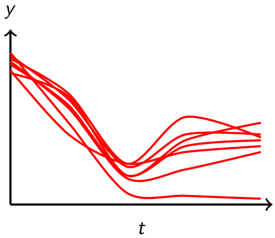
Problem: For sparse, noisy data many parameters are equally plausible.
$\Rightarrow$ How can this be taken into account?

How can measurement data be used in modeling?

Data + Estimation | Model | Prediction



$$\dot{x} = f(x, p^i, u)$$
$$y = h(x, p^i, u)$$
$$i \in \{1, \dots, N\}$$



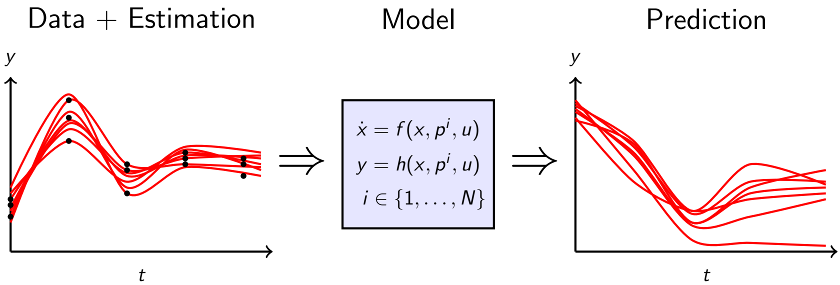
Sampling-based approach

1. Calculation of a sample of *good* parameters (e.g. Bayesian methods or bootstrapping)

$\Rightarrow$ sample of *good* models of the process

2. Model falsification/rejection and prediction using a sample of models

How can measurement data be used in modeling?



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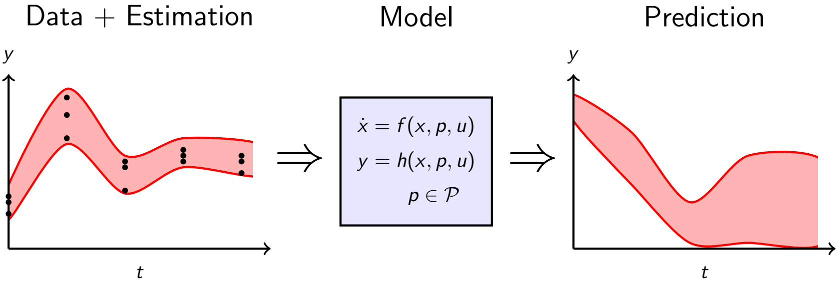
Advantage: More robust decision making.
Problem: The usage of a finite sample makes model falsification difficult.

How can measurement data be used in modeling?



Set-based approach [Jaulin2001]

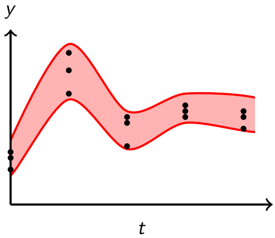
1. Calculation of the set of *consistent* parameters
   (e.g. interval arithmetics, SOS, or convex optimization)

$\Rightarrow$ all *consistent* models of the process (with a certain structure)

2. Model falsification/rejection and prediction using the set of models

How can measurement data be used in modeling?

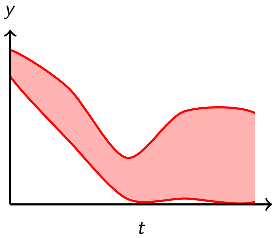
Data + Estimation | Model | Prediction



$\Rightarrow$

$$\dot{x} = f(x, p, u)$$
$$y = h(x, p, u)$$
$$p \in \mathcal{P}$$

$\Rightarrow$



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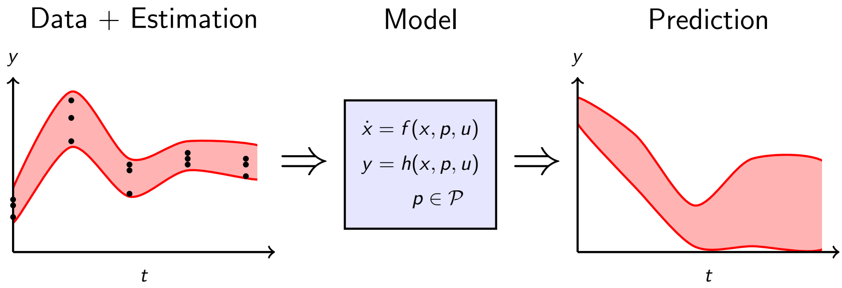
Advantage: Model falsification is very easy.
Problem: Analysis is computationally demanding.

How can measurement data be used in modeling?



measurement + measurement uncertainties

⇓

model + model uncertainties

⇓

prediction + prediction uncertainties

Goal of this talk: Illustration of the usage of different methods for the analysis of model and prediction uncertainties!

