Model-based design of experiments for model identification: advanced techniques and novel applications

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Outline

• Introduction: summary of my research activity
• Overview: design of experiments (DoE) and statistical planning
• Model-based Design of Experiments (MBDoE)
  – Introduction, open issues and limitations
  – Development of advanced MBDoE techniques for model identification
• Applications of MBDoE
  – Reaction Engineering
  – Bioengineering
  – Other applications
• Final remarks
A quick introduction

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Research interests
• Design of Experiments (DoE) and statistical planning
• Model-based Design of Experiments (MBDoE) for model identification
• Kinetic modelling, modelling of reaction systems
• Pharmacokinetics/pharmacodynamics modelling
• Modelling of physiological systems
• Parameter Estimation

Teaching interests
• CENGM01P/CENGG01P Process Systems Modelling and Design
• CENG207P Process Design Principles
• CENG302P/CENGGM22P/CENGG22P Process Dynamics and Control
Research activity: main topics

Development of advanced techniques for model-based design of experiments (MBDoE)

- Model-based design of parallel experiments (Galvanin et al., 2007)
- Online model-based design of experiments (Galvanin et al., 2009)
- A backoff strategy for design of experiments in the presence of uncertainty (Galvanin et al., 2010)
- A model-based design approach for continuous measurement systems (Galvanin et al., 2011)
- A disturbance estimation approach for model-based design of experiments (Galvanin et al., 2012)

Applications of MBDoE techniques and experiment design tools

- Identification physiological models of type I and II diabetes mellitus (Galvanin et al., 2009-2013)
- Optimal drug administration for the identification of cancer models (Galvanin et al., 2010)
- Development of physiological models for the study of rare coagulation diseases (Galvanin et al., 2014)
- Parallel design of experiments for the identification of bacterial inactivation models (Galvanin et al., 2014)
- Development of identifiable models of microalgal growth (Bernardi et al., 2014)
- Optimal design of experiments for the identification of electrodialysis models (Galvanin et al., 2016)
- Design of experiments for the identification of pharmacokinetic models (Galvanin et al., 2013-2014)
- Identification of kinetic models in microreactor platforms (Galvanin et al., 2015-2016)
Design of Experiments (DoE)

- **Design of Experiment (DoE)**\(^1\) is a systematic statistical method used to determine the relationship between different input factors \((X_i)\) affecting a process and the output \((Y)\) of that process.

\[
Y = \beta_0 + \sum_{i=1}^{N_u} \alpha_i X_i + ...
\]

Polynomial models («black box» models) used to build **response surfaces**

**TARGET**: improving the information content of an experiment from experimental data, progressively used to build **regression models**

Great reduction of the number of trials
Application-independent methodology

Model-based design of experiments (MBDoE)

Evolution of design of experiments (DoE)

Model-based Design of Experiment (MBDoE) → statistical DoE method\(^1\) based on a deterministic model of a physical system.

\[ Y = f(X, \theta) \]

\( f \) is a set of physical laws and correlations

**TARGET**: determining the experimental conditions providing the optimal information content of an experiment (optimal design), given a model and preliminary statistical information on its reliability

**Benefits**
- Minimisation of the experimental effort (time, money)
- Support to model development

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MBDoE for model identification

- Identification of a suitable model structure
- Identification of the model parameters

Set of an ideal experiment

- Optimally informative
- Feasible

Operability
Controllability
Safety

MBDoE for model discrimination
MBDoE for improving parameter precision

MBDoE for Model Identification: problem definition

Manipulated inputs

Model parameters $\theta_i$

Model prediction

Optimal input design for model identification\(^1\)

Conventional MBDoE procedure

Iterative sequence of 3 key activities

1. Optimal input design
2. Generation of information (experimental data)
3. Parameter estimation and statistics

Analysis of suitable model structures

Design of experiment

Experiment Execution

Parameter estimation

Is it satisfactory?

YES

STOP

NO
MBDoE: mathematical formulation (I)

Optimal design problem

\[ \phi^{\text{opt}} = \arg \min_{\phi} \left\{ \psi \left[ V_{\theta} (\theta, \phi) \right] \right\} = \arg \min_{\phi} \left\{ \psi \left[ H_{\theta}^{-1} (\theta, \phi) \right] \right\} \]

subject to

\[ f \left( \dot{x}, x, u, w, \theta, t \right) = 0 \quad \hat{y} = h(x) \]

\[ \tilde{C} = z \left( \dot{x}(t), x(t), \dot{u}(t), u(t), w, \theta \right) \leq 0 \]

- \( x(t) \) \( n_s \)-dimensional vector of state variables
- \( u(t) \) \( n_u \)-dimensional vector of manipulated inputs
- \( w \) \( n_w \)-dimensional vector of time-invariant inputs
- \( \hat{\theta} \) \( n_{\theta} \)-dimensional vector of model parameters
- \( \hat{y}(t) \) \( M \)-dimensional vector of measured variables

Design vector

\[ \phi = \left[ y \left( t_0 \right), u \left( t \right), w, t^{sp}, \tau \right] \]

DESIGN OPTIMALITY

DETERMINISTIC MODEL

FEASIBILITY CONDITIONS

(Constraints on State Variables)
MBDoE: mathematical formulation (II)

**Design Optimality Condition**

$$\phi = \text{arg min}_\psi \left\{ \left[ V_\theta \left( \theta, \phi \right) \right] \right\} = \text{arg min}_\psi \left\{ \left[ H_\theta \left( \theta, \phi \right) \right]^{-1} \right\}$$

**Fisher Information Matrix (FIM)**

$$H_\theta \left( \theta, \varphi \right) = \sum_{k=1}^{n_s} \sum_{i=1}^{N_y} \sum_{j=1}^{N_y} S_{ijk} Q_{ik}^T Q_{jk} + H_\theta^0$$

**Variance-covariance of measurements errors**

**Sensitivity Matrix**
Parallel experiments can be designed and executed simultaneously\(^1\):

\[
T = [N, N_R, C]
\]

- \(N\) = number of experiments
- \(N_R\) = number of available devices
- \(C\) = connection matrix

For the \(k\)-the experiment

\[
\min_{\varphi_k} \psi_k(V_0)
\]

Which is the \textit{shortest} route to \(\theta^*\)?

