Optimization Methods for Calibration and Validation of Dynamic Models

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Outline

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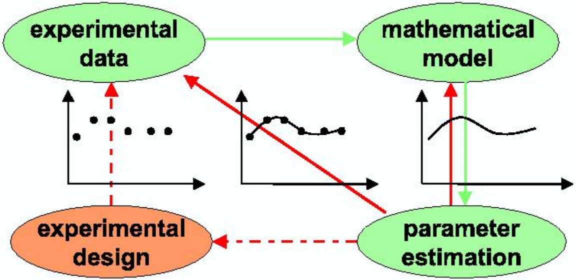
Model Validation:
Bringing Experiment and Modeling Together



We Need Models That Allow Simulation

From Merriam-Webster's Dictionary

Full Definition of *simulation*

1. *1* : the act or process of simulating
2. *2* : a sham object : counterfeit
3. *3a* : the imitative representation of the functioning of one system or process by means of the functioning of another *<a computer simulation of an industrial process>b* : examination of a problem often not subject to direct experimentation by means of a simulating device

Full Definition of *simulator*

1. : one that simulates; *especially* : a device that enables the operator to reproduce or represent under test conditions phenomena likely to occur in actual performance

Why Do We Need Simulation Models?

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GE Report Oct 4, 2015

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- Another example: development and admission of drugs
- Necessary precondition: validated models with reliable parameter estimates

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Dynamic Process Models

- Ordinary Differential Equations (ODE)
- Boundary Conditions
- Measurement Functions
- Differential Algebraic Equations (DAE)
- Partial Differential Equations (PDE) and Method of Lines (MOL)
- Models with Switches

Ordinary Differential Equations (ODE)

System dynamics is influenced by controls/inputs and unknown parameters

$$\dot{x}(t) = f(t, x(t), p, u(t))$$

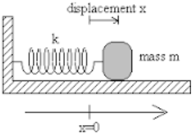
- simulation interval: $[t_0, t_{\text{end}}]$
- time $t \in [t_0, t_{\text{end}}]$
- state $x(t) \in \mathbb{R}^{n_x}$
- controls $u(t) \in \mathbb{R}^{n_u}$ $\longleftarrow$ inputs
- parameters $p \in \mathbb{R}^{n_p}$ $\longleftarrow$ unknown

ODE Example: Harmonic Oscillator

Mass m with spring constant k and unknown friction coefficient β:

$$\begin{aligned} \dot{x}_1(t) &= x_2(t) \\ \dot{x}_2(t) &= -\frac{k}{m}(x_1(t) - u(t)) \quad - \beta x_2(t) \end{aligned}$$

- state — $x(t) \in \mathbb{R}^2$
- position of mass — $x_1(t)$
- velocity of mass — $x_2(t)$
- control: acceleration — $u(t) \in \mathbb{R}$ $\longleftarrow$ given input
- parameter: friction — $\beta \in \mathbb{R}$ $\longleftarrow$ unknown



Boundary Conditions

Constraints on initial or intermediate values are important part of dynamic model

Standard Form:

$$r(x(t_0), x(t_1), \dots, x(t_{\text{end}}), p) = 0, \quad r \in \mathbb{R}^{n_r}$$

E.g., fixed or parameter dependent initial value x_0:

$$x(t_0) - x_0(p) = 0 \qquad (n_r = n_x)$$

or periodicity:

$$x(t_0) - x(t_{\text{end}}) = 0 \qquad (n_r = n_x)$$

Note: Initial values $x(t_0)$ need not always be fixed!

Measurement Functions

We can measure functions of states and parameters:

$$M_i(x(t_i), p) \qquad i = 1, \ldots, N$$

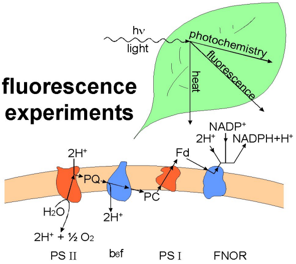
- $M_i \in \mathbb{R}^{m_i}$, often nonlinear
- altogether $\sum_{i=1}^{N} m_i$ measurements
- measurement times $t_1, \ldots, t_N \in [t_0, t_{\text{end}}]$

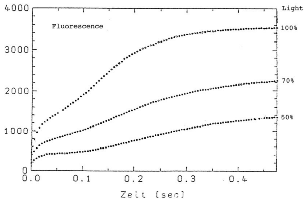
Example: The Light Reaction in Photosynthesis

Baake, Schlöder, 1992

three experiments with different light intensities

fluorescence experiments

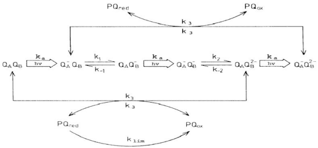




Laboratory Strasser, Stuttgart

Photosynthesis: ODE

electron transport chain
in photosynthesis:



- mathematical model:
  nonlinear ODE
  with 6 states and 4+2
  parameters

$$\begin{aligned}
\dot{x}_1 &= (k_a + k_3(p_{\text{tot}} - x_6))x_1 + k_3 x_5 x_6 \\
\dot{x}_2 &= k_a x_1 - (k_1 + k_3(p_{\text{tot}} - x_6))x_2 + k_{-1}x_3 + k_3 x_6 (1 - \textstyle\sum_{i=1}^{5} x_i) \\
\dot{x}_3 &= k_1 x_2 - (k_a + k_{-1})x_3 \\
\dot{x}_4 &= k_a x_3 - k_2 x_4 + k_{-2} x_5 \\
\dot{x}_5 &= k_3 x_1 (p_{\text{tot}} - x_6) + k_2 x_4 - (k_a + k_{-2} + k_3 x_6) x_5 \\
\dot{x}_6 &= -k_3 (1 - \textstyle\sum_{i=1}^{5} x_i) x_6 + k_3 (x_1 + x_2)(p_{\text{tot}} - x_6) + (p_{\text{tot}} - x_6) k_{\text{lim}}
\end{aligned}$$

with

$$k_a = \frac{I_2(1 - p_{2T})}{1 - p_{22} - p_{2T} + p_{22}p_{2T}(x_1 + x_3 + x_5)}$$

Photosynthesis: Boundary Conditions

- Initial values are given (partly depending on parameters):

$$r(x(0), p) = \begin{pmatrix} x_1(0) - c_1 \\ x_2(0) - c_2 \\ x_3(0) - c_3 \\ x_4(0) - c_4 \\ x_5(0) - c_5 \\ x_6(0) - p_{\text{tot}} \end{pmatrix} = 0$$

Photosynthesis: Measurement Function

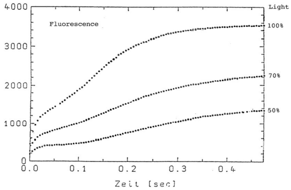
- Fluorescence is nonlinear function of states and parameters:

$$M_i(x(t_i), p) = \left\{ \frac{1 - p_{2T} - p_{22}}{p_{2T}} + \frac{1 - (x_1(t_i) + x_3(t_i) + x_5(t_i))}{1 + \frac{p_{22} p_{2T} (x_1(t_i) + x_3(t_i) + x_5(t_i))}{1 - p_{2T} - p_{22}}} \right\} \cdot S \cdot I_2$$

- Extra parameter (S) in measurement function (unknown gauge of apparatus)
- Fluorescence measured at 96 time points $t_1, \ldots, t_{96}$.
- Aim: Estimate model parameters from fluorescence measurements of living tobacco leaf

Photosynthesis: Multiple Experiment Structure

Data: 3 experiments with different light intensities (96 fluorescence measurements)



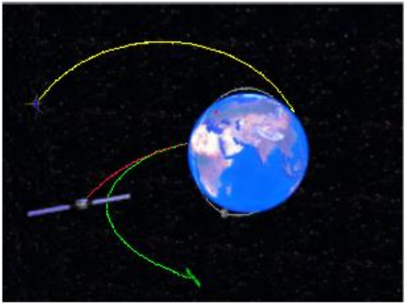
to be estimated:

4 system parameters $p_{\text{tot}}, p_{2T}, p_{22}, k_3$

\+ 1 measurement parameter S

\+ 3 x 2 parameters depending on experiment k_{lim}, I_2

Satellite Orbit Determination: False injection orbit

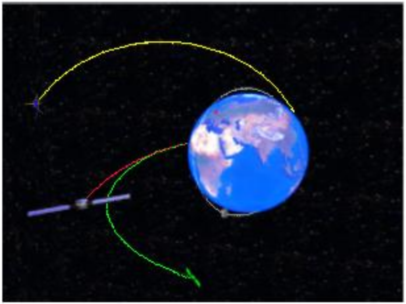


Actual injection orbit differs significantly due to launcher mal-function or underperformance

(SPACEFLIGHT NOW, 21.02.2002): ... the Ariane 5 launcher had propelled the Artemis satellite into a transfer orbit that was lower than expected, with the apogee at only 17 000 km rather than the nominal 36 000 km ...

Similar: Galileo satellite (August 2014)!

Satellite Orbit Determination: False injection orbit



Important: Fast and reliable determination of satellite orbit in order to

- predict future trajectory
- perform correction maneuvers

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Satellite Dynamics

Kepler equations augmented by perturbations

$$\dot{r}(t) = v(t), \qquad \dot{v}(t) = -\frac{GM_\oplus}{\|r(t)\|^3} r(t) + \text{pert}(r(t), v(t), t)$$

due to external forces

- gravitational forces of sun and moon
- inhomogeneities of earth' gravitational field
- air drag
- solar radiation pressure
- dynamic solid tide
- relativistic effects
- gravitational forces from Venus and Jupiter

$\vdots$

Satellite Dynamics

Kepler equations augmented by perturbations

$\dot{r}(t) = v(t), \qquad \dot{v}(t) = -\frac{GM_\oplus}{\|r(t)\|^3} r(t) + \text{pert}(r(t), v(t), t)$

- Results in small but complex nonlinear differential equation system in six states with discontinuities in right-hand side
- Orbit uniquely defined if full state vector $\begin{pmatrix} r(t_0) \\ \dot{r}(t_0) \end{pmatrix}$ known at a time t_0

Data

- Observations of the satellite from different ground stations

Typical measurements:

- range
- range rate
- azimuth and elevation angles

Malindi Ground Station

Range Measurements

distance between ground station and satellite

$$M_1(x(t_M), t_M) \quad = \quad m(x(t_M), t_M) + M_1^{corr}(x(t_M), t_M)$$

where
$m(x(t_M), t_M) = 2\|r(t_M) - r_{stat}(t_M)\|_2$

$x(t_M) = \binom{r(t_M)}{v(t_M)}$ - position of the satellite at the moment t_M

$r_{stat}(t_M)$ - position of the ground station at the moment t_M

correction term $M_1^{corr}(x(t_M), t_M)$ takes into account:

- motion of satellite and station during signal travel time
- systematic errors of physical nature (atmosphere)
- systematic errors of technical nature (biases, delays, ...)

Range Rate Measurements

change in distance between ground station and satellite

$$M_2(x(t_M), t_M) \quad = \quad \frac{m(x(t_M + h), t_M + h) - m(x(t_M), t_M)}{h} + M_2^{corr}(x(t_M), t_M)$$

where

$m(x(t_M), t_M) = 2\|r(t_M) - r_{stat}(t_M)\|_2$

$x(t_M) = \begin{pmatrix} r(t_M) \\ v(t_M) \end{pmatrix}$ - position of the satellite at the moment t_M

$r_{stat}(t_M)$ - position of the ground station at the moment t_M

correction term: motion of station and satellite, biases, ...

