Structural and Practical Identifiability Analysis

of partially observed dynamical systems

Andreas Raue[1]
with Thomas Maiwald[2], Clemens Kreutz[1] and Jens Timmer[1,3]

(1) University of Freiburg
(2) Harvard Medical School
(3) Freiburg Institute for Advanced Studies

Outline

- Introducing structural and practical identifiability
- **1. Profile Likelihood Approach**
  Detecting non-identifiabilities
- JAK-STAT Signaling Pathway
- **2. Mean *Optimal Transformation* Approach**
  Finding groups of functionally related parameters

Introduction

ODE models

species: $\dot{\vec{x}}(t) = f(\vec{x}(t), \vec{u}(t), \vec{p}, t)$

observables: $\vec{y}(t) = g(\vec{x}(t), \vec{s}) + \vec{\epsilon}(t)$

$$\theta = \{\vec{x}_0, \vec{p}, \vec{s}\} \in \mathbf{R}^+ \setminus \{0\}$$

Signaling pathways

	species	observables	parameters	data-points
JAK-STAT	4	2	7	32
EPO receptor	6	3	10	32
JAK2-STAT5	13	6	20	213
TNFα IL-1 IL-6	20	6	24	159
MAPK	24	12	68	168

Introduction

ODE models

$$
\begin{aligned}
&\text{species:} && \dot{\vec{x}}(t) &=& \; f(\vec{x}(t), \vec{u}(t), \vec{p}, t) \\
&\text{observables:} && \vec{y}(t) &=& \; g(\vec{x}(t), \vec{s}) + \vec{\epsilon}(t)
\end{aligned}
$$

$$
\begin{aligned}
\theta &= \{\vec{x}_0, \vec{p}, \vec{s}\} \\
&\in \mathbf{R}^+ \setminus \{0\}
\end{aligned}
$$

Objective function: Log-Likelihood

$$\chi^2(\theta) = \sum_{k=1}^{m} \sum_{l=1}^{d_i} \left(\frac{y_{kl}^D - y_k(\theta, t_{kl})}{\sigma_{kl}^D} \right)^2 \qquad \vec{\epsilon}(t) \sim N(0, \sigma^2)$$

$$\hat{\theta} = \arg\min \left[\chi^2(\theta) \right]$$

Introduction

Structural non-identifiability

$$\begin{aligned}\dot{\vec{x}}(t) &= f(\vec{x}(t), \vec{u}(t), \vec{p}, t) \\ \vec{y}(t) &= g(\vec{x}(t), \vec{s}) + \cancel{\vec{\epsilon}(t)}\end{aligned}$$

Simple example: A $\xrightarrow{k}$ B

$$\theta = \{A_0, B_0, k\}$$

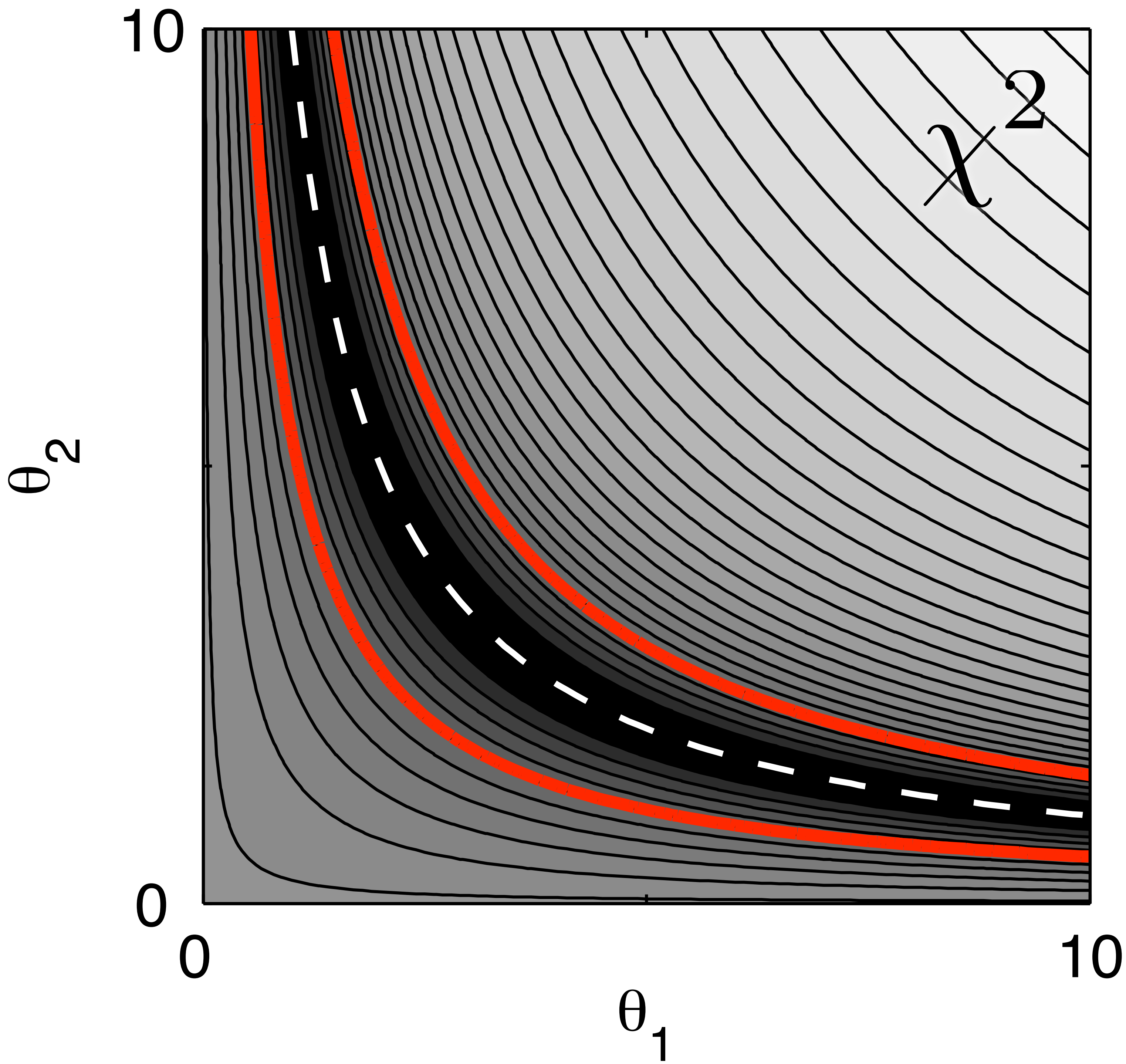
$$\begin{aligned}\dot{A}(t) &= -k \cdot A(t) \\ \dot{B}(t) &= +k \cdot A(t)\end{aligned}$$

$$\begin{aligned}y(t) &= A(t) + B(t) \\ &= A_0 \cdot e^{-k \cdot t} + [B_0 + A_0 \cdot (1 - e^{k \cdot t})] \\ &= A_0 + B_0\end{aligned}$$

Cobelli, C. and DiStefano, J. (1980). *Parameter and structural identifiability concepts and ambiguities: a critical review and analysis.* American Journal of Physiology- Regulatory, Integrative and Comparative Physiology, 239(1), 7–24.