Outline

1. Introduction

2. Parameter estimation and model falsification

3. Steady-state uncertainty

4. Summary/Conclusion

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1 Introduction

2 Parameter estimation and model falsification

3 Steady-state uncertainty

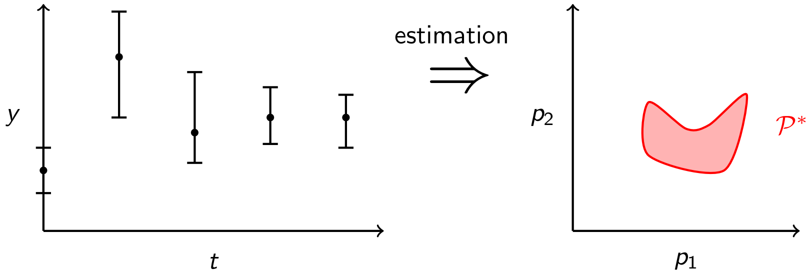
4 Summary/Conclusion

Introduction: Set-based parameter estimation

Problem of set-based parameter estimation

Given a set of measurement data $\bar{y}(t_k) = y(t_k) + \epsilon(t_k)$ and bounds for the measurement noise $\epsilon(t_k)$, determine the set of all parameters, which could have generated the measurement data.

$$\Rightarrow \text{set of consistent parameters } \mathcal{P}^*$$



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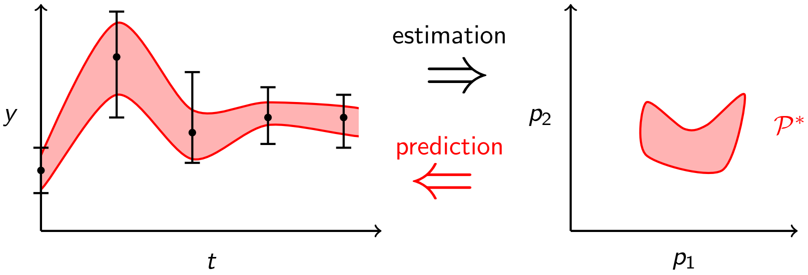

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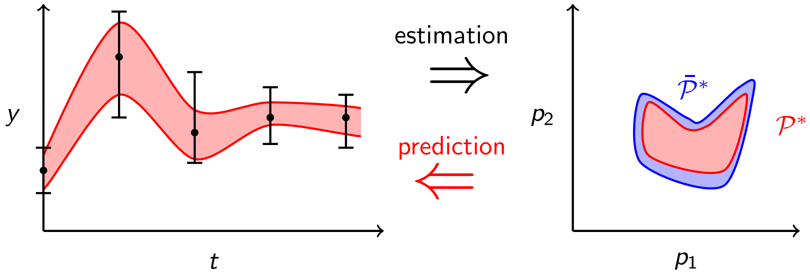

Problem: It is impossible to compute $\mathcal{P}^*$ precisely!
$\Rightarrow$ Computation of outer approximation $\bar{\mathcal{P}}^* \supseteq \mathcal{P}^*$

Introduction: Set-based parameter estimation

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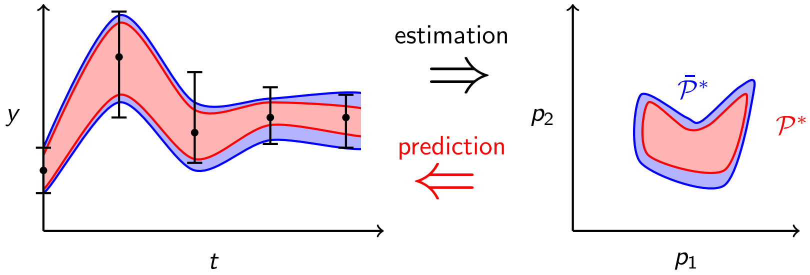


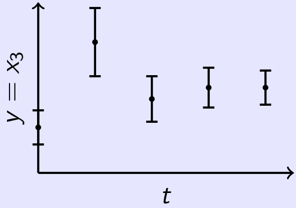
Why is the outer approximation $\bar{\mathcal{P}}^*$ useful?

Usage of $\bar{\mathcal{P}}^*$ for model falsification

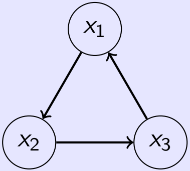
By definition the set of consistent parameters $\mathcal{P}^*$ contains all parameter p of a model which can explain the measurement data.

$\Rightarrow$ $\bar{\mathcal{P}}^*$ contains all parameter which can describe the data!

Let's assume we have two models and the corresponding sets $\bar{\mathcal{P}}^*$:

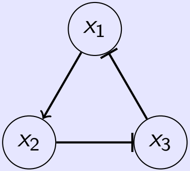


Model A



$\rightarrow \bar{\mathcal{P}}^* = \emptyset$

Model B



$\rightarrow \bar{\mathcal{P}}^* \neq \emptyset$

$\Rightarrow$ Model A is falsified as there are no consistent parameters.

$\Rightarrow$ Model B may be able to reproduce the data.