Angle Measurements

observation direction (azimuth and elevation angle)

$$M_{3,4}(x(t_M), t_M) \quad = \quad W_{3,4}(x(t_M), t_M) + M_{3,4}^{corr}(x(t_M), t_M)$$

where

$W_3(x(t_M), t_M) = \arctan\left(\frac{s_E}{s_N}\right)$ for azimuth angle

$W_4(x(t_M), t_M) = \arctan\left(\frac{s_Z}{\sqrt{s_E^2 + s_N^2}}\right)$ for elevation angle

$$\begin{pmatrix} s_E \\ s_N \\ s_Z \end{pmatrix} = \begin{pmatrix} -sin\lambda & -sin\varphi cos\lambda & cos\varphi cos\lambda \\ cos\lambda & -sin\varphi sin\lambda & cos\varphi sin\lambda \\ 0 & cos\varphi & sin\varphi \end{pmatrix} \cdot (r - r_{stat})$$

λ and φ are the longitute and altitude of the ground station respectively

Satellite Orbit Determination

Parameters to be estimated:

Six orbit elements at a given time (epoch)

in coop with ESA

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Differential-Algebraic Equations (DAE)

Augment ODE by **algebraic equations** g and **algebraic states** z

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

- differential states $y(t) \in \mathbb{R}^{n_x}$
- algebraic states $z(t) \in \mathbb{R}^{n_z}$
- algebraic equations $g(\cdot) \in \mathbb{R}^{n_z}$

Example: Index 1 DAE

$$
\begin{aligned}
0 &= g(t, y, z) \\
0 &= \frac{d}{dt} g(t, y, z) = \frac{\partial g}{\partial t} + \frac{\partial g}{\partial y} \dot{y} + \frac{\partial g}{\partial z} \dot{z}
\end{aligned}
$$

If the matrix $\frac{\partial g}{\partial z} \in \mathbb{R}^{n_z \times n_z}$ is invertible then we can compute

$$
\dot{z} = -\left(\frac{\partial g}{\partial z}\right)^{-1} \left(\frac{\partial g}{\partial t} + \frac{\partial g}{\partial y} \dot{y}\right)
$$

and obtain an ODE system for $x := \begin{pmatrix} y \\ z \end{pmatrix}$:

$$
\dot{x} = \begin{pmatrix} f(t, x) \\ -\left(\frac{\partial g}{\partial z}\right)^{-1} \left(\frac{\partial g}{\partial t} + \frac{\partial g}{\partial y} \dot{y}\right) \end{pmatrix}
$$

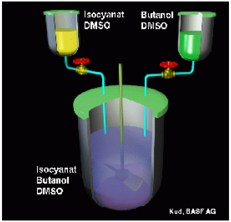
Example DAE: Urethane Reaction

S. Körkel, Cooperation with BASF SE

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

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

- Prototype for polyurethane production
- Main product C, byproduct D
- Composition of the products determines physical properties of the polyurethane plastic material



Example DAE: Urethane Reaction

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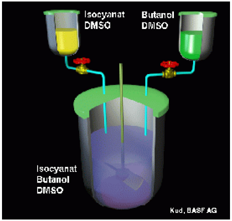


- Reactor: ideally stirred tank
- Two controlled feeds:
  A in DMSO and B in DMSO
- Control of reactor temperature

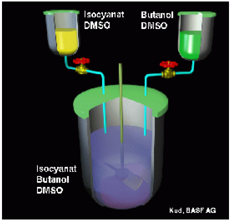
Example DAE: Urethane Reaction

S. Körkel, Cooperation with BASF SE

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

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

$$
\begin{aligned}
r_1 &= k_1 \cdot \frac{n_A}{V} \cdot \frac{n_B}{V} \qquad r_3 = k_3 \cdot \frac{n_D}{V} \\
r_2 &= k_2 \cdot \frac{n_A}{V} \cdot \frac{n_C}{V} \qquad r_4 = k_4 \cdot (\frac{n_A}{V})^2 \\
k_{i=1,2,4} &= k_{ref\,i} \cdot \exp\left(-\frac{E_{ai}}{R} \cdot \left(\frac{1}{T(t)} - \frac{1}{T_{ref\,i}}\right)\right) \\
\frac{k_2}{k_3} &= k_{c2} \cdot \exp\left(-\frac{dh_2}{R} \cdot \left(\frac{1}{T(t)} - \frac{1}{T_{c2}}\right)\right)
\end{aligned}
$$



Urethane Reaction: Features

Model

- 6 state variables $n_A, n_B, n_C, n_D, n_E, n_L$, nonlinear Arrhenius kinetics
- 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 $n_{A,e1,0}, n_{B,e2,0}, n_{L,e1,0}, n_{L,e2,0}$

Measurements

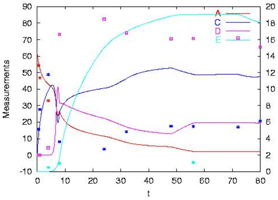
- 3 measurement methods (A, C/D, E) with different accuracies and different costs!

Urethane Example: Measurement Functions

Measurements: Mass percentage of A, C, D, E, e.g.

$$M_{n_C}(x,p) = 100 \cdot \frac{n_C M_C}{n_A M_A + \ldots + n_E M_E + n_L M_L}$$

Measurements and Simulated Model Response



Dynamical Process Models

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Partial Differential Equations

- Instationary partial differential equations (PDE) arise, e.g., in transport processes, wave propagation, ...
- Also called “distributed parameter systems”
- Often PDE of subsystems are coupled with each other (e.g., flow connections)
- Method of Lines (MOL): discretize PDE in space to yield ODE or DAE system

Partial Differential Equations: Example

- Convection-Diffusion-Reaction Equation

$$\frac{\partial y_i}{\partial t}(t,x) = \frac{\partial}{\partial x}\left(D\frac{\partial y_i}{\partial x}(t,x)\right) - v\frac{\partial y_i}{\partial x} + \sum_{j=1}^{m} r_j(y(t,x),\alpha(t,x),T(t,x),p)\cdot\nu_{ij},\ \ i = 1,\dots,n$$

- Catalyst deactivation

$$\frac{\partial \alpha}{\partial t}(t,x) = -k(y(t,x),\alpha(t,x),T(t,x),p)$$

+ Initial and Boundary Conditions

- $y_i(t,x)$: concentration of species $i, i = 1,\dots,n$
- $\alpha(t,x)$: catalyst activity

Possible Solution Approach: Method of Lines

- Discretize the state variables $y_i(t) := y(t, x_i)$ on a grid $(x_i,\ i = 1, \ldots, N)$ with $\Delta x = x_{i+1} - x_i$
- Replace spatial derivatives by finite differences, e.g.

$$\frac{y(t, x_{i+1}) - y(t, x_{i-1})}{2\Delta x} = \frac{\partial y}{\partial x}(t, x_i) + \mathcal{O}(\Delta x^2)$$

$$\frac{y(t, x_{i+1}) - 2y(t, x_i) + y(t, x_{i-1})}{\Delta x^2} = \frac{\partial^2 y}{\partial x \partial x}(t, x_i) + \mathcal{O}(\Delta x^2)$$

- Substitute into PDE equation, obtain high-dimensional stiff sparse ODE/DAE system

Example: Nonlinear Exchange Rate Dynamics

with S. Jäger

- Exchange rate is a stochastic process $S_t, t \in [t_0, T]$ and satisfies stochastic differential equation

$$dS = \mu dt + \sigma dW, \ W \text{ is a Wiener process}$$

- The distribution $F_t(s) = P(S_t \leq s)$ is defined by a drift term μ and a variance σ^2

$$S_t = S_{t_0} + \int_{t_0}^{t} \mu dt + \int_{t_0}^{t} \sigma dW,$$

- The drift term μ and the variance σ^2 of are supposed to depend non-linearly on the real exchange rate s and a set of market fundamental variables Z (e.g. money amounts, real incomes, nominal interests)

$$\mu = \mu(s, Z), \quad \sigma^2 = \sigma^2(s, Z)$$

- initial values S_{t_0}, μ and σ^2 are unknown and need to be identified!

Example: Nonlinear Exchange Rate Dynamics

with S. Jäger

- Model: μ and σ^2 satisfy the Fokker-Planck or forward Kolmogorov equation for the density function $f(t,s) = \frac{dF_t(s)}{ds}$ of the stochastic process S_t

$$\frac{\partial f}{\partial t} = -\frac{\partial(\mu f)}{\partial s} + \frac{1}{2}\frac{\partial^2(\sigma^2 f)}{\partial s^2}$$

Example: Nonlinear Exchange Rate Dynamics

with S. Jäger

- The drift is modelled by the 3d order polynome (Creedy et al, 96; multiple equilibria, regime switching, multimodality)

$$\mu = \mu(t,s,Z) = a_0(Z)(s-a_1(Z))(s-a_2(Z))(s-a_3(Z)),$$
$$a_i(Z) = C_i \prod_{j=1}^{K} Z_j^{\alpha_{ij}}$$

and the variance is

$$\sigma^2 = {\gamma_0}^2 + {\gamma_1}^2 s$$

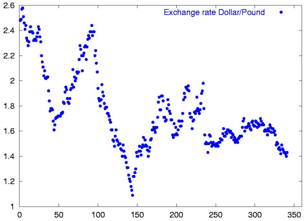
$Z_j, j = 1,...,K$ are the market fundamental variables

- Unknown parameters are $C_i,\ \alpha_{ij},\ j = 1,...,K,\ i = 0,1,2,3,\ \gamma_0,\ \gamma_1$

Example: Nonlinear Exchange Rate Dynamics

with S. Jäger

- Data η_j: monthly Dollar/Pound exchange rate



- Model response: expected value of the exchange rate

$$M(t_j) = \int_0^\infty f(t_j, s) s ds$$

Example: Nonlinear Exchange Rate Dynamics

with S. Jäger

- Boundary conditions:

$$\mu - \frac{1}{2}\frac{\partial(\sigma^2 f)}{\partial s}\bigg|_{s=s_{min}} = \mu - \frac{1}{2}\frac{\partial(\sigma^2 f)}{\partial s}\bigg|_{s=s_{max}} = 0,\ t \geq 0.$$

- Initial conditions: we assume that at the time moment $t = 0$ the stochastic process is stationary:

$$f(t,s)\mid_{t=0} = f^\star(s,p) = \exp\left(\int_0^s \frac{2\mu(\xi,p)}{\sigma^2(\xi,p)}d\xi - \ln\sigma^2(s,p) + \ln\sigma^2(0,p)\right)\eta^\star,$$

$\eta^\star$ is a normalizing constant

- alternative:

$$f(t,s)\mid_{t=0} = \exp\left(-(s-s_0)^2 a^2\right)\eta^\star,$$

with 2 additional parameters a and s_0 to estimate.

