Technische Universität Braunschweig

InES Institute of Energy and Process Systems Engineering

Flatness-Based Model Selection of Benzaldehyde Lyase Catalysed Biochemical Reaction Network

Moritz Schulze, René Schenkendorf, 26. May 2017

pvz Zentrum für Pharmaverfahrenstechnik

Center of Pharmaceutical Engineering (PVZ)

- TU Braunschweig
- founded in 2012
- 19 institutes, ca. 100 scientists
- $1500\,\mathrm{m}^2$ labs & $42\,\mathrm{m}^2$ pilot plant area

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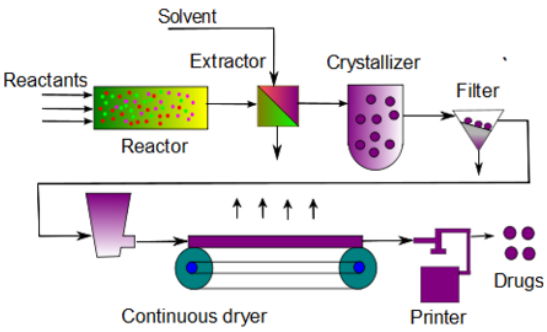
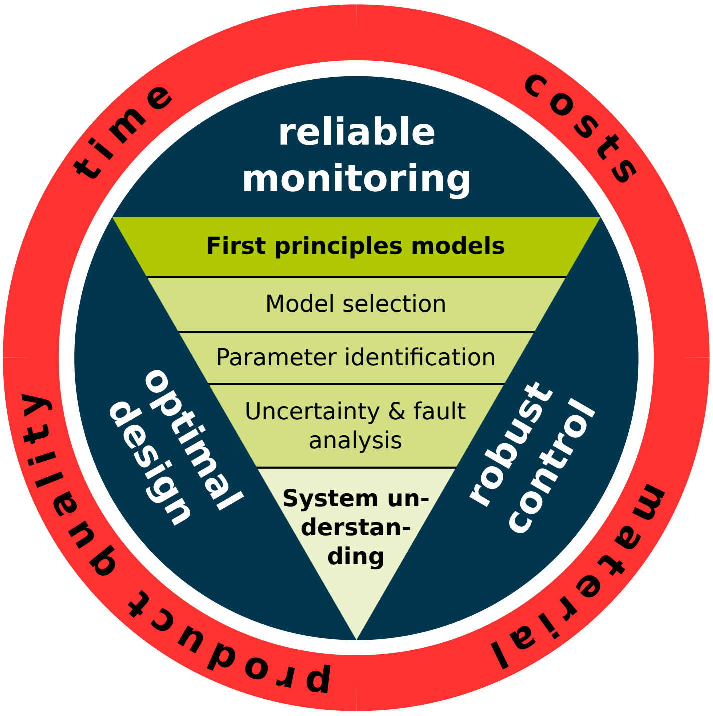
- interdisciplinary collaboration
- low-cost and effective APIs
- personalised therapy with individualised drug products



PSE group of InES

Pharmaceutical Systems Engineering group



Agenda

- Motivation
- Concept of flatness
- Results and challenges

Motivation

- Declining profit margins in pharmaceutical industry
  - Increasing R&D costs and time
  - Strengthened competition (generic drugs)

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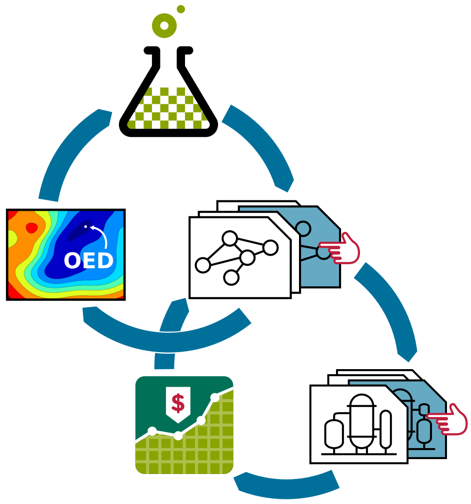
→ **Careful model selection and optimal design of experiments**



Model discrimination state-of-the-art

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  - Approximation of control inputs by e.g. orthogonal collocation or CVP techniques

