Parameter Estimation and Optimum Experimental Design for Dynamic Processes

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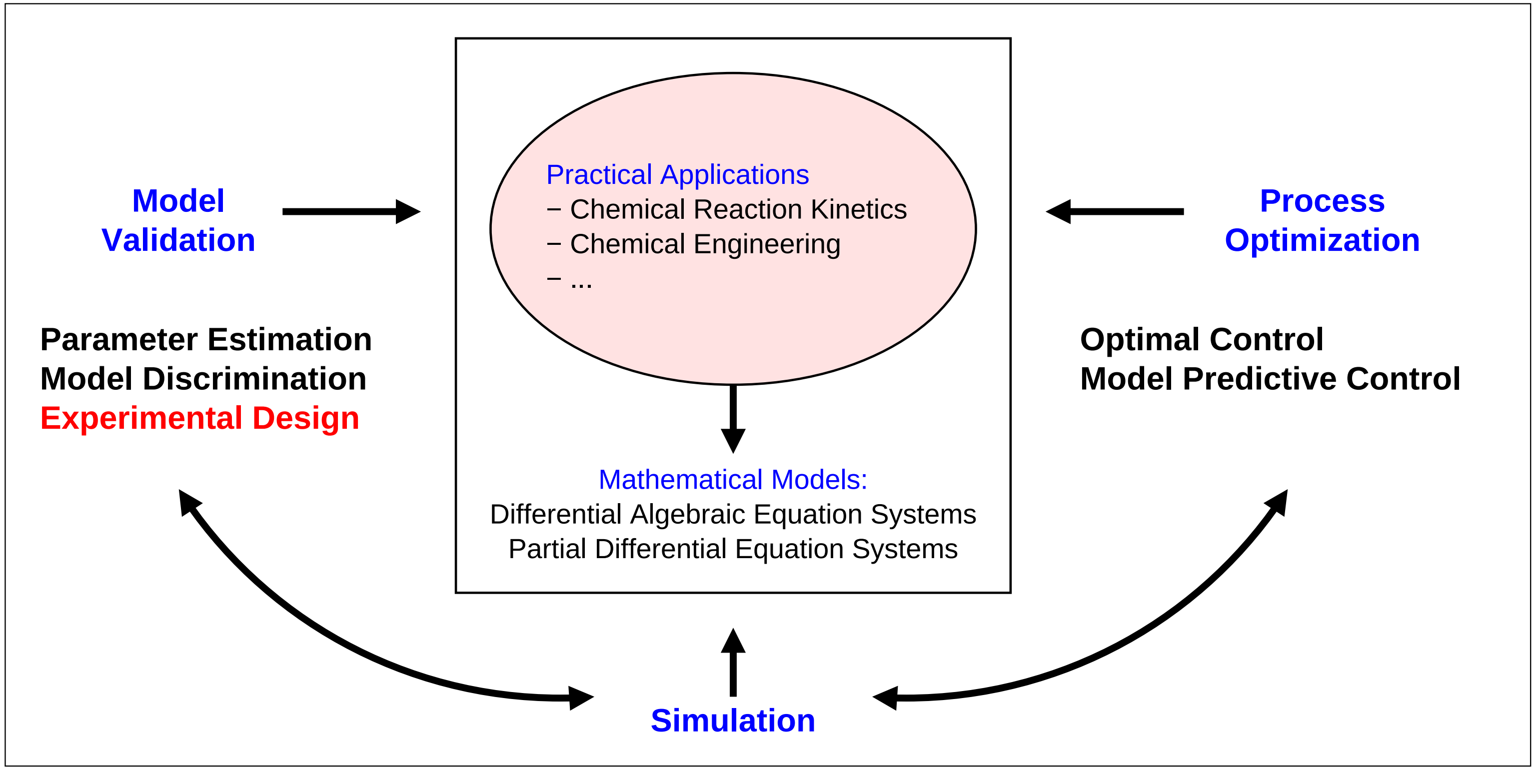
Overview


Model
Validation
Parameter Estimation
Model Discrimination
Experimental Design
Practical Applications
– Chemical Reaction Kinetics
– Chemical Engineering
– ...
Mathematical Models:
Differential Algebraic Equation Systems
Partial Differential Equation Systems
Process
Optimization
Optimal Control
Model Predictive Control
Simulation

Part I

Modeling, Simulation and Parameter Estimation

Example: Population Dynamics: SIR Model

Cooperation: German Federal Research Institute for Animal Health

SIR model (Kermack-McKendrick model):
Transmission of diseases and temporal spread of epidemics

Basic model: Susceptibles (S) → Infected (I) → Recovered (R)

$$\boxed{\frac{dS}{dt} = -r \cdot S \cdot I \qquad \frac{dI}{dt} = r \cdot S \cdot I - a \cdot I \qquad \frac{dR}{dt} = a \cdot I}$$

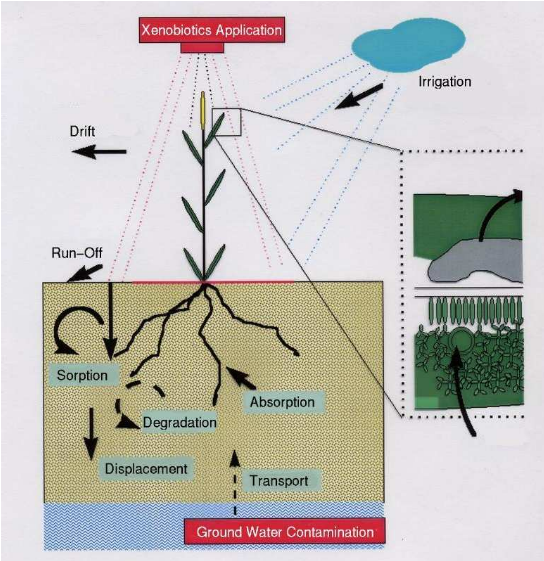
Extension: ($\rightarrow$ Partial Differential Equation system)

- Distribution over the age of the disease
- Spatial distribution

Goals:

- Parameter estimation
- Optimal strategies for fighting the disease

Example: Transport of Xenobiotics in Soil



PDE model: Fokker-Planck equation with convection and dispersion:

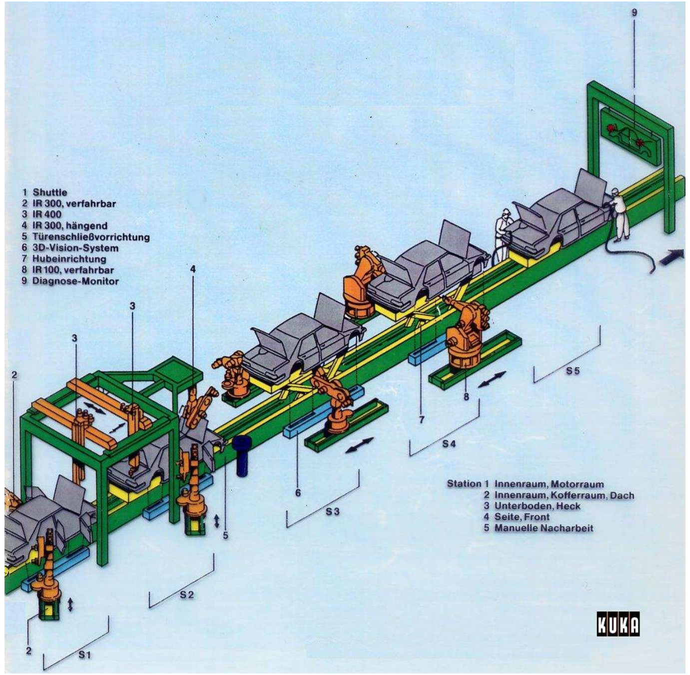
$$
\begin{aligned}
C(\psi; p)\frac{\partial \psi}{\partial t} &= \frac{\partial}{\partial z}\left(K(\psi; p)\frac{\partial}{\partial z}(\psi - z)\right) + S(\psi; p) \\
\frac{\partial \theta}{\partial t} &= \frac{\partial}{\partial z}\left(\bar{D}(\theta; p)\frac{\partial \theta}{\partial z} - \bar{K}(\theta; p)\right) + \bar{S}(\theta; p) \\
\frac{\partial(\theta c)}{\partial t} &= \frac{\partial}{\partial z}\left(\theta D_h(\theta; p)\frac{\partial c}{\partial z} - qc\right) - \frac{\partial(\rho s)}{\partial t} + Q(c; p)
\end{aligned}
$$

$+$ Initial and boundary conditions

Spatial discretization:
up to 2000 state variables

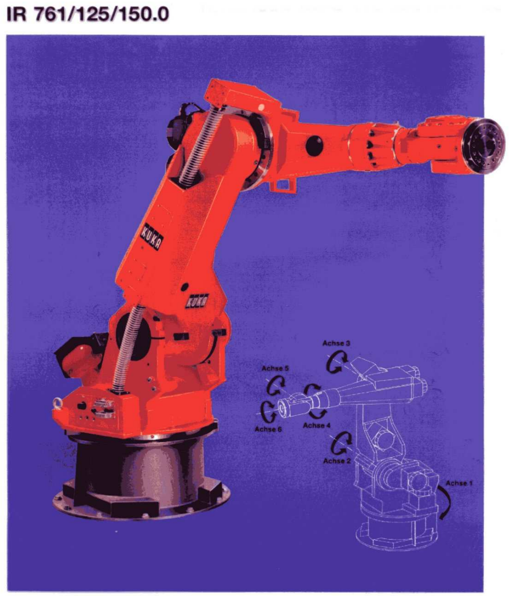
EU requires: Simulation of experiments which yield validated models. (Bock, Dieses, 2002)

Industrial Robots



welding — mounting — gluing — transporting

Can we speed up bottleneck maneuvers?



Find time optimal solutions based on dynamic interactions.

Model:
multibody system $\longrightarrow$ index-3-DAE system

The Red River System

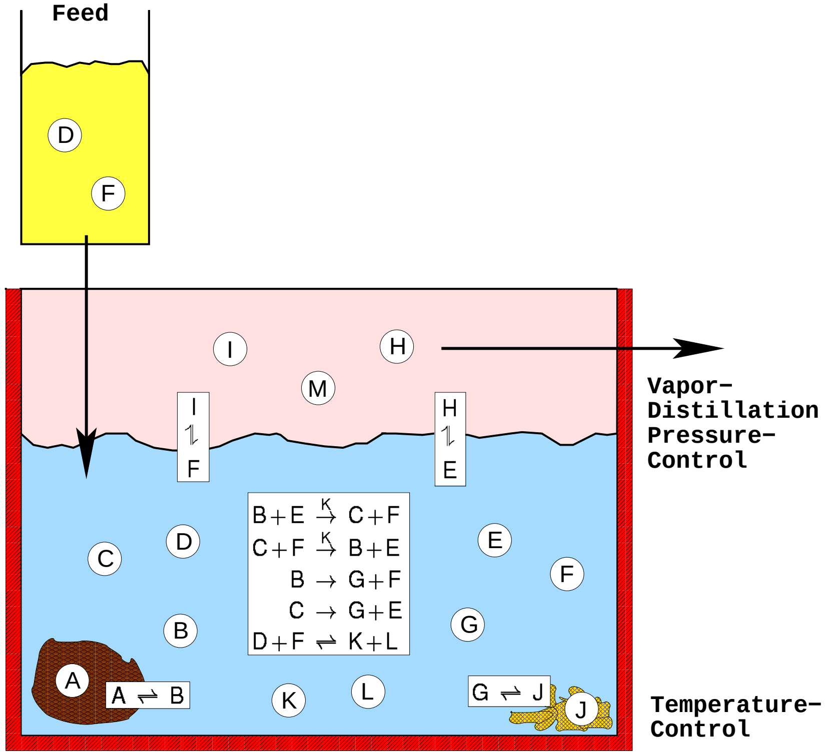
Saint-Venant equation

PDE-network model

first aim: get validated model of the river system

further aim: control water power plant in Hoa Binh in order to avoid floods in Hanoi

Example: A Multiphase Esterification Reaction



BASF

Model: Conservation of mass, mass action kinetics, Arrhenius kinetics, catalysis, NRTL model for phase transitions, thermodynamics of the reaction

Controls: initial molar numbers, feed profile, temperature profile, pressure, distillation rate

Measurements: HPLC: mass concentrations in solid, liquid and gas phase; pressure

DAE with 13 state variables, 6 parameters (Arrhenius-coefficients)

(800 lines of model code)

Modeling

Independent variable ("time"): t

State variables: $x(t) = (y(t), z(t)) : \boldsymbol{R} \longrightarrow \boldsymbol{R}^{n_x}$

Parameters: $p \in \boldsymbol{R}^{n}$
determined by nature

Control variables: $q \in \boldsymbol{R}^{n_q}$
and
Control functions $u(t) : \boldsymbol{R} \longrightarrow \boldsymbol{R}^{n_u}$
determined by the experimenter or observer

Differential Algebraic Equation Systems

$$\begin{aligned} \dot{y}(t) &= f(t, y(t), z(t), p, q, u(t)) \\ 0 &= g(t, y(t), z(t), p, q, u(t)) \end{aligned}$$

Simulation of the process:

- Given: initial states $y(t_0)$
- Compute solution $x(t) = (y(t), z(t))$ for $t \in [t_0, t_{end}]$

$\longrightarrow$ Solve an **Initial Value Problem**

Example: The Reaction of Urethane

Simultaneous and consecutive reaction: with

$$\begin{array}{rcl} A + B & \rightarrow & C \\ A + C & \rightleftharpoons & D \\ 3\,A & \rightarrow & E \end{array}$$

A: Isocyanate, B: Butanole,
C: Urethane, D: Allophanate,
E: Isocyanurate, L: Solvent DMSO

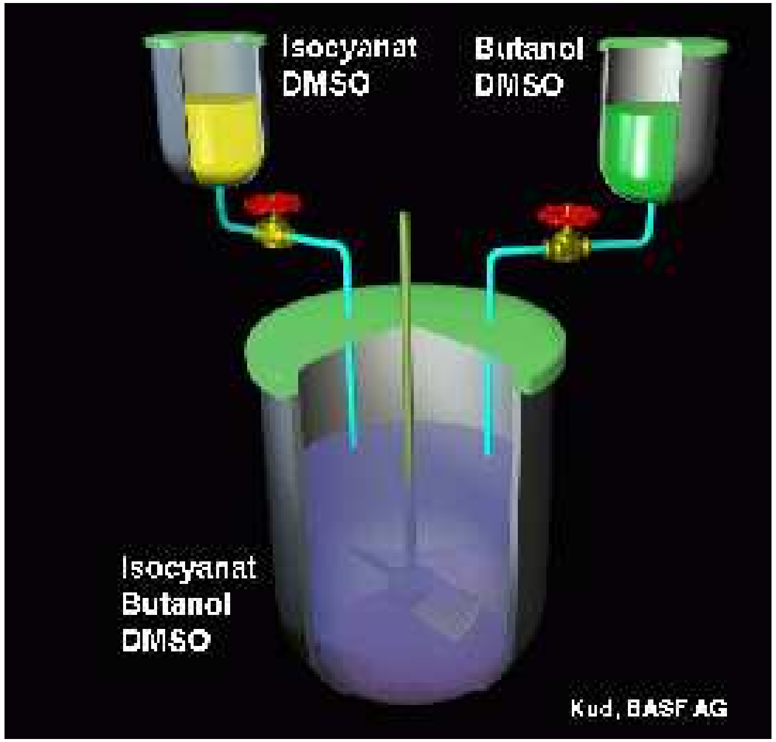
Prototype for polyurethane production

Main product A, byproduct D

Composition of the products determines physical properties of the polyurethane plastic material