Introduction

Structural non-identifiability (data-based view)



Functional relation:

$$\theta_1 \cdot \theta_2 = 10$$

Introduction

Practical non-identifiability & Confidence intervals

Asymptotic confidence intervals

$$\sigma_i^{\pm} = \hat{\theta}_i \pm \sqrt{\chi^2(1-\alpha, df) \cdot \mathbf{C}_{ii}}$$

$$\text{with} \quad \mathbf{C} = \mathbf{H}^{-1} \quad \text{and} \quad \mathbf{H} = \nabla^{\mathrm{T}} \nabla \, \chi^2 |_{\hat{\theta}_i}$$

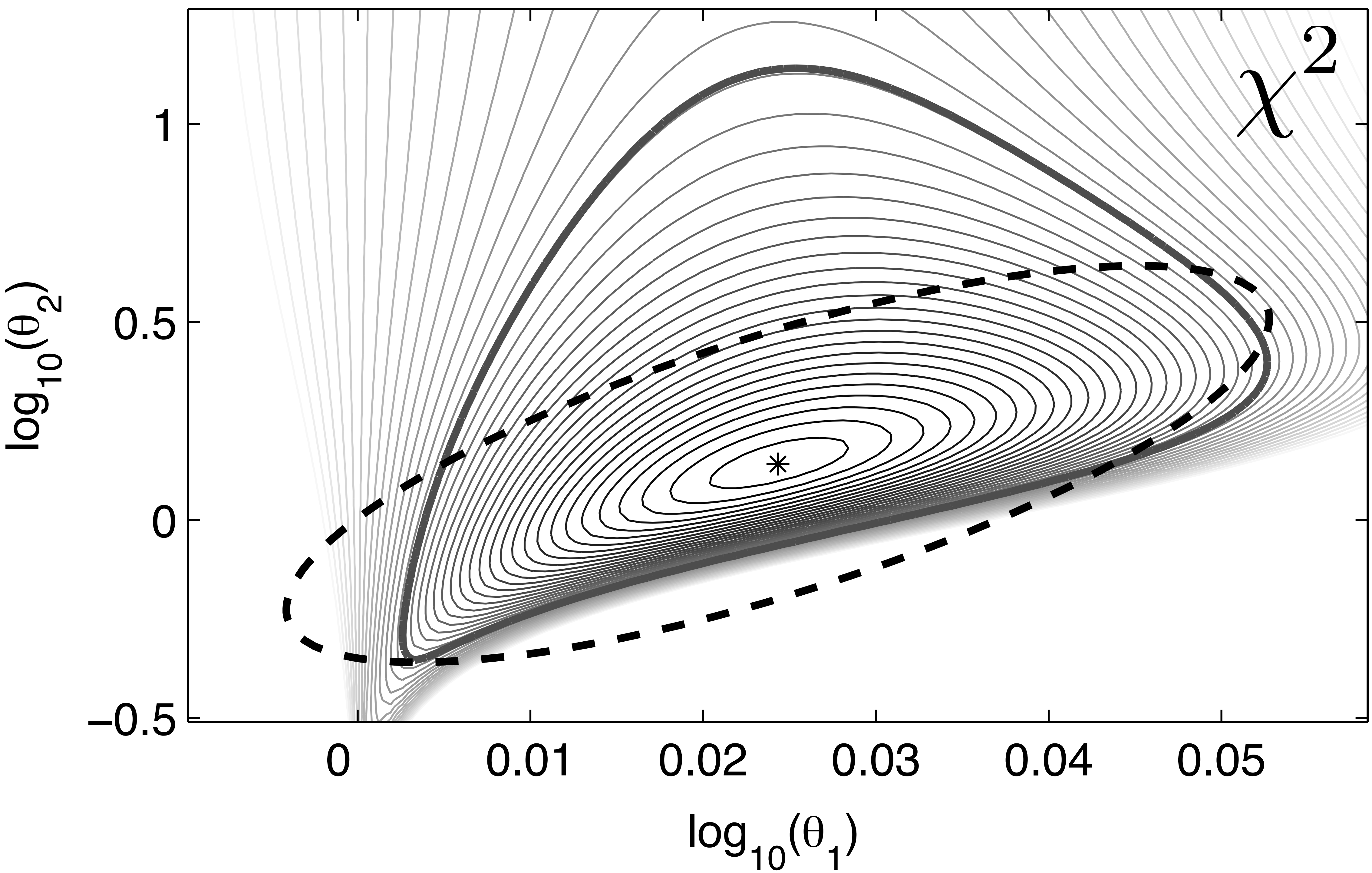
Likelihood-based confidence intervals

$$\{\theta \,|\, \chi^2(\theta) - \chi^2(\hat{\theta}) < \Delta_\alpha\}$$

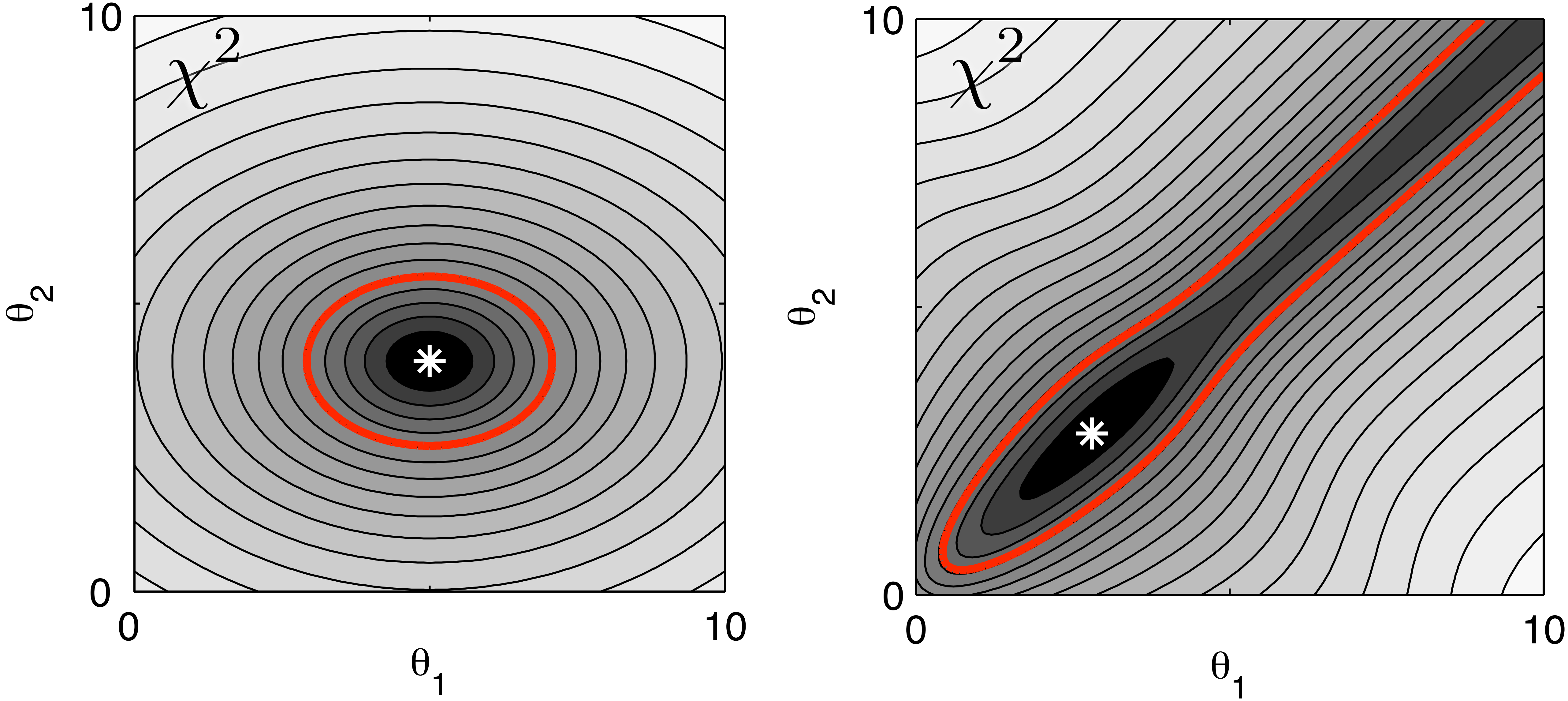
$$\text{with} \quad \Delta_\alpha = \chi^2(1-\alpha, df)$$

Introduction

Asymptotic vs. likelihood-based confidence intervals



Introduction



<u>Practical non-identifiability:</u> Likelihood-based confidence region infinitely extended.