---

MBDoE limitations: effect of uncertainty (I)

Effect on **design optimality**

- Dynamic sensitivity profile
- Uncertainty on Fisher information

**Expected variance** ≠ **Actual variance** on model parameters

Mismatch on information
MBDoE limitations: effect of uncertainty (II)

Effect on **design feasibility**

An example: identification of diabetes models (Galvanin et al., 2010)

**Optimal design result**

Patient incurring into hypoglycemia!
MBDoE under uncertainty (I)

- Parametric mismatch
  - It may cause **suboptimal** or **infeasible** experiments
- Correlation among parameters
- Parameters are “case-dependant”
  - Typical in biomedical/biological systems
  - Possible in other systems, too (“quality” is defined by an acceptable variance)
- Parameters may not be “constant”
  - In physiological/biological models systems response (e.g. model parameters) depend on environment, previous “history”, etc.
  - Catalysts reduces their activity over time, heat exchangers foul...
MBDoE under uncertainty (II)

- System response is always different from design (system stochastic behaviour)
- Limited knowledge of phenomena
  → Parameters are asked to compensate for “unknown”
- Model may represent a portion of existing phenomena
  – Physiological models
  – Oversize equipment
- Measurement systems
  – Effect of noise and frequency of the measurements
  – Correlated measurements
- Other disturbances
  – Unknown inputs
  – Systematic errors (biases in measurements)
MBDoE under uncertainty: proposed solutions

• Several approaches have appeared in the literature to deal with parametric uncertainty
  – Robust experiment design (Walter, 1987; Asprey and Macchietto, 2002; Rustem and Zakovic, 2003; Körkel et al., 2004; Dette et al., 2005; Bruwer and MacGregor, 2006; Rojas et al., 2007; Chu and Hahn, 2008) → mainly focused on design optimality

• My research contribution
  – Online re-design of experiments (OMBRE)\(^1\)
  – Explicit inclusion of the feasibility problem within MBDoE through a design with backoff from constraints\(^2\)
  – Online re-design of experiments with disturbance estimation (DE-OMBRE)\(^3\)
    → also focused on design feasibility

MBDoE and the uncertainty scenario

Model uncertainty

Parametric uncertainty
- Robust design
- Global sensitivity analysis (GSA)
- Bootstrapping methods

Measurements uncertainty
- Information is related to the shape of the likelihood function

OMBRE/MBDoE including backoff/disturbance estimation (DE)
A backoff strategy for MBDoE under parametric uncertainty

Designing the design space

MBDoE with backoffs: The basic idea

**Estimated Optimum**
\[ u = [u_1^*, u_2^*] \]

**Feasible region** for design inputs at initially assumed \( \theta^* \)

**Optimum**
\[ u = [u_1, u_2] \]

**Actual feasible region** at \( \theta \)

**Backoff Vector** \( \beta' \)
\[ \beta' = g (\theta^* - \theta) \]
\[ \beta' = g (p_\theta) \]

---

MBDoE with backoff from active constraints

MODEL

\[ f(\tilde{x}(t), \tilde{x}(t), u(t), w, \tilde{\theta}, t) = 0 \]

\[ \hat{y}(t) = g(\tilde{x}(t)) \]

DESIGN OPTIMALITY CONDITION

\[ \varphi = \arg \min \psi \left( V_{\theta} (\tilde{\theta}, \varphi) \right) \]

FEASIBILITY CONDITION

\[ C = x(t) - G(t) + \beta(\tilde{x}(t), \tilde{x}(t), u(t), w, \tilde{\theta}, t) \leq 0 \]

\[ \varphi_i^l \leq \varphi_i \leq \varphi_i^u \]
MBDoE with backoffs: the new iterative scheme
MBDoE with backoffs: optimisation loop

Stochastic simulation

Characterisation of parameters uncertainty

Mapping uncertainty $p_{x|\phi}(\xi_x(t), t)$

Backoff $\beta$ formulation

Constrained MBDoE

Experiment design

$\phi = \arg \min \psi(V_\theta)$

Constraints definition

$C = x(t) - G(t) + \beta$
MBDoE with backoffs: an illustrative example

Hyperglycemic conditions realised!

Optimal design result
MBDoE with backoffs: pros and cons

- Uncertainty is dealt with explicitly within the MBDoE framework
- Proved effectiveness at guaranteeing optimal and feasible experiments even for complex models

- Characterisation of parametric uncertainty is a complex task (global sensitivity analysis may help)
  - Model mismatch increase complexity considerably
- Representation of uncertainty in state variables is a critical issue
  - assuming a normal distribution may lead to erroneous definition of the design space
- High uncertainty may lead to null design space
- Heavy computation burden
Towards online redesign of experiments for model identification

Updating system knowledge

The information flux: gains and leakages

- **Prior Info**
- **Updated Prior Info**
- **Info Gain**
- **Expected Information**
- **Actual Information**
- **Information Extraction**

**INFORMATION SINK**
- Measurements error (correlation and distribution)
- Unmeasured disturbances

**INFORMATION SINK**
- Parameters mismatch and correlation
- Design optimality and efficiency

**INFORMATION SINK**
- Estimator efficiency
- Outliers, lack of fit
- Parameters correlation
Online Model-based re-design of experiment (OMBRE)

1. Design of experiment
2. Experiment execution
3. Parameter estimation
4. Redesign of experiment

The presence of a systematic error between the model and the system (bias) is not explicitly handled by OMBRE.
OMBRE procedure

1. Design experiment
2. Start experiment
3. Re-design? (NO: Continue, YES: Parameter estimation)
4. Parameter estimation
5. Satisfactory? (YES: STOP, NO: Re-design of experiment)
6. Re-design of experiment
7. End? (NO: Re-design of experiment, YES: STOP)
8. Stop
OMBRE including disturbance estimation (DE-OMBRE)

Design experiment
Start experiment
Re-design?
Disturbance pre-estimation
Parameter estimation
Satisfactory?
Disturbance post-estimation
Re-design of experiment
End?

Continue

First disturbance estimation step

Second disturbance estimation step

A disturbance model must be introduced to handle systematic errors.