Reactor and Mode of Operation

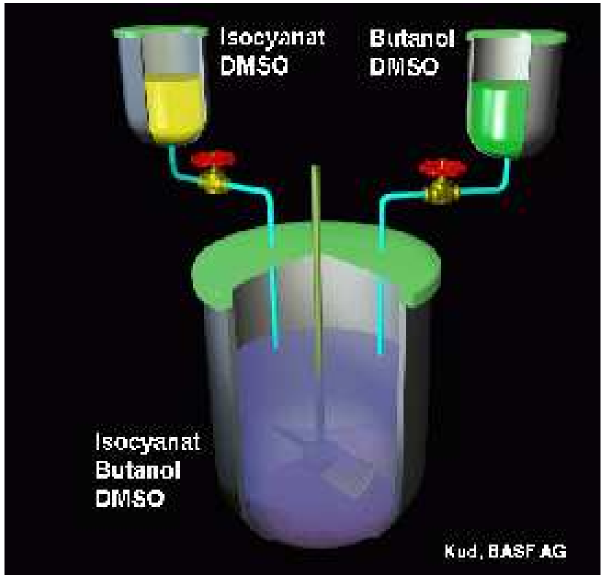
- Reactor: ideal stirring tank
- Receiver: A and B in L
- Semi-batch processing possible
- Two feeds: A in L and B in L
- Control of the internal reactor temperature



Mathematical Model

$$
\begin{aligned}
A + B &\rightarrow C \\
A + C &\rightleftharpoons D \\
3\,A &\rightarrow E
\end{aligned}
$$

A: Isocyanate	B: Butanole
C: Urethane	D: Allophanate
E: Isocyanurate	L: Solvent DMSO



$$
\begin{aligned}
\dot{n_C} &= V \cdot (r_1 - r_2 + r_3) \\
\dot{n_D} &= V \cdot (r_2 - r_3) \\
\dot{n_E} &= V \cdot r_4 \\
0 &= n_A + n_C + 2n_D + 3n_E - n_{A0} - n_{Aea}(t) \\
0 &= n_B + n_C + n_D - n_{B0} - n_{Beb}(t) \\
0 &= n_L - n_{L0} - n_{Lea}(t) - n_{Leb}(t)
\end{aligned}
$$

$$n_C(t_0) = n_D(t_0) = n_E(t_0) = 0$$

$$
\begin{aligned}
r_1 &= k_1 \cdot \frac{n_A}{V} \cdot \frac{n_B}{V} \qquad r_3 = k_3 \cdot \frac{n_D}{V} \\
r_2 &= k_2 \cdot \frac{n_A}{V} \cdot \frac{n_C}{V} \qquad r_4 = k_4 \cdot (\frac{n_A}{V})^2 \\
k_{i=1,2,4} &= k_{ref\ i} \cdot \exp\left(-\frac{E_{ai}}{R} \cdot \left(\frac{1}{T(t)} - \frac{1}{T_{ref\ i}}\right)\right) \\
\frac{k_2}{k_3} &= k_{c2} \cdot \exp\left(-\frac{dh_2}{R} \cdot \left(\frac{1}{T(t)} - \frac{1}{T_{g\,2}}\right)\right) \\
n_{A,e}(t) &= n_{A,e1,0} \cdot feed_1(t) \\
n_{B,e}(t) &= n_{B,e2,0} \cdot feed_2(t) \\
n_{L,e}(t) &= n_{L,e1,0} \cdot feed_1(t) + n_{L,e2,0} \cdot feed_2(t) \\
V &= \sum_{i=A}^{L} \frac{n_i \cdot M_i}{\rho_i}
\end{aligned}
$$

Mathematical Model

Model quantities:

- 6 state variables: n_A, n_B, n_C, n_D, n_E, n_L
- 8 unknown parameters p: steric factors $k_{ref\,i}$, activation energies E_{ai}, $i = 1, 2, 4$, equilibrium constant k_{c2}, reaction enthalpy dh_2
- 3 time dependent control functions $u(t)$: temperature $T(t)$, feed profiles $feed_1(t)$, $feed_2(t)$
- 7 control variables q: initial molar numbers in the reactor n_{A0}, n_{B0}, n_{L0} and in the feeds $n_{A,e1,0}$, $n_{B,e2,0}$, $n_{L,e1,0}$, $n_{L,e2,0}$
- constants

Constraints to the Controls

Molar fractions, percentage of active substances, volume

$$
\begin{aligned}
MV_1 &:= \frac{n_{B,0} + n_{B,e2,0}}{n_{A,0} + n_{A,e1,0}} && \in [0.1; 10] \\
MV_2 &:= \frac{n_{A,e1,0}}{n_{A,0}} && \in [0; 1000] \\
MV_3 &:= \frac{n_{B,e2,0}}{n_{A,0}} && \in [0; 10] \\
g_a &:= \frac{n_{A,0} \cdot M_A + n_{B,0} \cdot M_B}{n_{A,0} \cdot M_A + n_{B,0} \cdot M_B + n_{L,0} \cdot M_L} && \in [0; 0.8] \\
g_{a,e1} &:= \frac{n_{A,e1,0} \cdot M_A}{n_{A,e1,0} \cdot M_A + n_{L,e1,0} \cdot M_L} && \in [0; 0.9] \\
g_{a,e2} &:= \frac{n_{B,e2,0} \cdot M_B}{n_{B,e2,0} \cdot M_B + n_{L,e2,0} \cdot M_L} && \in [0; 1] \\
V_0 &:= \frac{n_{A,0} \cdot M_A}{\rho_A} + \frac{n_{B,0} \cdot M_B}{\rho_B} + \frac{n_{L,0} \cdot M_L}{\rho_L} && \in [0\, m^3; 0.00075\, m^3]
\end{aligned}
$$

Simulation

In general, a closed representation of the solution does not exist.
Hence: Numerical Solution

Properties of typical DAE systems from chemical engineering:

- Index 1
- stiff
- possibly need costly computations for the evaluation of the model functions f and g

Suited numerical methods:

- Implicit integration methods
- multistep methods

$\rightarrow$ **B**ackward-**D**ifferentiation-**F**ormulas, Software: DAESOL, lsoda, dassl

Simulation of the Reaction of Urethane

Starting values for the Parameters

$$
\begin{aligned}
k_{ref1} &= p_1 \cdot 5.0 \cdot 10^{-4}\, m^3/(h \cdot mol) \\
E_{a,1} &= p_2 \cdot 35240.0\, J/mol \\
k_{ref2} &= p_3 \cdot 8.0 \cdot 10^{-8}\, m^3/(h \cdot mol) \\
E_{a,2} &= p_4 \cdot 85000.0\, J/mol \\
k_{ref4} &= p_5 \cdot 1.0 \cdot 10^{-8}\, m^3/(h \cdot mol) \\
E_{a,4} &= p_6 \cdot 35000.0\, J/mol \\
\Delta H_2 &= p_7 \cdot -17031.0\, J/mol \\
K_{C2} &= p_8 \cdot 0.17\, m^3/mol.
\end{aligned}
$$

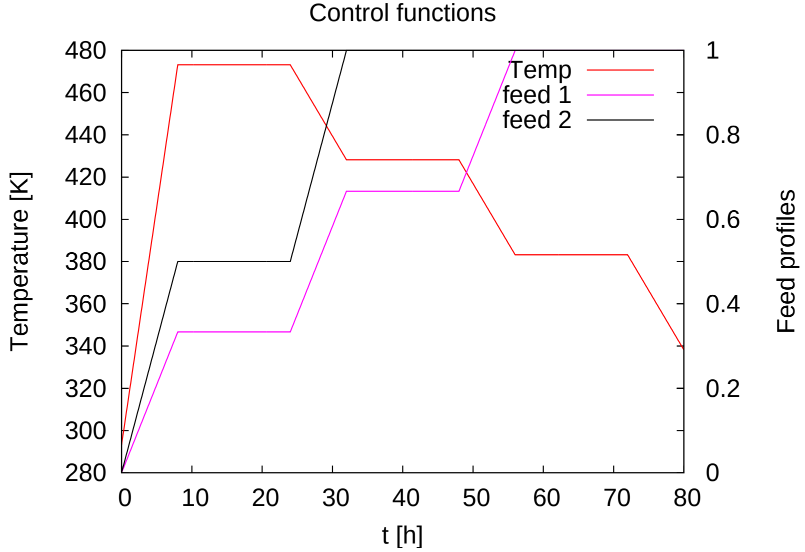
with $p_1 = \ldots = p_8 = 1.0$ (scaled, unit free)

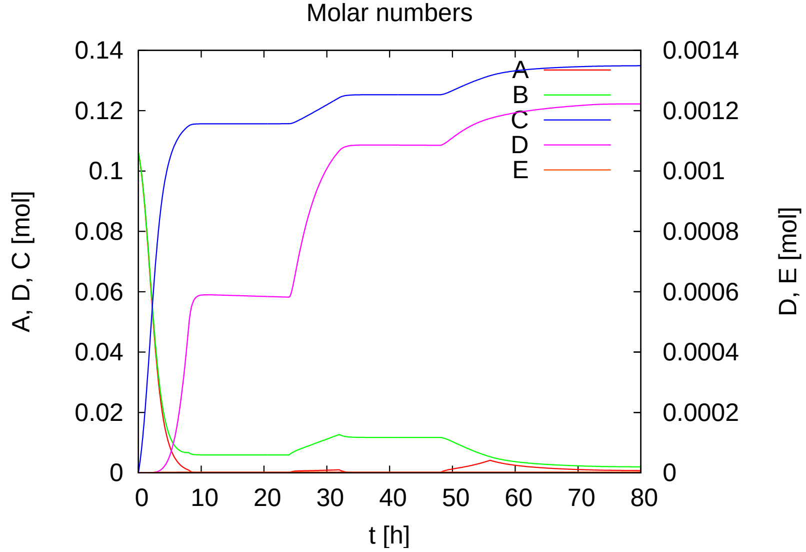
The control variables are chosen such that:

MV_1	MV_2	MV_3	g_a	$g_{a,e1}$	$g_{a,e2}$	V_0
1.0	0.3	0.3	0.75	0.5	0.4	$2.75 \cdot 10^{-5}\, m^3$

Simulation of the Reaction of Urethane

Control functions and trajectories:





Modeling of Measurements

Given for $i = 1, \ldots, M$:

- Measurement values η_i at measurement times t_i
- Measurement errors ε_i with variances σ_i^2
- Corresponding measurement methods $h_i(t_i, x(t_i), p, q)$

Nonlinear regression:

$$\eta_i = h_i(t_i, x(t_i), p, q) + \varepsilon_i$$

Assumption: measurement errors are normally distributed:

$$\varepsilon_i \sim \mathcal{N}(0, \sigma_i^2)$$

Parameter Estimation

Model Validation: determine the values of the parameters such that simulations reproduce the real process behavior correctly.

Parameter Estimation: Fit the model to the measurement data.

$$\min_{p,x} \sum_i \frac{(\eta_i - h_i(t_i, x(t_i), p, q))^2}{\sigma_i^2}$$

$$\begin{aligned} \dot{y} &= f(t, y, z, p, q, u) \\ 0 &= g(t, y, z, p, q, u) \end{aligned}$$

$$0 = r(x(t_1), \ldots, x(t_K), p, q)$$

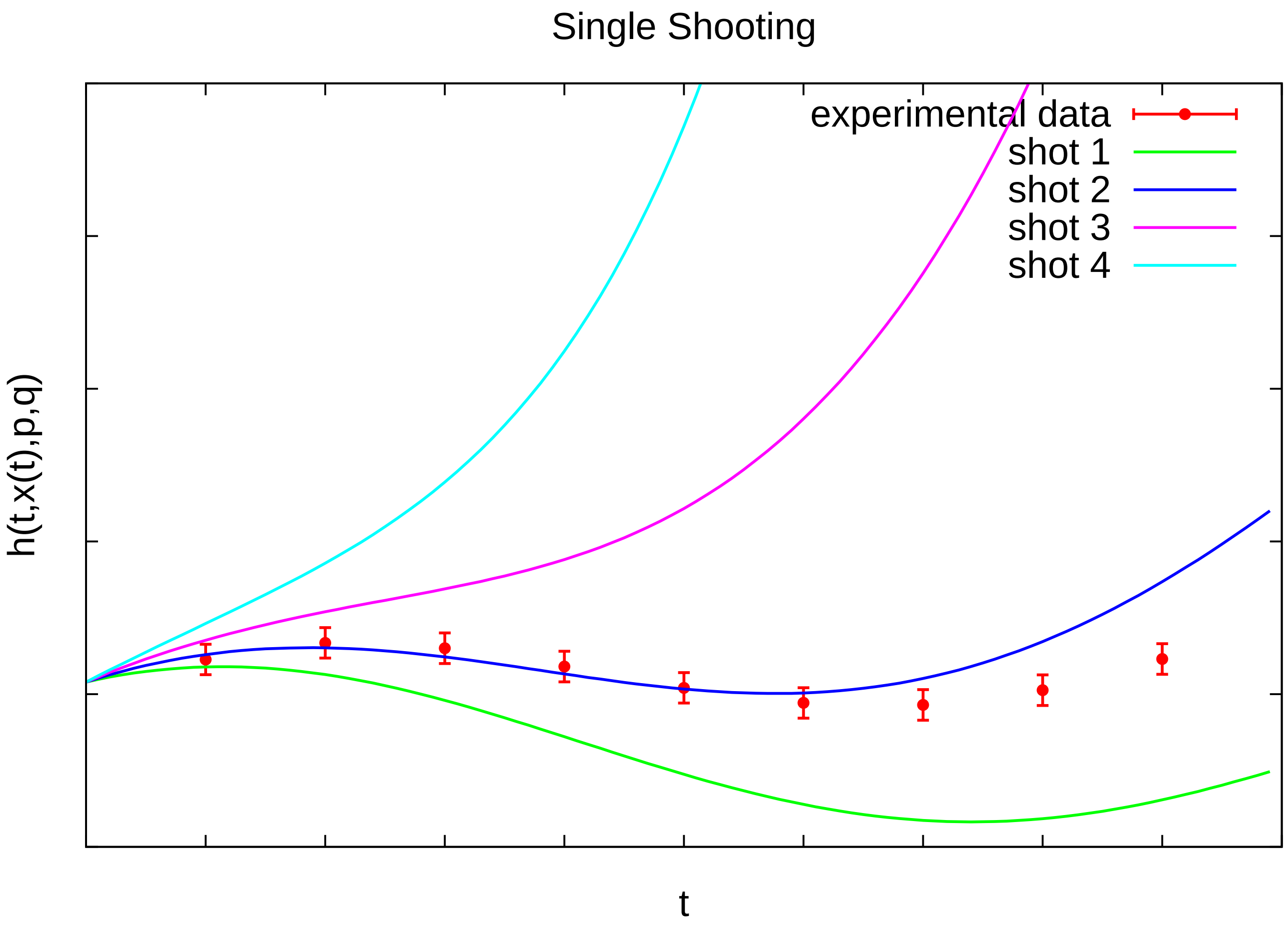
Numerical Methods for Parameter Estimation

(PARFIT, Bock et al. 1987ff.)