  $\rightarrow$ Large problems, high computational effort and efficient solvers required

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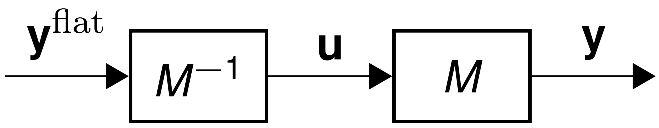
- Experimental conditions are derived analytically
- Feedforward control
- Analysis tool

Concept of flatness

$\mathbf{x}$: state variables, $\mathbf{u}$: inputs, $\mathbf{y}$: outputs

$$\underbrace{\begin{matrix} \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{u}) \\ \mathbf{y} = \mathbf{h}(\mathbf{x}, \mathbf{u}) \end{matrix}}_{\text{model } M} \overset{\mathbf{y}^{\text{flat}}}{\rightarrow} \underbrace{\begin{matrix} \mathbf{x} = \mathbf{f}_x(\mathbf{y}^{\text{flat}}, \dot{\mathbf{y}}^{\text{flat}}, \dots) \\ \mathbf{u} = \mathbf{f}_u(\mathbf{y}^{\text{flat}}, \dot{\mathbf{y}}^{\text{flat}}, \dots) \end{matrix}}_{\text{inverse model } M^{-1}}$$

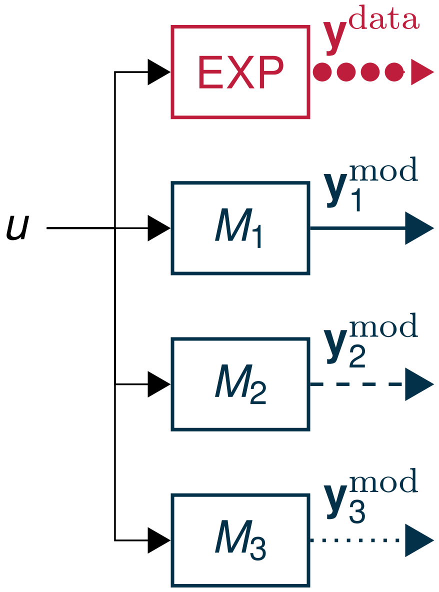


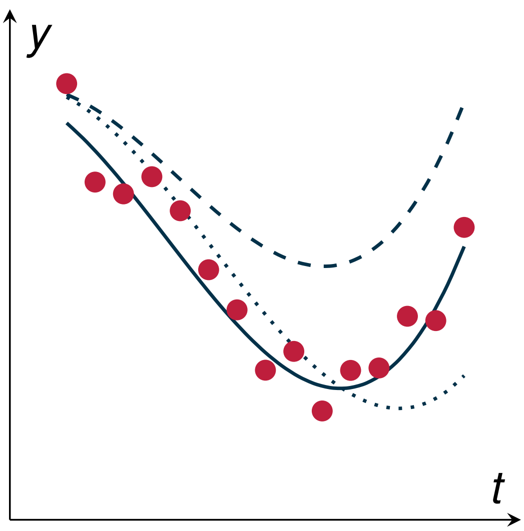
$\mathbf{y}^{\text{flat}} = \mathbf{f}^{\text{flat}}(\mathbf{x}, \mathbf{u}, \dot{\mathbf{u}}, \dots)$ and its derivatives fully describe dynamic behaviour of the system.

Model discrimination

$$\max_{\breve{\mathbf{y}}^{\text{flat}}} D(\breve{\mathbf{y}}^{\text{flat}}) \quad s.t.\ ||\Delta u|| < \epsilon$$