Method of Lines (MOL)

E.g. forward Kolmogorov equation for the density function $f(t,s) = \frac{dF_t(s)}{ds}$ of the stochastic process S_t

$$\frac{\partial f}{\partial t} = -\frac{\partial(\mu f)}{\partial s} + \frac{1}{2}\frac{\partial^2(\sigma^2 f)}{\partial s^2}$$

- introduce spatial grid points $s_0, \ldots, s_N$
- approximate spatial derivatives, e.g. by finite differences

$$\frac{\partial f(s_i)}{\partial s} \approx \frac{f(s_{i+1}) + f(s_i)}{h}, \quad \text{etc.}$$

- define state vector $y_{\text{col}} := (f(s_0), \ldots, f(s_N))^T$,
- obtain ODE

$$\dot{y}_{\text{col}}(t) = f_{\text{col}}(y_{\text{col}}(t), \mu(t), \sigma(t), p)$$

Transport and Degradation of Xenobiotics in Soil

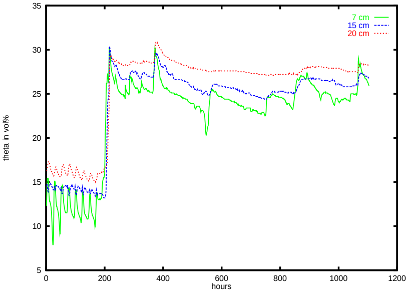
(..., A. Dieses, in coop. with O. Richter, TU Braunschweig)

Minilysimeter

- Investigation of fate of xenobiotics
- Expensive lysimeter experiments for registration
- To be replaced by computer experiments
- **Here: parameter estimation**
- **Later: Optimal lysimeter experiments**
  - + **optimal irrigation**
  - + **optimal solute application**
  - + **optimal sampling**

Field experiment: Water Transport (K. Aden)

- loamy sand without vegetation
- time-domain reflectrometry (TDR): hourly measurements of water content θ in 7, 15 and 20 cm
- period: Oct 28, 1997 - Dec 13, 1997



Model: Richards Equation

$$\frac{\partial \theta}{\partial t} = \frac{\partial}{\partial z}\left(D(\theta)\frac{\partial \theta}{\partial z} - K(\theta)\right)$$

$$K(\theta) = K_s \Theta^{1/2}\left[1 - \left(1 - \Theta^{n/(n-1)}\right)^{1-1/n}\right]^2, \qquad \Theta = \frac{\theta - \theta_r}{\theta_s - \theta_r}$$

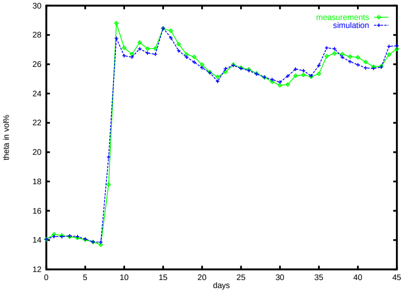
$$D(\theta) = K(\theta)\bar{C}(\theta)$$

$$\bar{C}(\theta) = \frac{1}{\alpha n m}\left(\Theta^{-1/m} - 1\right)^{-m}\Theta^{-1/m}\frac{1}{\theta - \theta_r}, \qquad m = 1 - \frac{1}{n}$$

- Initial condition: Linear interpolation of $\theta_{7cm}, \theta_{15cm}, \theta_{20cm}$ at begin of experiments (Oct 28, 1997)
- Upper boundary: Dirichlet condition (TDR data in 7 cm)
- Lower boundary: Dirichlet condition (TDR data in 20 cm)

Transport and Degradation of Xenobiotics in Soil

Result: Estimates for n, α and K_s
from TDR measurement data of water content in 15 cm depth



	guess	estimate
n	1.5	1.262 ± 0.0024
α	0.05	0.0324 ± 0.0024
K_s	35.0	20.92 ± 1.68

	α	K_s
n	0.14	-0.61
α	-	-0.94

Dynamical Process Models

- Ordinary Differential Equations (ODE)
- Boundary Conditions
- Measurement Functions
- Differential-Algebraic Equations (DAE)
- Partial Differential Equations (PDE) and Method of Lines (MOL)
- Models with Switches

Models with Switches

$$\begin{aligned} \dot{y}(t) = \quad & f(t, x(t), z(t), p, q, u(t), sign(\sigma(x(t), z(t), p)) \\ 0 = \quad & g(t, x(t), z(t), p, q, u(t), sign(\sigma(x(t), z(t), p)) \end{aligned} \quad t \in [t_0; t_f]$$

Discontinuous dynamics
Monitored by sign of ”switching functions” σ
E.g.

- modeling of phase transition in multi-phase reaction systems
- simplified modeling of fast transients in processes with varying time scales

Example: Growth of White Cabbage

Richter, Söndgerath 1990

- states: Cabbage's leaf biomass x_L, trunk biomass x_S and head biomass x_H
- 9 parameters a, r_L, μ_L, ρ, r_S, r_H, m_H, λ and t_H

$$\frac{dx_L}{dt} = r_L \frac{a+1}{a+\exp(\rho t)} x_L - \mu_L x_L$$

$$\frac{dx_S}{dt} = r_S x_L \left(\lambda - \frac{x_S}{x_L}\right)$$

$$\frac{dx_H}{dt} = \begin{cases} 0 & \text{for } t \le t_H \\ (r_H x_L - \mu_H x_H) & \text{for } t > t_H \end{cases}$$

- sign of "switching function" $\sigma := t - t_H$ determines which model is taken

Outline

Parameter Estimation Problems

- Parameter Estimation: Problem Formulation
- Boundary Value Problem Approach
- Generalized Gauss Newton Methods
  - Optimization Criteria and Convergence
  - Practical Solution
- Sensitivity Analysis
- Examples:
  - Lotka-Volterra, Unstable Process
  - Orbit Determination Problem for Satellites
  - Photosynthesis
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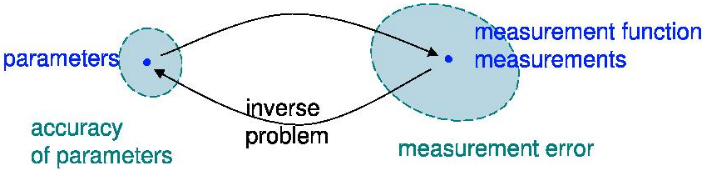
  - Enzyme Reaction Kinetics

What Is Parameter Estimation?

Determination of coefficients/parameters
in a model
from measured data
such that model matches data



Parameter Estimation Problem: Model

Model Equations? ("Forward Problem")

- Differential Algebraic Equations (DAE)

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

y: differential variables

z: algebraic variables, $x = (y, z)$

p: unknown parameters

q: design parameters

u: controls

stiff, nonlinear, with discontinuities, unstable modes, chaotic, ...

- Partial Differential Equations (PDE)

$$u_t - \nabla(K\nabla u) = f(u, p)$$

$\rightarrow$ semidiscretization in space

+ initial and boundary conditions!

Parameter Estimation Problem: Data

Experimental Data?

- Data from multiple experiments under varying experimental conditions
  - reactions with different initial composition of substances
  - different inputs (e.g., temperature, feedstreams, ...)
  - different experimental layout (e.g., a standing or sitting human being ...)

- Data for stationary or instationary states, bifurcations, oscillations, ...

  Each has specific model

- Outliers in the data

- Indirect observation functions ($\rightarrow$ and additional parameters), ...

Parameter Estimation Problem: Observation Model

$$\eta_{ij} \quad = \quad M_{ij}(x^{true}(t_j), p^{true}) + \varepsilon_{ij}$$

M: nonlinear function of states
(differential and algebraic)
and parameters

ε_{ij}: measurement error

- independent
- often normally distributed $\varepsilon_{ij} \in (\mathcal{N}(0, \sigma_{ij}^2))$

Parameter Estimation Problem: Match Model to the Data

Parameter Estimation Problem

$$\min_{x,p} \quad \sum_{i,j} \frac{(\eta_{ij} - M_{ij}(x(t_j), p))^2}{\sigma_{ij}^{\ 2}}$$

maximum likelihood

x, p satisfy

- DAE model
- additional constraints, e.g., boundary conditions, positivity, ...

$$r_2(x(t_1), \ldots, x(t_k), p) = 0 \text{ or } \geq 0$$

Parameter Estimation Problem: Match Model to the Data

Multiple Experiment Parameter Estimation Problem

$$\min_{x^l,p} \sum_{l=1}^{\#\,\text{Exp}} \sum_{i,j} \frac{(\eta_{ij}^l - M_{ij}^l(x^l(t_j^l),p))^2}{\sigma_{ij}^{l\,2}}$$

maximum likelihood

x^l, p satisfy

- DAE models, $l = 1, \ldots, \#\text{Exp}$
- additional constraints, e.g. boundary conditions, positivity, ...

$$r^l{}_2(x^l(t_1^l), ..., x^l(t_k^l), p) = 0 \text{ or } \geq 0 \,, \; l = 1, \ldots, \#\text{Exp}$$

Why Least-Squares Objective Function?

- Assumptions for distribution of measurement errors: $\varepsilon_{ij} \in \mathcal{N}(0, \sigma_{ij}^2)$
- Log-Likelihood function

$$
\begin{aligned}
\log \mathcal{L} &= \sum_{i,j} \log \left(\frac{1}{\sigma_{ij}\sqrt{2\pi}} \, e^{-\frac{(\eta_{ij} - M_{ij}(x,p))^2}{2\sigma_{ij}^2}} \right) \\
&= Const - \sum_{i,j} \frac{(\eta_{ij} - M_{ij}(x,p))^2}{2\sigma_{ij}^2} \\
\max_p \log \mathcal{L} &\equiv \min_p \sum_{i,j} \frac{(\eta_{ij} - M_{ij}(x,p))^2}{2\sigma_{ij}^2}
\end{aligned}
$$

- Then solution p^* of the parameter estimation problem is a maximum likelihood estimate for the parameters

Choice of Norm?

- if measurement errors are independent and normally distributed ($\varepsilon_{ij} \in N(0, \sigma_{ij}^2)$) then l_2 estimation is appropriate:

$$\min_{x,p} \sum_{i,j} \frac{(\eta_{ij} - M_{ij}(x(t_j), p))^2}{\sigma_{ij}^2} \quad \text{least squares}$$

$\rightarrow$ maximum likelihood: Legendre (1805), Gauss (1809)

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$$\min_{x,p} \sum_{i,j} \frac{(\eta_{ij} - M_{ij}(x(t_j), p))^2}{\sigma_{ij}^2}$$ least squares

$\rightarrow$ maximum likelihood: Legendre (1805), Gauss (1809)

- in case of Laplace distribution $\left(\frac{1}{2|\sigma_{ij}|} e^{-\frac{|t|}{|\sigma_{ij}|}} \right)$ l_1 estimation is appropriate:

$$\min_{x,p} \sum_{i,j} \frac{|\eta_{ij} - M_{ij}(x(t_j), p)|}{|\sigma_{ij}|}$$ least absolute deviation

$\rightarrow$ maximum likelihood: Boscovic (1758), Laplace (1812)

Properties of l_1-Parameter Estimation

under certain regularity assumptions

- l_1 optimal solution interpolates n "best" measurements
- consequently solution is less sensitive to outliers
- l_1 forms robust alternative to l_2 PE !

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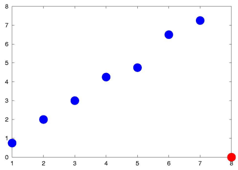
Data



● Outlier!

