Computational Life Sciences at MATHEON

Peter Deuflhard

DFG Research Center MATHEON
Mathematics for key technologies

February 21, 2008

Outline

Mathematical Fields

I Optimization and discrete mathematics
A. Griewank, M. Grötschel, G. M. Ziegler

II Numerical analysis and scientific computing
P. Deuflhard, V. Mehrmann, H. Yserentant

III Applied and stochastic analysis
A. Bovier, A. Mielke

Application Areas

A Life sciences
A. Bockmayr, P. Deuflhard, Ch. Schütte

B Logistics, traffic, and telecommunication networks
M. Grötschel, R. Möhring, M. Skutella

C Production
C. Carstensen, J. Sprekels, F. Tröltzsch

D Circuit simulation and opto-electronic devices
V. Mehrmann, F. Schmidt

E Finance
A. Bovier, P. Imkeller

F Visualization
K. Polthier, J. Sullivan, G. M. Ziegler

Z Education, Outreach, Administration
J. Kramer

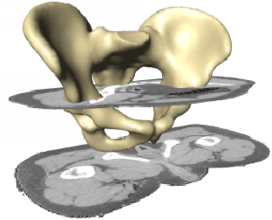
Outline

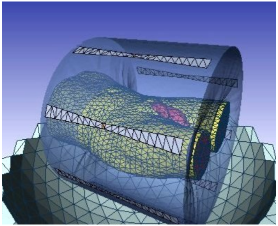
Projects:

- A1: Hyperthermia treatment planning (Deuflhard, Tröltzsch, Weiser)
- A2: Osteotomic surgery planning (Deuflhard, Kornhuber)
- A3: Noise Reduction in fMRI (Spokoyni)
- A4: Towards biomolecular flexibility (Schütte, Deuflhard)
- A5: Virtual screening by 3D similarity (Hougardy, Prömel)
- A6: Stochastic modelling in pharmacokinetics (Deuflhard, Schütte)
- A7: Numerical discretization methods in quantum chemistry (Schneider, Yserentant)
- A8: systems biology (Bockmayr)
- A9: Positive descriptor systems (Mehrmann)
- A11: Non-adiabatic effects in molecular dynamics (Lasser)

A1: Hyperthermia Treatment Planning

Regional Hyperthermia:	local tumor heating by radiowave radiation
Aim:	optimal control of antennas
Problems:	handling of state constraints perfusion modelling





Large Vessels

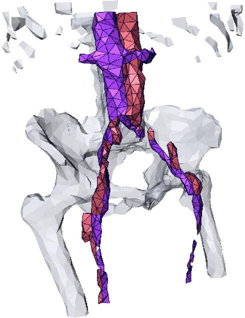
- 3D representation
- advection-diffusion equation

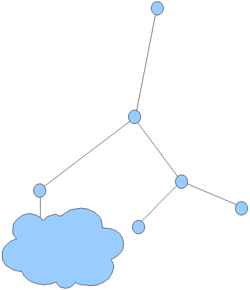
Medium Size Vessels

- 1D representation
- singular advection
- regional coupling

Capillaries

- no geometry available
- homogenization





Idea: model state constraints by barrier functionals

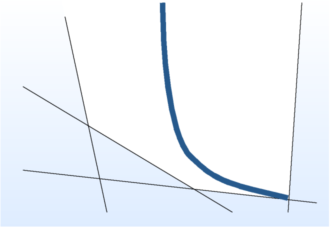
- ▷ homotopy in function space
- ▷ inexact Newton path-following
- ▷ adaptive multilevel method

Homotopy Path:

- ▷ existence and convergence
- ▷ Lipschitz continuity

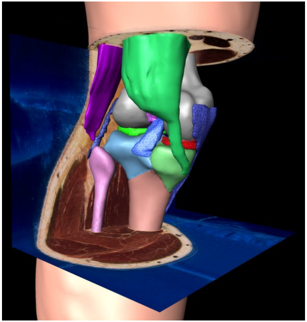
Lavrentiev Regularization:

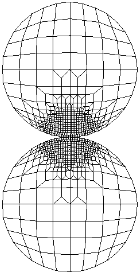
- ▷ regular Lagrange multipliers



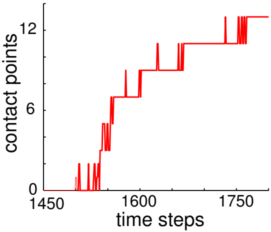
Towards forward dynamics for a human knee joint

