Hans Georg Bock, Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University

reporting on joint work with I. Bauer, D. Janka, C. Hoffmann, S. Körkel, E. Kostina, M. Mommer, S. Sager, J. Schlöder, S. Walter (Heidelberg), A. Badinski, A. Schreieck, S. Sauer, H. Schultze (BASF Scientific Computing Group), A. Bommarius, S. Estler (Degussa), S. Bandara, T. Meyer (Stanford) and others
The Industrial Problem: Mathematical modeling of complex industrial processes together with versatile mathematical simulation, optimization and control methods offer a huge potential for innovations in industrial applications ("rational design").

However, to base decisions about systems and process design and operation on MSO demands qualitatively and quantitatively validated models – and demands fundamental research into new mathematical methodologies!

Productive sector: Process engineering in the chemical industry – and beyond!

Simulation and Optimization Group, Interdisciplinary Center for Scientific Computing (IWR), Heidelberg University

BASF SE, Scientific Computing Group, Ludwigshafen
Overview

• Problem:
  • Optimum Experimental Designs (OED) to maximize information for the validation and calibration of Nonlinear Dynamic Process Models

• Approach: Optimization-based methods
  • Parameter estimation and assessment of statistical errors of parameter estimates
  • Design of optimized experiments
    • Solving non-standard optimal control problems
    • Sequential and parallel experiment designs

• Applications: Chemical and biochemical reactors, industrial case studies
Example 1: The Urethane Reaction
The Urethane Reaction

\[ A + B \rightarrow C \]
\[ A + C \rightleftharpoons D \]
\[ 3 \; A \rightarrow E \]

A: isocyanate    B: butanol
C: urethane      D: aliphaneate
E: isocyanurate  L: solvent DMSO

\[ \dot{n}_C = V \cdot (r_1 - r_2 + r_3) \]
\[ \dot{n}_D = V \cdot (r_2 - r_3) \]
\[ \dot{n}_E = V \cdot r_4 \]
\[ 0 = n_A + n_C + 2n_D + 3n_E - n_{AO} - n_{Aea}(t) \]
\[ 0 = n_B + n_C + n_D - n_{BO} - n_{Beb}(t) \]
\[ 0 = n_L - n_{L0} - n_{Lea}(t) - n_{Leb}(t) \]
\[ n_C(t_0) = n_D(t_0) = n_E(t_0) = 0 \]
\[ r_1 = k_1 \cdot \frac{n_A}{V} \cdot \frac{n_B}{V} \]
\[ r_2 = k_2 \cdot \frac{n_A}{V} \cdot \frac{n_C}{V} \]
\[ r_3 = k_3 \cdot \frac{n_D}{V} \]
\[ r_4 = k_4 \cdot \left( \frac{n_A}{V} \right)^2 \]

\[ k_{i=1,2,4} = k_{ref_i} \cdot \exp \left( -\frac{E_{ai}}{R} \cdot \left( \frac{1}{T(t)} - \frac{1}{T_{ref_i}} \right) \right) \]
\[ k_2 = k_{c2} \cdot \exp \left( -\frac{dh_2}{R} \cdot \left( \frac{1}{T(t)} - \frac{1}{T_{s2}} \right) \right) \]
The Urethane Reaction

Model

- 6 state variables, DAE, nonlinear Arrhenius kinetics
- 8 unknown parameters (frequency factors, Activation energies) of the reaction rates to be estimated

1: Can choose sampling design:

- 3 measurement methods (A, C/D, E) of different accuracy and costs, and measurement times (yes/no decisions!)

2. Can choose experimental conditions:

- 3 control functions $u(t)$: temperature, feed 1, feed 2
- 7 control parameters $q$: initial molar numbers, reaction volume

Subject to constraints!

- safety requirements, experimental costs, working hours (!!!)
The Problem Formulation
The Model Equations

\[ B(t, y, z, p) \dot{y} = f(t, y, z, p, q, u) \]
\[ 0 = g(t, y, z, p, q, u) \]

\( y \) „differential“ states
\( z \) „algebraic“ states

\( p \): (unknown) system parameters (PE)
\( q \): control parameters, \( u \): control functions (OED)

- ordinary differential equations
- non-stationary PDE

complexity:
- nonlinear, state dependent discontinuities
- stiff and/or unstable: different time-scales
The Parameter Estimation Problem