- Parameterization of the dynamic system: express the solution of the DAE system by finitely many variables s.
- Insert this representation of the solution into the parameter estimation problem.
- Eventually there are additional constraints from the parameterization.
- This yields a finite dimensional nonlinear constrained least squares problem.
- Solve this with a Gauss-Newton method.

Single Shooting

Idea: Solve the simulation problem and insert the solution into the optimization problem.



Relaxation of the Algebraic Equations

Solve

$$\begin{aligned}\dot{y} &= f(t, y, z, p, q, u)\\ 0 &= g(t, y, z, p, q, u) - g(t_0, y(t_0), s, p, q, u)\end{aligned}$$

with the initial values $y(t_0) = y_0(p, q), \quad z(t_0) = s$
in the whole interval $t \in [t_0, t_{end}]$.

The modified (relaxed) algebraic equations are automatically satisfied for arbitrary values of s.

Additionally: consistency conditions:

$$g(t_0, y(t_0), s, p, q, u) = 0$$

$\rightarrow$ additional constraints for the optimization problem.

Single Shooting

Disadvantages of Single Shooting:

- Small changes of the parameters may cause drastic changes of the trajectories.
- Then the convergence of the Gauss-Newton method may not be guaranteed, because we start very far away from the solution.
- Eventually the integration is not possible until t_{end}.

$\longrightarrow$ Method is simple, but not robust.

Remedy: Multiple Shooting

Multiple Shooting

Dissect the integration interval into partial intervals:

$t_0 < t_1 < \ldots < t_{N_{ms}} < t_{N_{ms}+1} = t_{end} \quad (t_i\text{: Multiple Shooting Nodes})$

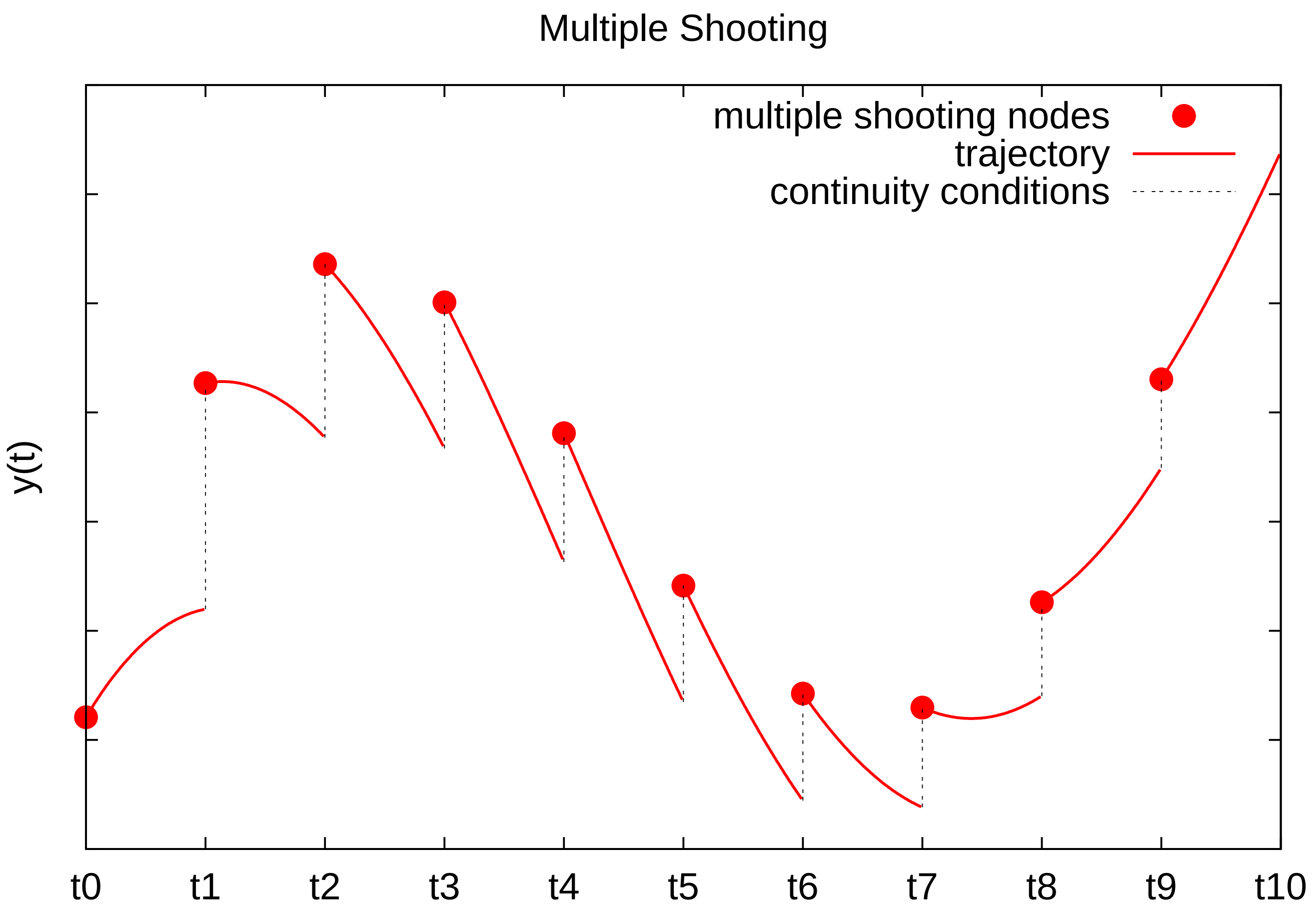
Integrate the relaxed DAE system on these partial intervals:

$$\begin{aligned} \dot{y} &= f(t, y, z, p, q, u) \\ 0 &= g(t, y, z, p, q, u) - g(t_i, y(t_i), z(t_i), p, q, u) \end{aligned}$$

with the initial conditions
$y(t_i) = s_{y,i}, \quad z(t_i) = s_{z,i}, \quad i = 0, \ldots, N_{ms}$ and $s_{y,0} = y_0(p, q)$.

The quantities $s_i = (s_{y,i}, s_{z,i})$ are additional variables of the problem.

Multiple Shooting



Multiple Shooting

The piecewise solution is not necessarily continuous in the multiple shooting nodes.

Hence in the multiple shooting nodes we formulate additionally:

Continuity conditions:

$$\lim_{t \to t_i} y_{i-1}(t, p, q, u, s_{i-1}) - s_{y,i} = 0, \quad i = 1, \ldots, N_{ms},$$

and consistency conditions

$$g(t_i, s_{y,i}, s_{z,i}, p, q, u) = 0, \quad i = 0, \ldots, N_{ms}$$

Continuity conditions and consistency conditions become additional constraints of the parameter estimation problem.

Multiple Shooting

- Multiple Shooting leads to significantly more additional variables and constraints than Single Shooting.
- But these can be eliminated easily because of the special structure of the continuity and consistency constraints.
- Hence the computational effort for Multiple Shooting is comparable to the computational effort for Single Shooting.
- The Multiple-Shooting variables can often be initialized with good starting values, e.g. from measurement values.
- Thus we can start near the solution, and convergence of the Gauss-Newton method is assured.
- The piecewise defined solution of the DAE system always exists.
- Multiple Shooting is reducing the nonlinearity of the problem.

Nonlinear Constrained Least-Squares Problem

By the parameterization of the dynamic system we obtain a finite-dimensional nonlinear constrained least-squares problem:

$$\min_v \|F_1(v)\|_2^2$$
$$F_2(v) = 0$$

with the variables $v = (p, s)$ and

$$F(v) = \begin{pmatrix} F_1(v) \\ F_2(v) \end{pmatrix} = \begin{pmatrix} \left(\frac{\eta_i - h_i(t_i, x(t_i, p, q, u, s), p, q)}{\sigma_i}\right)_{i=1,\dots,M} \\ r(p, q, u, s) \end{pmatrix}$$

Jacobian:

$$J(v) = \begin{pmatrix} J_1(v) \\ J_2(v) \end{pmatrix} = \begin{pmatrix} \frac{\partial F_1}{\partial v}(v) \\ \frac{\partial F_2}{\partial v}(v) \end{pmatrix}$$

Gauss-Newton Method

Solve iteratively a sequence of linear least-squares problems:

1. Start with a starting value v_0.
2. For $k = 0, 1, 2, \ldots$:
   2.1 Solve the linearized problem

$$\begin{aligned} \min_{\Delta v_k} \quad & \|J_1(v_k)\Delta v_k + F_1(v_k)\|_2^2 \\ & J_2(v_k)\Delta v_k + F_2(v_k) = 0. \end{aligned}$$

   2.2 Compute the new iterate

$$v_{k+1} := v_k + \alpha \cdot \Delta v_k$$

   with $\alpha \in (0; 1]$ from a strategy for globalization of the convergence.

   2.3 Is $\|\Delta v_k\|_2 \leq \epsilon$, the stop the algorithm with the solution $\hat{v} := v_{k+1}$.

Generalized Inverse

The solution of the linearized problem

$$\min_{\Delta v} \|J_1(v)\Delta v + F_1(v)\|_2^2$$
$$J_2(v)\Delta v + F_2(v) = 0$$

is

$$\begin{aligned}
\Delta v &= -\begin{pmatrix} I & 0 \end{pmatrix} \begin{pmatrix} J_1(v)^T J_1(v) & J_2^T(v) \\ J_2(v) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1(v)^T & 0 \\ 0 & I \end{pmatrix} \begin{pmatrix} F_1(v) \\ F_2(v) \end{pmatrix} \\
&= -J(v)^+ \begin{pmatrix} F_1(v) \\ F_2(v) \end{pmatrix}
\end{aligned}$$

with the *Generalized Inverse*

$$J^+ = \begin{pmatrix} I & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T & 0 \\ 0 & I \end{pmatrix}$$

Parameter Estimation for the Reaction of Urethane

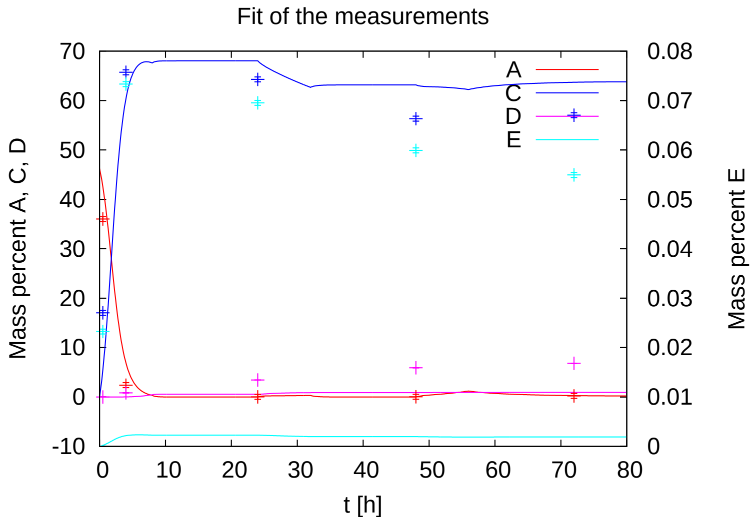
Available measurement methods:

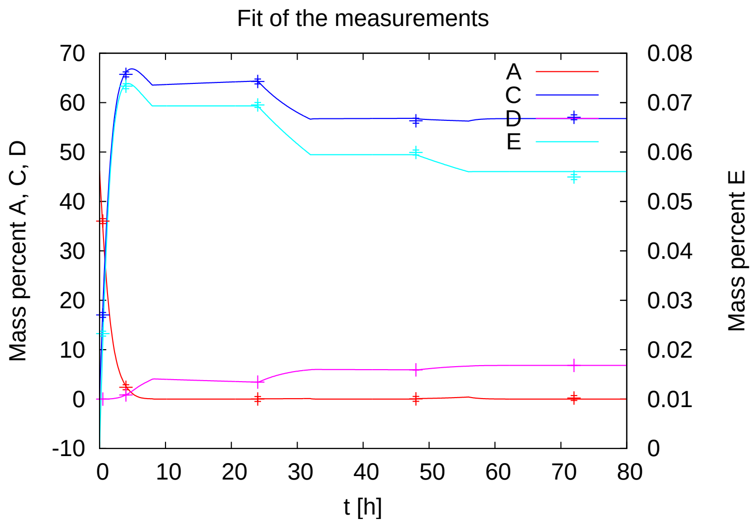
- Titration: measurement of mass percent of A with an absolute measurement error of 0.5,
- HPLC-1: measurement of mass percent of C with an absolute measurement error of 0.5 and of D with an absolute measurement error of 0.005,
- HPLC-2: measurement of mass percent of E with an absolute measurement error of 0.0005.

Measurement times:

$$t = 0.5, 4.0, 24.0, 48.0, 72.0\, h$$

Parameter Estimation for the Reaction of Urethane





Reduction of the total residual from $2.8 \cdot 10^6$ to $3.8 \cdot 10^1$

Parameter estimate:

$$\begin{aligned} p_1 &= 2.40769 \\ p_2 &= 0.796408 \\ p_3 &= 89.9524 \\ p_4 &= 0.791621 \\ p_5 &= 70.6908 \\ p_6 &= 0.76358 \\ p_7 &= 3.4727 \\ p_8 &= 26.643 \end{aligned}$$

Statistical Analysis

Error propagation: The statistical errors of the measurement data yield statistical errors of the parameter estimate $\hat{v}$.

We have (in first order):

$$\hat{v} \sim \mathcal{N}(v_{true}, C)$$

C is the **Variance-Covariance Matrix** of the parameter estimate.