$\rightarrow$ shape functions for $\breve{\mathbf{y}}^{\text{flat}}$





Case study 1: Academic example

Discrimination criterion ("T-optimal design")

$$D = \sum_{i=1}^{m-1} \sum_{j=i+1}^{m} \left| u_i(y^{\mathrm{flat}}) - u_j(y^{\mathrm{flat}}) \right|^2$$

m model candidates M_i:

$$M_1: \quad \dot{x} = -0.1x + u$$

$$M_2: \quad \dot{x} = -0.2x + u$$

$$M_3: \quad \dot{x} = -0.01x^2 + u$$

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$$y^{\mathrm{flat}} = x$$

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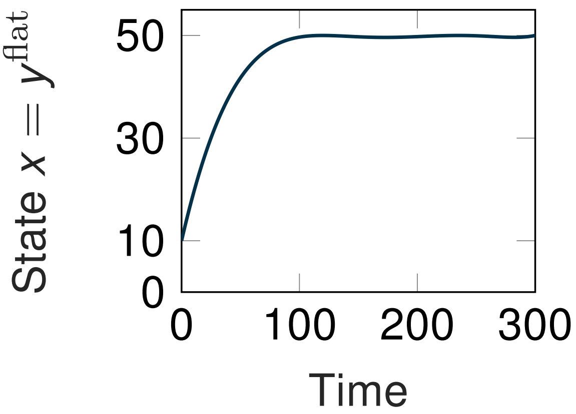
$$\max_{y^{\mathrm{flat}}} D(y^{\mathrm{flat}}, \dot{y}^{\mathrm{flat}})$$

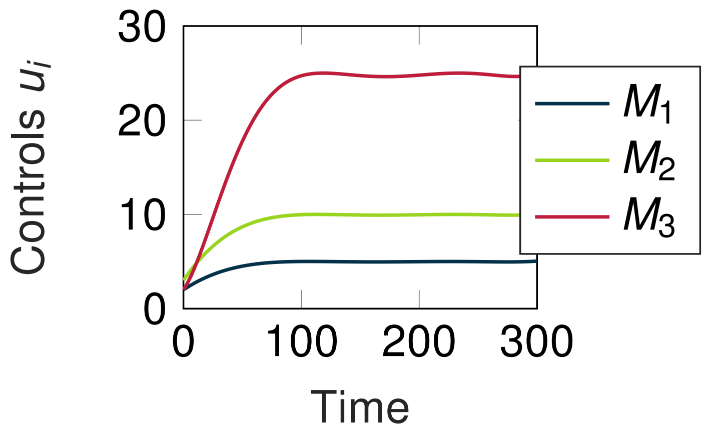
$s.t.$

$$x < 50$$

$$x_0 < 10$$

Case study 1: Optimisation results





$$\max_{y^{\text{flat}}} D(y^{\text{flat}}, \dot{y}^{\text{flat}})$$

$s.t.$

$x < 50$

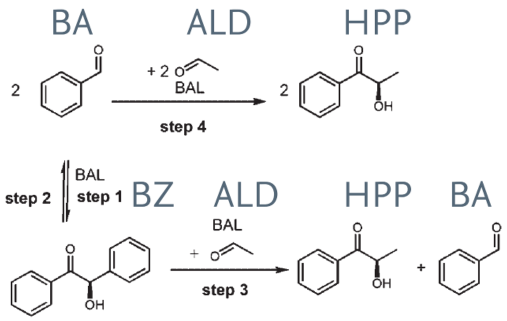
$x_0 < 10$

$$y^{\text{flat}}(t) = \sum_{i=0}^{6} C_i t^i$$

D increases as $y^{\text{flat}} = x$ incr.
$\rightarrow$ optimisation as expected

Case study 2: BAL catalysed reaction network

Symbol	Derivative
BA	benzaldehyde
ALD	acetaldehyde
BZ	benzoin
HPP	hydroxy-phenyl-propan



Reaction network [1]

Mechanistics

$$2\,\mathrm{BA} \xrightarrow[\text{step1}]{\text{BAL}} 1\,\mathrm{BZ}$$

$$1\,\mathrm{BZ} + 1\,\mathrm{ALD} \xrightarrow[\text{step3}]{\text{BAL}} 1\,\mathrm{HPP} + 1\,\mathrm{BA}$$

[1] Falk Hildebrand et al. en. In: *Biotechnology and Bioengineering* 96.5 (Apr. 2007), pp. 835–843.