• Given: data/measurements

\[ \eta_{ij} = b_j (t_i, x(t_i), p) + \varepsilon_{ij}, e.g., \varepsilon_{ij} \in \mathbb{N} \ 0, \sigma_{ij}^2 \] 

x=(y,z)

Constrained Approximation Problem:

• determine parameters p and solution trajectory x such that

\[
\begin{align*}
\min_{x,p} \| \eta - F_1[x,p] \| \\
\text{s.t. } F_2[x,p] = 0, \text{ or } \geq 0
\end{align*}
\]

• suitably weighted norm of deviation between data and model minimized (\(l_2, l_1\), hybrid, …)

• model equations and constraints satisfied

Methods of choice:

• **Generalized Gauss-Newton** methods and their variants for DE constrained problems

Gauss 1809
After Discretization: Large-Scale Constrained Nonlinear Least Squares Problem with Special Structure \((l^2\text{ case})\)

\[ \begin{align*}
\text{[CNLS]} & \quad \min_X \| F_1(X) \|_2^2 \\
\text{s.t.} & \quad F_2(X^k) = 0, \text{ or } \geq 0
\end{align*} \]

\(X = (p, s_0, s_1, \ldots, s_m)\) parameters and discretized states

solution by "Generalized Gauss-Newton Method"

\[ X^{k+1} = X^k + t^k \Delta X^k \]

where \(\Delta X^k\) solves a constrained linear least squares problem

\[ \begin{align*}
\text{[CLLS]} & \quad \min_{\Delta X} \left\| F_1(X^k) + J_1(X^k) \Delta X \right\|_2^2 \\
\text{s.t.} & \quad F_2(X^k) + J_2(X^k) \Delta X = 0, \text{ or } \geq 0
\end{align*} \]

Note: solution can be expressed in terms of a generalized inverse

\[ \Delta X^k := -J(X^k)^+F(X^k) \]

\[ J_i := \frac{\partial F_i}{\partial X} \]

\[ J^+ = J^+JJ^+ \]

PARFIT
Example 2: Enzyme Reaction Kinetics
• expensive evaluation of long-term stability behavior ("half-life", "total turn-over")
• in practice: many long lasting and expensive experiments

reaction

N: native enzyme
U: unfolded enzyme
D: deactivated enzyme
Enzyme Reaction Kinetics: Experiments with Candida Antarctica on Ionic Resin ("Novozym")

Model:
- mass action kinetics ODE, nonlinear Arrhenius-type reaction kinetics for temperature dependence

- 8 unknown reaction rate parameters $p$ to be estimated
  - wanted: stability quantities "total turnover", "half-life"

- experimental choice:
  - 1 control function $u(t)$ only: temperature profile
  - 1 indirect measurement device only: amount of base added to neutralize acid production (side-reaction)

will see: problem very ill-conditioned, cannot estimate parameters from a single "industry standard" experiment
Enzyme Reaction Kinetics: Experiments with *Candida Antarctica* on Ionic Resin ("Novozym")

Temperature profile of a standard experiment

Measurements, and fit to experimental data

Are parameter estimates reliable?
Assessment of Statistical Error of Parameter Estimate
Assessment of Statistical Error of Estimate

- Good fit insufficient, need error of parameter estimates as function of measurements errors $\varepsilon$, because even small errors in measurements ...

\[ \varepsilon \in N(0, \beta^2 I) \]

\[ X^*(\varepsilon) \in N(X^*, C) \]

\[ J^+ \]

- consequence: additional and better experiments must be designed!

- errors of parameters and / or model prediction quantifiable by generalized inverse $J^+$ and covariance matrix $C$

\[
C := E \left( J(X^*) + \begin{pmatrix} \varepsilon \\ \varepsilon^T \\ 0 \\ 0 \end{pmatrix} J(X^*)^+ \right)^T \left( \begin{pmatrix} \beta^2 I & 0 \\ 0 & 0 \end{pmatrix} \right) J(X^*)^+ T
\]
Difficulties:

- estimated values of parameters ± standard deviations after one standard experiment
- fit looks okay, but ...

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated Value</th>
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Optimum Experimental Design
And How to Optimize Experimental Conditions?

• Choose optimal experimental conditions \( \xi = (u, q, w) \) …

  • \( u \): control functions - temperature profiles, feed-streams,
  • \( q \): control parameters - volume, initial conditions,
  • \( w \): sampling design - measurement devices and times (integer!)