Usage of $\bar{\mathcal{P}}^*$ for model falsification

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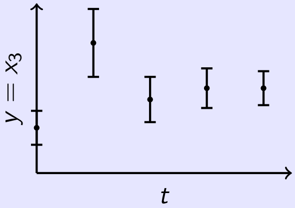

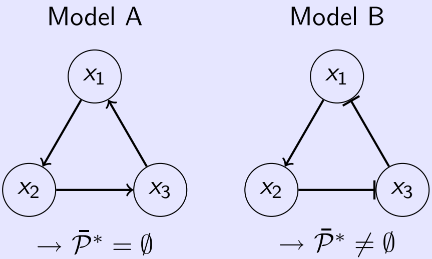

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Calculation of $\bar{\mathcal{P}}^*$?

Problem setup of set-based parameter estimation

System class

We consider nonlinear discrete time systems,

$$x^{(k+1)} = F(x^{(k)}, p), \quad x^{(0)} = x_0$$
$$y^{(k)} = H(x^{(k)}, p),$$

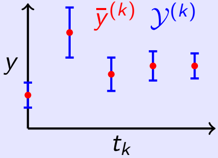
in which $x^{(k)} \in \mathbb{R}^n$ is the state, $y^{(k)} \in \mathbb{R}^m$ is the output, $p \in \mathbb{R}^q$ the vector of unknown parameters, and F and H are rational functions.

F can be obtained by discretizing a continuous process ($\rightarrow$ ODE solver).

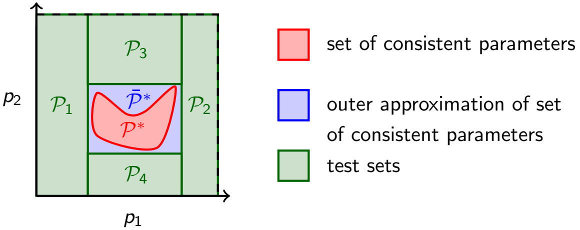
Measurement data

$$\bar{y}^{(k)} = y^{(k)} + \epsilon^{(k)}, \quad k \in \{1, \dots, N\},$$

in which $y^{(k)} \in \mathbb{R}^m$ is the measured noise corrupted output, and $\epsilon^{(k)} \in \mathbb{R}^m$ is the bounded measurement noise. $\Rightarrow y^{(k)} \in \mathcal{Y}^{(k)}$



Computation of $\bar{\mathcal{P}}^*$ via a series of feasibility problems



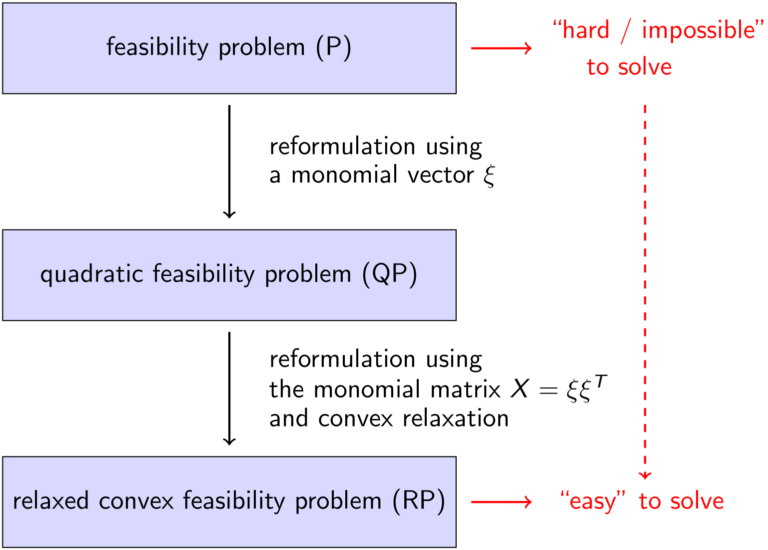
Feasibility problem [Hasenauer2010a]

- verification that a set $\mathcal{P}_i$ cannot contain consistent parameters
- feasibility problem for test set $\mathcal{P}_i$:

$$
(\mathrm{P}):\begin{cases}\text{find} & p \in \mathcal{P}_i,\; x^{(k)} \in \mathcal{X},\; y^{(k)} \in \mathcal{Y}^{(k)} \\ \text{subject to} & x^{(k+1)} = F(x^{(k)}, p),\; \forall k \quad \rightarrow \text{dynamics} \\ & y^{(k)} = H(x^{(k)}, p),\; \forall k \quad \rightarrow \text{measurement}\end{cases}
$$

(P) infeasible $\Longleftrightarrow$ $\mathcal{P}_i$ does not contain consistent parameters