Dynamic system

$$\mathrm{BA}: \quad \dot{x}_1 = -2\nu_{\mathrm{step1}} + \nu_{\mathrm{step3}} + u_1$$

$$\mathrm{ALD}: \quad \dot{x}_2 = -\nu_{\mathrm{step3}} + u_2$$

$$\mathrm{BZ}: \quad \dot{x}_3 = \nu_{\mathrm{step1}} - \nu_{\mathrm{step3}}$$

$$\mathrm{HPP}: \quad \dot{x}_4 = \nu_{\mathrm{step3}}$$

Case study 2: Model candidates

Candidates (kinetics)

M_1: Michaelis-Menten with inhibition

M_2: Michaelis-Menten (set $K_{\mathrm{I},2} = \infty$)

M_3: Power law

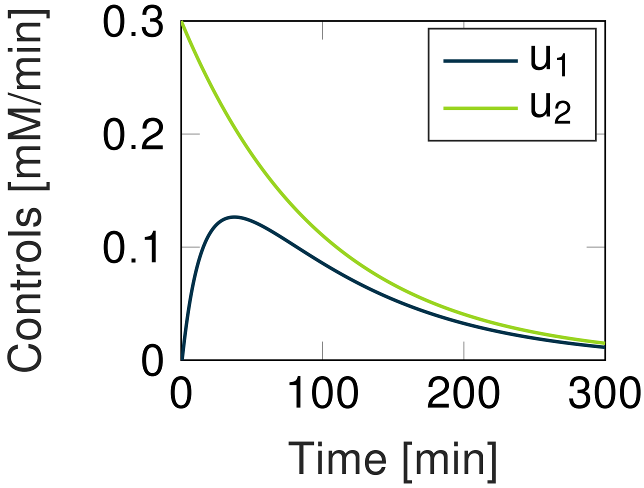
$$M_1, M_2 \begin{cases} \nu_{\mathrm{step1}} &= [E]\, V_{\mathrm{max},1} \left(\frac{x_1}{K_{\mathrm{M,BA}}(1+x_2/K_{\mathrm{I},2})+x_1} \right)^2 \\ \nu_{\mathrm{step3}} &= [E]\, V_{\mathrm{max},3} \frac{x_3}{K_{\mathrm{M,BZ}}(1+x_2/K_{\mathrm{I},2})+x_3} \end{cases}$$

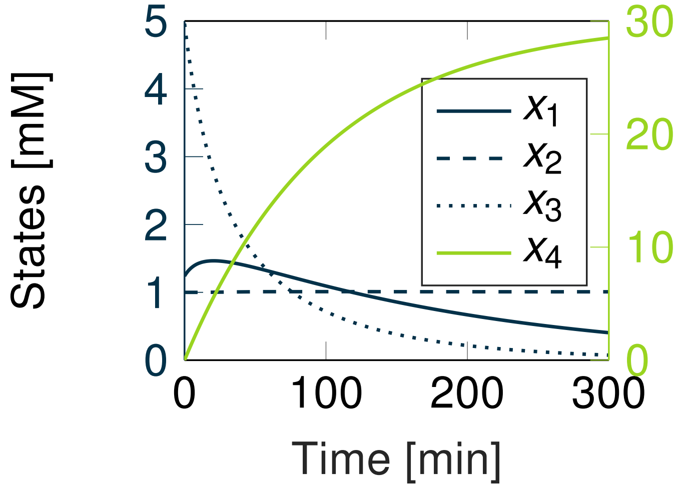
$$M_3 \begin{cases} \nu_{\mathrm{step1}} &= k_1 x_1^2 \\ \nu_{\mathrm{step3}} &= k_3 x_2 x_3 \end{cases}$$

