Model-based Experimental Design for Process Optimization

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Two examples

- Biocatalyst stability testing
- World scale production plant
Scientific Computing
Competence center for mathematical modeling

Competencies

- Quantum Chemistry, Molecular Modeling
- Modeling of Dynamic Systems, Model Validation
- Statistics, Data Mining, Risk Management
- Mathematical Optimization in Business and Operations

Application Areas

- Thermodynamics and Kinetics
- Reaction Mechanisms
- Catalysis
- Materials Properties
- Solvent Selection, Formulation
- Active Substances
- Process Optimization
- Process- & Quality-Control
- Risk Management
- Supply Chain Management
- Purchase
- Marketing
High Throughput Screening for Enzymes

- Short experiments at constant conditions: **initial activity and selectivity**

- **Stability** (i.e. long-term performance) is no criterion for enzyme screening
Biocatalyst Stability Testing

- Status Quo: **Very long** experiments in late development stage
- Experiments are time consuming and provide few information

Duration of experiments is very long (months)

Analytic data (e.g. half life time) for single point of operation
Objective for process optimization

Total Turn Over

Additional Controls
Target: **Fast method** for high throughput screening by

Optimal experimental design and MTP experimentation

⇒ **Reduction of R&D expenses and time to market**
Model-based Optimum Experimental Design
Sequential Proceeding

Application

Model

Optimal Design

Process Optimum

Fit & Test

Experiments
Model-based Optimum Experimental Design
Minimization of Uncertainties

Experimental conditions:
- Constant temperatures

Experimental conditions:
- Temperature profiles

Parameter 1 (e.g. activation energy)

Parameter 2 (e.g. deactivation barrier)
Reaction Scheme: Biocatalyst Stability

Water- & Buffer-Ions

\[ S \rightarrow P \]

\[ S \rightarrow P \quad \text{pH} \rightarrow \]
Sketch of dynamic model

- Dynamic states \( \frac{dx(t)}{dt} = f(x(t), u(t), q, p) \)
- Experimental controls \( u(t), q \)
- Model parameters \( p \)
- Observable \( m(x(t), u(t), q, p) \)
- Measurement error \( s(\ldots) \)
- Coupled constraints w.r.t. \( m(\ldots), u(t), q \)

- Parameter estimation with PARFIT by Bock et al.
- Experimental design with VPLAN by Körkel et al.
Kirill Rachinskiy (Group Büchs, RWTH Aachen)
Enzyme Test Bench
Biocatalyst Stability Testing
Turn Over for Process Optimization
Validation in 1L Stirred Reactor
Optimal Designed Screening Process:

- **Standard method:** 2200h  ➤ **New method:** 120h (includes modeling)
- Parallelized and automated experimentation in MTP
World scale production site

- Plant produces **intermediate for plastics** (thousands of tons per year)
- Multi step **fluid phase** synthesis with solid intermediates
- **Solids have costly consequences** for layout and operation of plants
- Reactions have very different **time scales** and dependencies
- Status Quo: **no appropriate quantitative model** concerning solids
Sketch of production plant

1. Educt

Reaction Step 1

2. Educt

Reaction Step 2

Reaction Step 3

Separation

Product purification
Liquid phase
- Educt A forms solid with X
- Educts A and Y form B
- Intermediate B forms product C

Gaseous phase
- Educts X, Y and solvent L

Observable: pressure
Target: residence time of particles
Particle size distribution

![Graph showing particle size distribution with a peak at 1.0E-08 projection area, decreasing as projection area increases. The y-axis represents amount, ranging from 0.0E+00 to 5.0E-04. The graph includes a line labeled 'initial'.]
Particle Size Distribution

Time evolution of particle size distribution

Projection area

Amount

- Initial
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 20
- 30
- 40
- 50
- 60
Process performance under production-like conditions

- Particle Diameter
- Time

Graph showing the relationship between particle diameter and time. The graph indicates a decrease in particle diameter over time, with specific points marked for residence time with 95% confidence.
Summary
Predictive models by optimal design

Cooperations:
S. Körkel,
H.G. Bock,
J. Schlöder,
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