Summary: Reformulation of the feasibility problem



Quadratic decomposition

Reformulation of dynamics and measurement

- Monomial vector: $\xi^T = (1, p, x^{(k)}, y^{(k)}, p \cdot x^{(k)}, \dots) \in \mathbb{R}^\kappa$
- Dynamics/Measurement:

$$0 = x^{(k+1)} - F(x^{(k)}, p) := G(x^{(k+1)}, x^{(k)}, p)$$

$$\Rightarrow 0 = G_i(x^{(k+1)}, x^{(k)}, p) = \xi^T Q_i \xi, \quad \forall i$$

Quadratic feasibility problem

$$(\mathrm{QP}) : \begin{cases} \text{find} & \xi \in \mathbb{R}^\kappa & \\ \text{subject to} & \xi^T Q_i \xi = 0 & i = 1, \dots, c \\ & B\,\xi \geq 0 & \\ & \xi_1 = 1 & \end{cases}$$

in which $p \in \mathcal{P}_i$, $x^{(k)} \in \mathcal{X}^{(k)}$, $y^{(k)} \in \mathcal{Y}^{(k)} \iff B(\mathcal{P}_i, \mathcal{X}^{(k)}, \mathcal{Y}^{(k)})\,\xi \geq 0$

(QP) infeasible $\iff$ (P) infeasible

Convex relaxation

Feasibility problem

- Symmetric monomial matrix: $X = \xi\xi^T$
- Feasibility problem in X:

$$(\widetilde{\mathrm{QP}}) : \begin{cases} \text{find} & X \in \mathcal{S}^\kappa \\ \text{subject to} & \mathrm{tr}(Q_i X) = 0 \quad i = 1, \ldots, c \\ & BXe_1 \geq 0 \\ & \mathrm{tr}(e_1 e_1^T X) = 1 \\ & \mathrm{rank}(X) = 1 \\ & X \succcurlyeq 0 \end{cases}$$

in which $e_1 = [1,\ 0,\ \ldots,\ 0]^T$

Convex relaxation

Relaxed feasibility problem

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in which $e_1 = [1,\ 0,\ \dots,\ 0]^T$

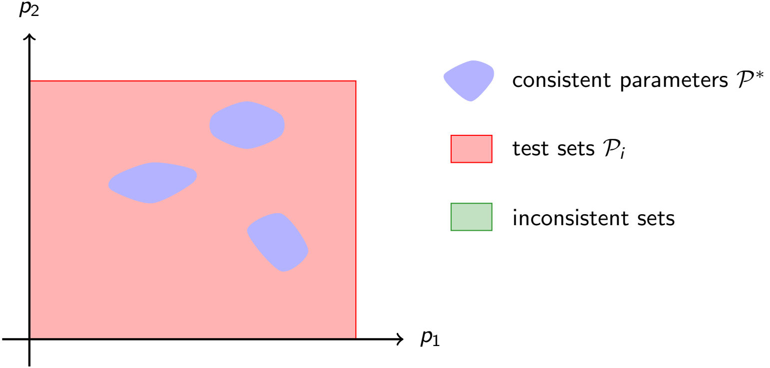
(RP) infeasible $\Longrightarrow$ (QP) infeasible $\Longrightarrow$ (P) infeasible

$\Rightarrow$ (RP) to verify that $\mathcal{P}_i$ cannot contain consistent parameters

Computation of the set of consistent parameters

Algorithm

- computation of $\bar{\mathcal{P}}^*$ based on a bisection algorithm
- in each bisection step the matrix $B(\mathcal{P}_i, \mathcal{X}^{(k)}, \mathcal{Y}^{(k)})$ is modified
- lower and upper bounds for all parameters known initially



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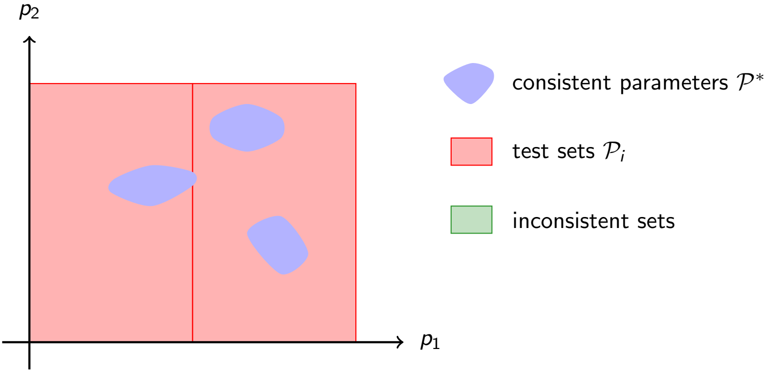

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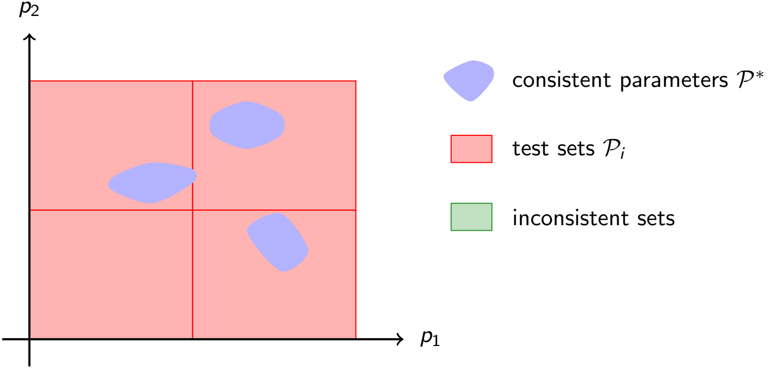