Augmented model including disturbances $d$:

\[
\begin{align*}
    f(\dot{x}, x, u, w, \theta, t) &= 0 \\
    \hat{y} &= h(x) + d \\
    \dot{d} &= 0
\end{align*}
\]

$N_y$-dimensional set of lumped disturbances on the outputs

FEASIBILITY CONDITION

\[
H(h(x) + d) - D(t) \leq 0
\]

Systematic update of constraints
Disturbance estimation (DE step)

\( d \) can be estimated through a **two step procedure**:

1) **Prediction**: simulation of the augmented model with \( d = d_{k|k-1} \)

2) **Filtering**: given the measurement \( y_k \) the prediction error is

\[
 e_k = y_k - h(x_k) - d_{k|k-1} \\
 d_{k|k} = d_{k|k-1} + L_d e_k 
\]

\( L_d = \text{tuning parameter} \)

Based on the actual measurement confidence
1. fixed to 1
2. estimated by an extended Kalman filter (EKF)
Example: identification of type 1 diabetes models

**Diabetes**: metabolic disease characterised by high concentrations of fasting blood glucose
- no production of insulin (Type I)
- partial production (Type II)

**Hyperglycaemia**
- Kidney failure, Blindness, Stroke 
  (prolonged period)

**Hypoglycaemia**
- Loss of consciousness, Coma 
  (short period)

**Artificial pancreas** → automatic insulin delivery for maintaining normoglycaemia

- GLUCOSE SENSOR FOR MEASUREMENTS
- INSULIN INFUSION PUMP
- CONTROL ALGORITHM → DIABETES MODELS
Comparison of design configurations

Optimal design of clinical tests for the identification of diabetes models

**Design variables**
- time allocation and amount of 4 fast acting Lispro boluses
- time allocation and amount of carbohydrates of 4 meals

**Constraints**
- upper ($D_1 = 180 \text{ mg/dL, “soft”}$) and lower ($D_2 = 60 \text{ mg/dL, “hard”}$) thresholds on $G$
- simple bounds on design variables

Initial guess on model parameters: $\theta^0 = [1.000 \ 1.000 \ 1.000]^T$

True set defining the diabetic subject: $\theta = [0.025 \ 1.250 \ 5.400]^T$

**Compared design configurations**
- **OMBRE**: E-optimal redesign (a redesign is scheduled every $\Delta t_{up} = 6 \text{ hours}$)
- **DE-OMBRE**: E-optimal redesign including disturbance estimation ($\Delta t_{up} = 6 \text{ hours}$)
Case Study: OMBRE

- hypoglycemia occurs
- the OMBRE approach is not able to preserve the feasibility of the test
- poor predictive capability of the model
Case Study: DE-OMBRE

- the test is safe and optimally informative
- very good predictive capability of the model
DE-OMBRE: disturbance estimation

DE-OMBRE (\(L_d = 1\))

- Design value
- Estimated disturbance
- Disturbance

DE-OMBRE (EKF)

- Estimated disturbance
- Disturbance

DE-OMBRE allows for the detection of systematic errors

DE-OMBRE including extended Kalman filtering:
- disturbance estimation is more stable
- parameter estimation can be improved
OMBRE/DE-OMBRE: Pros and cons

👍 Very pragmatic approach to deal with uncertainty
👍 Significant reduction in the optimisation problem complexity (and computational burden)
👍 Highly flexible
  • Possible to include backoffs
  • Possible to change design criterion during the same experiment
👍 DE-OMBRE handle the presence of systematic modelling errors or disturbances allowing for the best possible estimation of model parameters
👍 Robustness increased

👎 Difficult to tune “complexity” in the disturbance estimation (DE) method
  • Some disturbance estimation methods may “compensate too much”
    → is the resulting model helpful without the disturbance model?
👎 No sound rule to choose among different updating approaches
Remarks: what we have

- An application-independent methodology for DoE/MBDoE
- A suite of advanced techniques and procedures for the optimal design of experiments in the presence of uncertainty
- A framework for the applications of advanced MBDoE techniques to the online identification of deterministic models

Now some applications more in detail ...
A model-based design of experiments approach for the identification of kinetic models of methanol oxidation on silver catalyst

A systematic approach to kinetic modeling
Outline

• Introduction and problem definition
  – Development of kinetic models for methanol oxidation on silver catalyst
• Microstructured reactors for kinetics evaluation
• Candidate kinetic mechanisms
• Microreactor model
• Model-based Design of Experiments (MBDoE)
  – Experimental design procedure
  – Definition of the experimental design space
  – Information maps and ranking of experiments
  – Multi-objective design formulation
• Results
• Final remarks
Introduction and problem definition (I)

Formaldehyde is one of the world’s most important chemicals.

Industrial formaldehyde synthesis → catalytic oxidation of methanol

- **Silver catalyst process** (50% of the total in Western Europe)
  - Catalyst: Ag under lean air conditions
- **Formox process**
  - Catalyst: Ferric molybdate at excess air condition

Polyurethane and polyester plastics

- Resins
- Dyes
- Tanning, coating and bonding agents
- Disinfectant, tissue fixative, …
Introduction and problem definition (II)

Silver catalyst process: industrial conditions
- Atmospheric pressure
- 1:1 oxygen-methanol mixture
- Temperature range 850 – 923 K
- If steam is introduced (H$_2$O/CH$_3$OH = 0.67) and CH$_3$OH/O$_2$ = 2.4-2.5
  $\rightarrow$ CH$_2$O selectivity $\sim$ 90%

Overall oxidation process

Partial methanol oxidation
$CH_3OH + \frac{1}{2}O_2 \rightarrow CH_2O + H_2O$ $-159$ kJ mol$^{-1}$

Methanol dehydrogenation
$CH_3OH \rightarrow CH_2O + H_2$ $+84$ kJ mol$^{-1}$

Goals of the study
- Kinetic modeling of the process at industrial conditions (T) in microfluidic devices
- Detection of the most informative experimental regions for model development
  $\rightarrow$ Model-based design of experiments (MBDoE)

Observed by-products
- H$_2$, CO, H$_2$O, CO$_2$
- HCOOCH$_3$, CH$_2$O$_2$
Microreactors for kinetics evaluation