  ... in order to maximize information gain, here:
  minimize uncertainty of parameter estimate, resp.,
  prediction errors of model!

• subject to numerous state, control and parameter constraints, e.g.,
  • costs, safety, feasibility (shifts!), domain of model validity (!),...
Optimum Experimental Design is a Complex Non-Standard Optimal Control Problem

- Mathematically: minimize a function of covariance matrix $C$
  \[
  \min = \Phi(C(X,\xi)) \quad \text{e.g. } \Phi(C) := \text{trace}C
  \]

- subject to discretized model equations, state and control constraints
  \[
  \mathcal{g}(X,\xi) = 0 \text{ or } \geq 0
  \]

Numerous numerical challenges:
- **nonlinear mixed-integer** optimal control problem
- cost function *implicity defined* by generalized inverse
- hence **higher order derivatives** needed for optimization
- **robustification against uncertainties** …
A Competition Between Human Expert and Optimization: The Urethane Reaction
A competition:
new mathematical methods vs. chief expert in BASF main lab!

BASF 1887

proved to be very important for acceptance!
The Urethane Reaction Experiment

The expert's design:

• 15 experiments at different constant temperatures, 90 measurements
• results: parameter errors still up to 32%

\[ k_{\text{ref1}}: \pm 0.93\%, \ E_a1: \pm 0.88\%, \ k_{\text{ref2}}: \pm 0.72\%, \ E_a2: \pm 0.26\%, \]
\[ k_{\text{ref4}}: \pm 0.01\%, \ E_a4: \pm 0.01\%, \ dH_2: \pm 32.98\%, \ K_c2: \pm 22.41\% \]

New optimum experimental design methods, sequential approach:

• 2 consecutive experiments, varying temperatures, 32 measurements
• results: all parameter errors < 1%

\[ k_{\text{ref1}}: \pm 0.23\%, \ E_a1: \pm 0.17\%, \ k_{\text{ref2}}: \pm 0.02\%, \ E_a2: \pm 0.01\%, \]
\[ k_{\text{ref4}}: \pm 0.01\%, \ E_a4: \pm 0.03\%, \ dH_2: \pm 0.54\%, \ K_c2: \pm 0.78\% \]
The Urethane Reaction Experiment

Experiment 1: controls and states

Experiment 2: controls and states
Result:

• optimally designed experiments contain orders of magnitude more information than expert design

• costs: reduced to 2000 instead of 6000 EUR - and much less time

BASF: "We save up to 80% costs with these methods and get much more precise results!"
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The "Bildzeitung" (German yellow press)
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"Success Story":
BASF funding of an IWR Research Group on OED
2.5 K€/a for 7 years!

The "Bildzeitung" (German yellow press)
Many More Applications …

- now in routine application at BASF (in cooperation with IWR)

E.g., OED for parameter estimation for a **catalytic flow reactor**
- reduction of experimental cost and time by 75%
- results of much higher accuracy
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E.g., OED for parameter estimation for a catalytic flow reactor

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- results of much higher accuracy

Impact? => leverage! made a 10 MEUR difference by causing a decision for different reactor design!
However, Designing *One Experiment at a Time* Often Cannot Solve the Problem – Needs Design of *Parallel Experiments*!

Here: the *Enzyme Problem*!
Enzyme Reaction Kinetics: Experiments with Candida Antarctica on Ionic Resin (“Novozym”)

Result:

- 2, 3 or 4 *simultaneously* optimized experiments still insufficient!
- but **5 simultaneously optimized complementary experiments** allow to identify all 8 reaction rate coefficients up to first decimal

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The 5 complementary temperature control profiles:

- The standard temperature control profile
- 5 additional "simultaneously optimized" temperature profiles

Enzyme Reaction Kinetics: Experiments with *Candida Antarctica* on Ionic Resin ("Novozym")

The optimality is hidden in the complementarity!
Thanks to all partners!

bmb+f

SimOpt

BASF

degussa.
And Thank You Very Much for Your Attention!
Constrained Linearized Problem Is Solved by a "Generalized Inverse" $J^+$

Note: CLLS solution expressed in terms of a generalized inverse $J^+$

\[ \Delta X^k := -J(X^k)^+F(X^k) \]

\[ F := \begin{pmatrix} F_1 \\ F_2 \end{pmatrix}, J := \begin{pmatrix} J_1 \\ J_2 \end{pmatrix} \]

\[ J^+ = J^+JJ^+ \]

satisfying