Variance-Covariance Matrix

Mathematical representation:

for constraint parameter estimation problems
$\min \|F_1(v)\|_2^2,\ F_2(v) = 0$

$$
\begin{aligned}
C &= J^+ \begin{pmatrix} E(F_1 F_1^T) & 0 \\ 0 & 0 \end{pmatrix} J^{+\,T} = J^+ \begin{pmatrix} I & 0 \\ 0 & 0 \end{pmatrix} J^{+\,T} \\
&= \begin{pmatrix} I & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T J_1 & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-T} \begin{pmatrix} I \\ 0 \end{pmatrix}
\end{aligned}
$$

Special case for unconstraint parameter estimation problems
$\min \|F(v)\|_2^2$

$$C = (J^T J)^{-1}$$

Confidence Region

The $(100 \cdot \alpha)\%$ confidence region contains the true (but unknown) parameters with the probability $\alpha \in [0,1]$.

$$G(\alpha, v_{true}) = \left\{ v \in \boldsymbol{R}^n : F_2(v) = 0,\ \|F_1(v)\|_2^2 - \|F_1(v_{true})\|_2^2 \leq \gamma^2(\alpha) \right\}$$

($\gamma^2(\alpha)$: Quantile of the χ^2 distribution with argument α)

Linearized approximation: confidence ellipsoid

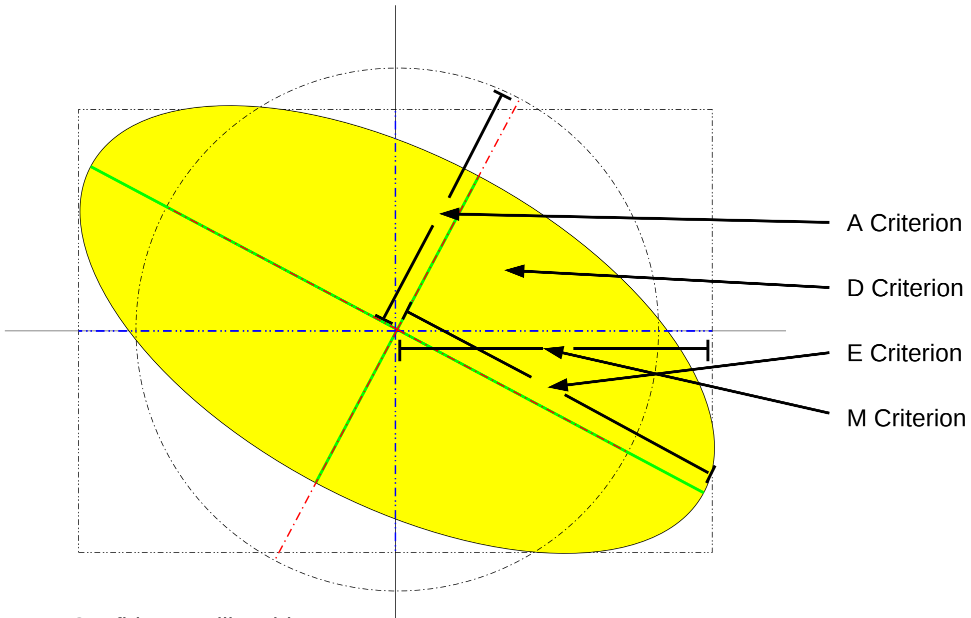
$$\begin{aligned} G_L(\alpha, \hat{v}) \quad &:= \quad \{ v \in \boldsymbol{R}^n :\ F_2(\hat{v}) + J_2(\hat{v})(v - \hat{v}) = 0, \\ &\qquad \|F_1(\hat{v}) + J_1(\hat{v})(v - \hat{v})\|_2^2 - \|F_1(\hat{v})\|_2^2 \leq \gamma^2(\alpha) \} \\ &= \quad \left\{ v \in \boldsymbol{R}^n :\ v = \hat{v} - J^+(\hat{v}) \begin{pmatrix} \delta w \\ 0 \end{pmatrix},\ \|\delta w\|_2 \leq \gamma(\alpha) \right\} \end{aligned}$$

Confidence Ellipsoid

The variance-covariance matrix C describes the confidence ellipsoid.

Geometrical properties:

- A criterion:
  $\frac{1}{n} \cdot \mathrm{trace}\, C$
- D criterion:
  $(\det C)^{\frac{1}{n}}$
- E criterion:
  $\max\{\text{eigenvalues}(C)\}$
- M criterion:
  $\max \sqrt{C_{ii}}$



Confidence Ellipsoid

Parameter Estimation for the Reaction of Urethane

Parameter values with corresponding standard deviations:

$$
\begin{array}{llll}
p_1 & = & 2.40769 & \pm & 0.218221 \\
p_2 & = & 0.796408 & \pm & 0.037436 \\
p_3 & = & 89.9524 & \pm & 4.87002 \\
p_4 & = & 0.791621 & \pm & 0.0287973 \\
p_5 & = & 70.6908 & \pm & 7.29698 \\
p_6 & = & 0.76358 & \pm & 0.0451626 \\
p_7 & = & 3.4727 & \pm & 1.93125 \\
p_8 & = & 26.643 & \pm & 60.2027
\end{array}
$$

Though the trajectories are fitted well after the parameter estimation, the confidence intervals of some of the parameters are so large that these parameters are practically undetermined.

Part II

Optimum Experimental Design

Linear Experimental Design

Kiefer, Wolfowitz 1959, Pukelsheim 1993

Distinguish:

- *Responses*: experimental results, dependent variables, measurable quantities η
- *Inputs*: adjustable quantities, independent variables, controls q

General relation: linear regression with parameters p

$$\eta_i = h_i(q)^T p + \epsilon_i, \quad i = 1, \ldots, M$$

e.g. polynomial fit models:

$$h_i(q)^T p = \sum_{k=0}^{n} \sum_{\substack{i_1, \ldots, i_k = 1 \\ i_1 \leq \ldots \leq i_k}}^{n} p_i \cdot q_{i_1} \cdot \ldots \cdot q_{i_k}$$

Linear Experimental Design

Goal: Design experiments such that the influence of the measurement errors on the parameter fit becomes as small as possible.

Approaches:

- Repetition of experiments
- Random experiments
- Factorial experiments
- Orthogonal experiments
- Block experiments

Nonlinear Regression

Nonlinear regression models

$$\eta_i = h_i(p, q) + \epsilon_i, \quad i = 1, \ldots, M$$

For dynamic processes:

$$\eta_i = h_i(t, x(t), p, q, u) + \epsilon_i, \quad i = 1, \ldots, M,$$

where $x(t) = (y(t), z(t))$ is the solution of a nonlinear DAE system:

$$\begin{aligned} \dot{y}(t) &= f(t, y(t), z(t), p, q, u) \\ 0 &= g(t, y(t), z(t), p, q, u). \end{aligned}$$

Experiments

An experiment is characterized by the

- experimental setup
- mode of processing
- choice of initial conditions
- choice of process conditions
- control of the process behavior
- realization of measurements

Planning of Measurements

What can be measured? Where? When? How often?

Points in time when measurements are possible: $t_1, \ldots, t_M$

Decision, if a possible measurement is actually realized:
variable *(weight)* $w_i \in \{0, 1\}$, $i = 1, \ldots, M$

$$w_i = \begin{cases} 1, & \text{measurement } i \text{ is realized,} \\ 0, & \text{measurement } i \text{ is not realized.} \end{cases}$$

Modified measurement error distribution:

$$\epsilon_i \sim \mathcal{N}(0, \sigma_i^2 / w_i).$$

Not realized measurements (weight 0) have an infinite variance, realized measurements (weight 1) have the variance σ_i^2.

Choice of Measurements

Typical constraints on the weights:

- Maximum number of measurements per point in time
- Maximum number of measurements per measurement method
- Maximum number of measurements per experiment

$$L_J \leq \sum_{i \in J} w_i \leq U_J \quad \text{for subsets } J \subseteq \{1, \ldots, M\}$$

- Cost of the measurements

$$\sum_{i=1}^{M} c_i^w \cdot w_i \leq c_{max}$$

$\longrightarrow$ Linear constraints for 0-1 variables

Modified Parameter Estimation Problem

For experimental design we now consider the modified parameter estimation problem

$$\min_{p,x} \sum_i w_i \cdot \frac{(\eta_i - h_i(t_i, x(t_i), p, q))^2}{\sigma_i^2}$$

$$\begin{aligned} \dot{y} &= f(t, y, z, p, q, u) \\ 0 &= g(t, y, z, p, q, u) \end{aligned}$$

$$0 = r(x(t_1), \dots, x(t_K), p, q)$$

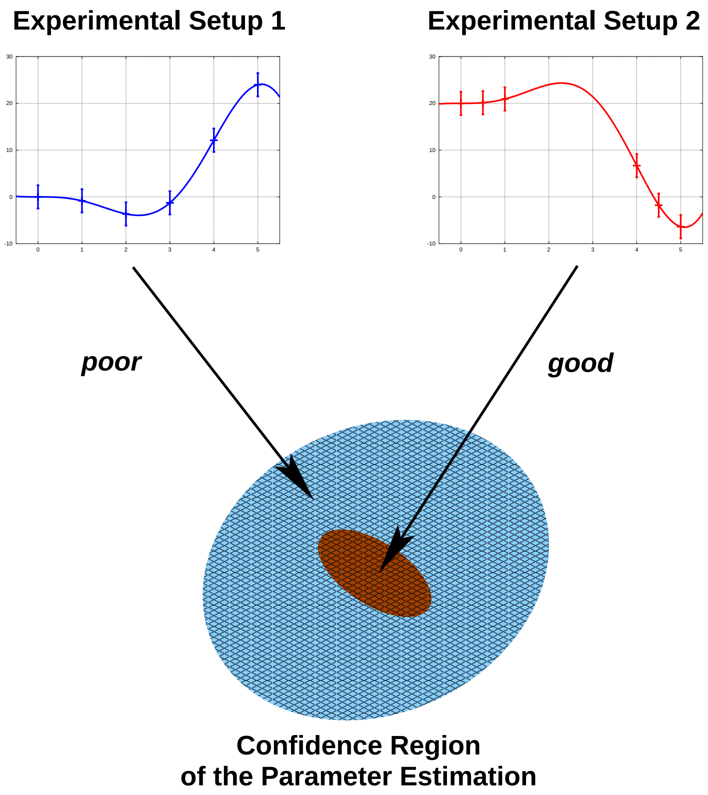
Let C be the variance-covariance matrix for the solution of this problem.

Experimental Design Variables

The variables q, $u(t)$ and w determine the experiment, we call them **experimental design variables** ξ.

$$\xi := (q, u, w)$$

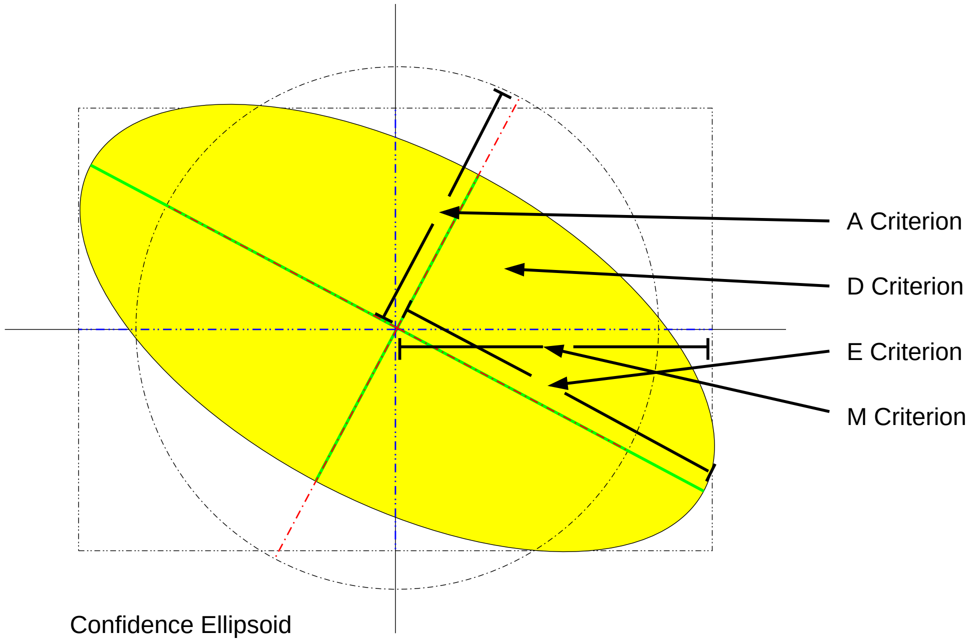
The confidence region depends on the values of the experimental design variables.



Objective Function of Experimental Design

Objective function for experimental design: function on the variance-covariance matrix:

- A criterion:
  $\frac{1}{n} \cdot \mathrm{trace}\, C$
- D criterion:
  $(\det C)^{\frac{1}{n}}$
- E criterion:
  $\max\{\text{eigenvalues}(C)\}$
- M criterion:
  $\max \sqrt{C_{ii}}$



Constraints for Experimental Design: Experiment Space

Control constraints:

$$\begin{array}{rcl} q_i & \in & [L_{q_i}, U_{q_i}] \\ u_i(t) & \in & [L_{u_i}, U_{u_i}] \\ L_c \leq & c(q) & \leq U_c \end{array}$$

State constraints:

$$L_b \leq b(t, x(t, p, q, u, s), p, q, u) \leq U_b,$$

Choice of measurements, weight constraints:

$$L_J \leq \sum_{i \in J} w_i \leq U_J \quad (J \subseteq \{1, \ldots, M\} \text{ subset of the possible measurements}),$$

Cost constraint:

$$\sum_{i=1}^{M} c_i^w w_i + \sum_{i=1}^{n_q} c_i^q q_i + \sum_{i=1}^{n_u} \int_{t_0}^{t_{end}} c_i^u(t) u_i(t) dt \leq c_{max},$$

Experiment Space

Formally summarized:

Inequality constraints:

$$L \leq \psi(t, x, p, q, u, w) \leq U$$

Equality constraints:

$$\chi(t, x, p, q, u, w) = 0$$

0-1 constraints for the weights:

$$w_i \in \{0, 1\}, \ i = 1, \dots, M.$$

Experimental Design Optimization Problem

$$\min_{x,q,u,w} \phi(C)$$

$$\begin{aligned} \dot{y} &= f(t, y, z, p, q, u) \\ 0 &= g(t, y, z, p, q, u) \end{aligned}$$

$$L \leq \psi(t, x, p, q, u, w) \leq U$$

$$\chi(t, x, p, q, u, w) = 0$$

$$w \in \{0, 1\}^M$$

Mathematical Properties of the Experimental Design Optimization Problem

- Constrained nonlinear optimal control problem
- Intricate non-standard objective function which is defined implicitly on derivatives
- Mixed-integer variables
- Multiple experiments yield structures
- DAE model equations are in general stiff

$\longrightarrow$ very challenging problem class,
cannot be treated with standard software