• **Microreactors** are miniaturized reaction systems
• **Dimensions**: 10s - 100s micron scale
• **Main uses**
  – Reaction Kinetic Studies
  – Catalytic Testing
  – High Pressure/Temperature Chemistries
  – Nanoparticle Synthesis

**Advantages of microreactors**

• Allow to exploit continuous processes
• High heat and mass transfer
• Minimal consumption of reagents/catalyst
• Millisecond residence time to study fast reactions
• Suitable to numbering-out (as opposed to scale-up)
• Safer systems for managing hazardous chemistries
• Ability to explore a wide reaction space
Kinetic models of methanol oxidation on silver

Oxidative dehydrogenation of methanol: understanding the role of adsorbed oxygen

- Bhattacharyya (1967-1971)
- Juusola et al. (1970)
- Graydon et al. (1970)
- Robb and Harriott (1974)
- Wax and Madix (1978)
- Lefferts et al. (1986-1987)
- Andreasen et al. (2003)
- Andreasen et al. (2005)

Steady-state adsorption model (537-563 K)
Steady-state adsorption model: generalisation
Langmuir-Hinshelwood mechanism: total methanol reaction rate
Mechanism via methoxy intermediate ($\text{CH}_3\text{O}^*$) is introduced
Different oxygen species at the catalyst surface
Full microkinetic model
Microkinetic model simplified

Full understanding of kinetics of the reaction on silver at industrially relevant reaction temperature still to be established!
**Andreasen microkinetic model**\(^1\)**

Microkinetic model based on Langmuir-Hinshelwood mechanism 
→ Wachs and Madix (1978) suggested mechanism (via methoxide)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Description</th>
<th>Equilibrium equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3\text{OH} + * \rightleftharpoons \text{CH}_3\text{OH}^*)</td>
<td>Methanol adsorption</td>
<td>(\theta_{\text{CH}<em>3\text{OH}^*} = K_1 p</em>{\text{CH}_3\text{OH}} \theta^*)</td>
</tr>
<tr>
<td>(\text{O}_2 + * \rightleftharpoons \text{O}_2^*)</td>
<td>Molecular oxygen adsorption</td>
<td>(\theta_{\text{O}<em>2^*} = K_2 p</em>{\text{O}_2} \theta^*)</td>
</tr>
<tr>
<td>(\text{O}_2^* \rightleftharpoons 2\text{O}^*)</td>
<td>Atomic oxygen adsorption</td>
<td>(\theta_{\text{O}^<em>} = (K_3 p_{\text{O}_2} \theta^</em>)^{1/2})</td>
</tr>
<tr>
<td>(2\text{CH}_3\text{OH}^* + \text{O}^* \rightleftharpoons \text{CH}_3\text{O}^* + \text{H}_2\text{O}^*)</td>
<td>Methanol selective oxidation</td>
<td>(\theta_{\text{CH}<em>3\text{O}^*} = \theta</em>{\text{CH}<em>3\text{OH}^*} \left(\frac{K_4 \theta</em>{\text{O}^<em>} \theta_{\text{H}_2\text{O}^</em>}^1}{\theta^*}\right)^{1/2})</td>
</tr>
<tr>
<td>(\text{CH}_3\text{O}^* + * \rightleftharpoons \text{H}_2\text{CO}^* + \text{H}^*) (SLOW)</td>
<td>Formaldehyde from methoxide</td>
<td>(r_5 = K_5 \theta_{\text{CH}<em>3\text{O}^<em>} \theta^</em> - k</em>{-5} \theta_{\text{H}<em>2\text{CO}^*} \theta</em>{\text{H}^*})</td>
</tr>
<tr>
<td>(\text{CH}_2\text{O}^* \rightleftharpoons \text{H}_2\text{CO} + *)</td>
<td>Products desorption</td>
<td>(\theta_{\text{CH}<em>2\text{O}^*} = K_6^{-1} p</em>{\text{CH}_2\text{O}} \theta^*)</td>
</tr>
<tr>
<td>(2\text{H}^* \rightleftharpoons \text{H}_2 + *)</td>
<td>Products desorption</td>
<td>(\theta_{\text{H}^<em>} = K_7^{-1/2} p_{\text{H}_2}^{1/2} \theta^</em>)</td>
</tr>
<tr>
<td>(\text{H}_2\text{O}^* \rightleftharpoons \text{H}_2\text{O} + *)</td>
<td>Products desorption</td>
<td>(\theta_{\text{H}<em>2\text{O}^*} = K_8^{-1} p</em>{\text{H}_2\text{O}} \theta^*)</td>
</tr>
<tr>
<td>(\text{H}_2\text{CO}^* + \text{O}^* \rightleftharpoons \text{HCOO}^* + \text{H}^*)</td>
<td>Formate formation</td>
<td>(\theta_{\text{HCOO}^<em>} = K_9 \theta_{\text{H}_2\text{CO}^</em>} \theta_{\text{O}^<em>} / \theta_{\text{H}^</em>})</td>
</tr>
<tr>
<td>(\text{HCOO}^* + * \rightleftharpoons \text{CO}_2^* + \text{H}^*) (SLOW)</td>
<td>Formate decomposition</td>
<td>(r_5 = K_{10} \theta_{\text{HCOO}^<em>} \theta^</em> - k_{-10} \theta_{\text{CO}<em>2^*} \theta</em>{\text{H}^*})</td>
</tr>
<tr>
<td>(\text{CO}_2^* \rightleftharpoons \text{CO}_2 + *)</td>
<td>Products desorption</td>
<td>(\theta_{\text{CO}<em>2^*} = p</em>{\text{CO}<em>2} \theta^* / K</em>{11})</td>
</tr>
</tbody>
</table>
Andreasen simplified model\(^1\)

The full microkinetic model is limited to the representation of the rate limiting steps. The following two overall reactions may be derived:

1) \[ CH_3OH + \frac{1}{4} O_2 \rightleftharpoons H_2CO + \frac{1}{2} H_2 + \frac{1}{2} H_2O \]  
   Methanol oxidation to formaldehyde

2) \[ H_2CO + \frac{1}{2} O_2 \rightleftharpoons CO_2 + H_2 \]  
   Oxidation of formaldehyde to carbon dioxide