1. Profile Likelihood Approach

Structural non-identifiability → Likelihood perfectly flat

Practical non-identifiability → Likelihood flattens out

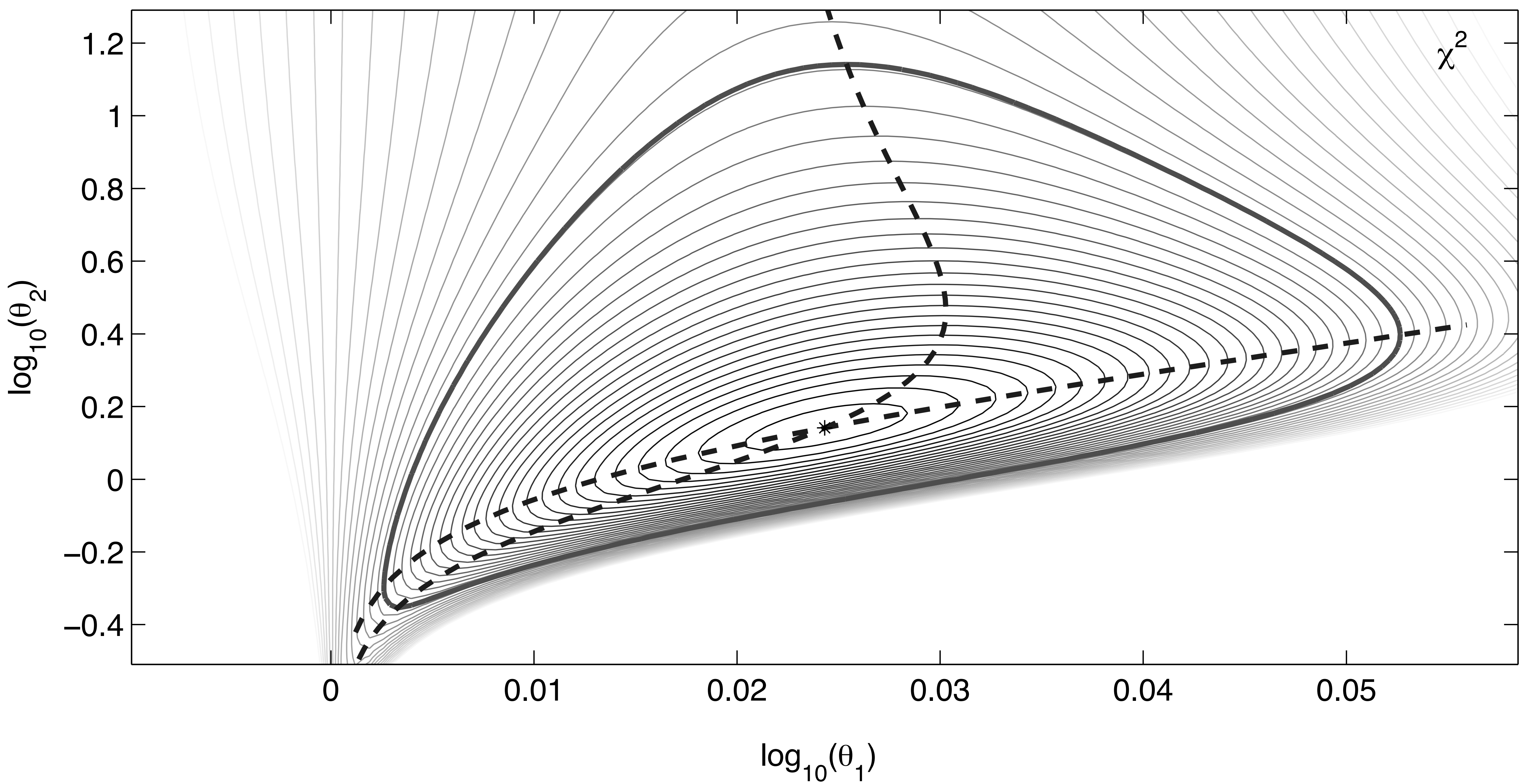
<u>Idea:</u> Sample the profile likelihood

$$\chi^2_{PL}(\theta_i) = \min_{\forall \theta_{j \neq i}} \left[\chi^2(\theta) \right]$$

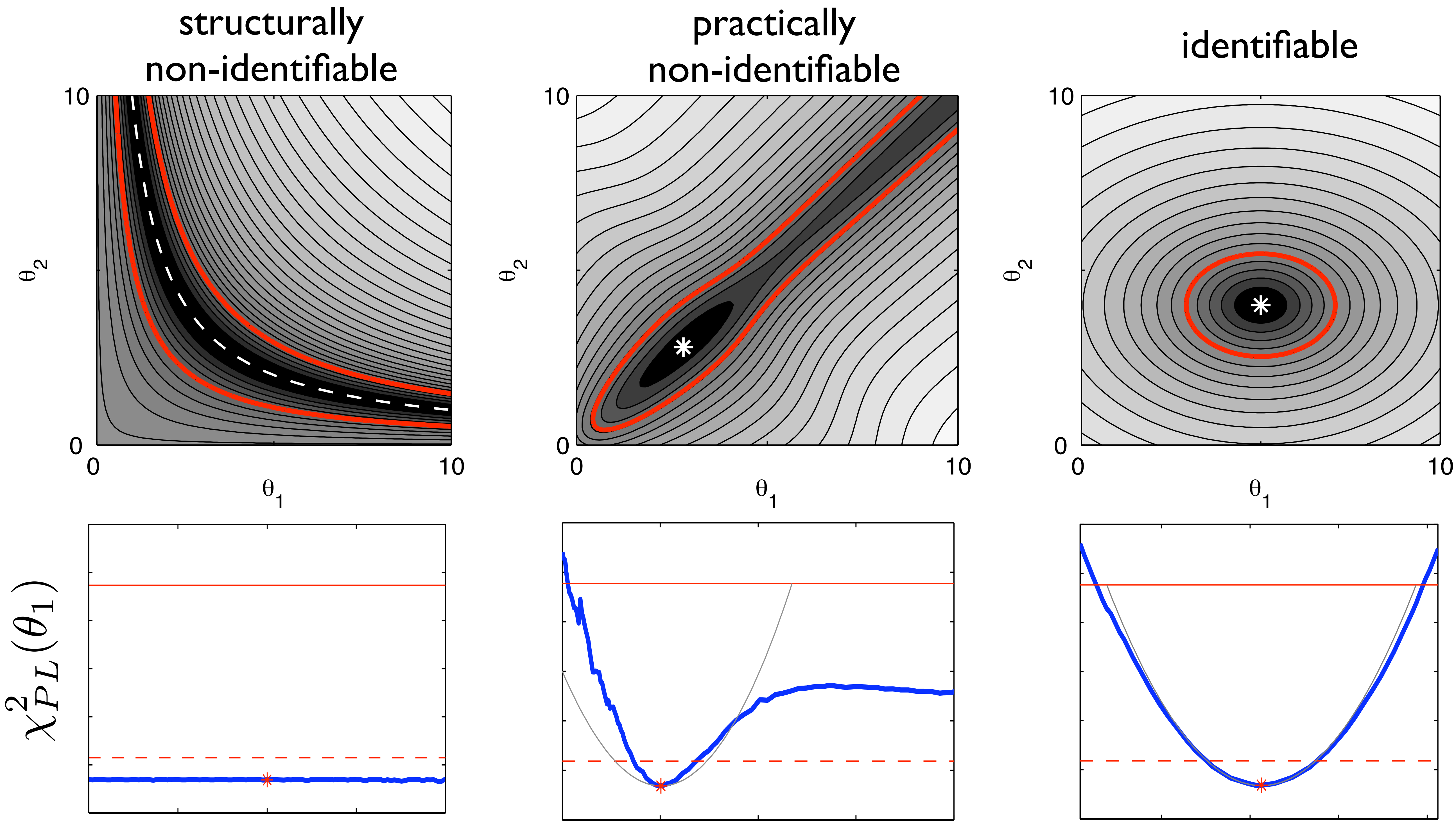
Murphy, S. and van der Vaart, A. (2000). *On profile likelihood.* Journal of the American Statistical Association, 95(450), 449–485.