Results: System trajectories

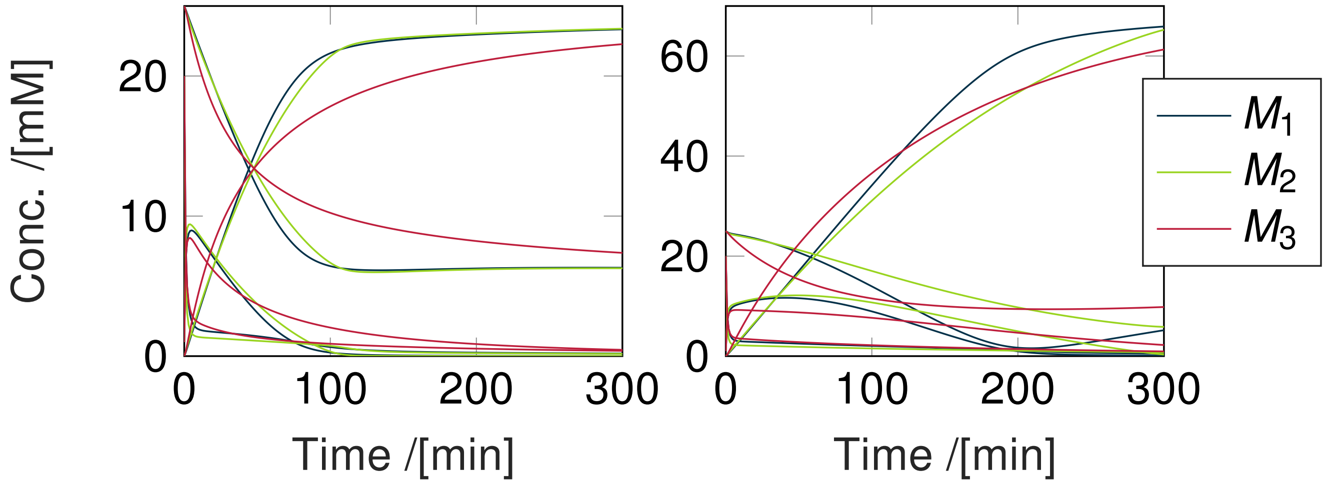
Model 2: $\mathbf{y}^{\text{flat}} = \begin{pmatrix} x_2 \\ x_4 \end{pmatrix} = \begin{pmatrix} 1 \\ 30(1 - \exp[-t/100]) \end{pmatrix}$

Flat outputs → controls → states



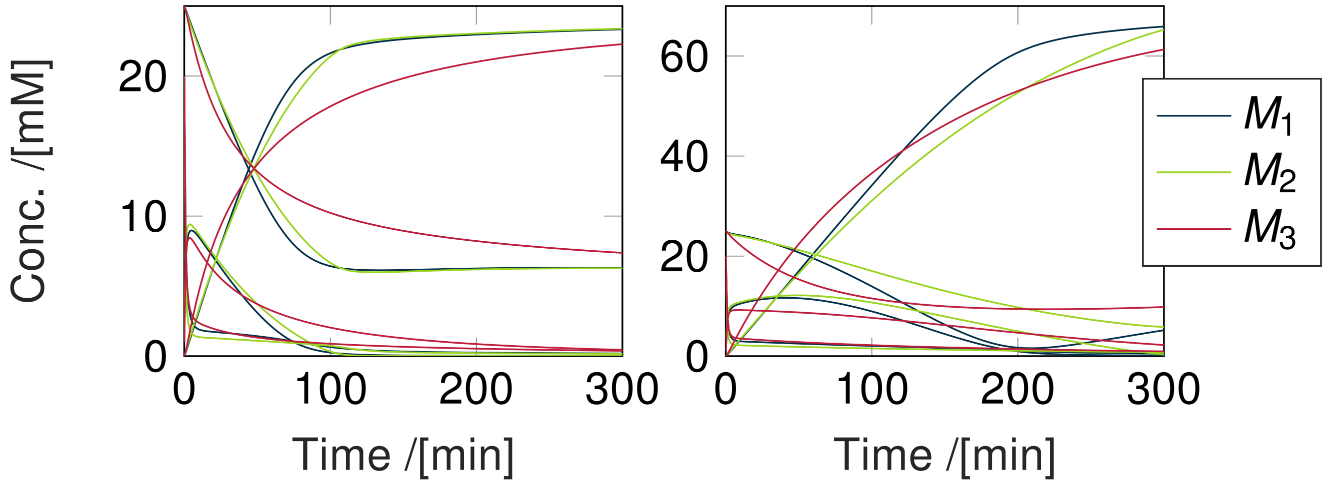


Case study 2: Optimisation



Controls 1 → Controls 2

Case study 2: Optimisation



Controls 1 → Controls 2

Is this the optimal discriminating input?

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  - Complex regions
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  - Diverse local and global solvers (MATLAB, e.g. fminsearch, fmincon, particlesearch, patternsearch)

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Outlook: Splines (increasing degrees of freedom)

Thanks for your attention!