Properties of l_1-Parameter Estimation

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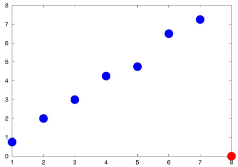
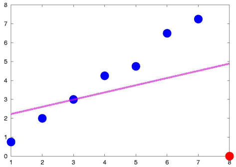
Data



l_2



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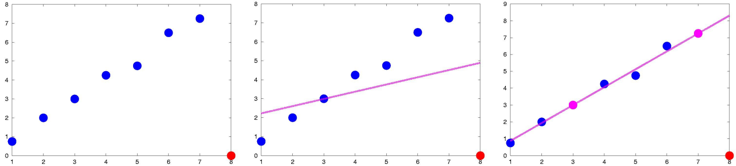
Data $\quad$ l_2 $\quad$ l_1



● Outlier!

Robust Parameter Estimation

- robustness means “insensitivity to small deviations from the assumptions” (Huber 1981)
- even high-quality measurements are not exactly normally distributed, but typically longer-tailed
  (for scientific routine data 1–10% gross errors are the rule rather than the exception)
- gross errors often show up as outliers (although not all outliers are gross errors)
- a single outlier can completely spoil a least squares analysis

Robust PE: Choice of Cost Functional

- least squares norm of measurement errors (normally distributed measurement error)

$$\min \frac{1}{2} \sum_{i}^{\#Meas.} \left(\frac{\varepsilon_i}{\sigma_i} \right)^2$$

- robust against outliers l_1 norm of measurement errors (Laplace distributed measurement error)

$$\min \sum_{i}^{\#Meas.} \left| \frac{\varepsilon_i}{\sigma_i} \right|$$

- another robust estimator: hybrid “norm”, Huber-estimator

$$\min \frac{1}{2} \sum_{i:|\varepsilon_i/\sigma_i| \leq \gamma} \left(\frac{\varepsilon_i}{\sigma_i} \right)^2 + \sum_{i:|\varepsilon_i/\sigma_i| > \gamma} \left(\gamma \left| \frac{\varepsilon_i}{\sigma_i} \right| - \frac{1}{2} \gamma^2 \right)$$

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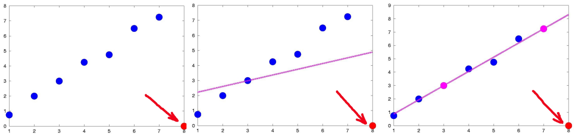
- partition constant γ can be determined by the ratio of “bad” data points in the measurement data for an assumed error probability $\epsilon = \frac{\varepsilon_i}{\sigma_i}$:

$\epsilon \to 0 \;\Rightarrow\; \gamma \to \infty$: converges to solution of least squares method,

$\epsilon \to 1 \;\Rightarrow\; \gamma \to 0$: converges to solution of l_1 approximation

Example: a Single Outlier

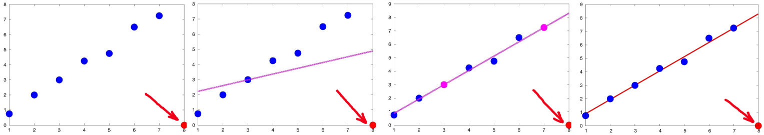
Data l_2 l_1



- Outlier!

Example: a Single Outlier

Data l_2 l_1 Huber ($\gamma = 0.02$)



- Outlier!

Parameter Estimation Problems

- Parameter Estimation: Problem Formulation
- Boundary Value Problem Approach
- Generalized Gauss Newton Methods
  - Optimization Criteria and Convergence
  - Aspects of Practical Solution
- Sensitivity Analysis
- Examples:
  - Lotka-Volterra, Unstable Process
  - Orbit Determination Problem for Satellites
  - Photosynthesis
  - Bistable Belousov-Zhabotinskii Reaction
  - Enzyme Reaction Kinetics

Direct "All-at-Once" Boundary Value Problem Methods

- the IVP approach: "single shooting"
  - integrate DAE over whole interval to yield $x(t; x_0, p)$
  - eliminate - infinite - state variables in favour of unknown parameters p, plug into suitable optimizer

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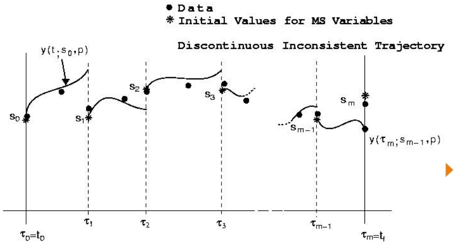
Bock and coworkers, 81, . . .

- the BVP approach: discretize DAE and solve simultaneously
  - optimization problem
  - discretized BVP as equality constraint
  - further constraints

  in one loop!

Flexible realization: multiple shooting
analogous for FD, collocation (e.g. Biegler)

The Multiple Shooting Method



- choose mesh $t_0 = \tau_0 < \tau_1 < \ldots < \tau_m = t_f$
- choose initial values $s_j = (y(\tau_j), z(\tau_j))$ as additional variables
- solve relaxed DAE IVP at each interval

$$\begin{aligned} \dot{y} &= f(y, z, p) \\ 0 &= g(y, z, p) \\ &\quad -\alpha(t) g(s_j, p) \end{aligned}$$

$\alpha(\tau_j) = 1$, $\alpha(t) \to 0$ for $t \to \infty$

- DAE discretization leads to additional matching conditions
  - for continuity: $s^y_{j+1} - y(\tau_{j+1}; s_j, p) = 0$
  - for consistency: $g(s_j, p) = 0$

After discretization: large scale nonlinear constrained approximation problem

$$\min_X \quad \frac{1}{2}||F_1(X)||_2^2$$

$$F_2(X) = 0 \qquad \text{(contains discretized BVP)} \quad \text{or } \geq 0$$

Difficulties

- nonlinear equality - and inequality - constrained optimization problem
- large number of variables from discretization

  e.g., in case multiple shooting: # of parameters +
  # of differential and algebraic variables
  × # of multiple shooting points
  × # of experiments!
- but special block structures

So Multiple Shooting Makes Things More Difficult?

FAQ: Why Multiple Shooting?

- key property: discretized states as add'l optimization variables
  - allows for *better initial guesses* using information about the process, helps to avoid ”far away” local minima
  - damps influence of poor parameter guesses
  - *reduces nonlinearity* and speeds up convergence (even up to one step convergence!)
  - method is *numerically stable* even for potentially instable, e.g. chaotic, differential equations
- efficient parallel implementation
- adaptive accuracy discretization strategies
- state-of-the-art solvers for DAE IVP applicable

An Unstable Test Problem

- state equations:

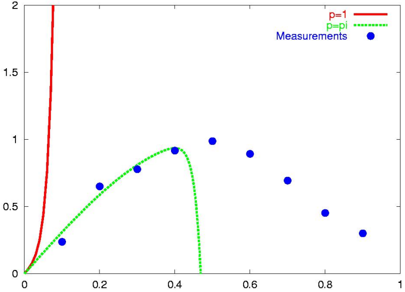
$$\dot{x}_1 = x_2 \qquad \dot{x}_2 = \mu^2 x_1 - (\mu^2 + p^2) \sin pt, t \in [0, 1]$$
$$x_1(0) = 0, \qquad x_2(0) = \pi$$

- special solution for “true” parameter value $p = \pi$:

$$x_1(t) = \sin \pi t, \qquad x_2(t) = \pi \cos \pi t.$$

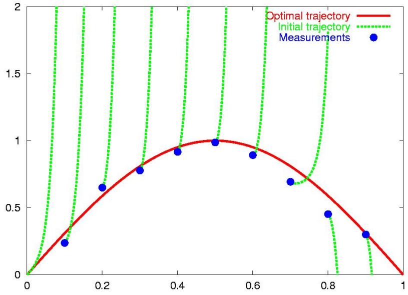
- $\mu = 60$, i.e. error propagation over $[0, 1]$ is $\exp \mu \approx 10^{27}$ - highly unstable
- pseudo random measurement noise, $\sigma = 0.05$

An Unstable Test Problem - Single Shooting - FAILS!



initial trajectory with $p = 1$ and with $p = \mathit{float}(\pi)$ in 64 bit

An Unstable Test Problem - Multiple Shooting - WORKS!



initial trajectory with $p = 1$ - convergence after 4 iterations in 64 bit

Multiple Shooting Reduces Nonlinearity: One Step Convergence

If:

- Dense data for all states are available
- Problem equations are linear in parameters
- Lengths of multiple shooting interval $h \to 0$

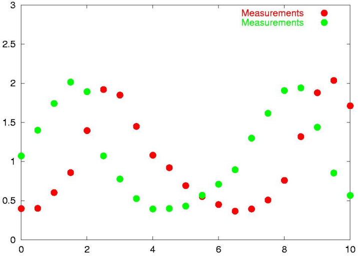
Then:

- One-step-convergence to true parameter values

$$p^1 = p^0 + \Delta p^0 = p^{true} + O(h^s)$$

Lotka-Volterra Problem: Model and Data

$$\begin{aligned} \dot{x}_1 &= -p_1 x_1 + p_2 x_1 x_2 \\ \dot{x}_2 &= +p_3 x_2 - p_4 x_1 x_2 \end{aligned}$$

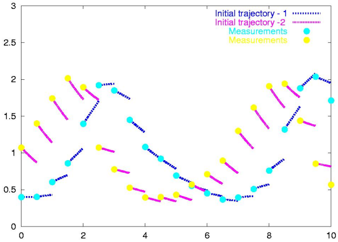


x_1: predators
x_2: preys
DE linear in parameters

Data: $\sigma = 5\%$

Lotka-Volterra Problem:
Solution with Multiple Shooting

Initial trajectory

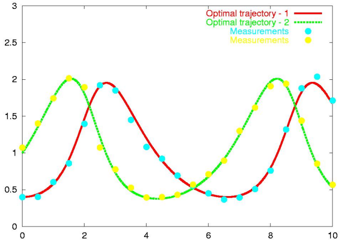


Initial guesses:

$p_1 = 0.5 \qquad p_2 = 0.5$

$p_3 = -0.5 \qquad p_4 = -0.2$

Solution trajectory



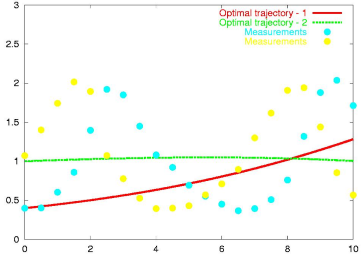
Solution:

$p_1 = 1.01 \pm 0.02 \qquad p_2 = 1.01 \pm 0.03$

$p_3 = 0.99 \pm 0.02 \qquad p_4 = 1.01 \pm 0.03$

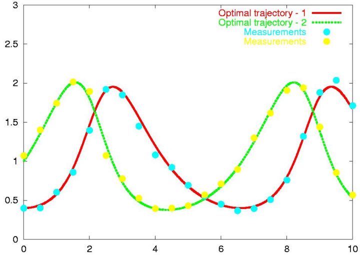
Comparison: Single vs. Multiple Shooting