1. Profile Likelihood Approach

The profile likelihood $$\chi^2_{PL}(\theta_i) = \min_{\forall \theta_{j \neq i}} \left[\chi^2(\theta)\right]$$



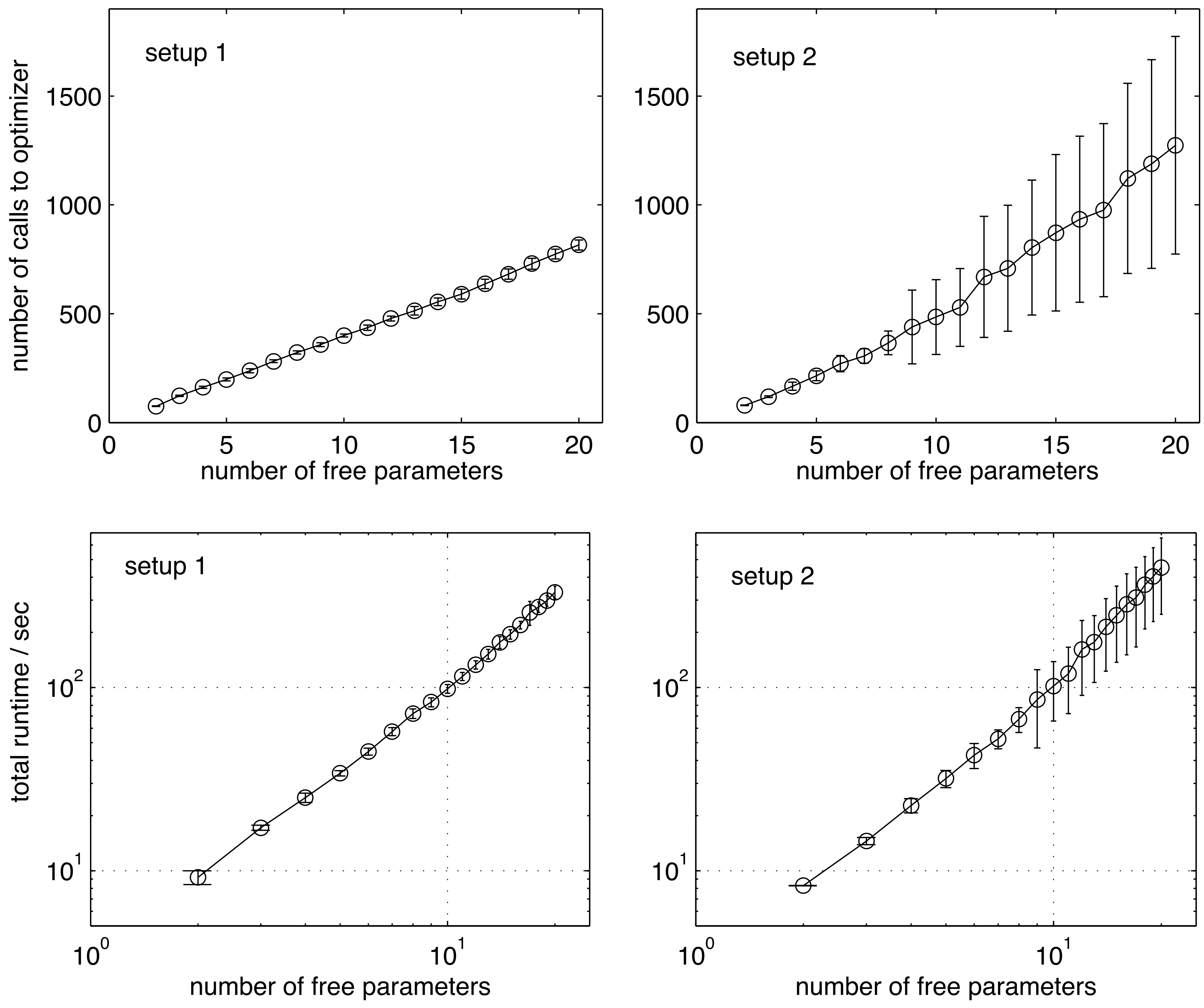
1. Profile Likelihood Approach



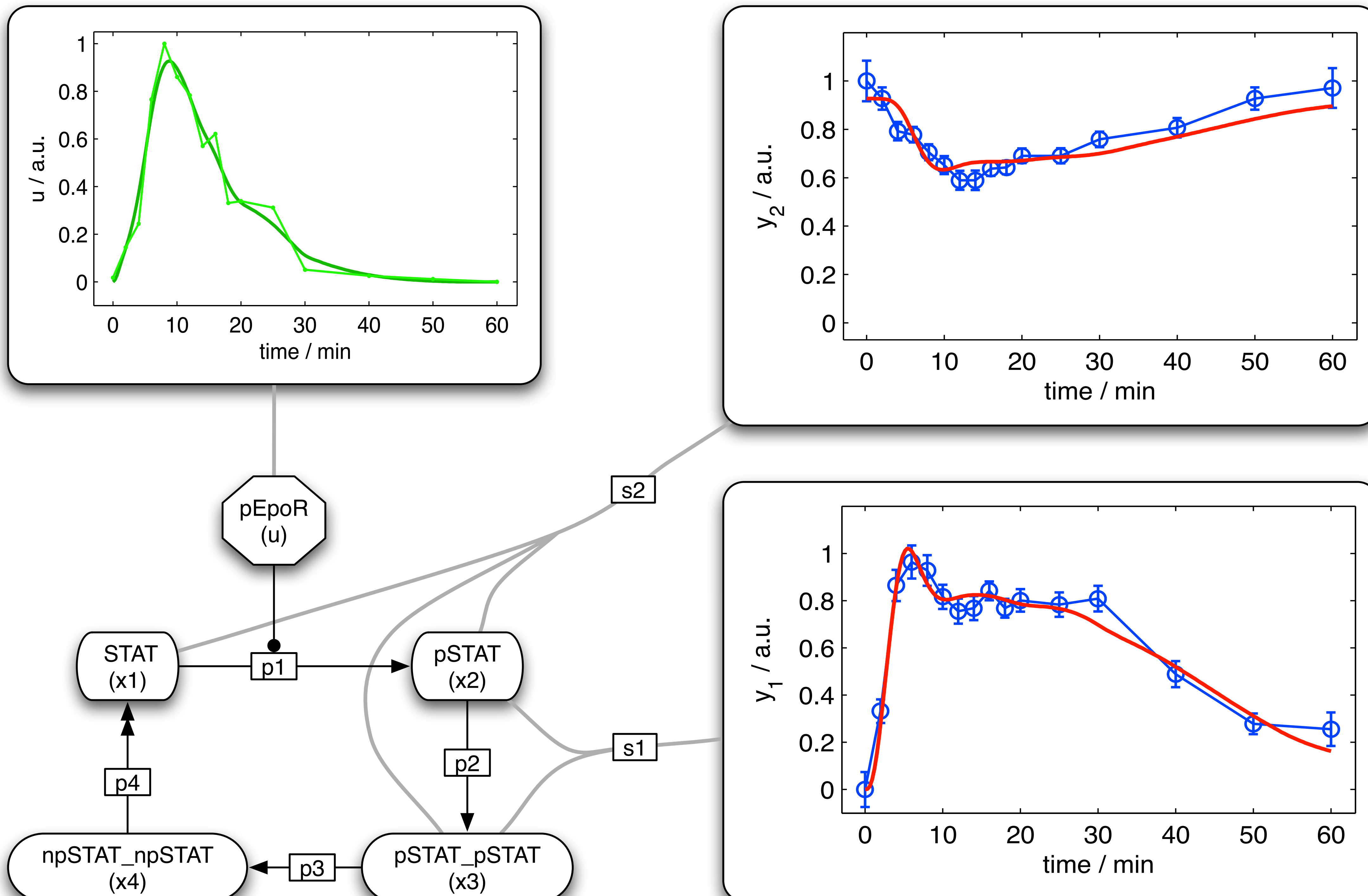
Raue A., Kreutz C., Maiwald T., Bachmann J., Schilling M., Klingmüller U., Timmer J. *Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood.* Bioinformatics, in press