Mathematical Methods for Nonlinear Experimental Design

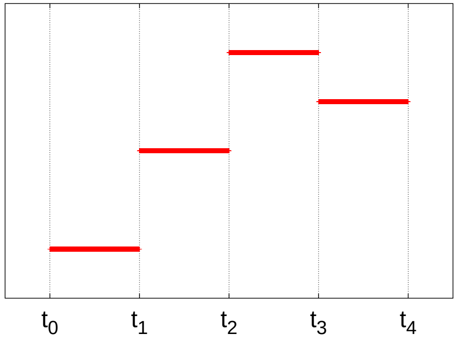
Overview:

- Direct approach of optimal control
- Discretization of the state constraints
- SQP method for nonlinear constrained optimization problems
- Solution of the DAE systems with a BDF method (DAESOL)
- Tailored derivative computation: Internal Numerical Differentiation in combination with Automatic Differentiation
- Relaxation of the integrality constraints, application of heuristics
- Exploitation of multiple experiment structures
- Modification for robust experimental design

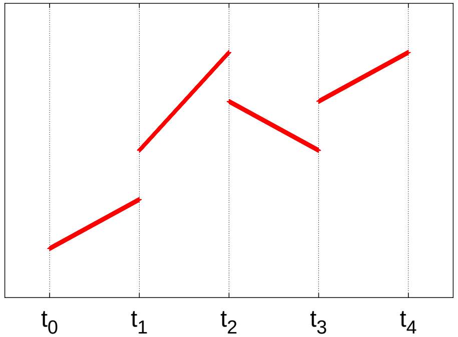
Direct Approach

Parameterization of the control functions, for example

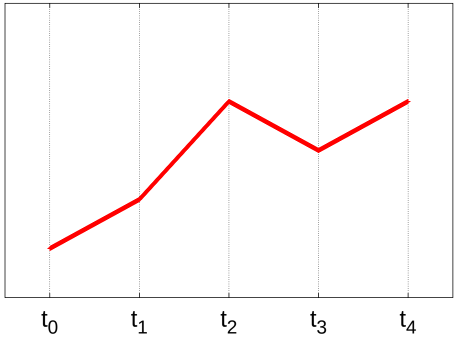
piecewise constant



piecewise linear



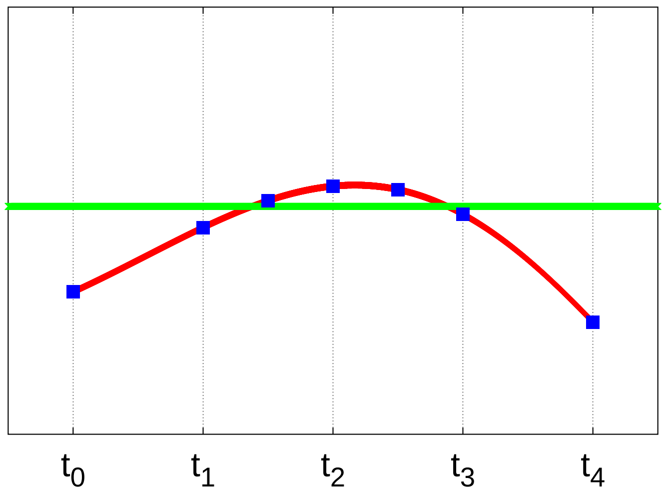
piecew. linear and cont.



$\longrightarrow$ Finitely many degrees of freedom

Discretization of the Control Constraints

Consider the control constraints on a finite grid:



$\longrightarrow$ finite number of constraints

- user defined grid
- eventually iteratively refined

Relaxation of the Integrality

Substitute $w_i \in \{0, 1\}$ by $w_i \in [0, 1]$, $i = 1, \ldots, M$.

Interpretation of this relaxation:

A measurement with (fractional) weight w_i is

- w_i times as precise: variance σ_i^2 / w_i
- w_i times as expensive: cost $c_i \cdot w_i$

as a measurement with weight 1

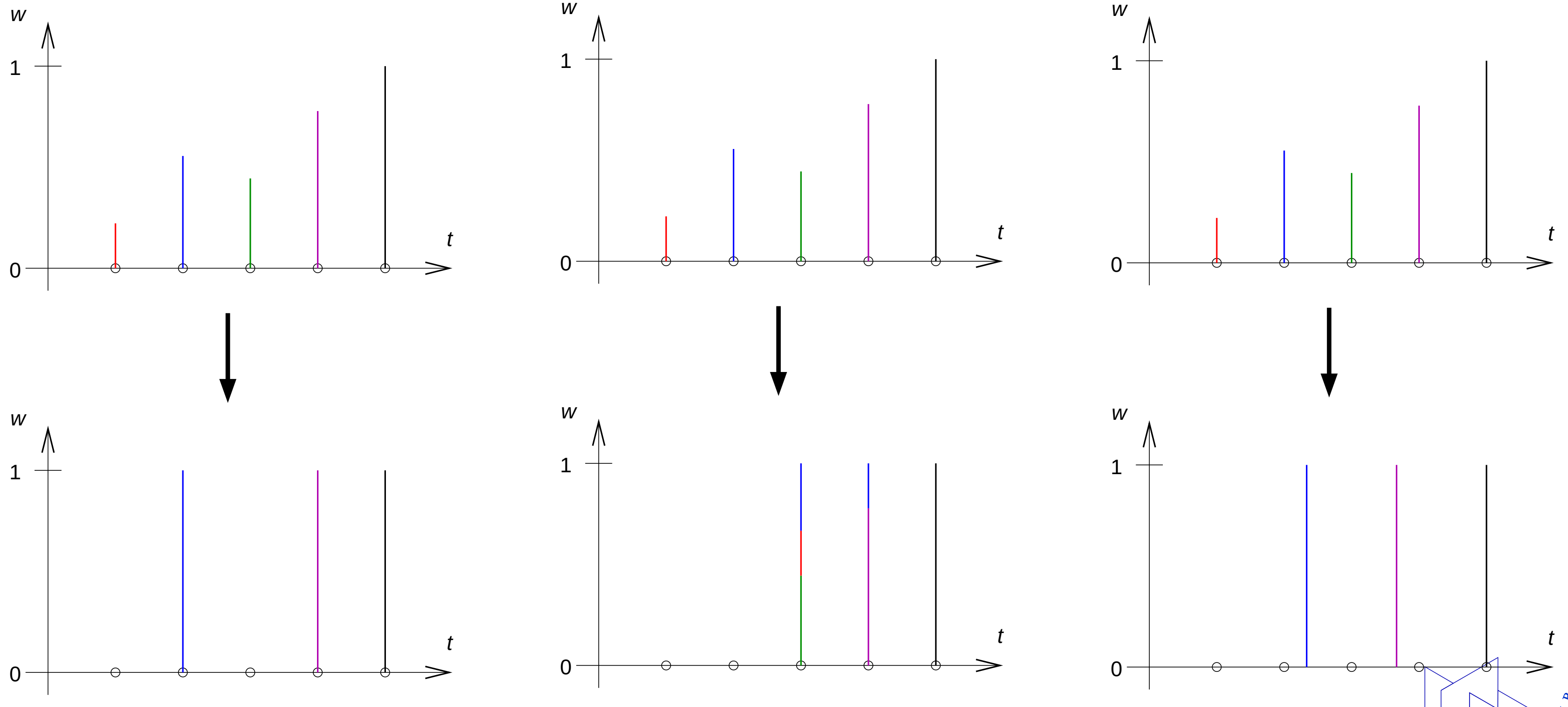
$\longrightarrow$ w_i-fold measurement.

Analogously: weights $w_i \in \boldsymbol{R}_+$.

Heuristics for the Generation of Integer Solutions

For example:

simple rounding | sum-up rounding | shifting of measurements



Exact Design

Observation:

Solutions of the relaxed problem with typical constraints on the weights satisfy the integrality constraints already completely or at least nearly.

Explanation: (Pukelsheim, Rieder, 1992)

For linear polynomial fit models of degree d:

A design is optimal if and only if is unequal 0 on exactly $d + 1$ points.

Sequential Quadratic Programming (SQP)

Nonlinear constrained optimization problem	$\min f(x)$ $0 = g(x)$ $0 \leq h(x)$

Idea: Solve a sequence of quadratic problems
($\equiv$ Newton's method for KKT conditions)

1. $k = 0$. Starting value x_0
2. Solve quadratic problem

$$\begin{aligned} &\min \Delta x_k^T H_k \Delta x_k + \nabla f(x_k)^T \Delta x_k \\ &0 = g(x_k) + \nabla g(x_k)^T \Delta x_k \\ &0 \leq h(x_k) + \nabla h(x_k)^T \Delta x_k \end{aligned}$$

3. Iteration: $x_{k+1} = x_k + \alpha_k \Delta x_k$
4. Stop or continue with 2. and $k := k + 1$.

with

$$H_k \approx \nabla_x^2 \mathcal{L}(x_k, \lambda_k, \mu_k)$$

approximation of the Hessian of the Lagrangian

$$\mathcal{L}(x, \lambda, \mu) = f(x) - \lambda^T g - \mu^T h$$

Computation of the Objective

$$\phi(C) = \mathrm{trace}(C) \text{ or } \det(K^T C K) \text{ or } \max\{\lambda : \lambda \text{ eigenvalue of } C\} \text{ or } \max\{C_{ii}\}$$

$$C = \begin{pmatrix} I & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T J_1 & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-T} \begin{pmatrix} I \\ 0 \end{pmatrix}$$

$$J_i = \frac{\partial F_i}{\partial x}\frac{\partial x}{\partial p} + \frac{\partial F_i}{\partial p}, \quad i = 1, 2$$

Derivative of the Objective

Given: direction Δq *Wanted:* directional derivative $\Delta \phi = \frac{d\phi}{dq} \Delta q$

$\phi(C) = \mathrm{trace}(C)$ or $\det(K^T C K)$ or $\max\{\lambda : \lambda$ eigenvalue of $C\}$ or $\max\{C_{ii}\}$

$\Delta \phi = \frac{d\phi}{dC} \Delta C$ (derivative of the objective w.r.t. the variance-cov. matrix)

$$C = \begin{pmatrix} I & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T J_1 & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-T} \begin{pmatrix} I \\ 0 \end{pmatrix}$$

$\Delta C = \frac{dC}{dJ} \Delta J$ (derivative of the variance-cov. matrix w.r.t. the Jacobian)

$J_i = \frac{\partial F_i}{\partial x} \frac{\partial x}{\partial p} + \frac{\partial F_i}{\partial p}, \quad i = 1, 2$ (deriv. of the Jacobian w.r.t. the controls)

$$\Delta J_i = \frac{dJ_i}{dq} \Delta q = \frac{\partial F_i}{\partial x} \frac{\partial^2 x}{\partial p \partial q} \Delta q + \frac{\partial^2 F_i}{\partial x \partial x} \frac{\partial x}{\partial p} \frac{\partial x}{\partial q} \Delta q + \frac{\partial^2 F_i}{\partial x \partial q} \frac{\partial x}{\partial p} \Delta q + \frac{\partial^2 F_i}{\partial p \partial x} \frac{\partial x}{\partial q} \Delta q + \frac{\partial^2 F_i}{\partial p \partial q} \Delta q$$

Derivative of the Objective

Given: direction Δq *Wanted:* directional derivative $\Delta\phi = \frac{d\phi}{dq}\Delta q$

$\phi(C) = \mathrm{trace}(C)$ or $\det(K^T C K)$ or $\max\{\lambda : \lambda$ eigenvalue of $C\}$ or $\max\{C_{ii}\}$

$\Delta\phi = \frac{d\phi}{dC}\Delta C$ (derivative of the objective w.r.t. the variance-cov. matrix)

$$C = \begin{pmatrix} I & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1^T J_1 & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} J_1^T J_1 & J_2^T \\ J_2 & 0 \end{pmatrix}^{-T} \begin{pmatrix} I \\ 0 \end{pmatrix}$$

$\Delta C = \frac{dC}{dJ}\Delta J$ (derivative of the variance-cov. matrix w.r.t. the Jacobian)

$J_i = \frac{\partial F_i}{\partial x}\frac{\partial x}{\partial p} + \frac{\partial F_i}{\partial p}, \quad i = 1,2$ (deriv. of the Jacobian w.r.t. the controls)

$$\Delta J_i = \frac{dJ_i}{dq}\Delta q = \frac{\partial F_i}{\partial x}\frac{\partial^2 x}{\partial p \partial q}\Delta q + \frac{\partial^2 F_i}{\partial x \partial x}\frac{\partial x}{\partial p}\frac{\partial x}{\partial q}\Delta q + \frac{\partial^2 F_i}{\partial x \partial q}\frac{\partial x}{\partial p}\Delta q + \frac{\partial^2 F_i}{\partial p \partial x}\frac{\partial x}{\partial q}\Delta q + \frac{\partial^2 F_i}{\partial p \partial q}\Delta q$$

Needs: Numerical solution $x(t) = (y(t), z(t))$ of the DAE

and derivatives $\frac{\partial x}{\partial p}(t)$, $\frac{\partial x}{\partial q}(t)$, $\frac{\partial^2 x}{\partial p \partial q}(t)$

$\rightarrow$ *Internal Numerical Differentiation*

Derivative Computation: Numerical Differentiation

Use finite differences, e.g. $f'(x) \cdot s = \dfrac{f(x + h \cdot s) - f(x)}{h} + O(h)$

Example: $f(x) = x^2$, $f'(x) = 2x$, $x = 1$, $s = 1$, 16 digits accuracy

h	$\frac{f(x+h)-f(x)}{h}$	error
10^{-2}	2.0100000000	0.0100000000
10^{-4}	2.0001000000	0.0001000000
10^{-6}	2.0000009999	0.0000009999
10^{-8}	1.9999999878	0.0000000122
10^{-10}	2.0000001655	0.0000001655
10^{-12}	2.0001778012	0.0001778012
10^{-14}	1.9984014443	0.0015985557
10^{-16}	0.0000000000	2.0000000000

h too big: too imprecise $\longrightarrow$ approximation error
h too small: also too imprecise $\longrightarrow$ cancellation error

Derivative Computation: Symbolic Differentiation

Compute the derivative function:

Example: $f(x) = \frac{3x^3+2x-6}{-x^2-4x+3}$

Computer algebra program MAPLE:

$$f := x \rightarrow \frac{(3x\text{^}3 + 2x - 6)}{(-x\text{^}2 - 4x + 3)}$$

$$x \rightarrow \frac{3x^3 + 2x - 6}{-x^2 - 4x + 3} \qquad (1)$$

$$\frac{\partial}{\partial x} f(x)$$

$$\frac{9x^2 + 2}{-x^2 - 4x + 3} - \frac{(3x^3 + 2x - 6)(-2x - 4)}{(-x^2 - 4x + 3)^2} \qquad (2)$$

$$\frac{\partial^2}{\partial x^2} f(x)$$

$$\frac{18x}{-x^2 - 4x + 3} - \frac{2(9x^2 + 2)(-2x - 4)}{(-x^2 - 4x + 3)^2} + \frac{2(3x^3 + 2x - 6)(-2x - 4)^2}{(-x^2 - 4x + 3)^3} + \frac{2(3x^3 + 2x - 6)}{(-x^2 - 4x + 3)^2} \qquad (3)$$

Expressions become more and more complicated.