Single Shooting



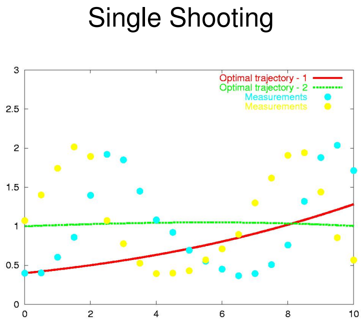
Convergence after 8 iterations

Multiple Shooting

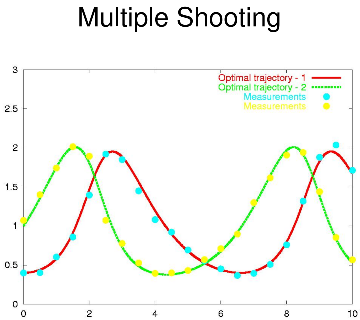


Convergence after 4 iterations

Comparison: Single vs. Multiple Shooting



Convergence after 8 iterations



Convergence after 4 iterations

- Multiple Shooting helps to avoid local minima

Generation of Initial States for Multiple Shooting Nodes

- important for problem solution $\rightarrow$ generation of good initial guesses for multiple shooting variables
- one possibility: solve *special nonlinear constrained least squares problem* at each multiple shooting node τ_j:

$$\min_{s} \quad \|s^j_{ref} - s\|_2^2$$
$$\text{s.t.} \quad \phi^j(s, \eta) = 0 \text{ or } \geq 0$$

s^j_{ref} is a reference value, e.g. the value of the computed trajectory at the end of the previous interval

constraints $\phi^j(s, \eta) = 0$ or ≥ 0 include, e.g., the requirement that initial values should satisfy the measurements at τ_j

Orbit Determination Problem

Minimize deviation of model response $M(y(t), p)$ from measurement values η

$$\min_{y,p} \sum_{j=1}^{l} \sum_{i=1}^{m_j} \left(\frac{\eta_{ij} - M_{ij}(y(t_j), p)}{\sigma_{ij}} \right)^2,$$

s.t. satellite dynamics is fulfilled

$$\begin{aligned} \dot{y}(t) &= f(t, y(t), p) \\ y(t_0) &= y_0(p) \end{aligned}$$

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s.t. satellite dynamics is fulfilled

$$\begin{aligned} \dot{y}(t) &= f(t, y(t), p) \\ y(t_0) &= y_0(p) \end{aligned}$$

Parameters to estimate are initial values for the states
$+$ callibration parameters in measurement functions
$+$ coefficients for air drag model and/or solar radiation pressure
$+$ ...

Orbit Determination Problem

Minimize deviation of model response $M(y(t), p)$ from measurement values η

$$\min_{y,p} \sum_{j=1}^{l} \sum_{i=1}^{m_j} \left(\frac{\eta_{ij} - M_{ij}(y(t_j), p)}{\sigma_{ij}} \right)^2,$$

s.t. satellite dynamics is fulfilled

$$\begin{aligned} \dot{y}(t) &= f(t, y(t), p) \\ y(t_0) &= y_0(p) \end{aligned}$$

Difficulties: No complete state observation
Outliers in the data

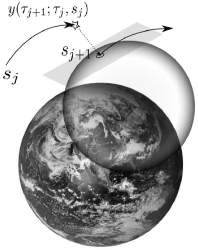
Generation of Initial States for Multiple Shooting Nodes: Orbit Determination for Satellites

S. Lenz in coop with ESA

Example:

Range Measurement $\eta_{r,j+1}$ at time τ_{j+1}

- Positions that fulfill the measurement are on a sphere around the station



1. Decompose solution of IVP in position and velocity

$$y(\tau_{j+1};\tau_j,s_j) \rightarrow \left((r_{j+1}^{int})^T, (\dot{r}_{j+1}^{int})^T \right)^T$$

2. Transform position vector into local tangent coordinate system: $r_{j+1}^{int} \rightarrow r_{j+1}^{lt}$
3. Scale position vector to measured range:

$$r_{j+1}^{lt,new} = \frac{\eta_{r,j+1}}{2} \frac{r_{j+1}^{lt}}{||r_{j+1}^{lt}||_2}$$

4. Transform new position vector back into inertial frame: $r_{j+1}^{lt,new} \rightarrow r_{j+1}^{new}$
5. Combine new position and unchanged velocity into a vector

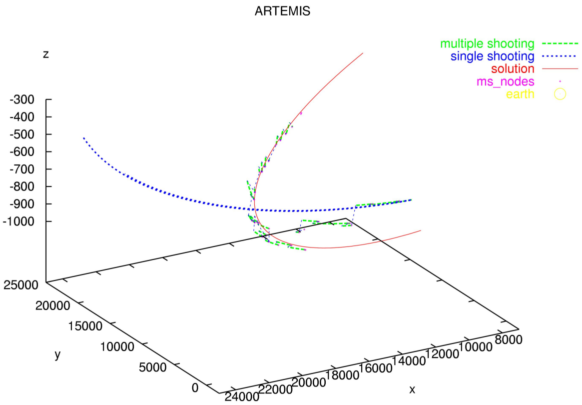
$$\left((r_{j+1}^{new})^T, (\dot{r}_{j+1}^{int})^T \right)^T \rightarrow s_{j+1}$$

6. Continue integration

Generation of Initial States for Multiple Shooting Nodes: Analytical Projection

Example: Orbit Determination for Satellites (ESA)

S. Lenz



Application: Orbit Determination Problems for Satellites (ARTEMIS-Launch)

initial multiple shooting trajectory (including projections)

(Loading ...)

Satellite Orbit Determination: Result

nominal orbit, actual orbit

(Loading ...)

Parameter Estimation Problems

- Parameter Estimation: Problem Formulation
- Boundary Value Problem Approach
- Generalized Gauss Newton Methods
  - Optimization Criteria and Convergence
  - Practical Solution
- Sensitivity Analysis
- Examples:
  - Lotka-Volterra, Unstable Process
  - Enzyme Reaction Kinetics
  - Photosynthesis
  - Bistable Belousov-Zhabotinskii Reaction

After discretization: large scale nonlinear constrained approximation problem

$$\min_X \quad \frac{1}{2}||F_1(X)||_2^2$$

$$F_2(X) = 0 \qquad \text{(contains discretized BVP)} \quad \text{or} \geq 0$$

numerical treatment with Newton type methods

unconstrained case (IVP methods)

constrained case (BVP methods)

examples for structure exploitation

Solution Methods - IVP Approach

- **Nonlinear unconstrained least squares problem**

$$\min \varphi(X) = \frac{1}{2} F_1^T(X) F_1(X), \quad X \in \mathbb{R}^n, \quad F_1 : \mathbb{R}^n \to \mathbb{R}^{m_1}$$

- optimal solution X^* solves the system of nonlinear equations

$$\nabla \varphi(X^*) = J_1^T(X^*) F_1(X^*) = 0$$

- Newton iteration: $X^+ = X^- + \Delta X$ for improving an approximate solution X of optimality equations, ΔX solves $\nabla^2 \varphi(X) \Delta X = -\nabla \varphi(X)$, or, equivalently,

$$\left(J_1^T J_1 + \sum_{i=1}^{m_1} F_{1,i} \nabla_{XX} F_{1,i} \right) \Delta X = -J_1^T F_1, \quad J_1 = \nabla F_1(X)$$

- variations of Newton's method involve the approximation of the term

$$S = \sum_{i=1}^{m_1} F_{1,i} \nabla_{XX} F_{1,i}(X).$$

- **Gauss-Newton:** $S = 0$

Solution Methods - BVP Approach

- **Nonlinear constrained least squares problem**

$$\min \varphi(X) = \frac{1}{2} F_1^T(X) F_1(X) \qquad s.t. \quad F_2(X) = 0$$

- Iteration: $X^{k+1} = X^k + \Delta X^k$
- The increment ΔX^k solves the quadratic problem:

$$\begin{array}{ll} \min\limits_{\Delta X \in \Omega^k} & \frac{1}{2} \Delta X^T A^k \Delta X + \nabla \varphi(X^k)^T \Delta X \\ \text{s.t.} & F_2(X^k) + J_2(X^k)^T \Delta X = 0 \end{array}$$

- A^k is an approximation of the Hessian of the Lagrangian:

$$\begin{array}{rcl} A^k & \approx & \nabla_{XX} L(X^k, \lambda^k), \quad L(X, \lambda) = \varphi(X) - \lambda^T F_2(X), \\ & \approx & J_1^T(X^k) J_1(X^k) + F_1(X^k)^T \nabla_{XX} F_1(X^k) - \lambda^T \nabla_{XX} F_2(X^k). \end{array}$$

Generalized Gauss-Newton

- **Generalized Gauss-Newton: ignore second order derivatives**

$$A^k = J_1(X^k)^T J_1(X^k)$$

- ΔX^k solves linear constrained problem

$$\min_{\Delta X \in \Omega^k} \quad \frac{1}{2}||F_1(X^k) + J_1(X^k)\Delta X||_2^2$$

$$\text{s.t.} \quad F_2(X^k) + J_2(X^k)\Delta X = 0$$

Optimality Criteria

- Constraint Qualification
  X is regular if Constraint Qualification (CQ) holds:

$$\text{rank}(J_2(X)) = \#Constraints$$

- Lagrange function:

$$L(X, \lambda) = \frac{1}{2}||F_1(X)||_2^2 - \lambda^T F_2(X)$$

Optimality Criteria

Necessary Conditions:

Let

- X^* be a regular solution of the nonlinear problem.

Then

- X^* is feasible $F_2(X^*) = 0$
- there exists a unique vector λ^* such that

$$\nabla_X L(X^*, \lambda^*) = 0 \qquad \leftarrow \text{Stationarity}$$

- furthermore, second order necessary conditions hold:

$$d^T \nabla_{XX} L(X^*, \lambda^*) d \geq 0, \forall d \in \{w | J_2(X^*) w = 0\}$$

Optimality Criteria

Sufficient Condition:

Let

- (X^*, λ^*) satisfy first-order necessary conditions
- Positive Definiteness (PD) condition holds:

$$d^T \nabla_{XX} L(X^*, \lambda^*) d > 0, \forall d \in \{w \neq 0 | J_2(x^*) w = 0\}$$

Then

- X^* is a strict local minimum.