1. Profile Likelihood Approach

Computational complexity

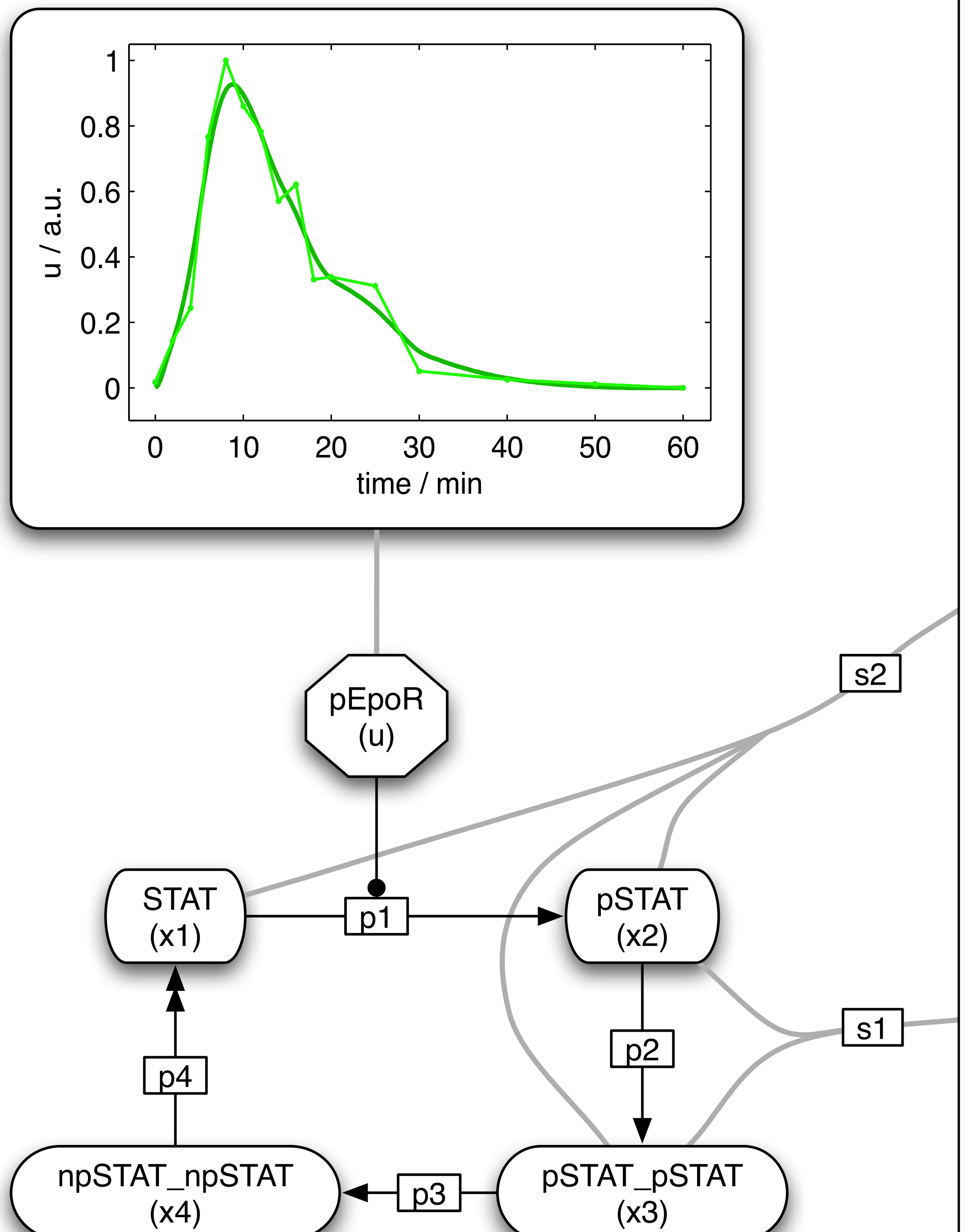


JAK-STAT Signaling Pathway



Swameye, I., Müller, T. G., Timmer, J., Sandra, O., and Klingmüller, U. (2003). *Identification of nucleocytoplasmic cycling as a remote sensor in cellular signaling by databased modeling*. PNAS, 100(3), 1028–1033.

JAK-STAT Signaling Pathway



ODE model

$$\begin{aligned}
\dot{x}_1 &= -p_1 x_1 u + 2 p_4 x_4^{\tau} \\
\dot{x}_2 &= +p_1 x_1 u - p_2 x_2^2 \\
\dot{x}_3 &= +0.5 p_2 x_2^2 - p_3 x_3 \\
\dot{x}_4 &= +p_3 x_3 - p_4 x_4^{\tau}
\end{aligned}$$