Derived kinetic expressions:

\[ r_5 = k_5 K_A \frac{p_{CH_3OH}}{p^\Theta} \left( \frac{p_{O_2}}{p^\Theta} \right)^{1/4} \left( \frac{p_{H_2O}}{p^\Theta} \right)^{-1/2} (1 - \beta_I) \theta^* \]

\[ r_{10} = k_{10} K_B \frac{p_{H_2CO}}{p^\Theta} \left( \frac{p_{H_2}}{p^\Theta} \right)^{-1/2} \left( \frac{p_{O_2}}{p^\Theta} \right)^{1/2} (1 - \beta_{II}) \theta^* \]

\[ \beta_I, \beta_{II} = \text{approach to the equilibrium} \]

\[ \theta^* = \text{global coverage} \]

\[ N = \text{number of species on the surface} \]
Oxidation pathways

Together with 1) and 2), also the combustion reactions have to be taken into account:

- Selectivity towards formaldehyde is limited by combustion reactions (favoured at lower T).
- CO formation is negligible under $T = 900\, \text{K}$ (pyrolytic gas phase reaction).

Proposed competitive kinetic mechanisms

<table>
<thead>
<tr>
<th>$N^{\text{rea}}$</th>
<th>Reactions</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{CH}_3\text{OH} + 1/4\text{O}_2 \rightleftharpoons \text{CH}_2\text{O} + 1/2\text{H}_2 + 1/2\text{H}_2\text{O}$</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>$\text{CH}_2\text{O} + 1/2\text{O}_2 \rightleftharpoons \text{H}_2 + \text{CO}_2$</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3</td>
<td>$\text{CH}_3\text{OH} + 3/2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{CO}_2$</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4</td>
<td>$\text{CH}_2\text{O} + \text{O}_2 \rightarrow \text{H}_2\text{O} + \text{CO}_2$</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5</td>
<td>$\text{CH}_3\text{OH} \rightleftharpoons \text{CH}_2\text{O} + \text{H}_2$</td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>6</td>
<td>$\text{CH}_3\text{OH} + 1/2\text{O}_2 \rightleftharpoons \text{CH}_2\text{O} + \text{H}_2\text{O}$</td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>7</td>
<td>$\text{H}_2 + 1/2\text{O}_2 \rightarrow \text{H}_2\text{O}$</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Number of kinetic parameters ($N_{\theta}$)</td>
<td>6</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Comments

- **Model 1**: reaction 1-2 from Andreasen model, reaction 7 occurring at high T\(^1\)
- **Model 2**: like Model 1, includes combustion reactions
- **Model 3**: includes separate methanol dehydrogenation (5) and oxidation pathways (6)

Microreactor model

Modeled as a plug flow reactor (PFR)

\[ \frac{\partial c_i}{\partial t} + v_z \frac{\partial c_i}{\partial z} = \sum_{j=1}^{N_{\text{reaz}}} v_{ij} r_j \]

- \( c_i \) is the species concentration
- \( r_j \) and \( v_{ij} \) are the reaction rate and the stoichiometric coefficient of the \( i \)-th species in the \( j \)-th reaction
- \( z \) is the axial coordinate
- \( v_z \) is the speed of fluid flow in the \( z \)-direction
- \( t \) the integration time

Mass balance for component \( i \)

System of Differential and Algebraic Equations (DAEs)

\[
\begin{align*}
    f(\dot{x}(z,t), x(z,t), u(z,t), \theta, t) & = 0 \\
    \hat{y}(z,t) & = g(x(z,t))
\end{align*}
\]

- \( x \) = reactant/products concentrations
- \( u \) = input variables \((T, P, F)\)
- \( \hat{y} \) = set of measured concentrations
- \( \theta \) = set of model parameters

Reaction channel

\( H = 0.12 \text{ mm} \)

\( W = 0.6 \text{ mm} \)

Estimation of kinetic parameters

\[
k_i = \exp\left[\ln(A_i) \left(\frac{T}{T_0} - E_i\right)\right] \quad i = 1 \ldots N_{\text{reaz}}
\]

Pre-exponential factors \((A_i)\) and activation energies \((E_i)\)
Experimental design procedure

1. Propose (probable) reaction mechanisms
2. Formulation of competitive kinetic models
3. Evaluation of model complexity/model reduction
4. Model-Based Design of Experiments
   - For model discrimination
   - For improving parameter precision
5. Experiment execution
6. Parameter Estimation
7. Discard inadequate models

Consideration:
- Yes: Continue
- No: Discard

References:
Model-based design of experiments: formulation

New MBDoE formulation for microreactor platforms

Fisher information matrix (FIM)

\[
H_{\theta}(\theta, \varphi) = H^0_{\theta} + \sum_{k=1}^{n_w} \sum_{i=1}^{N_x} \sum_{j=1}^{N_y} S_{ij} \left[ \frac{\partial \hat{y}_i(z_k, t_k)}{\partial \theta_i} \frac{\partial \hat{y}_j(z_k, t_k)}{\partial \theta_m} \right]_{I,m=1...N_{\theta}}
\]

Optimal design for improving parameter estimation

\[
\varphi^{PE} = \arg \min_{\varphi \in D} \left\{ \psi \left[ V_{\theta}(\theta, \varphi) \right] \right\} = \arg \min_{\varphi \in D} \left\{ \psi \left[ H^{-1}_{\theta}(\theta, \varphi) \right] \right\}
\]

Design vector

\[
\varphi = \left[ y_0, u, t^{sp}, \tau \right]^T
\]

- \(y_0\) set of initial conditions on the measured variables \((C_i)\)
- \(u\) set of manipulated inputs \((T, P, F)\)
- \(t^{sp}\) set of time instants at which the measured variables are sampled
- \(\tau\) the experiment duration (possibly)
Information maps and ranking of experiments

Amount of information which can be obtained for the estimation of the \( j \)-th model parameters from the \( i \)-th experiment

→ Relative Fisher Information (RFI) index

\[
RFI_{ij} = \frac{\|H_{ij}\|}{\sum_{i=1}^{N_{\text{exp}}} \|H_{ij}\|} = \frac{\|H_{ij}\|}{\|H_j\|}
\]

FIM related to the \( i \)-th experiment for the \( j \)-th competitive model

Global FIM obtained from the \( N_{\text{exp}} \) experiments for the identification of the \( j \)-th model

\| - \| is a matrix norm (trace, determinant, maximum eigenvalue).