Optimality Criteria

for linear systems regularity conditions (CQ) and (PD) are equivalent to

$$\text{rank}(J_2(X)) = \#constraints$$

$$\text{rank}(J(X)) = \#variables, \quad J(X) = J = \begin{pmatrix} J_1 \\ J_2 \end{pmatrix}$$

Optimality Criteria

- Karush-Kuhn-Tucker Conditions: Feasibility + Stationarity

$$F_1^T(X^*)J_1(X^*) = 0$$
$$F_2(X^*) = 0$$

- (X^*, λ^*) is called a KKT-Point
- Under regularity conditions:
  (X^*, λ^*) is a KKT-Point of the nonlinear problem $\Leftrightarrow$ $(0, \lambda^*)$ is a KKT-Point of the linear problem

Solution of the Linear Least-Squares Problem

- At each GN iteration we need to solve:

$$\begin{array}{rl} \min & \frac{1}{2}||F_1(X^k) + J_1(X^k)\Delta X||_2^2, \\ \text{s.t.} & F_2(X^k) + J_2(X^k)\Delta X = 0 \\ \text{where} & J_i(X) = \nabla F_i(X) \end{array}$$

- KKT conditions:

$$\begin{pmatrix} J_1^T(X)J_1(X) & J_2^T(X) \\ J_2(X) & 0 \end{pmatrix} \begin{pmatrix} \Delta X \\ -\lambda \end{pmatrix} = \begin{pmatrix} -J_1^T(X)F_1(X) \\ F_2(X) \end{pmatrix}$$

- The linear system has unique solution, if (CQ) and (PD) are fulfilled

Solution of the Linear Least-Squares Problem

- ΔX^k can be formally written with the help of a solution operator J^+

$$\Delta X^k = -J^+(X^k)F(X^k)$$

J^+ is a generalized inverse: $J^+JJ^+ = J^+$

$$J = \begin{pmatrix} J_1 \\ J_2 \end{pmatrix}, \; F = \begin{pmatrix} F_1 \\ F_2 \end{pmatrix}$$

- The solution operator J^+ is explicitly given by

$$J^+(X) = \begin{pmatrix} \mathbb{I} & 0 \end{pmatrix} \begin{pmatrix} J_1^T(X)J_1(X) & J_2(X)^T \\ J_2(X) & 0 \end{pmatrix}^{-1} \begin{pmatrix} J_1(X)^T & 0 \\ 0 & \mathbb{I} \end{pmatrix}.$$

Local Contraction

Bock, 1987

Let (weighted) Lipschitz conditions be true for J und J^+:

$$(J) \qquad \frac{\|J^+(Y)[J(X+t(Y-X))-J(X)](Y-X)\|}{t\,\|Y-X\|^2} \leq \omega(X) \leq \omega < \infty \qquad \text{nonlinearity}$$

$$(J^+) \qquad \frac{\|[J^+(Z)-J^+(X)]R(X)\|}{\|Z-X\|} \leq \kappa(X) \leq \kappa < 1 \qquad \text{incompatibility}$$

$$\forall t \in [0,1], \quad X - Y = J^+(X)F(X), \quad R(X) := F(X) - J(X)J(X)^+F(X)$$

Then: For X^0 with $\|J(X^0)^+F(X^0)\|\omega/2 + \kappa < 1$

$X^{j+1} = X^j - J(X^j)^+F(X^j)$ is well defined

$X^k \rightarrow X^*$ stationary point with $J(X^*)^+F(X^*) = 0$

and $\|\Delta X^{j+1}\| \leq (\|\Delta X^j\|\,\omega/2 \,+\, \kappa)\,\|\Delta X^j\|$

linear convergence (convergence rate $\rightarrow \kappa$)

Local Contraction

Bock, 1987

Interpretation:
Nonlinearity ω

- ω is a measure for nonlinearity (weighted second derivative)
- ω^{-1} characterizes region of validity of the linear model

Incompatibility constant κ

- $\kappa < 1$: necessary for identifiability
- depends on compatibility of the model with measurements
- a stationary point with $\kappa < 1$ is statistically stable
- GGN method does not converge to large residual solutions (Advantage!)

Globalization Strategies

Line Search

- Iteration: $X^{k+1} = X^k + t^k \Delta X^k, \quad t^k \in]0,1]$, where t^k is a stepsize
- stepsize t^k is chosen such that the next iterate X^{k+1} is “better” than X^k: $T_1(X^{k+1}) < T_1(X^k)$
- exact penalty function as merit function

$$T_1(X) := \frac{1}{2}||F_1(X)||_2^2 + \sum_{i,Eq.} \alpha_i |F_{2i}(X)|$$

  with sufficiently large weights $\alpha_i > 0$
- t^k is (approximate) minimum of the merit function

$$t^k = \text{arg} \min_{0<t\leq 1} T_1(X^k + t\Delta X^k)$$

Globalization Strategies

Line Search

- Iteration: $X^{k+1} = X^k + t^k \Delta X^k, \quad t^k \in]0,1]$, where t^k is a stepsize
- stepsize t^k is chosen such that the next iterate X^{k+1} is "better" than X^k: $T_1(X^{k+1}) < T_1(X^k)$
- exact penalty function as merit function

$$T_1(X) := \frac{1}{2}||F_1(X)||_2^2 + \sum_{i,Eq.} \alpha_i |F_{2i}(X)|$$

  with sufficiently large weights $\alpha_i > 0$
- alternative: line search based on the natural level functions

$$T^k(X^k + t^k \Delta X^k) \quad = \quad ||J^+(X^k) F(X^k + t^k \Delta X^k)||_2^2$$

  $\rightarrow$ new effective "affine invariant" globalization strategy - guarantees full step in local convergence domain (Bock, K., Schlöder, 2000, K. 2004)

Numerical Solution of Linear Least-Squares Problems

Unconstrained case:

- QR factorization with column pivoting on the matrix J_1:

$$J_1 P = Q \begin{pmatrix} R \\ 0 \end{pmatrix} = (Q_1, \quad Q_2) \begin{pmatrix} R \\ 0 \end{pmatrix} = Q_1 R,$$

  where

  P is an $n \times n$ permutation matrix (orthogonal);
  Q is $m_1 \times m_1$ orthogonal;
  $Q_1 \in \mathbb{R}^{m_1 \times n}$, $Q_2 \in \mathbb{R}^{m_1 \times (m_1 - n)}$;
  R is $n \times n$ upper triangular.

- We get

$$||F_1 + J_1 \Delta X||_2^2 = ||Q_1^T F_1 + R P^T \Delta X||_2^2 + ||Q_2^T F_1||_2^2$$

- We minimize $||F_1 + J_1 \Delta X||_2^2$ by driving the first term in to zero:

$$\Delta X = -P R^{-1} Q_1^T F_1$$

Numerical Solution of Linear Least-Squares Problems

- alternative: use SVD of Jacobian J_1

$$J_1 = U \begin{pmatrix} S \\ 0 \end{pmatrix} V^T = (U_1, \quad U_2) \begin{pmatrix} S \\ 0 \end{pmatrix} V^T = U_1 S V^T,$$

  where

  U is an orthogonal $m_1 \times m_1$ matrix;
  $U_1 \in \mathbb{R}^{m_1 \times n}$, $U_2 \in \mathbb{R}^{m_1 \times (m_1 - n)}$;
  V is an orthogonal $n \times n$ matrix;
  S is a diagonal $n \times n$ matrix with elements $\sigma_1 \geq \sigma_2 \geq \ldots \geq \sigma_n \geq 0$.

- the solution ΔX:

$$\Delta X = -VS^{-1} U_1^T F_1 = -\sum_i \frac{u_i^T F_1}{\sigma_i} v_i$$

Numerical Solution of Linear Least-Squares Problems

Constrained case:

- Orthogonal decomposition of J_2: $J_2 = LQ^T$ where
  - $L \in \mathbb{R}^{m_2 \times n}$,
  - $L = [L', \mathbf{0}]$, $L' \in \mathbb{R}^{m_2 \times m_2}$ is a lower triangular matrix,
  - $Q \in \mathbb{R}^{n \times n}$, $Q^T Q = I$.
- Linear problem can be rewritten:

$$
\begin{aligned}
\min \quad & \frac{1}{2}||F_1 + J_1 Q \Delta Y||_2^2, \\
\text{s.t.} \quad & F_2 + L \Delta Y = 0,
\end{aligned}
$$

with $\Delta Y = Q^T \Delta X$

Numerical Solution of Linear Least-Squares Problems

- The solution ΔY is:

$$\Delta Y = \begin{pmatrix} \Delta Y_2 \\ \Delta Y_1 \end{pmatrix},$$

where ΔY_2 is computed by

$$\Delta Y_2 = -(L')^{-1} F_2$$

and ΔY_1 solves unconstrained linear least squares problem:

$$\min_{\Delta Y_1} \quad \frac{1}{2} ||\tilde{F}_1 + \tilde{J}_1 \Delta Y_1||_2^2 = ||(F_1 - J_1 Q_1 (L')^{-1} F_2) + (J_1 Q_2) \Delta Y_1||_2^2.$$

- solution in original coordinates by back-transformation

$$\Delta X = Q \Delta Y$$

Treatment of Ill-Conditioned Problems

Regularization by a-priori information:

- Given a-priori information on values of variables $\tilde{X}_i$
- Given variances for this information σ_i^2
- i.e $X_i = \tilde{X}_i \pm \sigma_i$
- Then: Modify cost functional:

$$||F_1(X)||_2^2 \rightarrow ||F_1(X)||_2^2 + \sum_i^n \frac{(X_i - \tilde{X}_i)^2}{\sigma_i^2}$$

- $J_1^T J_1 \rightarrow J_1^T J_1 + \Sigma^{-2}$
- analogous: a-priori information with covariance matrix Cov

$\rightarrow$ important for moving horizon estimation in real-time

Treatment of Ill-Conditioned Problems

Regularisation by Rank Reduction

- in each iteration solve

$$\min_x \|Ax + b\|_2^2$$

- perform SVD, decompose $A = USV^T$

$$\min_y \|Sy + \hat{b}\|_2^2$$

where $y = V^T x, \quad \hat{b} = U^T b$ and
$S = \text{Diag}(s_i), \quad s_1 \geq s_2 \geq \dots \geq s_n \geq 0$

- condition $\quad cond(S) = \frac{s_1}{s_n} \qquad$ too large?
- rank reduction!
criterion: set rank to j^* where $j^* = max\{j | s_j \geq C\}$
choice of C ? $\qquad$ note: $\text{var}(y_j) = \frac{\beta^2}{s_j^2}$
for σ_{max}^2 maximal acceptable variance: choose $C \geq \frac{\beta}{\sigma_{max}}$

Treatment of Ill-Conditioned Problems

Regularisation by Rank Reduction

- alternative: QR-decomposition (with pivoting) $A = QR$
- estimate for the condition number

$$cond_{QR}: \quad \frac{|r_{11}|}{|r_{nn}|}$$

- rank citerion set rank to j^* where $j^* = max\{j||r_{jj}| \geq C\}$

How to Solve Linear Constrained l_1 Problem?

$$\min_{\Delta X \in \Omega^k} \quad ||F_1(X^k) + J_1(X^k)\Delta X||_1,$$

$$\text{s.t.} \quad F_2(X^k) + J_2(X^k)\Delta X = 0 \quad \text{or} \quad \geq 0$$

- cost function is piecewise-linear, very special structure that can be effectively epxloited $\rightarrow$ so called multiple pivoting or long steps (Osborne 76, Gabasov et al 79, K. et al 98, Osborne, K. 2006)

(Block-)Sparse Structures (Multiple Shooting)

Bock 81, 87, Schlöder 83

- large block sparse super-structures from multiple experiments

$$
\begin{pmatrix}
\begin{matrix} E_{L1} \\ U_{L1} \end{matrix} & 0 & 0 & & 0 & \begin{matrix} E_{G1} \\ U_{G1} \end{matrix} \\
0 & \begin{matrix} E_{L2} \\ U_{L2} \end{matrix} & 0 & & 0 & \begin{matrix} E_{G2} \\ U_{G2} \end{matrix} \\
0 & 0 & \boxed{\begin{matrix} E_{L3} \\ U_{L3} \end{matrix}} & & 0 & \boxed{\begin{matrix} E_{G3} \\ U_{G3} \end{matrix}} \\
 & & & \ddots & & \vdots \\
0 & 0 & 0 & & \begin{matrix} E_{LN} \\ U_{LN} \end{matrix} & \begin{matrix} E_{GN} \\ U_{GN} \end{matrix}
\end{pmatrix}
\begin{matrix} \\ \\ \leftarrow \\ \\ \\ \end{matrix}
$$