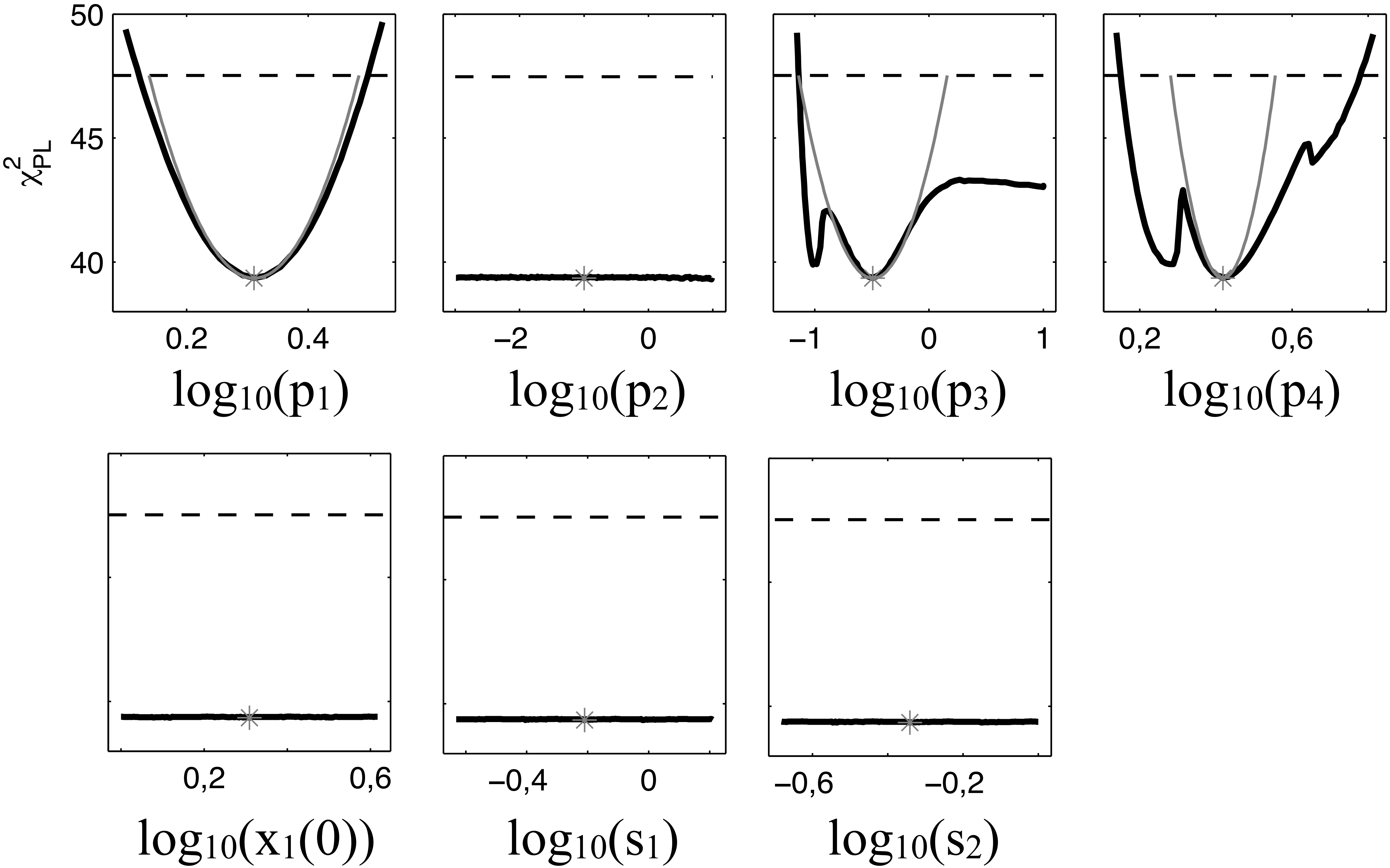
$$\begin{aligned}
y_1 &= s_1 (x_2 + 2x_3) \\
y_2 &= s_2 (x_1 + x_2 + 2x_3)
\end{aligned}$$

Structural non-identifiability

$$\{p_2, x_1(0), s_1, s_2\}$$

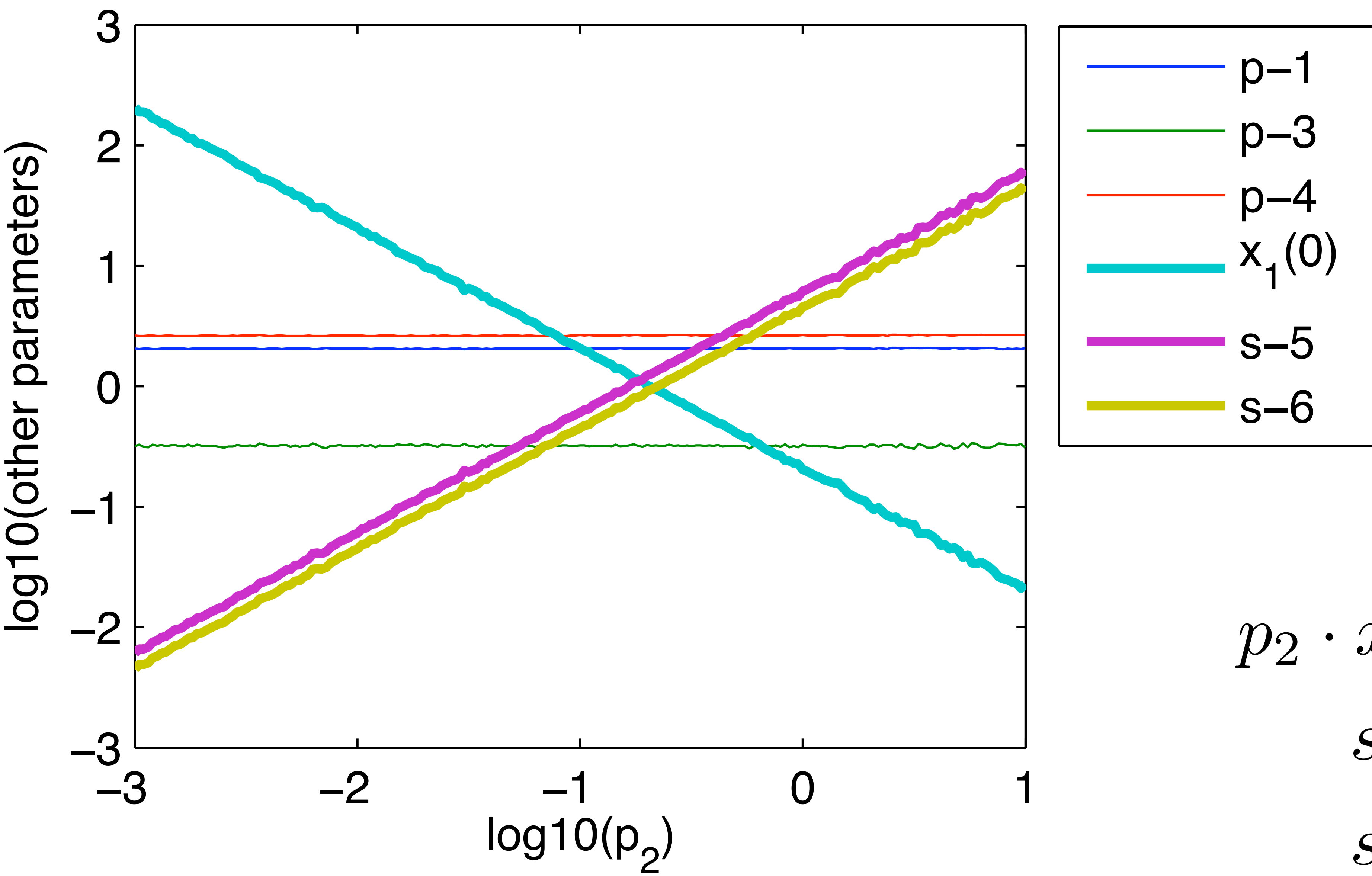
Swameye, I., Müller, T. G., Timmer, J., Sandra, O., and Klingmüller, U. (2003). *Identification of nucleocytoplasmic cycling as a remote sensor in cellular signaling by databased modeling*. PNAS, (3), 1028–1033.

JAK-STAT Signaling Pathway



JAK-STAT Signaling Pathway

Functional relations between $\{p_2, x_1(0), s_1, s_2\}$



$$
\begin{aligned}
p_2 \cdot x_1(0) &= const \\
s_1/p_2 &= const \\
s_2/p_2 &= const
\end{aligned}
$$

2. Mean *Optimal Transformation* Approach

	Profile Likelihood Approach	Mean Optimal Transformation Approach
Parameter 1		
Parameter 2	structurally non-identifiable	Group 1
Parameter 3	structurally non-identifiable	Group 2
Parameter 4		
Parameter 5	structurally non-identifiable	Group 1
Parameter 6		
Parameter 7	structurally non-identifiable	Group 1
Parameter 8	structurally non-identifiable	Group 2
Parameter 9		
...	...	...