Derivative Computation: Automatic Differentiation

(Bischof 1994, Griewank 2000)

- Merge derivative code into function evaluation code
- Namely computational step by computational step
- Apply the chain rule
- But: do not differentiate decisions, branches, loops, ...

Result:

- Derivatives have the same accuracy as the function evaluation.
- Computational effort for computation of a derivative is only at most by a factor 4 bigger than for function evaluation.

Derivative Computation: Automatic Differentiation

Example: $f(x) = \frac{3x^3+2x-6}{-x^2-4x+3}$

$$
\begin{array}{rcl|rcl}
v_0 & = & x & \dot{v}_0 & = & s \\
\hline
v_1 & = & 3v_0^3 + 2v_0 - 6 & \dot{v}_1 & = & (9v_0^2 + 2)\dot{v}_0 \\
v_2 & = & -v_0^2 - 4v_0 + 3 & \dot{v}_2 & = & (-2v_0 - 4)\dot{v}_0 \\
v_3 & = & 1/v_2 & \dot{v}_3 & = & -v_3^2\dot{v}_2 \\
v_4 & = & v_1 v_3 & \dot{v}_4 & = & \dot{v}_1 v_3 + v_1 \dot{v}_3 \\
\hline
f(x) & = & v_4 & f'(x) & = & \dot{v}_4
\end{array}
$$

Here: forward (direct) mode

Alternative: backward (adjoint) mode

Internal Numerical Differentiation for BDF Methods

Apply the AD principles to the BDF integration method:

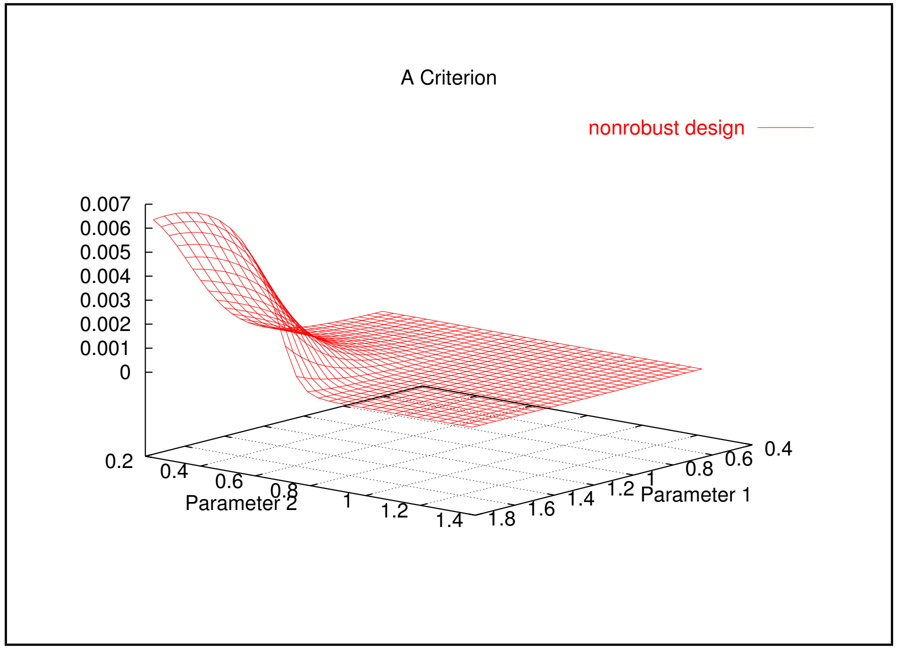
(ODE) $\dot{x} = f(x,p)$	(VDE) $\dot{G}^p = \frac{\partial f}{\partial x} G^p + \frac{\partial f}{\partial p} \quad \left(G^p = \frac{\partial x}{\partial p} \right)$
x_{n+1} approximation of the solution $x(t_{n+1})$	G^p_{n+1} approximation of the solution $G^p(t_{n+1})$
BDF discretization scheme step with order k and stepsize h:	BDF discretization scheme step with order k^p and stepsize h^p:
$\dot{x}_{n+1} = \frac{1}{h} \cdot \sum_{i=0}^{k} \alpha_i \cdot x_{n+1-i}$	$\dot{G}^p_{n+1} = \frac{1}{h^p} \cdot \sum_{i=0}^{k^p} \alpha^p_i \cdot G^p_{n+1-i}$
$\sum_{i=0}^{k} \alpha_i \cdot x_{n+1-i} = h f_{n+1}$	$\sum_{i=0}^{k^p} \alpha^p_i \cdot G^p_{n+1-i} = h^p \left(\frac{\partial f_{n+1}}{\partial x} G^p_{n+1} + \frac{\partial f_{n+1}}{\partial p} \right)$
differentiate BDF scheme:	freeze adaptive components:
$\sum_{i=0}^{k} \alpha_i \cdot G^p_{n+1-i} = h \cdot \left(\frac{\partial f_{n+1}}{\partial x} G^p_{n+1} + \frac{\partial f_{n+1}}{\partial p} \right)$	order $k^p = k$ stepsize $h^p = h$, $\Rightarrow$ BDF coefficients $\alpha^p_i = \alpha_i$

Derivative of the BDF scheme for (ODE) with frozen adaptive components is the same BDF scheme applied to (VDE).

Robust Experimental Design

For nonlinear models: The variance-covariance matrix depends on the model parameters:

$$C = C(\xi, p)$$



Reaction of Urethane, A criterion

Worst-Case Approach

Approach: Worst-Case Design

Compute significant experiments
for a distribution of the parameters:

$$\min_{\xi \in \Omega} \max_{\|p - p_0\|_{2,\Sigma^{-1}} \leq \gamma} \phi(C(\xi, p))$$

This is a **semi-infinite optimization problem**!

Methods require computation of global optima.

$\rightarrow$ Complexity: exponential in n_p

Our Approach

Approach: develop w.r.t. p

$$\min_{\xi\in\Omega} \max_{\|p-p_0\|_{2,\Sigma^{-1}}\leq\gamma} \left(\phi(C(\xi,p_0)) + \frac{d}{dp}\phi(C(\xi,p_0))(p-p_0)\right)$$

The inner problem can be solved explicitly:

$$\max_{\|p-p_0\|_{2,\Sigma^{-1}}\leq\gamma} \phi(C(\xi,p_0)) + \frac{d}{dp}\phi(C(\xi,p_0))(p-p_0)$$

$$= \phi(C(\xi,p_0)) + \gamma \left\| \frac{d}{dp}\phi(C(\xi,p_0)) \right\|_{2,\Sigma}$$

(Constraints: analogously)

Robust Experimental Designs Problem

$$\min_{\xi \in \Omega} \left(\phi(C(\xi, p_0)) + \gamma \left\| \frac{d}{dp} \phi(C(\xi, p_0)) \right\|_{2,\Sigma} \right)$$

The uncertainty quantile γ gives a **coupling** between

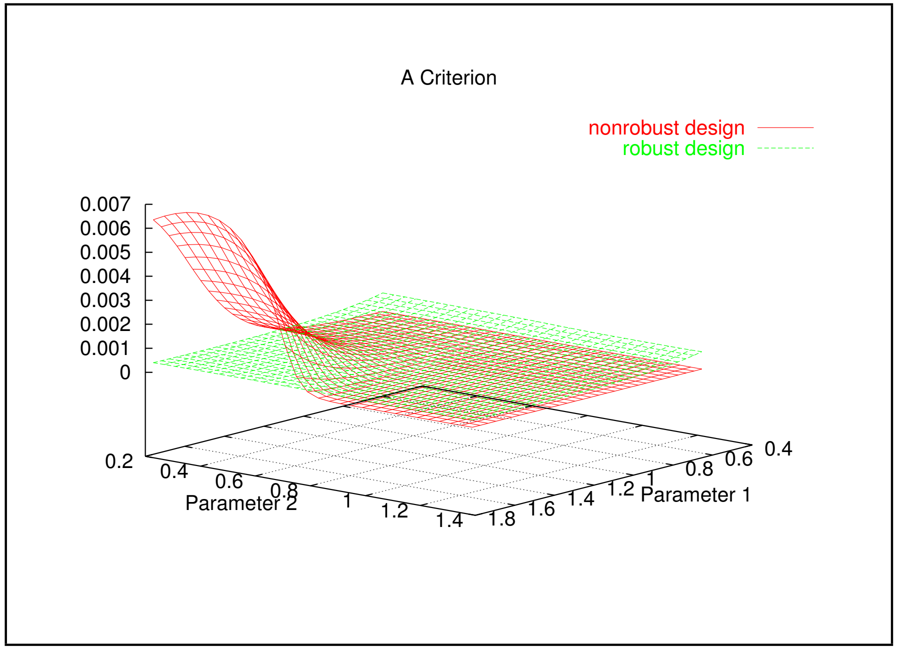
- the "non-robust part" $\phi(C(\xi, p_0))$
- and the "robustness part" $\left\| \frac{d}{dp} \phi(C(\xi, p_0)) \right\|_{2,\Sigma}$

of the objective function.

$\rightarrow$ Complexity: linear in n_p

Robust Experimental Design: Results

Comparison between "non-robust design" and "robust design"



Reaction of Urethane, A criterion

Robustness is improved drastically!

Multiple Experiments

Instead of single experiments, we can design series of experiments.

- **In parallel:** design of several experiments at the same time
  $\longrightarrow$ different experiments provide complementary information
- **Sequentially:** design of new experiments under consideration of the information from existent old experiments
  $\longrightarrow$ maximum gain in information

Multiple Experiments

Multiple experiments yield structures in the Jacobian:

$$
J_1 = \left(\begin{array}{c|cccc|cccc}
J^{1}_{1,p} & J^{1}_{1,s^1} & 0 & \cdots & 0 & & & & \\
\vdots & & \ddots & & & & 0 & & \\
J^{N_{\mathit{fix}}}_{1,p} & 0 & \cdots & 0 & J^{N_{\mathit{fix}}}_{1,s^{N_{\mathit{fix}}}} & & & & \\ \hline
J^{N_{\mathit{fix}}+1}_{1,p} & & & & & J^{N_{\mathit{fix}}+1}_{1,s^{N_{\mathit{fix}}+1}} & 0 & \cdots & 0 \\
\vdots & & & 0 & & & \ddots & & \\
J^{N_{ex}}_{1,p} & & & & & 0 & \cdots & 0 & J^{N_{ex}}_{1,s^{N_{ex}}}
\end{array}\right),
$$

Numerical treatment:

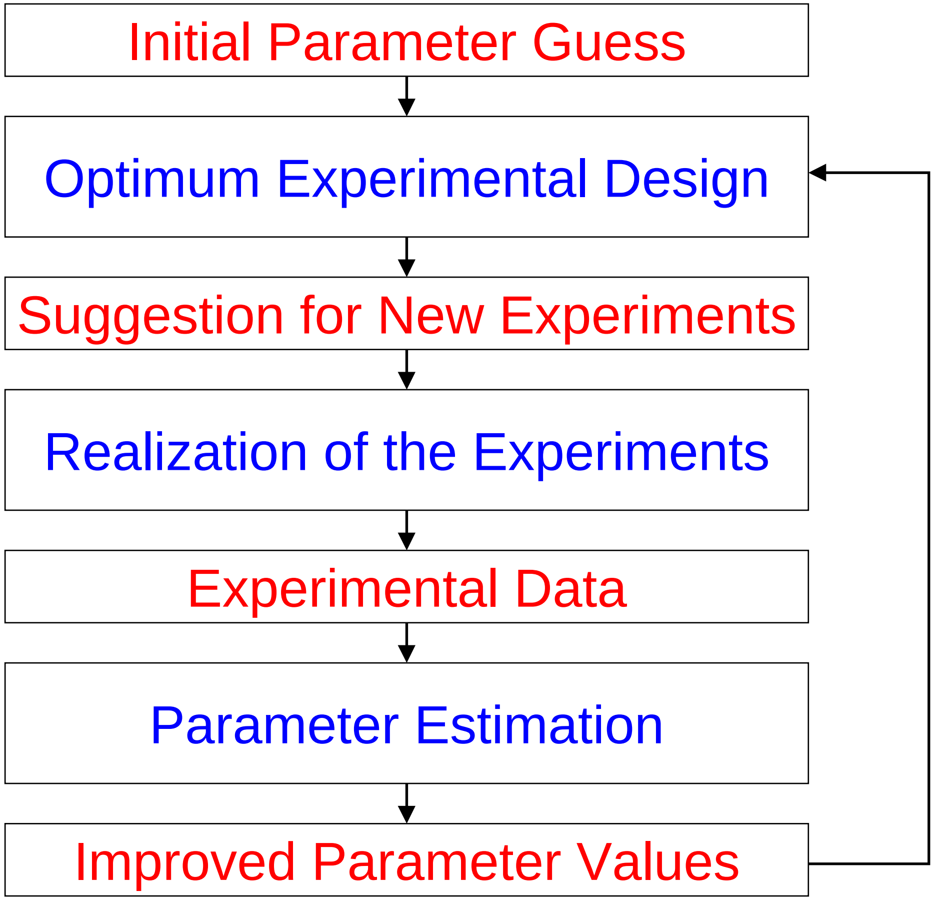
- separate integration and derivative computation for the particular experiments
- exploitation of the block structure of the Jacobian
- can be parallelized, prototype implemented

Summary Model Validation

	Parameter Estimation	Optimum Experimental Design
optimization problem	$\min\limits_{p,x} \sum_i w_i \cdot \frac{(\eta_i - h_i(x(t_i), p, q))^2}{\sigma_i^2}$ $r(x(t_0), \ldots, x(t_f), p, q) = 0$	$\min\limits_{\xi,x} \phi(C(x, p, \xi))$ $L \leq \psi(t, x, p, \xi) \leq U$ $\chi(t, x, p, \xi) = 0$
underlying DAE model	$\dot{y} = f(t, x(t), p, q, u(t))$ $0 = g(t, x(t), p, q, u(t))$	
variables	p	$\xi = (q, u(t), w)$
fixed	$\xi = (q, u(t), w)$	p

Sequential Approach

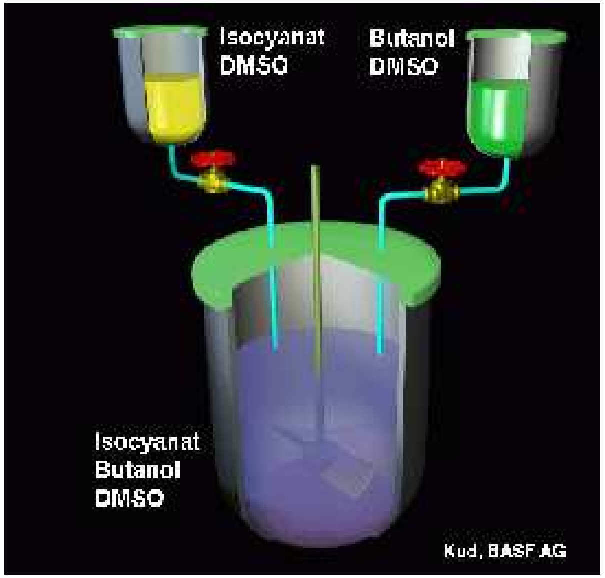
Goal: Determine Parameters and optimal experiments simultaneously.