Computation of the set of consistent parameters

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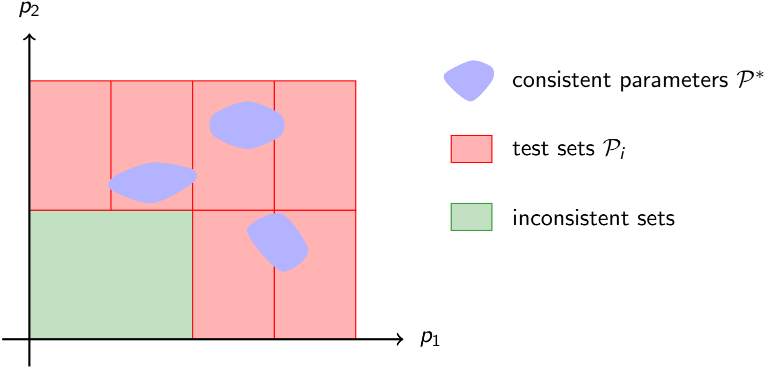

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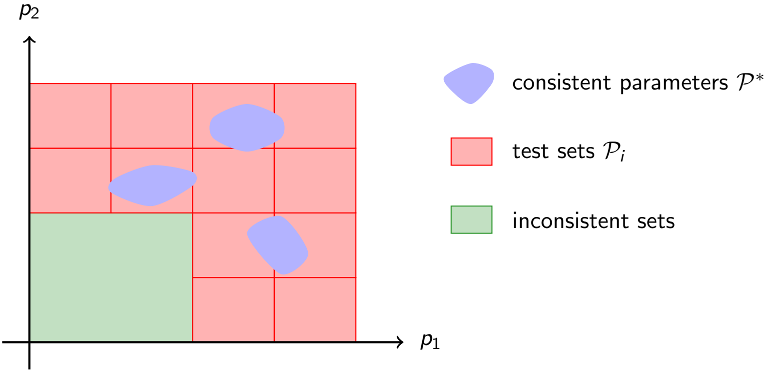

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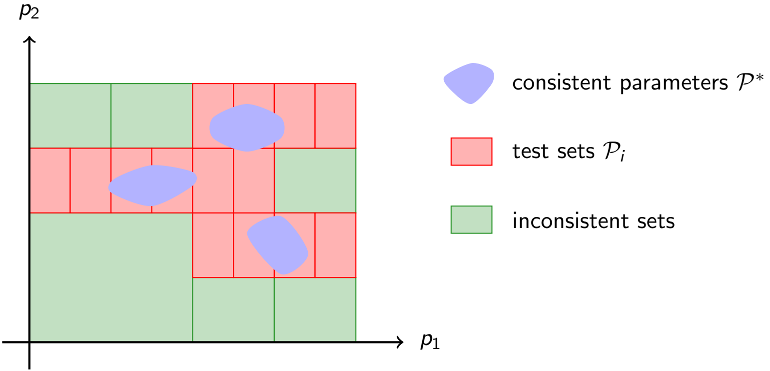

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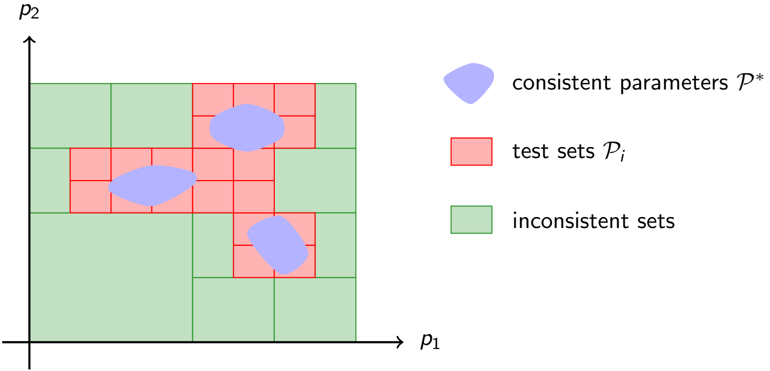

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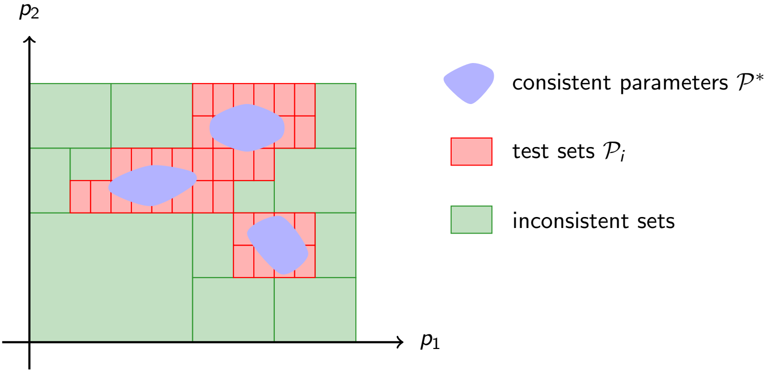