2. Mean *Optimal Transformation* Approach

Hengl S., Kreutz C., Timmer J., Maiwald T. *Data-dased identifiability analysis of nonlinear dynamical models*. Bioinformatics 23, 2007, 2612-2618

<u>Idea</u>:

1. Multiple fitting

2. *Optimal Transformation*

$$\{\Theta, \Phi\} = \sup_{\hat{\Theta}, \hat{\Phi}} |R(\hat{\Theta}(p_i), \hat{\Phi}(p_j))|$$

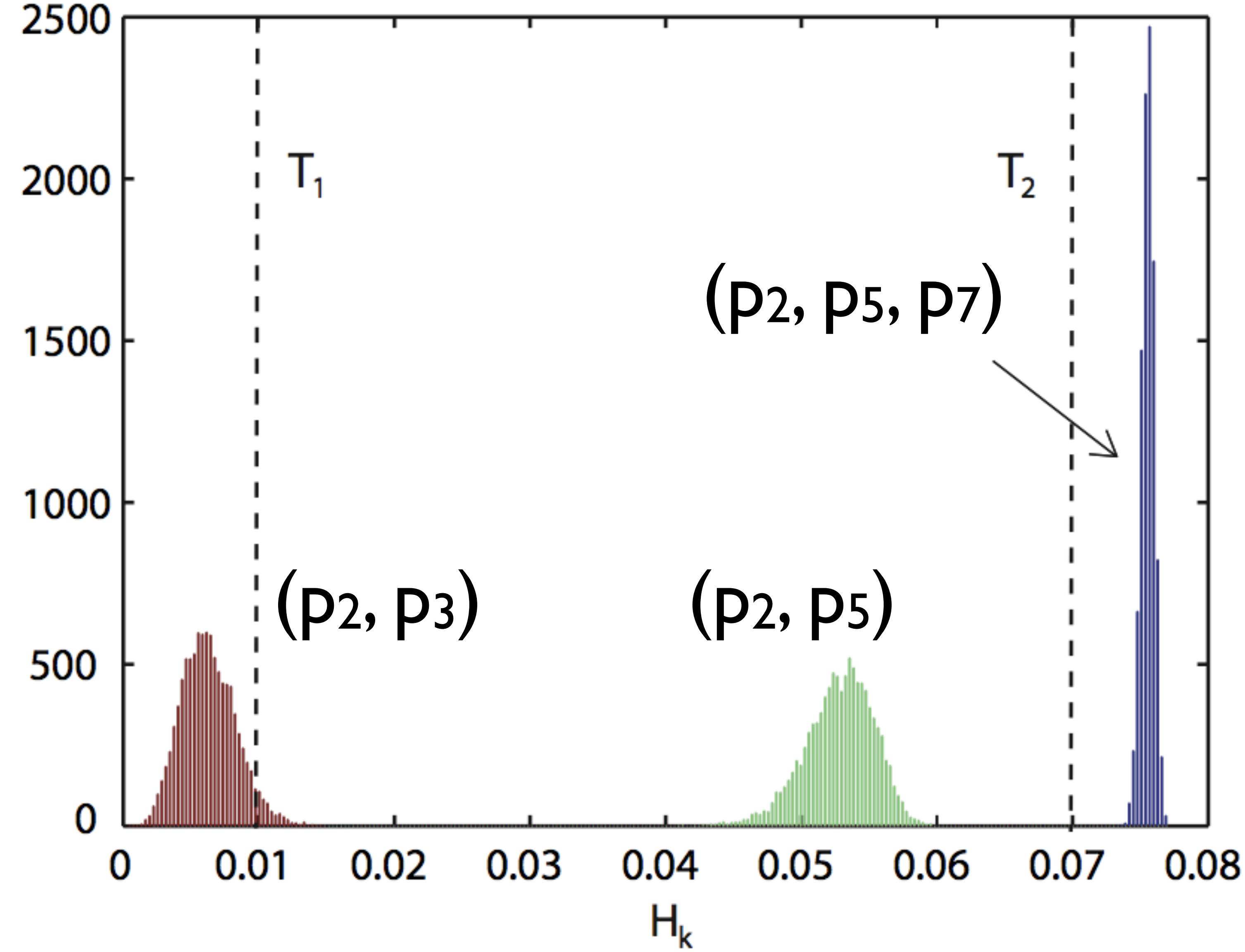
by *Alternating Conditional Expectation* algorithm.

3. Bootstrap

Breiman L., Friedman J. H. *Estimating optimal transformations for multiple regression and correlation.* Journal American Statistical Association 80, 1985, 580–598

2. Mean *Optimal Transformation* Approach

Test statistics H_k



Independency Optimal transformations change every time

Not yet decidable

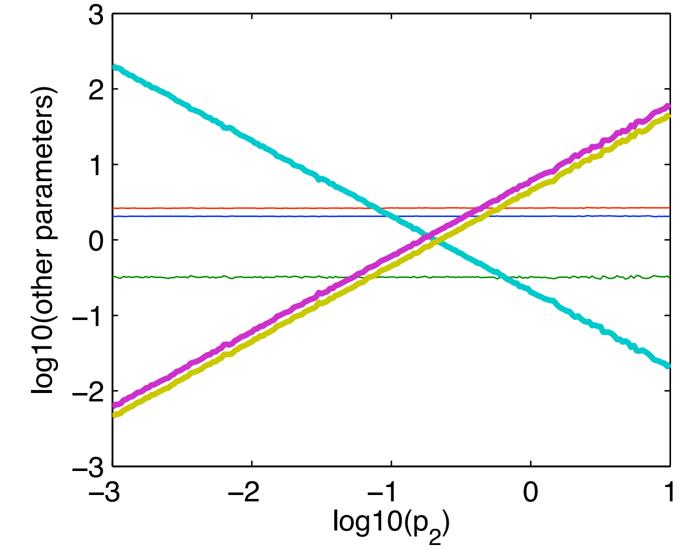
Dependency Optimal transformation is reproduced