Experimental Design for the Reaction of Urethane

$$
\begin{array}{ccc}
A + B & \rightarrow & C \\
A + C & \rightleftharpoons & D \\
3\ A & \rightarrow & E
\end{array}
$$

A: Isocyanate B: Butanole
C: Urethane D: Allophanate
E: Isocyanurate L: Solvent DMSO



$$
\begin{aligned}
\dot{n_C} &= V \cdot (r_1 - r_2 + r_3) \\
\dot{n_D} &= V \cdot (r_2 - r_3) \\
\dot{n_E} &= V \cdot r_4 \\
0 &= n_A + n_C + 2n_D + 3n_E - n_{A0} - n_{Aea}(t) \\
0 &= n_B + n_C + n_D - n_{B0} - n_{Beb}(t) \\
0 &= n_L - n_{L0} - n_{Lea}(t) - n_{Leb}(t)
\end{aligned}
$$

$$n_C(t_0) = n_D(t_0) = n_E(t_0) = 0$$

$$
\begin{aligned}
r_1 &= k_1 \cdot \frac{n_A}{V} \cdot \frac{n_B}{V} \qquad r_3 = k_3 \cdot \frac{n_D}{V} \\
r_2 &= k_2 \cdot \frac{n_A}{V} \cdot \frac{n_C}{V} \qquad r_4 = k_4 \cdot (\frac{n_A}{V})^2 \\
k_{i=1,2,4} &= k_{ref\ i} \cdot \exp\left(-\frac{E_{ai}}{R} \cdot \left(\frac{1}{T(t)} - \frac{1}{T_{ref\ i}}\right)\right) \\
\frac{k_2}{k_3} &= k_{c2} \cdot \exp\left(-\frac{dh_2}{R} \cdot \left(\frac{1}{T(t)} - \frac{1}{T_{g\,2}}\right)\right) \\
n_{A,e}(t) &= n_{A,e1,0} \cdot feed_1(t) \\
n_{B,e}(t) &= n_{B,e2,0} \cdot feed_2(t) \\
n_{L,e}(t) &= n_{L,e1,0} \cdot feed_1(t) + n_{L,e2,0} \cdot feed_2(t) \\
V &= \sum_{i=A}^{L} \frac{n_i \cdot M_i}{\rho_i}
\end{aligned}
$$

Expert Design (BASF)

Based on longtime experimental experience.

• Batch reactor • Isothermal experiments • Separation of the reactions

Formation of Urethane:
4 experiments with $97, 117, 127^\circ C$, measurements of Isocyanate

Formation of Allophanate:
6 experiments with $67, 97, 127, 147^\circ C$, measurements of Urethane/Allophanate

Formation of Isocyanurate:
5 experiments with $127, 157, 187^\circ C$, measurements of Isocyanurate

Altogether 90 measurements

Parameter Estimation for the Intuitive Experiments

Parameter	Estimation after 15 experiments		
$k_{ref\,1}$	$\underline{0.0012}5$	$\pm$	$1.2 \cdot 10^{-5}$
E_{a1}	$\underline{294}42$	$\pm$	$2.6 \cdot 10^{+2}$
$k_{ref\,2}$	$\underline{7.3}0 \cdot 10^{-6}$	$\pm$	$5.2 \cdot 10^{-8}$
E_{a2}	$\underline{709}24$	$\pm$	$1.9 \cdot 10^{+2}$
$k_{ref\,4}$	$\underline{5.799}0 \cdot 10^{-7}$	$\pm$	$8.5 \cdot 10^{-11}$
E_{a4}	$\underline{2300}4$	$\pm$	3
dh_2	$\underline{-1}5148$	$\pm$	$5 \cdot 10^{+3}$
k_{c2}	$\underline{0.1}9$	$\pm$	0.04

$\Longrightarrow$ Worst parameter has uncertainty of $\approx 30\%$.

Constraints for Experimental Design

- Control constraints:

$$
\begin{aligned}
MV_1 &:= \frac{n_{B,0} + n_{B,e2,0}}{n_{A,0} + n_{A,e1,0}} && \in && [0.1; 10] \\
MV_2 &:= \frac{n_{A,e1,0}}{n_{A,0}} && \in && [0; 1000] \\
MV_3 &:= \frac{n_{B,e2,0}}{n_{A,0}} && \in && [0; 10] \\
g_a &:= \frac{n_{A,0} \cdot M_A + n_{B,0} \cdot M_B}{n_{A,0} \cdot M_A + n_{B,0} \cdot M_B + n_{L,0} \cdot M_L} && \in && [0; 0.8] \\
g_{a,e1} &:= \frac{n_{A,e1,0} \cdot M_A}{n_{A,e1,0} \cdot M_A + n_{L,e1,0} \cdot M_L} && \in && [0; 0.9] \\
g_{a,e2} &:= \frac{n_{B,e2,0} \cdot M_B}{n_{B,e2,0} \cdot M_B + n_{L,e2,0} \cdot M_L} && \in && [0; 1] \\
V_0 &:= \frac{n_{A,0} \cdot M_A}{\rho_A} + \frac{n_{B,0} \cdot M_B}{\rho_B} + \frac{n_{L,0} \cdot M_L}{\rho_L} && \in && [0\ m^3; 0.00075\ m^3]
\end{aligned}
$$

- Cost constraint:
  at most 16 measurements per experiment
- Day-night-shift operation:
  during the night-shifts: no measurements, no changes of the control functions

Optimum Experimental Design

Design of the first experiment

before optimization: $\phi_A = 35.5481$

after optimization: $\phi_A = 0.00113361$

after simple rounding of three weights: $\phi_A = 0.00113406$

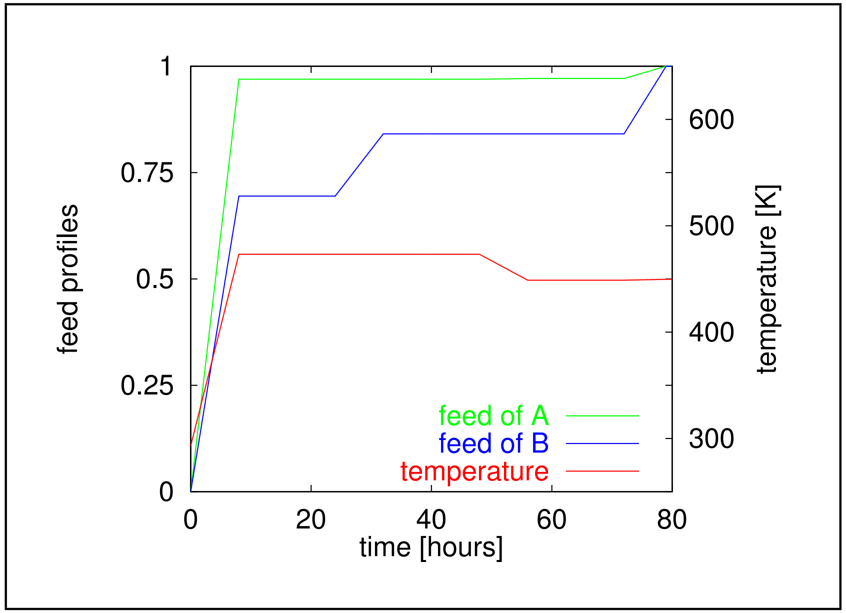
Design of the second experiment

before optimization: $\phi_A = 0.00213083$

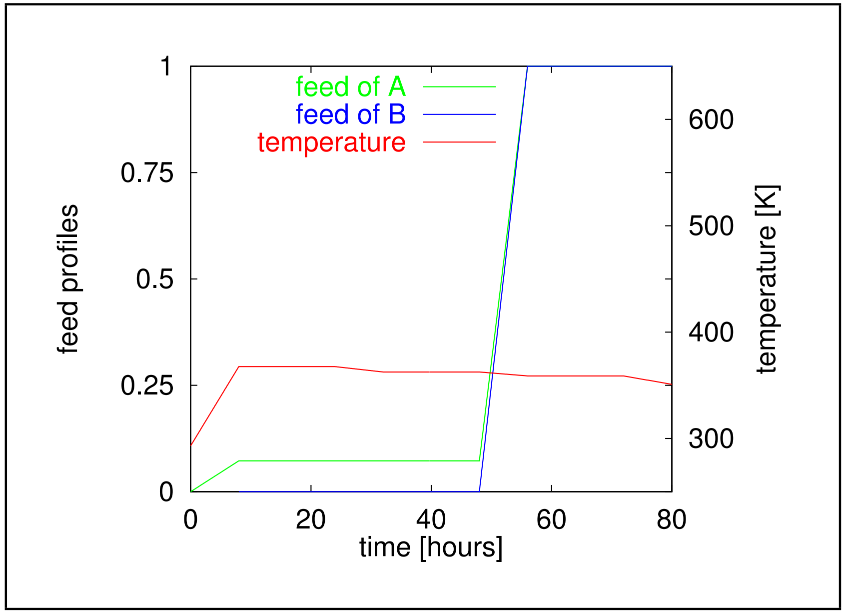
after optimization: $\phi_A = 0.0000557949$

all weights already integer

Optimized Control Functions

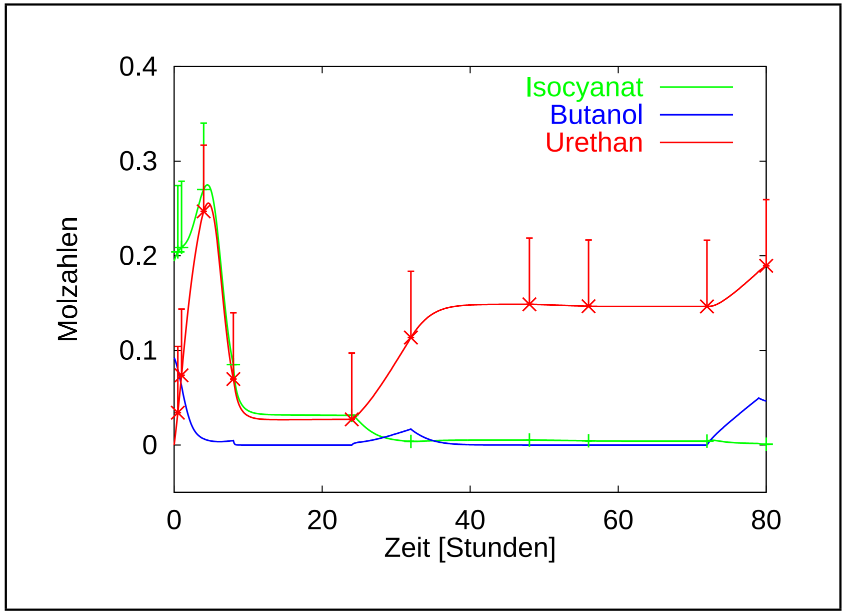


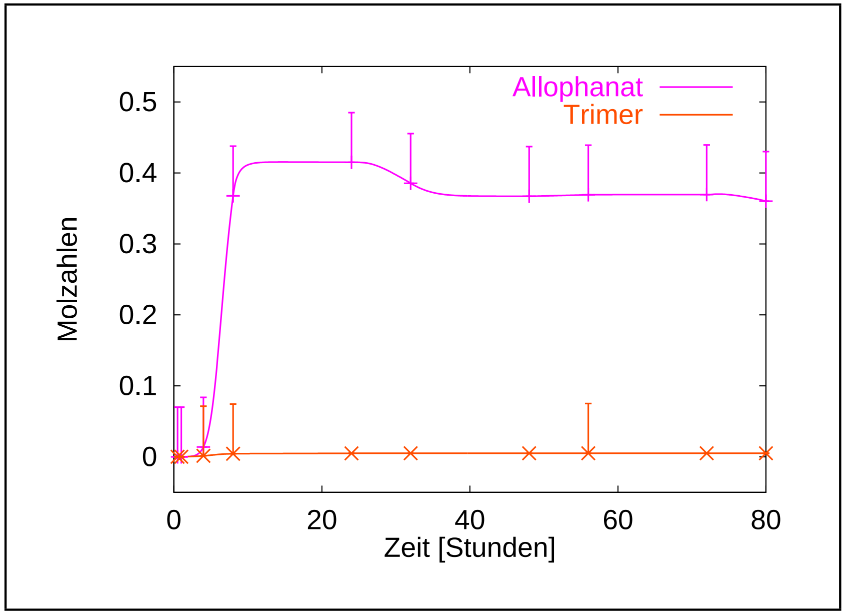
First experiment



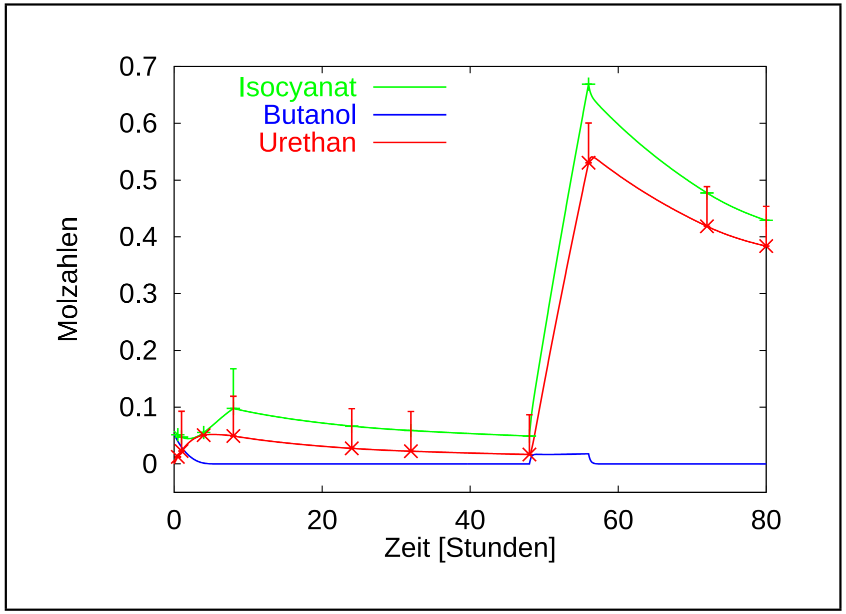
Second experiment

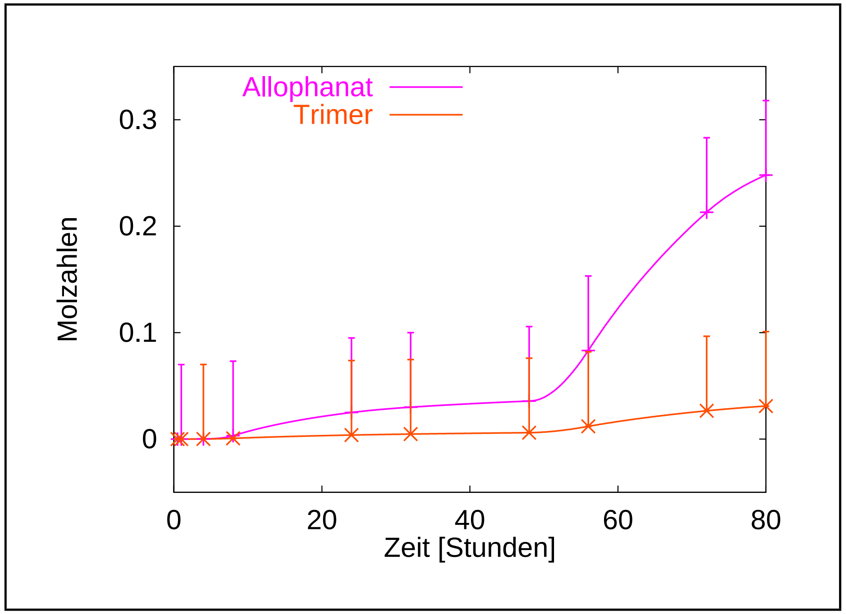
Trajectories and Measurements of the First Optimized Experiment