- Patient-specific geometry
- Finite element discretization
- Time integration with inequality constraints
  - Energy dissipative
  - No spurious oscillations
- Static two-body contact problems
  - Mortar discretization
  - Parametrized boundaries
  - Multigrid convergence

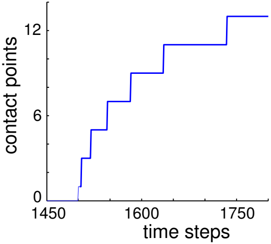




Hertzian Contact Problem



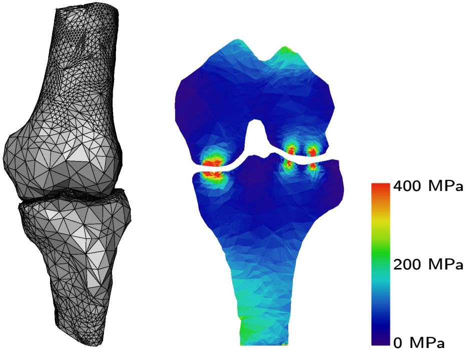
Improved Newmark (Caltech)

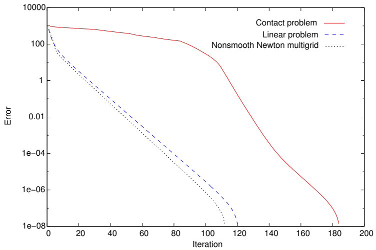


Contact-stabilized Newmark (Matheon)

Newmark schemes for dynamical contact problems

- Improved Newmark scheme [Kane, Repetto, Ortiz, Marsden 99]: Energy dissipative, spurious contact oscillations
- Contact-stabilized Newmark scheme [Deuflhard, Krause, Ertel 06]: Energy dissipative, no spurious contact oscillations

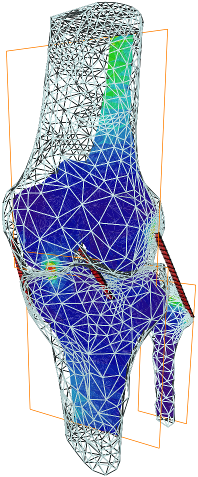




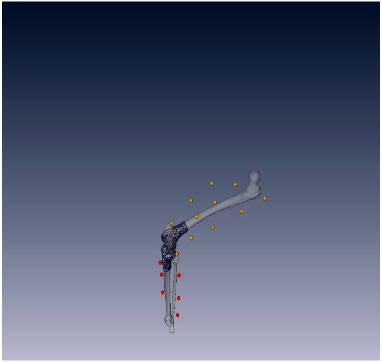
Fast solvers for multi-body contact problems

- Monotone multigrid: asymptotic multigrid convergence rate
- Nonsmooth Newton multigrid: faster than equivalent linear problem! [Kornhuber, Krause, Sander, Deuflhard, Ertel 06]


M. quadriceps femoris, Tendo
Femur
Patella
Epicondylus medialis
Lig. patellae
Meniscus medialis
Lig. collaterale tibiale
Tuberositas tibiae
Tibia
Fibula



A2: Knee Climbing Stairs

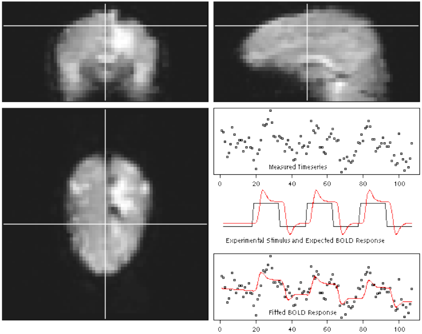


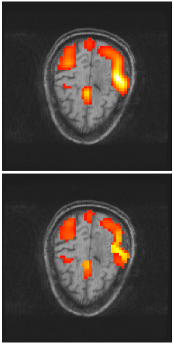
Example using real-world data

- ▷ Distal femur and proximal tibia from the Visible Human data set
- ▷ Contact between the bones; foundation as rigid obstacle
- ▷ Three grid levels, $\approx$ 220,000 degrees of freedom