Given a candidate model it is possible

• To detect the best experimental conditions for model identification
• To evaluate the amount of information related to one or more experiments
  (→ ranking of performed experiments)

Relative Fisher Information

Number of experiments

Model 1
Joint Model-based Design of Experiments

Multi-objective MBDoE formulation

- Optimal design for discriminating between $N_M$ competing kinetic models\(^1\)
- Optimal design for improving the estimation of kinetic parameters\(^2\)

$$
\phi^{MD} = \arg \max_{\phi \in D} \left\{ \psi^{MD} \right\} = \arg \max_{\phi \in D} \left\{ \sum_{M,N=1}^{N_M} P_M P_N \left[ \sum_{i=1}^{N_i} \frac{(\hat{y}_{M,i} - \hat{y}_{N,i})^2}{\sigma_{y,i}^2} \right]_M,N \right\}
$$

$$
\psi^{PE} = \sum_{j=1}^{N_M} \| H_j \| \leq N_M \leq \varepsilon
$$

\text{st} \ \varepsilon^{MIN} \leq \varepsilon \leq \varepsilon^{MAX}

“\varepsilon\text{-constraint method}”\(^3\)

MBDoE for model discrimination

MBDoE for improving parameter estimation

Design of experimental conditions providing the greatest difference between model predictions

... ensuring at the same time the best possible reduction of parametric uncertainty

\(P_i = \text{probability of the i-th model to be the “true” model}\)

\(\hat{y}_{ji} = i\text{-th predicted response of the } j\text{-th model}\)


MBDoE: definition of the experimental design space D

Elements of the design vector $\phi$ and design space $D$

- Composition of reactants in terms of molar fractions
  - methanol (0.07-0.14)
  - oxygen (0.03-0.10)
  - water (0.02-0.22)
- Temperature $T$ ($725 \text{ K} < T < 826 \text{ K}$)
- Pressure $P$ (1.6-1.7 atm)
- Flow rate $F$ (25-27 mL/min)

Number of performed experiments $N^{\text{exp}} = 21$

- Experiments E1-5: $T$ varied from 725 to 826 K ($y_{\text{CH}_3\text{OH}} = 0.10$, $y_{\text{O}_2} = 0.04$, $y_{\text{H}_2\text{O}} = 0.07$)
- Experiments E6-9: $T$ varied from 725 to 826 K ($y_{\text{CH}_3\text{OH}} = 0.15$, $y_{\text{O}_2} = 0.06$, $y_{\text{H}_2\text{O}} = 0.11$)
- Experiments E10-21: $T$ kept at 733 K, variable $y_{\text{CH}_3\text{OH}}$ (range 0.07-0.14, E10-E14), $y_{\text{O}_2}$ (range 0.03-0.10, E15-E17) and $y_{\text{H}_2\text{O}}$ (range 0.02-0.21, E18-E21)

Concentration measurements

$\rightarrow$ CH$_3$OH, O$_2$, CH$_2$O, H$_2$, H$_2$O and CO$_2$ at the inlet ($z = 0$) and outlet ($z = l$) of the reactor (3% max error)
Results: model discrimination (I)

Results after model identification: molar fraction profiles Vs temperature

**Comments**
- Model 1 fails to represent O\textsubscript{2} concentration profiles
- Great improvement if combustion reactions are included in the model formulation
- Model 2/3 providing good results in terms of CH\textsubscript{3}OH, O\textsubscript{2} and H\textsubscript{2}O representation
Results: model discrimination (II)

Results after model identification: molar fraction profiles Vs temperature

Comments
• Model 1 fails to represent CO₂ and CH₂O at lower temperatures
• Model 3 provides an excellent fitting of CH₂O concentrations
  → importance of competitive methanol dehydrogenation/selective oxidation pathways
• Model 3 is the only model able to represent the CO₂ trend
Results: model discrimination (III)

Trade-off between **model complexity** \( (N_\theta) \) and **model adequacy** \( (\chi^2, P_i) \)

\[ \text{AIC} = 2N_\theta - 2\ln \chi^2 \quad \text{(Akaike Information Criterion)} \]

<table>
<thead>
<tr>
<th>Model</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \chi^2 )</td>
<td>9762</td>
<td>7721</td>
<td>6874</td>
</tr>
<tr>
<td>( N_\theta )</td>
<td>6</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>AIC</td>
<td>-6.4</td>
<td>2.1</td>
<td>6.3</td>
</tr>
<tr>
<td>( P_i )</td>
<td>27%</td>
<td>34%</td>
<td>39%</td>
</tr>
</tbody>
</table>

**Model 3**: best fitting, but higher number of model parameters
### Results: Model Discrimination (III)

| Param.   | Estimated Value       | 95% conf. interval | t-value  
|----------|-----------------------|--------------------|----------
| $A_1$ [mol/m$^2$ s] | 308.360 ($\times 10^4$) | 328.008            | 0.940    |
| $A_2$ [mol/m$^2$ s] | 23.760 ($\times 10^4$)  | 104.800            | 0.227    |
| $A_3$ [mol/m$^2$ s] | 3.176 ($\times 10^4$)   | 3.976              | 0.799    |
| $A_4$ [mol/m$^2$ s] | 13.016 ($\times 10^4$)  | 296.641            | 0.044    |
| $A_5$ [mol/m$^2$ s] | 16.48 ($\times 10^4$)   | 8.8$\times 10^8$   | 2.3$\times 10^{-8}$ |
| $A_6$ [mol/m$^2$ s] | 0.201 ($\times 10^4$)   | 1.011              | 0.199    |
| $E_1$ [kJ/mol]     | 128.82                 | 6.88               | 18.620   |
| $E_2$ [kJ/mol]     | 146.41                 | 28.96              | 5.061    |
| $E_3$ [kJ/mol]     | 86.72                  | 8.01               | 10.830   |
| $E_4$ [kJ/mol]     | 124.24                 | 146.16             | 0.849    |
| $E_5$ [kJ/mol]     | 416.25                 | 3.7$\times 10^7$   | 1.4$\times 10^{-7}$ |
| $E_6$ [kJ/mol]     | 48.37                  | 32.63              | 1.48     |
After model discrimination ($N^{exp} = 21$ performed experiments)