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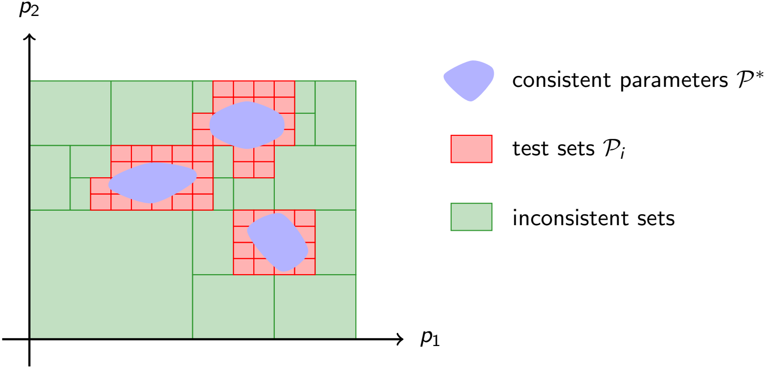

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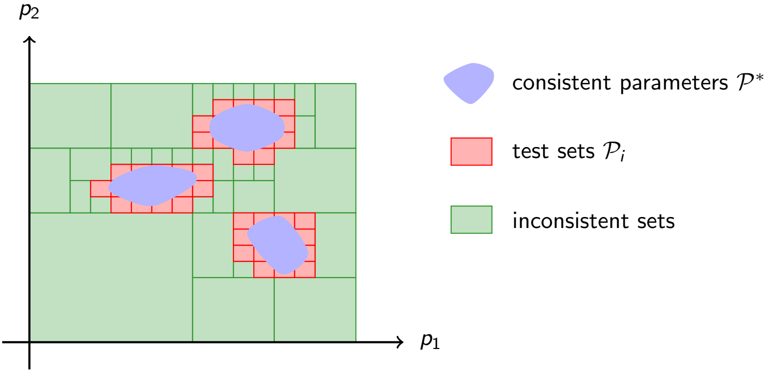

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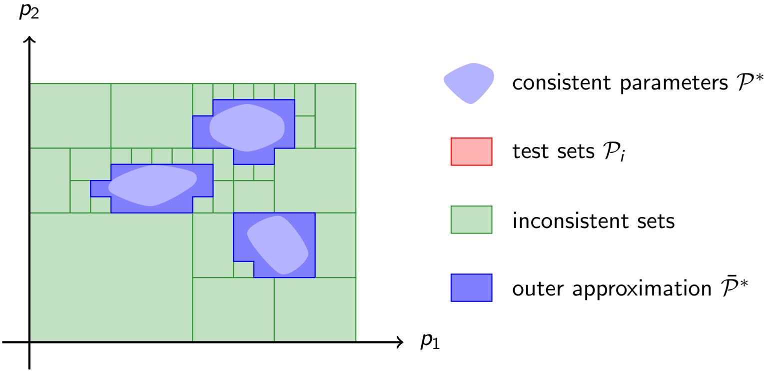
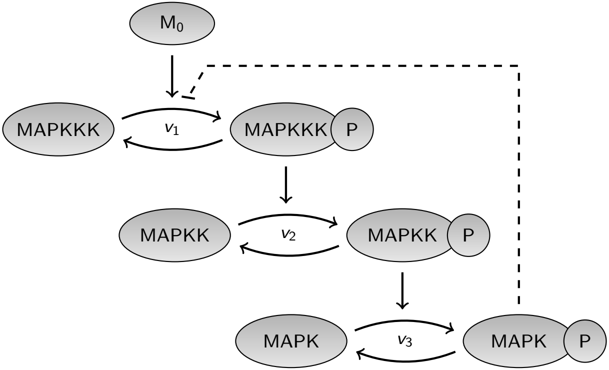


$\Longrightarrow$ outer approximation of the set of consistent parameters

Example: MAP-kinase-cascade (1)



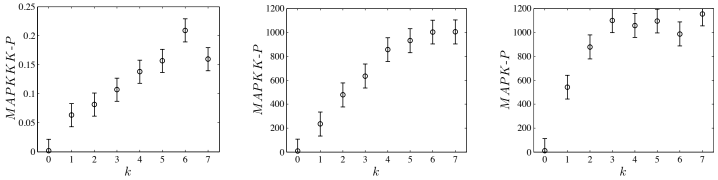
Model alternatives

- Model A: without feedback (—) $\Rightarrow 0 = F^{A}(x^{(k+1)}, x^{(k)}, p)$
- Model B: with feedback (— / – –) $\Rightarrow 0 = F^{B}(x^{(k+1)}, x^{(k)}, p)$

Which model is correct?