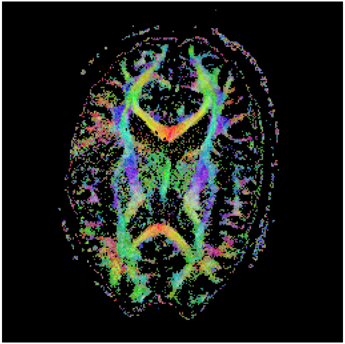
fMRI – functional Magnetic Resonance Imaging

Aim: Noise reduction while preserving shapes of activation areas.
Method: Structural adaptive denoising (lower right)





DTI – Diffusion Tensor Imaging

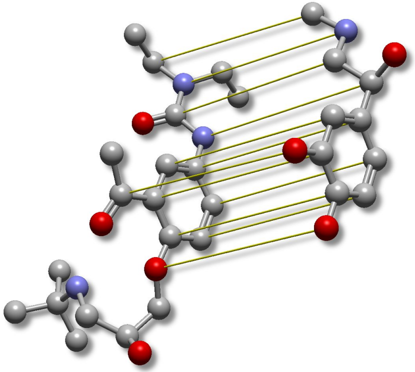


- Measuring anisotropic diffusion in tissue
- Accurate determination of diagnostic measures …
- … and fiber tracking!

A5: Virtual Screening by 3D Similarity

Aim: Designing new Drugs

- ▷ minimize side effects
- ▷ lower production costs
- ▷ sidestep existing patents



Problem: Candidate Search

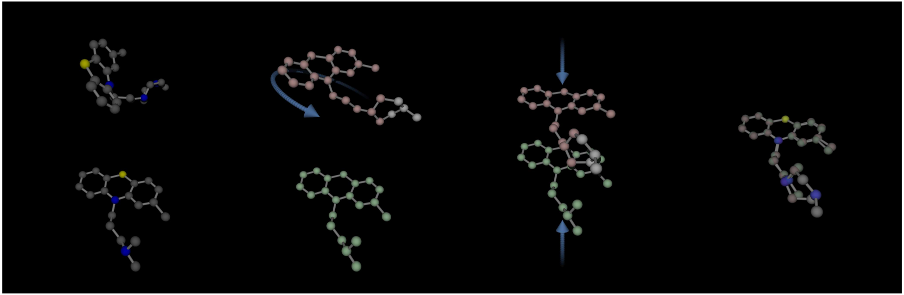
- ▷ screening of drug candidates expensive
- ▷ millions of potentially active compounds

Solution: 3D Virtual Screening

- ▷ computer aided search for good candidates in databases using a sophisticated 3D similarity measure

Superposition by rigid motion, such that

- "many" atoms of both molecules are superimposed
- distances between superimposed atoms are "small"



maximize score function: $n_s \cdot e^{-rmsd}$

n_s	=	fraction of superimposed atoms
$rmsd$	=	root mean square distance between superimposed atoms

A5: Algorithmic Solution for 3D Virtual Screening

Hard Computational Problem

- brute force algorithm on n atoms $\Rightarrow 2^{2^n} \cdot n!$ operations
  $n = 8$: 1 second $\quad$ $n = 16$: 10^6 years
- heuristics fail to find partial similarity

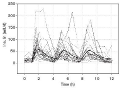
MATHEON Algorithm

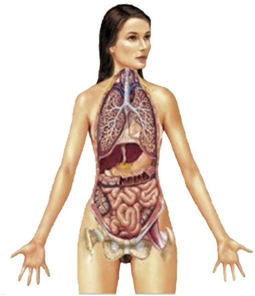
- handles multiple conformations and flexibility
- no heuristic – finds optimal solution within seconds
- optimization of other 3D score functions possible
- patent pending (Germany and PCT application)

Pharmacokinetics:

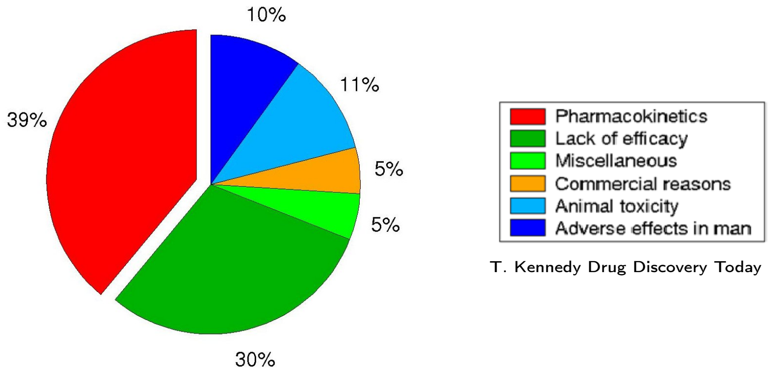
- ▷ Absorption
- ▷ Distribution
- ▷ Metabolism
- ▷ Excretion