- Model 3 is the best model in terms of fitting capability
- With the available set of experiments it is not possible to estimate the set of kinetic parameters in a statistically sound way

Model 3 is structurally identifiable

→ a number of experiments is poorly informative for model identification in the design space $D$

Need to detect the most informative experimental conditions

→ MBDoE and ranking of performed experiments
Results: ranking of performed experiments

Performed experiments: evaluation of RFI for each candidate kinetic model

Each model needs specific experimental conditions for the precise estimation of the kinetic parameters

Comments

- Increment on temperature → beneficial for Model 2
  → unhelpful for Model 1 and 2
- Increment on oxygen concentration in the feed → always beneficial
- High methanol concentration in the feed → beneficial for Model 2 and 3
  → maximum in the information realised for Model 1
- Increment on water concentration in the feed → increases the information for Model 1 and 2
  → it does not particularly affect Model 3 identification
Highly informative experiments are characterised by high methanol, oxygen and water concentration.

The optimal experimental conditions are:
- \( T = 800 \, K \), \( P = 165000 \, \text{Pa} \), \( F = 26 \, \text{mL/min} \);
- methanol, oxygen and water initial molar fractions:
  \[ y_0 = [y_{\text{CH}_3\text{OH}} \, y_{\text{O}_2} \, y_{\text{H}_2\text{O}}]^T = [0.14 \, 0.10 \, 0.22]^T \]
Joint MBDoE: computation of trade-off solutions

Optimal conditions:

\[
\mathbf{y}_0 = [y_{\text{CH}_3\text{OH}} \ y_{\text{O}_2} \ y_{\text{H}_2\text{O}}] \mathbf{T} = [0.14 \ 0.10 \ 0.22] \mathbf{T}
\]

\[F = 26.0 \text{ mL/min}\]
\[P = 1.6 \text{ atm}\]

Variable temperature:

\[T^4 = 826 \text{ K}\]
\[T^3 = 796 \text{ K}\]
\[T^2 = 765 \text{ K}\]
\[T^1 = 732 \text{ K}\]
Joint MBDoE: optimal design of temperature profile

**GOAL:** optimal design of a sequence of steady state experiments for *simultaneous* improvement of parameter precision and model discrimination

![Graph showing temperature profile and design optimization points](image)
Joint MBDoE: optimal design results

j-MBDoE allows for a **substantial reduction of parametric uncertainty** related to critical kinetic parameters\(^1\).

Model prediction of j-MBDoE experiments

- **Model 3** is the only model predicting an increase of CH\(_2\)O selectivity with T.

---

Final remarks

• Candidate kinetic models for methanol oxidation on Ag have been developed
• Model discrimination results
  – Model 1 → fails on representing $O_2$ and $CO_2$ concentrations
  – Model 3 → best model in terms of fitting capability
    • Methanol selective oxidation and dehydrogenation pathways are included
    • Total oxidation pathways for $CH_3OH$ and $CH_2O$ are included
  – Critical issue: **precise estimation of the model parameters**
• Model-based design of experiments (MBDoE)
  – Screening of the design space for the precise estimation of the model parameters
    • Quantitative evaluation of information: **ranking of experiments**
  – Joint Model-based Design of Experiments (j-MBDoE)
    • simultaneous **model discrimination** and **improvement of parameter precision**
Towards a model-based diagnosis of Von Willebrand disease

A systems engineering approach for pharmacokinetic modeling

Outline

• Introduction
  – Von Willebrand Disease (VWD)
  – Clinical evaluation of subjects affected by VWD
• Model development and identification from clinical tests
  – Suitable model structures
  – Parameter estimation results for distinct classes of subjects
• Model-based diagnosis: a case study
  – Classification of subjects affected by VWD type 1
• Model-based design of clinical tests
• Final remarks
**Von Willebrand Disease (VWD)**

**Von Willebrand disease (VWD)**
- the most common inherited coagulation disorder described in humans (~1% the global incidence in the world)
- characterised by a deficiency and/or dysfunction of the *von Willebrand factor* (VWF)
- **VWF** is a large multimeric glycoprotein
  - mediates the aggregation of platelets
  - promotes the coagulation factor VIII (FVIII) in the blood stream

**Typical VWD symptoms:** nosebleeds, excessive bleeding from small lesions in skin, menorrhagia

**VWD classification**

**Type 1** → VWF quantitative defect
- very heterogeneous nature

**Type 2** → VWF functional defect
- 2A, 2B, 2N, 2M

**Type 3** → virtual absence of VWF

**Vicenza** → no anomalies in multimer distribution, reduced VWF levels

Base mechanisms of VWF release and distribution

- **VWF RELEASE**
  - secretion of super ultra-large multimers (SUL)

- **VWF PROTEOLYSIS**
  - proteolysis of SUL to smaller species operated by a specific enzyme (ADAMTS 13)

- **VWF CLEARANCE**
  - elimination from plasma (independent by multimer size)
Medical evaluation of a subject affected by VWD

- Evaluation of the patient history and general physical examination

  **Preliminary VWD tests**
  - VWF levels (Ag/RCo/CB) and activity (FVIII)

  **Advanced VWD tests**
  - DDAVP, multimer distribution, platelet/FVIII binding

- DDAVP test
  - Antigen (VWF:Ag) measurements
  - Collagen-binding (VWF:CB) measurements
  - Multimeric assay (gel electrophoresis)

VWD diagnosis → analysis of the available data from preliminary and advanced laboratory tests
The available data set: average profiles

Clinical data

Antigen measurements

Collagen-binding measurements
The available data set: individual profiles

1. Strong heterogeneity between subjects (and different dynamics)
2. Presence of strong oscillations (outliers?) on measurements
The available data set

Multimeric analysis via gel electrophoresis

- Evaluation of UL, H, and L multimeric species
Model discrimination: suitable model structures

Compartmental pharmacokinetic models → systems of differential and algebraic equations (DAEs)

Main issue: ensuring model identifiability from VWF:Ag/CB measurements only → Model 2