Experiments N: $1 \sim 100$

(Block-)Sparse Structures (Multiple Shooting)

Bock 81, 87, Schlöder 83

- large block sparse super-structures from multiple experiments
- structures from parametrization in time, e.g. induced by multiple shooting $\rightarrow$ typical staircase structure

$$
\begin{array}{l}
U_{Lk} = \\ \\ E_{Lk} =
\end{array}
\left[\begin{array}{cccccc}
D_1^1 & D_1^2 & \cdot & \cdot & \cdot & D_1^q \\
D_2^1 & D_2^2 & \cdot & \cdot & \cdot & D_2^q \\
G_1^l & G_1^r & & & & G_1^q \\
& \boxed{G_2^l} & G_2^r & & & \boxed{G_2^q} \\
& & \ddots & \ddots & & \vdots \\
& & & G_{m-1}^l & G_{m-1}^r & G_{m-1}^q
\end{array}\right]
\qquad
\begin{array}{l}
U_{Gk} = \\ \\ E_{Gk} =
\end{array}
\left[\begin{array}{c}
D_1^p \\
D_2^p \\
G_1^p \\
\boxed{G_2^p} \\
\vdots \\
G_{m-1}^p
\end{array}\right]
$$

Meshpoints $m : 2 \rightarrow \geq 100$

Evaluation of Linear Systems
DAE Initial Value Problems and Derivatives

- BDF discretization for stiff systems
- adaptive integrators for ODE and relaxed DAE
- treatment of implicitly given discontinuities and jumps in dynamics
- fast and accurate computation of 1. and 2. order derivatives
  Combining
  > ”automatic differentiation” of model equations and
  > ”internal numerical differentiation” of adaptive discretization scheme
- in forward or reverse mode

⋮

e.g. DAESOL, RKFSWT (Bauer et al ’98, Albersmeyer ’05, Kirches ’06)

Parameter Estimation Problems

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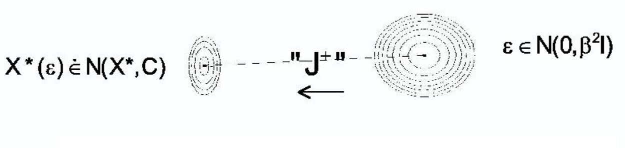
- Generalized Gauss Newton Methods
  - Optimization Criteria and Convergence
  - Practical Solution
- Sensitivity Analysis
- Examples:
  - Lotka-Volterra, Unstable Process
  - Orbit Determination Problem for Satellites
  - Photosynthesis
  - Bistable Belousov-Zhabotinskii Reaction
  - Enzyme Reaction Kinetics

Assessment of Uncertainties in Parameter Estimates for Constrained Case (l_2)

- "good fit" is not sufficient - we need to know uncertainty of parameter estimate $X^\star(\varepsilon)$ depending on measurement errors, e.g. $\varepsilon \in N(0, \beta^2 \mathbb{I})$

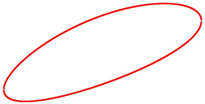


- first order expansion at $X^\star = X^\star(0)$:
  $$\Delta X = X^\star(\varepsilon) - X^\star \approx -J(X^\star)^+ \begin{pmatrix} \varepsilon \\ 0 \end{pmatrix}$$
- yields covariance-matrix approximation for states and parameters
  $$C := \mathcal{E}\left(\Delta X \Delta X^T\right) = \left(J(X^\star)^+ \begin{pmatrix} \varepsilon \\ 0 \end{pmatrix} \begin{pmatrix} \varepsilon \\ 0 \end{pmatrix}^T J(X^\star)^{+T} \right) =$$
  $$J(X^\star)^+ \begin{pmatrix} \beta^2 \mathbb{I} & 0 \\ 0 & 0 \end{pmatrix} J(X^\star)^{+T}$$

Assessment of Uncertainties in Parameter Estimates for Constrained Case (l_2)

- Nonlinear confidence region $G_N(\alpha)$ for the state and parameter estimates with error probability α is

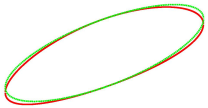
$$G_N(\alpha) := \{X |\, F_2(X) = 0,\ \|F_1(X)\|_2^2 - \|F_1(X^\star)\|_2^2 \leq \gamma^2(\alpha)\}$$



Assessment of Uncertainties in Parameter Estimates for Constrained Case (l_2)

- $G_N(\alpha)$ can be approximated through the linearized confidence region $G_L(\alpha)$

$$G_L(\alpha) := \{X \quad | \quad F_2(X^\star) + J_2(X^\star)(X - X^\star) = 0, \\ \|F_1(X^\star) + J_1(X^\star)(X - X^\star)\|_2^2 - \|F_1(X^\star)\|_2^2 \leq \gamma^2(\alpha)\}.$$



Assessment of Uncertainties in Parameter Estimates for Constrained Case (l_2)

- $G_L(\alpha)$ can be equivalently represented using generalized inverse J^+:

$$G_L(\alpha) = \{X | X = X^\star - J(X^\star)^+ \begin{pmatrix} \varepsilon \\ 0 \end{pmatrix}, ||\varepsilon||_2^2 \leq \gamma(\alpha)\}$$

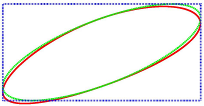
Assessment of Uncertainties in Parameter Estimates for Constrained Case (l_2)

- $G_L(\alpha)$ is contained in confidence box

$$G_L(\alpha) \quad \subset \quad \Pi_{i=1}^{n}[X_i^\star - \delta_i, X_i^\star + \delta_i], \quad \delta_i = C_{ii}^{1/2}\gamma(\alpha)^{1/2}$$

exactly, that is

$$\max_{X \in G_L(\alpha)} \qquad |X_i - X_i^\star| = \delta_i, \;\; i = 1, ..., n.$$



- $C_{ii}^{1/2}$ - standard deviations of parameters can be computed fast

Assessment of Uncertainties in Parameter Estimates for Constrained Case (l_2)

- Covariance matrix can be computed for all variables:

  $\rightarrow$ for parameters and state variables, $\rightarrow$ Prediction
- Diagonal elements of covariance matrix C_{ii} are variances of corresponding variables

Important: Variances for functions $g(x,p)$ of parameters and states can also easily be determined.
Procedure: Introduce new parameter p_{neu} and additional equality constraint $p_{new} = g(x,p)$.
Confidence interval for p_{new} describes quality of $g(x,p)$.

Characterization of Confidence Ellipsoids

Functions Φ_α of the covariance matrix $C(p, q, u, w)$ (unconstrained problem)

- A optimal: Average of the variances of the estimates

$$\Phi_1(C) = \frac{1}{n} trace C$$

- B optimal: maximal square root of diagonal elements of the covariance matrix (“maximal standard deviation”, proportional to maximal edge of enclosing box) (Bock, 1987)

$$\Phi_M(c) = \max_i (C_{ii}^{1/2})$$

- D optimal: Determinant of covariance matrix (“volume”)

$$\Phi_0(C) = det(C)$$

- E optimal: Maximum Eigenvalue of covariance matrix (“maximal semi axis”)

$$\Phi_\infty(c) = \lambda_{max}(C)$$

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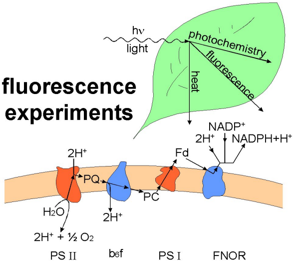
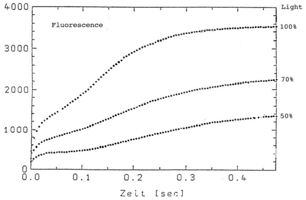
  - Enzyme Reaction Kinetics

Example: The Light Reaction in Photosynthesis

Baake, Schlöder, 1992

three experiments with different light intensities:

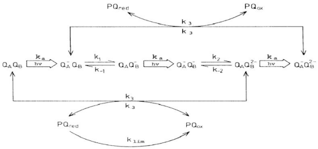




Laboratory Strasser, Stuttgart

Photosynthesis: ODE Model

electron transport chain in photosynthesis:



- mathematical model: nonlinear ODE with 6 states and 6 parameters

$$
\begin{aligned}
\dot{x}_1 &= (k_a + k_3(p_{tot} - x_6))x_1 + k_3 x_5 x_6\\
\dot{x}_2 &= k_a x_1 - (k_1 + k_3(p_{tot} - x_6))x_2 + k_{-1}x_3 + k_3 x_6 (1 - \textstyle\sum_{i=1}^{5} x_i)\\
\dot{x}_3 &= k_1 x_2 - (k_a + k_{-1})x_3\\
\dot{x}_4 &= k_a x_3 - k_2 x_4 + k_{-2} x_5\\
\dot{x}_5 &= k_3 x_1 (p_{tot} - x_6) + k_2 x_4 - (k_a + k_{-2} + k_3 x_6)x_5\\
\dot{x}_6 &= -k_3(1 - \textstyle\sum_{i=1}^{5} x_i)x_6 + k_3(x_1 + x_2)(p_{tot} - x_6) + (p_{tot} - x_6)k_{lim}
\end{aligned}
$$

with

$$
k_a = \frac{I_2(1 - p_{2T})}{1 - p_{22} - p_{2T} + p_{22}p_{2T}(x_1 + x_3 + x_5)}
$$

Photosynthesis: Measurement Function

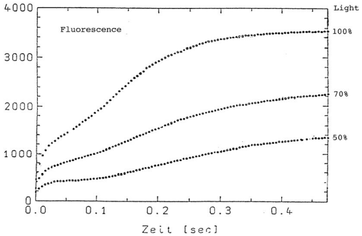
- Fluorescence is nonlinear function of states and parameters:

$$b_i(x(t_i), p) = \left\{ \frac{1 - p_{2T} - p_{22}}{p_{2T}} + \frac{1 - (x_1(t_i) + x_3(t_i) + x_5(t_i))}{1 + \frac{p_{22}p_{2T}(x_1(t_i)+x_3(t_i)+x_5(t_i))}{1-p_{2T}-p_{22}}} \right\} \cdot S \cdot I_2$$

- extra parameter (S) in measurement function (unknown gauge of apparatus)
- Fluorescence measured at 96 time points $t_1, \ldots, t_{96}$.
- Aim: Estimate model parameters from fluorescence measurements of living tobacco leaf

Photosynthesis: Multiple Experiment Structure

Data: 3 experiments with different light intensities (96 fluorescence measurements)



to be estimated:

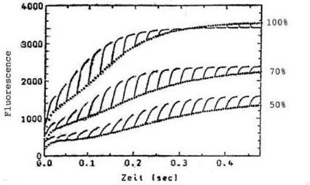
4 system parameter $p_{\text{tot}}, p_{2T}, p_{22}, k_3$