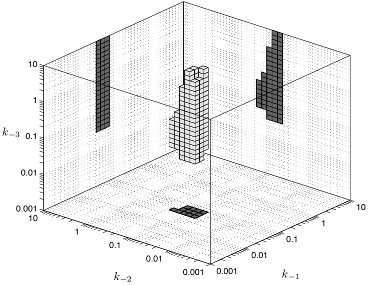
Example: MAP-Kinase-Cascade (2)

Artificial measurement data: (generated from Model A)



Set of consistent parameters:

Model A (without feedback)



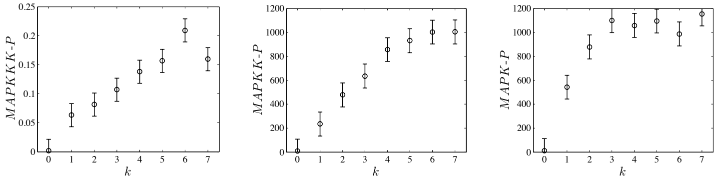
Model B (with feedback)

$\bar{\mathcal{P}}^* = \emptyset \Rightarrow$ Model B cannot describe the above artificial data.

(Only guaranteed for discrete time model!)

Example: MAP-Kinase-Cascade (2)

Artificial measurement data: (generated from Model A)



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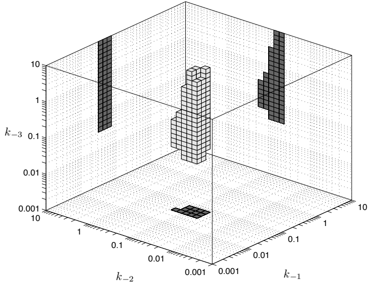


Model B (with feedback)

$\bar{\mathcal{P}}^* = \emptyset \Rightarrow$ Model B cannot describe the above artificial data.

(Only guaranteed for discrete time model!)

How can the knowledge we gained by doing set-based estimation be used?

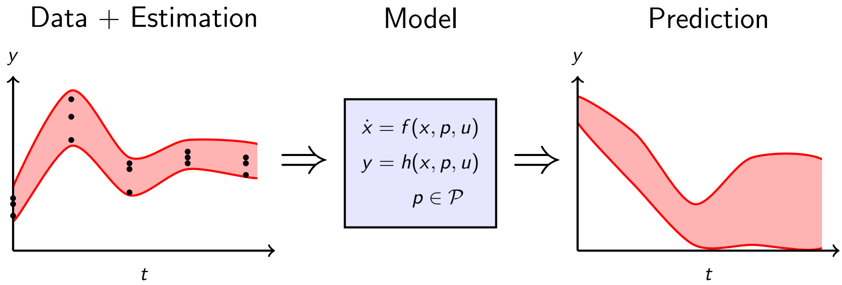
Outline

1. Introduction
2. Parameter estimation and model falsification
3. Steady-state uncertainty
4. Summary/Conclusion

What do we really know?

A question every modeler should ask:

Given certain measurement data, can I trust the model predictions?



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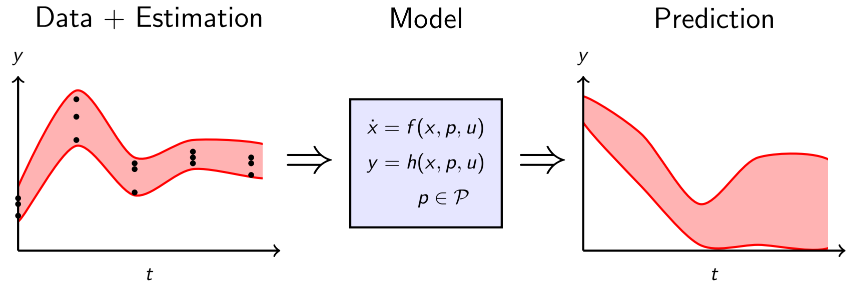
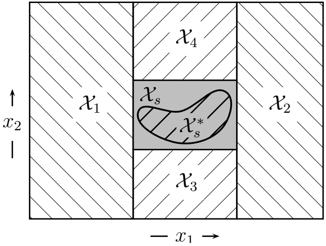


key property: asymptotic behavior

Formulation of uncertainty analysis as feasibility problem



$\mathcal{X}_s^*$ = set of feasible steady states of an uncertain system (in general not computable analytically!)

$\mathcal{X}_i$ = set for which infeasibility certificates can be computed

$\mathcal{X}_s$ = obtained outer approximation of $\mathcal{X}_s^*$

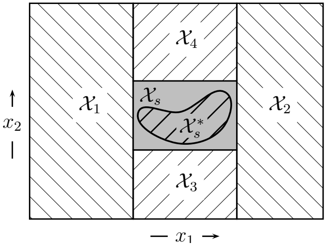
Feasibility problem

- verification that a set $\mathcal{X}_i$ cannot contain steady states
- feasibility problem (for $\dot{x} = f(x, p)$):

$$(P) : \begin{cases} \text{find} & x \in \mathcal{X}_i,\ p \in \mathcal{P} \\ \text{subject to} & f(x,p) = 0 \end{cases}$$