Trajectories and Measurements of the Second Optimized Experiment





Results of the Parameter Estimation

Parameter	Starting value	Estimation after 2 experiments		
$k_{ref\,1}$	0.0005	$\underline{0.00125}2$	$\pm$	$3 \cdot 10^{-6}$
E_{a1}	35240	$\underline{294}40$	$\pm$	$5 \cdot 10^{+1}$
$k_{ref\,2}$	$8 \cdot 10^{-8}$	$\underline{7.298}1 \cdot 10^{-6}$	$\pm$	$8 \cdot 10^{-10}$
E_{a2}	85000	$\underline{7101}4$	$\pm$	$8 \cdot 10^{+0}$
$k_{ref\,4}$	$1 \cdot 10^{-8}$	$\underline{5.799}6 \cdot 10^{-7}$	$\pm$	$4 \cdot 10^{-11}$
E_{a4}	35000	$\underline{230}20$	$\pm$	$1 \cdot 10^{+1}$
dh_2	-17031	$\underline{-183}00$	$\pm$	$1 \cdot 10^{+2}$
k_{c2}	0.17	$\underline{0.21}7$	$\pm$	$2 \cdot 10^{-3}$

$\Longrightarrow$ All parameters can be estimated with a variance smaller than 1 percent.

Comparison: Intuitive Experimental Design vs. Optimum Experimental Design for the Reaction of Urethane

	number of experiments	number of measurements	maximum error
intuitive	15	90	$> 30\%$
with optimization	2	32	$< 1\%$

Conclusion: Enormous potential:
Cost-saving by application of optimization methods.

The Software Package VPLAN

VPLAN is a software package for the formulation and solution of simulation and optimization tasks for multiple experiments with underlying DAE models.

Virtual Laboratory:

- *Simulation Tool:* Numerical solution of the DAE systems for all experiments, graphical output of the trajectories. Evaluation of the measurement response functions, computation of residuals. Computation of the variance-covariance matrix, optimality criteria and standard deviations. Check if the constraints are satisfied.
- *Parameter Estimation:* Solution of multiple experiment parameter estimation problems.
- *Experimental Design:* Solution of nonlinear optimum experimental designs problems.

Software Concepts of VPLAN

- Strict separation of the program and the formulation and implementation of the application problems.
- Description of application problems by ASCII files, hence connection to graphical user interfaces, model generators and process control systems easily possible.
- Output of the results via ASCII files, interface for visualization available.
- Use of techniques of automatic derivative generation, for the user derivative-free.
- VPLAN uses the program packages SNOPT, ADIFOR and LAPACK. As components, DAESOL and PARFIT are contained.

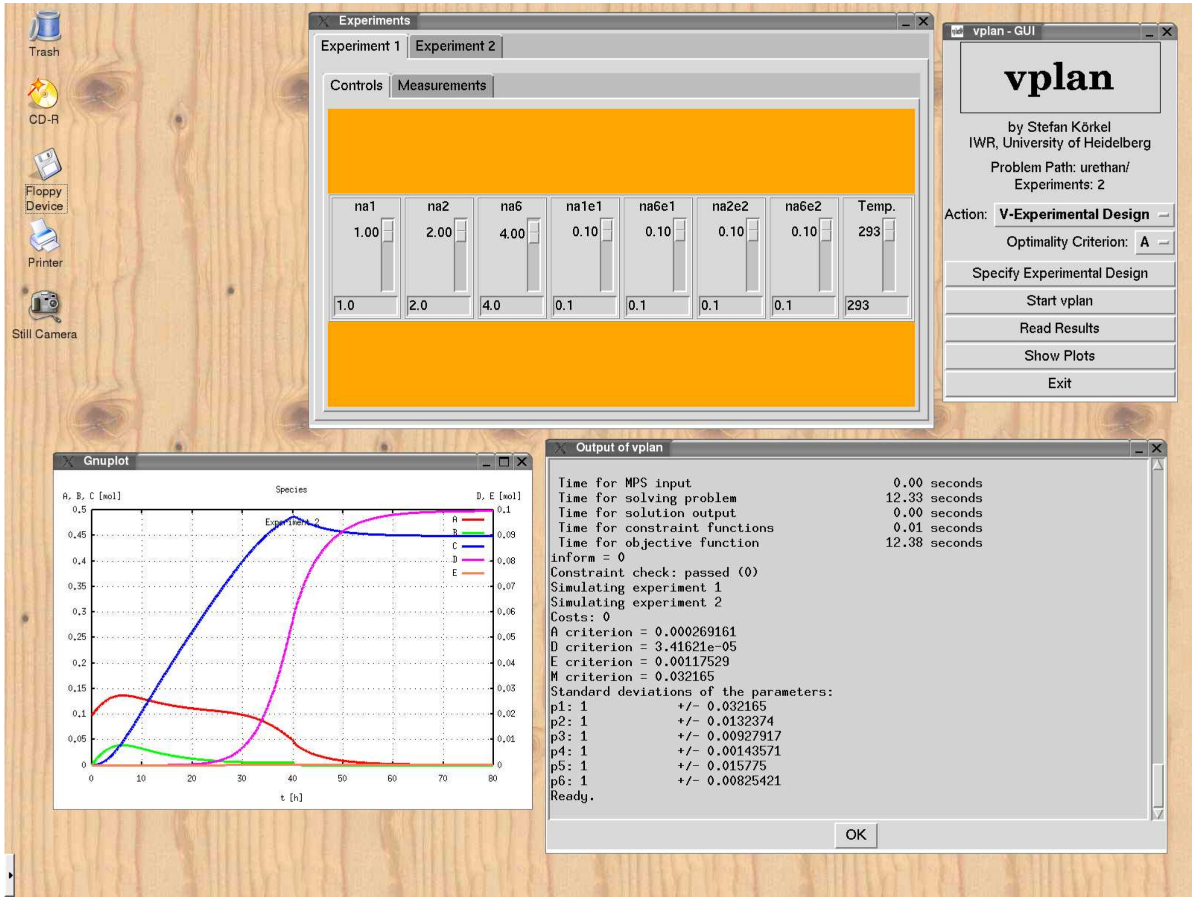
Usage of VPLAN

Working with an application problem:

1. Creation of the problem directory
2. Creation of model and data files in the problem directory
3. Automatic derivative generation and making of the problem module
4. Execution of numerical computations with one of the modes described above
5. Access to output files in the problem directory

Output files have the same structure as input files. Hence it is easily possible to call VPLAN repeatedly and successively.

GUI for VPLAN



Development of VPLAN

- In the past: development mainly in the group of Prof. Bock at the IWR in Heidelberg.
- BMBF Project: Optimum Experimental Design, partners: IWR, FH Frankfurt, BASF, Aventis
- SFB 359 at the IWR
- Dissertation K., Heidelberg, 2002
- Further developers: I. Bauer, S. Sager, G. Rücker
- Ongoing utilization at BASF
- Since 2005 development also at HU Berlin
- New BMBF Project NOVOEXP, partners: IWR Heidelberg, HU Berlin, TU Berlin, U Marburg, BASF, Knauer

Summary and Outlook

- Modeling of dynamic processes leads to systems of differential equations.
- Parameter Estimation: validation of the model by fitting to experimental data.
- Experimental Design: determine experiments from which the parameters can be estimated significantly.
- For validated processes simulation based process optimization methods can be applied.
- Suited mathematical methods for optimization: Newton-type methods.
- Available: powerful mathematical software.
- Necessary: interdisciplinary cooperations to bring together know-how about the processes and the mathematical methods.

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VPLAN-Wiki: novoexp.mathematik.hu-berlin.de

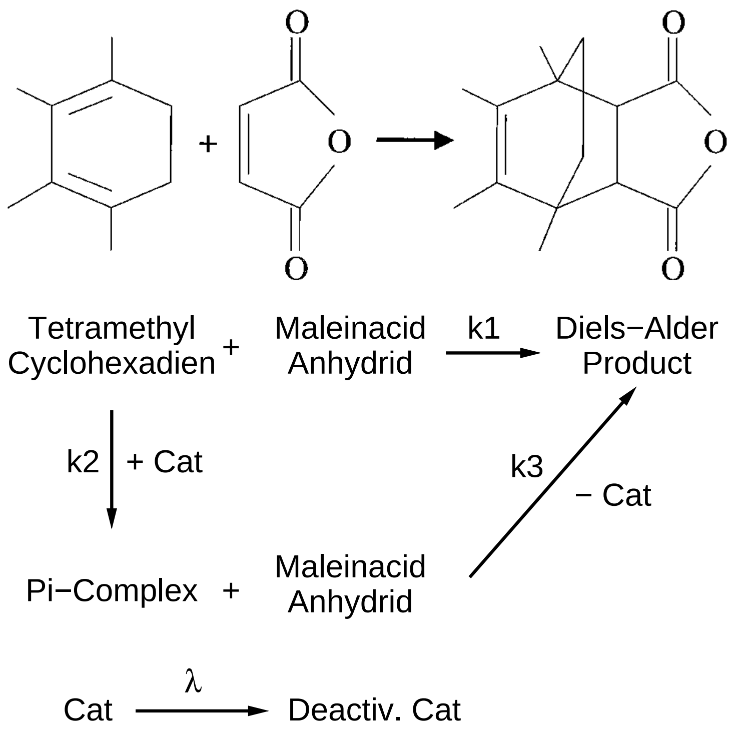
Part III

Practical Computer Course

Example: Bimolecular Catalysis

Diels-Alder reaction

Mechanism of the reaction:



non-catalyzed and catalyzed reaction path

deactivation of the catalyst

Mathematical Model

Differential equation system:

$$\begin{aligned}
\dot{n}_1 &= -k \cdot \frac{n_1 \cdot n_2}{m_{tot}} \\
\dot{n}_2 &= -k \cdot \frac{n_1 \cdot n_2}{m_{tot}} \\
\dot{n}_3 &= k \cdot \frac{n_1 \cdot n_2}{m_{tot}}
\end{aligned}$$

Initial values:

$$\begin{aligned}
n_1(0) &= n_{a1} \\
n_2(0) &= n_{a2} \\
n_3(0) &= 0
\end{aligned}$$

Mathematical Model

Reaction velocity constant:

$$\begin{aligned} k &= k_1 \cdot \exp\left(-\frac{E_1}{R} \cdot \left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\right) \\ &+ k_{kat} \cdot c_{kat} \cdot \exp\left(-\lambda \cdot t\right) \cdot \exp\left(-\frac{E_{kat}}{R} \cdot \left(\frac{1}{T} - \frac{1}{T_{ref}}\right)\right) \end{aligned}$$

Solvent:

$$n_4 = n_{a4}$$

Total mass:

$$m_{tot} = n_1 \cdot M_1 + n_2 \cdot M_2 + n_3 \cdot M_3 + n_4 \cdot M_4$$

Temperature in Kelvin:

$$T = \vartheta + 273$$

Model Quantities

- State variables: molar numbers n_1, n_2, n_3
- Parameters: steric factors k_1, k_{kat}, activation energies E_1, E_{kat}, catalyst deactivation coefficient λ
- Control variables: initial molar numbers n_{a1},n_{a2}, $n_{a4} \in [0.4, 9]$, concentration of the catalyst $c_{kat} \in [0, 6]$, Celsius temperature $\vartheta(t) \in [20, 100]$
- Constants: molar masses $M_1 = 0.1362$, $M_2 = 0.09806$, $M_3 = 0.23426$, $M_4 = 0.236$, universal gas constant $R = 8.314$, reference temperature $T_{ref} = 293$

Model Quantities

Control of the temperature:

$$\vartheta(t) = \begin{cases} \vartheta_1 & \text{for } t \leq 2 \\ \vartheta_1 + \frac{t-2}{6}(\vartheta_2 - \vartheta_1) & \text{for } 2 \leq t \leq 8 \\ \vartheta_2 & \text{for } t \geq 8 \end{cases}$$

Starting values for the parameters:

$$\begin{aligned} k_1 &= p_1 \cdot 0.01 \\ E_1 &= p_2 \cdot 60000 \\ k_{kat} &= p_3 \cdot 0.10 \\ E_{kat} &= p_4 \cdot 40000 \\ \lambda &= p_5 \cdot 0.25 \end{aligned}$$

with $p_j = 1,\ j = 1, \ldots, 5$

Measurement Functions

The product C of the reaction can be measured with an HPLC.

$$h = \frac{n_3 \cdot M_3}{m_{tot}} \cdot 100$$

Standard deviation of the measurement error:

$$\sigma = 1$$

Constraints

Initial mass:

$$0.1 \leq n_{a1} \cdot M_1 + n_{a2} \cdot M_2 + n_{a4} \cdot M_4 \leq 10$$

Fraction of active substances:

$$0.1 \leq \frac{n_{a1} \cdot M_1 + n_{a2} \cdot M_2}{n_{a1} \cdot M_1 + n_{a2} \cdot M_2 + n_{a4} \cdot M_4} \leq 0.7$$

Steps in the Practical

1. Get used to Knoppix
2. Modeling of processes in VPLAN
3. Automatic derivative generation
4. Call of VPLAN
5. GUI: simulation tool, trial and error
6. GUI: optimum experimental design
7. Parameter estimation