2. Mean *Optimal Transformation* Approach

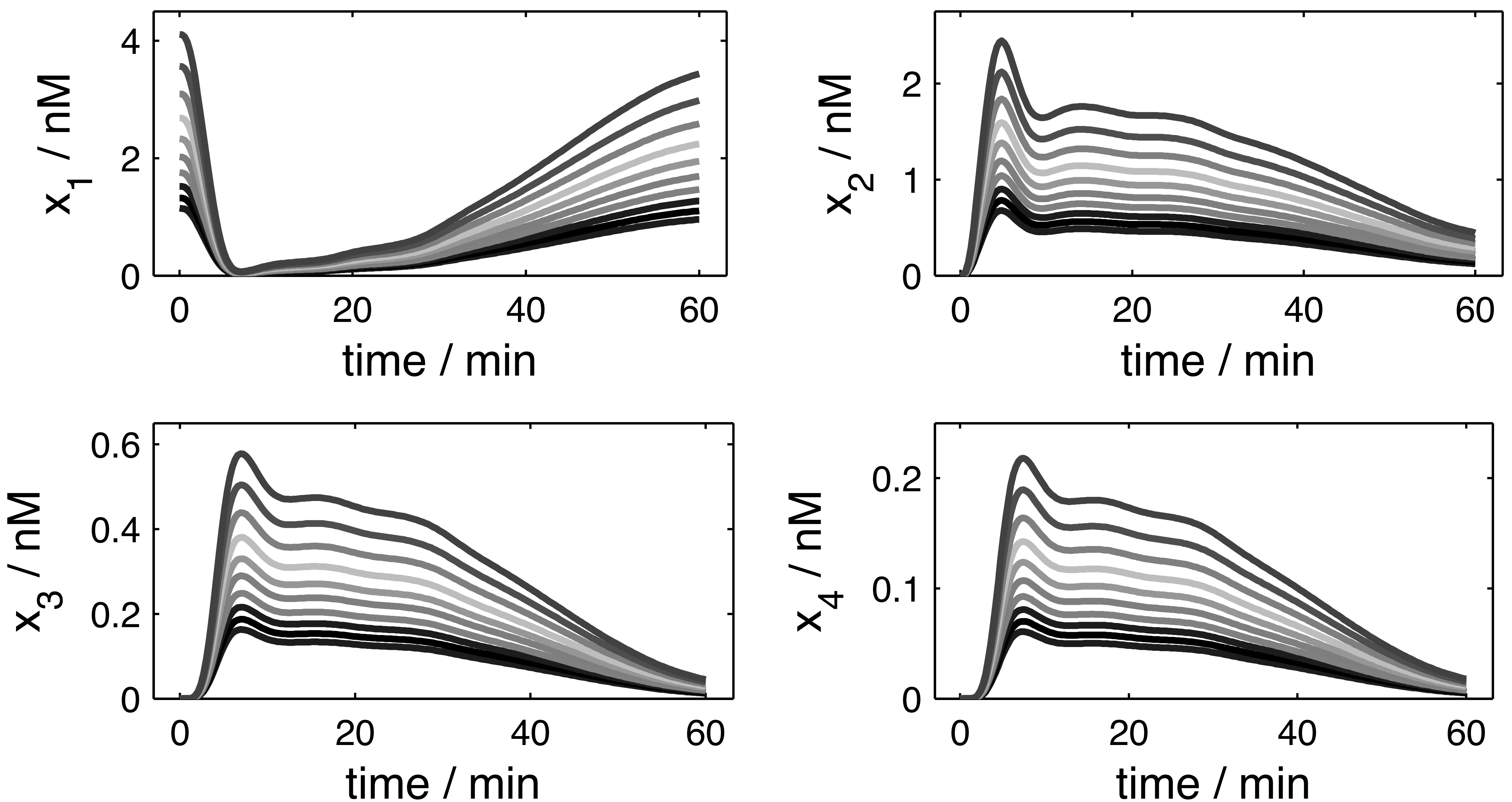
Parameter 2	1	1	1	0	0
Parameter 5	1	1	1	0	0
Parameter 7	1	1	1	0	0
Parameter 3	0	0	0	1	1
Parameter 8	0	0	0	1	1

Experimental Design

Structural non-identifiability



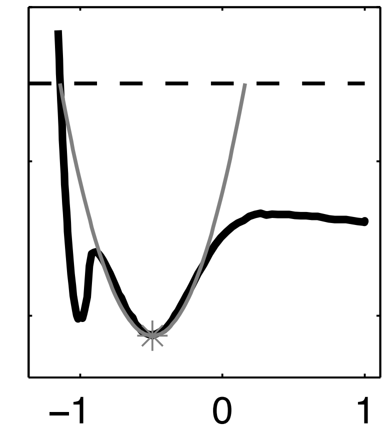
$$\{p_2, x_1(0), s_1, s_2\}$$

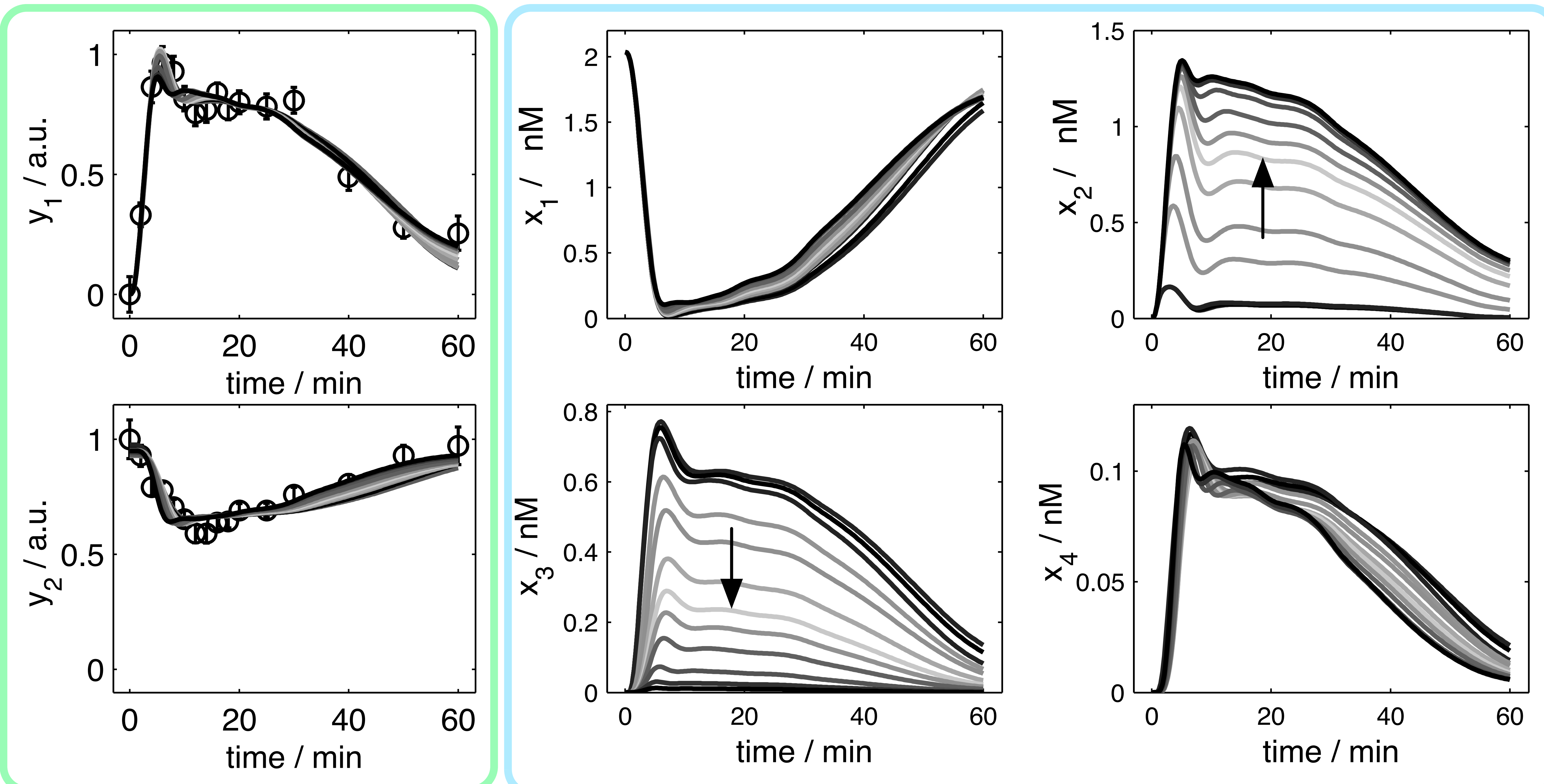


Experimental Design

Practical non-identifiability

$\log_{10}(p_3)$





Summary

- Two data-based approaches to detect and analyse structural and practical non-identifiabilities
- Facilitating experimental design to build predictive models

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dkfz.

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HepatoSys