\+ 1 measurement parameter S

\+ 3 x 2 parameter depending on experiment k_{lim}, I_2

Initital Trajectories for Multiple Shooting Photosynthesis

Multiple shooting with 20 gridpoints

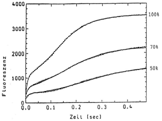


	k_3	p_{22}	p_{2T}	p_{tot}	S	I_2	k_{lim}
Exp 1	20	0.5	0.4	10	10	300	1
Exp 2						210	1
Exp 3						150	1

initial guesses

Photosynthesis: 3-Experiment Solution

Acc:10^{-3}, 12 Iterations, 3 damped



	k_3	p_{22}	p_{2T}	p_{tot}	S
solution	17.3	0.0710	0.841	11.5	18.1
standard error[1]	± 0.76	± 0.015	± 0.015	± 0.84	± 1.0

	100%		70%		50%	
	I_2	k_{lim}	I_2	k_{lim}	I_2	k_{lim}
solution	195.	1.07	143.	1.92	101.	1.67
standard error[1]	± 9.0	± 0.36	± 6.9	± 0.26	± 5.3	± 0.17

[1] estimated; multiplication by 4.5 yields 95% confidence intervals

Belousov Zhabotinskii Reaction

Nonlinear ODE

9 chem. species 5 control parameters

14 unknown parameters

The stochiometric system

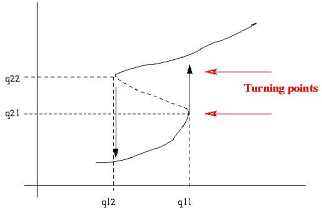
NOYES-FIELD-THOMPSON-MECHANISMUS

$$
\begin{aligned}
BrO_3^- + Br^- + 2H^+ &\underset{p_{-1}}{\overset{p_1}{\rightleftharpoons}} HBrO_2 + HOBr \\
HBrO_2 + Br^- + H^+ &\underset{p_{-2}}{\overset{p_2}{\rightleftharpoons}} 2HOBr \\
HOBr + Br^- + H^+ &\underset{p_{-3}}{\overset{p_3}{\rightleftharpoons}} Br_2 + H_2O \\
BrO_3^- + HBrO_2 + H^+ &\underset{p_{-4}}{\overset{p_4}{\rightleftharpoons}} 2BrO_2^- + H_2O \\
Ce^{3+} + BrO_2^- + H^+ &\underset{p_{-5}}{\overset{p_5}{\rightleftharpoons}} Ce^{4+} + HBrO_2 \\
Ce^{4+} + BrO_2^- + H_2O &\underset{p_{-6}}{\overset{p_6}{\rightleftharpoons}} Ce^{3+} + BrO_3^- + 2H^+ \\
2HBrO_2 &\underset{p_{-7}}{\overset{p_7}{\rightleftharpoons}} BrO_3^- + HOBr + H^+
\end{aligned}
$$

$$
\begin{aligned}
[HBrO_2] \quad \dot{A} &= p_1 BCH^2 - p_{-1}AD - p_2 ACH + p_{-2}D^2 \\
&\quad - p_4 ABH + p_{-4}F^2 + p_5 FGH - p_{-5}AI \\
&\quad - 2p_7 A^2 + 2p_{-7}BDH - k_E A \\
[BrO_3^-] \quad \dot{B} &= -p_1 BCH^2 + p_{-1}AD - p_4 ABH + p_{-4}F^2 \\
&\quad + p_6 FI - p_{-6}BGH^2 + p_7 A^2 - p_{-7}BDH - k_E(B - B_E) \\
[Br^-] \quad \dot{C} &= -p_{-1}BCH^2 + p_{-1}AD - p_2 ACH + p_{-2}D^2 \\
&\quad - p_3 CDH + p_{-3}E - k_E(C - C_E) \\
[HOBr] \quad \dot{D} &= p_1 BCH^2 - p_{-1}AD + 2p_2 ACH - 2p_{-2}D^2 \\
&\quad - p_3 CDH + p_{-3}E + p_7 A^2 - p_{-7}BDH - k_E D \\
[Br_2] \quad \dot{E} &= p_3 CDH - p_{-3}E - k_E E \\
[BrO_2] \quad \dot{F} &= 2p_4 ABH - 2p_{-4}F^2 - p_5 FGH + p_{-5}AI \\
&\quad - p_6 FI + p_{-6}BGH^2 - k_E F \\
[Ce^{3+}] \quad \dot{G} &= -p_5 FGH + p_{-5}AI + p_6 FI - p_{-6}BGH^2 \\
&\quad - k_E(G - G_E) \\
[H^+] \quad \dot{H} &= -2p_1 BCH^2 + 2p_{-1}AD - p_2 ACH + p_{-2}D^2 \\
&\quad - p_3 CDH + p_{-3}E - p_4 ABH + p_{-4}F^2 - p_5 FGH \\
&\quad + p_{-5}AI + 2p_6 FI \\
&\quad - 2p_{-6}BGH^2 + p_7 A^2 - p_{-7}BDH - k_E(H - H_E) \\
[Ce^{4+}] \quad \dot{I} &= p_5 FGH - p_{-5}AI - p_6 FI + p_{-6}BGH^2 - k_E I
\end{aligned}
$$

Belousov Zhabotinskii Reaction – PE Problem

Description of experiments

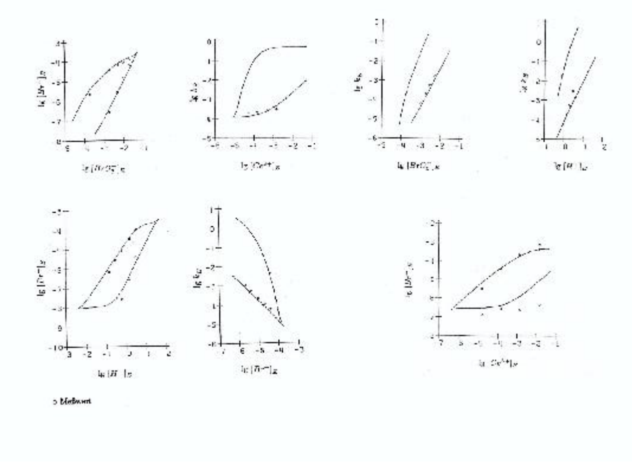


$$\left.\begin{array}{rcl} f(y, q, p) & = & 0 \\ f_y(y, q, p) \cdot h & = & 0 \\ h^T \cdot h & = & 1 \end{array}\right\} \otimes$$

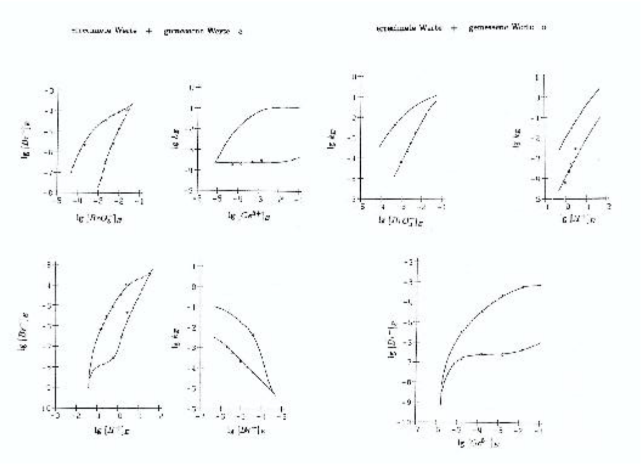
- Measurement points: 44 points on 4-dim manifold of turning points (Geiseler, Bar-Eli '81)
- Manifold depends on 14 unknown parameters (rate constants)
- Problem: fit 4-dim manifold on 44 5-dim points, which are implicitly given by $\otimes$

$\rightarrow$ 894 variables; 838 nonlinear equations 88 least squares terms 498 positivity constraints

Belousov Zhabotinskii Reaction: Simulation for Initial Guesses

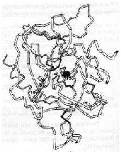


Belousov Zhabotinskii Reaction – Solution



Enzyme Reaction Kinetics

K. et al 2001



- enzymes = biocatalysts, highly active
- demand from industry since they accelerate biochemical reactions
- but: great expenses for the evaluation of the long-term behaviour
- practice: very many expensive experiments are carried out

Enzyme Reaction Kinetics

K. et al 2001

$$
\begin{array}{ccc}
\text{N} & \overset{k_{NU}}{\underset{k_{UN}}{\rightleftarrows}} & \text{U} \\
k_{ND} \searrow & & \swarrow k_{UD} \\
 & \text{D} &
\end{array}
$$

N: native enzyme, measurable
U: unfolded enzyme, not measurable
D: deactivated enzyme, not measurable

Enzyme Reaction Kinetics

K. et al 2001

$$\frac{d\ C_D}{d\ t} = \left(k_d^0 \exp\left(\frac{-\Delta h_u^*}{RT}\right) K_U + k_N^0 \exp\left(\frac{-\Delta h_N^*}{RT}\right)\right) \frac{C_{E_0} - C_D}{1 + K_U},$$

$$\frac{d\ C_S}{d\ t} = \frac{\dot{V}}{V}\left(C_S^0 - C_S\right) - r_{max}\frac{C_S}{k_m + C_S},$$

$$C_D(0) = 0, \qquad C_S(0) = C_S^0,$$

$$K_U = \exp\left(\frac{-\Delta h_u^0}{RT}\right) \exp\left(\frac{\Delta S_u^0}{R}\right),$$

$$r_{max} = A \exp\left(\frac{-\Delta h_E^*}{RT}\right) \frac{C_{E_0} - C_D}{1 + K_U}.$$

Application: Enzyme Reaction Kinetics

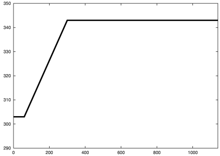
Cooperation with degussa.

- nonlinear Arrhenius kinetics
- 8 unknown parameters p
- 1 time dependent control function $u(t)$: temperature
- 1 indirect measurement: consumption of base necessary to neutralize the acidic reaction product (side-reaction!)
- quantities describing stability (total turn-over number and half-life) are of interest!
- problem is too ill-conditioned, impossible to identify parameters from 1 experiment!

Experiments with *Candida antarctica* on ionic resin ("Novozym")

l_2 parameter estimation from the standard experiment: estimated values of parameters $\pm$ standard deviation after parameter estimation

	initial profile
p_1	27.86 $\pm$ 4.42
p_2	48.98 $\pm$ 10.92
p_3	1.73 $\pm$ 2.39 $\times 10^5$
p_4	634.20 $\pm$ 806.00 $\times 10^6$
p_5	-1.43 $\pm$ 1.50 $\times 10^7$
p_6	-7.50 $\pm$ 4.16 $\times 10^7$
p_7	-4.15 $\pm$ 0.091
p_8	-8.63 $\pm$ 2.00



Can we find better experiments?

Question: Can We Determine Better Experimental Conditions?

Aim:

- choose experimental conditions $\xi = (u, q, w)$,
  - control functions: temperature profiles, feed streams,
  - control parameters: volume, initial conditions,
  - sampling design: measurement devices and times
- aim: “to maximize information gain”, here: “to minimize uncertainty of resulting parameter estimate”
- subject to state, control and parameter constraints
  - safety, domain of model validity, costs, feasibility of experiments

Outline

Summary

- numerical methods and applications
  - parameter estimation for DAE
- based on multiple shooting
- Generalized Gauss-Newton
  for l_2 and l_1 problems
- sensitivity analysis as basis for optimum experimental design
- complex nonlinear problems can be treated
- next: methods for nonlinear optimum experimental design

THANK YOU VERY MUCH FOR YOUR ATTENTION!

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