Galvanin et al. (2014), AIChE J, 60, 1718-1727.
Model 2: features and assumptions

Features
1. D release of super ultralarge (SUL) multimers
2. Proteolysis of SUL to ultralarge/high (UL+H) and low (L) molecular weight multimers
3. Reduction of (UL+H) to L
4. Correction on CB measurements

\[ y^{CB'} = k_y^{CB} \frac{y_b^{AG}}{y_b^{CB}} = k_y^{CB} \left( 1 + \frac{x_b^L}{x_b^H} \right) \]

Assumptions
1. At the basal state only H and L are present (UL = SUL = 0)
2. VWF:AG reproduces the evolution in time of UL+H+L, whereas VWF:CB reproduces UL+H
3. SUL cannot be measured directly
Flux analysis and model parameters

**Identifiable set of model parameters**

\[ \theta = \begin{bmatrix} k_0 D / k_e & k_1 & k_2 & k_3 & k_e & D \end{bmatrix} \]
**Standard PK parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (Clearance)</td>
<td>$CL = k_e V_d$</td>
<td>mL/kg/h</td>
</tr>
<tr>
<td>$Q$ (Amount of VWF released)</td>
<td>$Q = BW^{-1} \int \limits_0^\infty k_0 D \exp(-k_0(t-t_{max})) dt$</td>
<td>U/kg</td>
</tr>
<tr>
<td>$T_{1/2el}$ (Elimination half-life)</td>
<td>$T_{1/2el} = \frac{\ln 2}{k_e}$</td>
<td>h</td>
</tr>
</tbody>
</table>

**Heuristic indicators**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Formula</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_1$ (VWF release rate)</td>
<td>$I_1 = k_0 \int \limits_0^\infty F_0 dt$</td>
<td>U/h</td>
</tr>
<tr>
<td>$I_2$ (Proteolysis rate)</td>
<td>$I_2 = k_3 \int \limits_0^\infty F_3 dt$</td>
<td>U/h</td>
</tr>
<tr>
<td>$I_3$ (Clearance rate)</td>
<td>$I_3 = k_e \int \limits_0^\infty F_4 dt + k_e \int \limits_0^\infty F_5 dt$</td>
<td>U/h</td>
</tr>
</tbody>
</table>
Estimation of PK parameters

The model representation of key PK parameters is in **very good agreement** with available physiological data.
Individual VWF:Ag/CB data are available for two (supposed) unknown subjects
1. **Subject A** (healthy non-O)
2. **Subject B** (VWD type 2B)
Model-based diagnosis: results (I)

Results after parameter estimation are analysed in terms of sum of squared weighted residuals (SSWR):

$$SSWR = \sum_{i=1}^{N} \sum_{j=1}^{M} \sum_{k=1}^{N_{sp}} r_{ijk}^2 / \sigma_{ijk}^2 = \sum_{i=1}^{N} \sum_{j=1}^{M} \sum_{k=1}^{N_{sp}} \left(y_{ijk} - \hat{y}_{ijk}\right)^2 / \sigma_{ijk}^2$$

<table>
<thead>
<tr>
<th>Subject</th>
<th>Healthy O</th>
<th>Healthy non-O</th>
<th>2A</th>
<th>2B</th>
<th>Vicenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5350</td>
<td>3409</td>
<td>7268</td>
<td>8311</td>
<td>9148</td>
</tr>
<tr>
<td>B</td>
<td>92</td>
<td>87</td>
<td>50</td>
<td>20</td>
<td>177</td>
</tr>
</tbody>
</table>

model-based diagnosis consistent with clinical diagnosis
Model-based diagnosis: results (II)

Diagnosis is **clear**
- **Subject A** → healthy non-O
- **Subject B** → VWD type 2B

Excellent fitting of VWF levels is realised
Classification of VWD type 1: problem definition

Classification of type 1 subjects from individual VWF:Ag/CB data is a complex and not fully resolved issue.

5 distinct pools of genetically characterised subjects from preliminary studies\(^1\):

- No Mutation
- Missense mutation
- Nonsense mutation
- Missense C1130F
- Normal subjects

\(^1\)Casonato et al. (2010), *Transl Res*, 155, 200-208
Despite the great simplification with respect to genetic investigation, the model can represent with good accuracy most classes VWD type 1 through much less expensive clinical tests. Several complex genetic exceptions are detected, too.
Final remarks

- Development of two identifiable mechanistic models for the description of VWD
  - Quantitative assessment of biochemical pathways for pools of subjects
  - Either model can be used depending on quality of available measurements
- Potential for representing specificity of single subjects
- Faster and more effective diagnosis from clinical data.
- Design for shorter and easier clinical tests
  - Minimum stress for the subject
  - Strong impact on the economy of diagnostic procedures
- Future work
  - Investigating the relationship between PK parameters and genetics in type 1 VWD
  - In silico experiments for the development of customized therapeutic procedures
Other MBDoE applications: bioengineering (I)

- Optimal design of clinical tests for the identification of complex physiological models of type I and II diabetes mellitus (Galvanin et al., 2009-2013)
  - wearable artificial pancreas (WAP) project
  - impact of the use of continuous glucose monitoring systems (CGMs) on model identification

- Optimal chemotherapeutic drug administration for the identification of cancer models (Galvanin et al., 2010)
  - managing the delivery of chemotherapeutic agents under the uncertainty scenario
Advanced model-based design of experiments for the identification of PK-PD models (Galvanin et al., 2013)

→ optimisation of antibiotic dosage
→ optimal design of parallel PK-PD experiments

An identifiable state model to describe light intensity influence on microalgae growth (Bernardi et al., 2014)

→ model discrimination
→ development of structurally identifiable models of algal growth
Other MBDoE applications: process systems engineering

- Parallel design of experiments for the identification of bacterial inactivation models (Galvanin et al., 2014)
  - bacterial inactivation by supercritical CO₂
  - optimal sampling and investigation of the process conditions (T,P)

- Design of experiments for the identification of models for electrodialysis desalting (Galvanin et al., under review)
  - modeling an electrodialysis process for the treatment of liquids in food industry
  - optimal design managing electric current intensity profile
  - great reduction of experimental time if the current intensity profile is managed by MBDoE
Thank you for your attention