(P) infeasible $\Longleftrightarrow$ $\mathcal{X}_i$ does not contain steady states for $p \in \mathcal{P}$

Formulation of uncertainty analysis as feasibility problem



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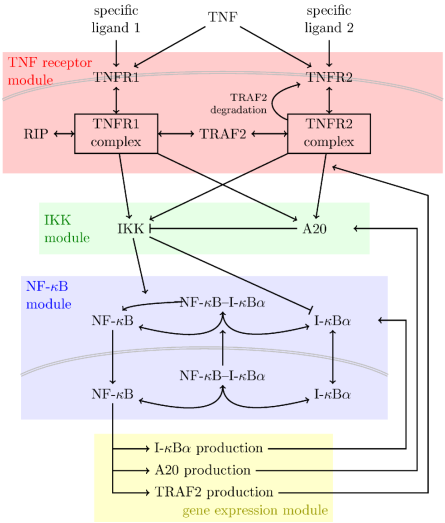
Computation of the set of feasible steady states employes the same methods as the computation of the set of consistent parameters!

Example: TNF-induced anti-apoptotic signaling

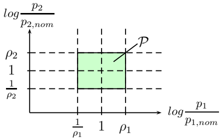


Schematic of antiapoptotic signaling pathway

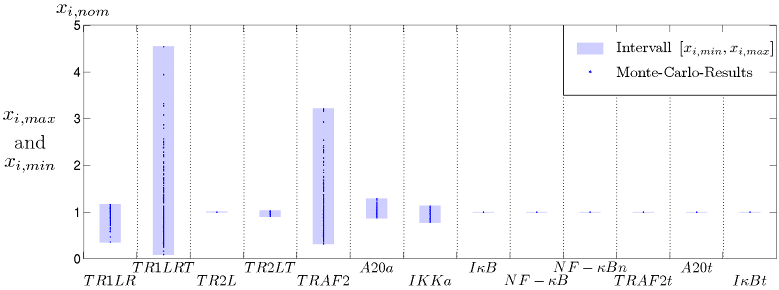
- Biological relevance:
  - apoptosis
  - proliferation
  - inflammation
- Components:
  - TNF-receptors
  - NF-κB signaling pathway
- Model:
  - 24 state variables
  - 56 parameter
- Inputs:
  - TNF1
  - TNF2

Computation of $\mathcal{X}_s$

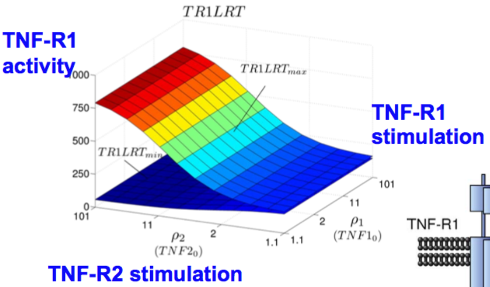
- Parameter uncertainties of factors:
  $$\rho^T = (\rho_1, \ldots, \rho_q)$$
- Parameter set $\mathcal{P}$ is a hyperrectangle

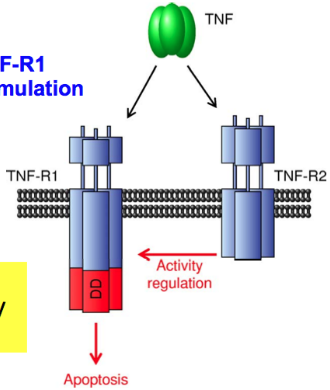


Set of feasible steady states for a variation: $\rho^T = (2, 2, 2, 2)$



Biological findings





Model prediction:
Receptor 2 regulates activity of receptor 1

Surprising results

The signal transduction process via the *TNF* receptor 1 complex is more sensitive to *TNF*2 than to *TNF*1. ⇒ strong crosstalk!

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Summary

Coherent framework for set-based ...

- parameter estimation [Küpfer2007, Hasenauer2010a, Rumschinski2010],
- model falsification [Anderson2009, Hasenauer2010a, Rumschinski2010], and
- steady state predictions [Waldherr2008, Hasenauer2010b, Waldherr2011a],

by employing powerful tools from convex optimization.

Alternative to: interval analysis and constraint propagation [Jaulin2001, Tucker2006, Walter2007]

Extensions to perform set-based ...

- experimental design [Hasenauer2010a], and
- robustness analysis [Waldherr2011b]

Toolbox: `bioSDP` for SDP-based analysis of dynamical systems.

Challenges

- Discretization error → *Torkel Glad*
- Computational complexity → *Pelle Lundberg*
- Application to real world examples → *Pelle Lundberg*

Conclusion / Opinion

Shift towards rigorous analysis of uncertainties required!

measurement + measurement uncertainties

$\Downarrow$

model + model uncertainties

$\Downarrow$

prediction + prediction uncertainties

$\Downarrow$

new experiments + new experiments uncertainties

Uncertainty analysis is a crucial task in systems biology. There are some methods available, but they are limited and not widely used!

$\Rightarrow$ many challenging open problems

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Thanks for your attention!