of drugs in the body



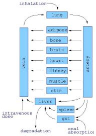


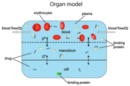
Aim: Mathematical modelling and theoretical analysis of pharmacokinetics processes, including variability & uncertainty



T. Kennedy Drug Discovery Today 2 (1997)

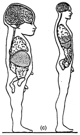
Emerging interest in advanced in silico approaches to support drug discovery and development

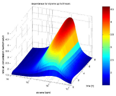




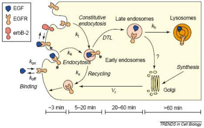
Model design: development of consistent and modular pharmacokinetic models

Non-linear sensitivity analysis: analyzing the effects of parameter variability



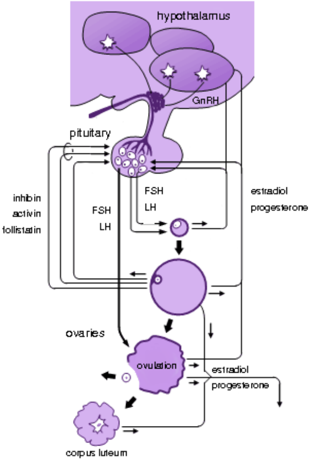


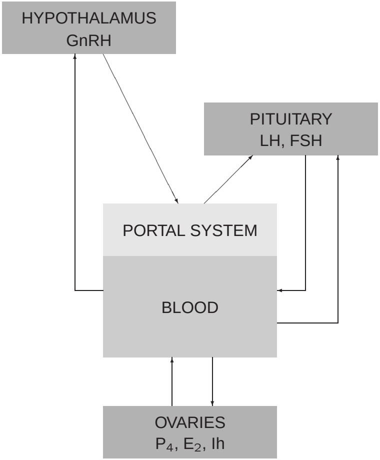
$$\partial_t u(t) = -\mathrm{div}(F \cdot u(t))$$



Hybrid stochastic-deterministic models: coupling pharmacokinetic models to cellular processes

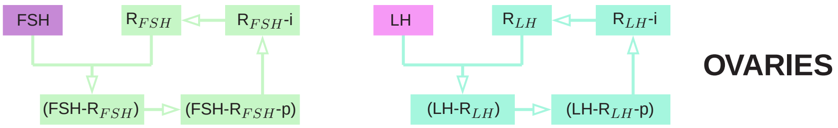
Software: Virtual Lab for Modelling and Simulation in Pharmacokinetics (coop CiT)


hypothalamus
GnRH
pituitary
inhibin
activin
follistatin
FSH
LH
FSH
LH
estradiol
progesterone
ovaries
ovulation
estradiol
progesterone
corpus luteum


HYPOTHALAMUS
GnRH
PITUITARY
LH, FSH
PORTAL SYSTEM
BLOOD
OVARIES
P_4, E_2, Ih

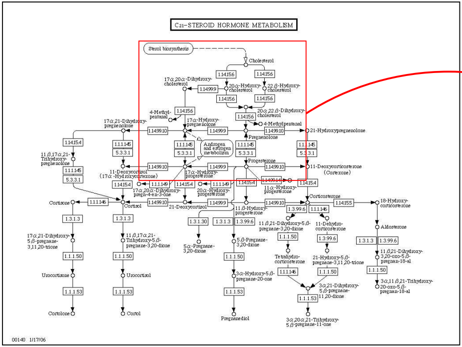
Receptor Binding and Recycling

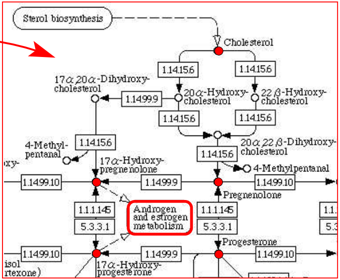
- FSH and LH bind to their receptors and form a complex
- The bound receptor becomes phosphorylated, internalized and returns, finally, to unbound state



- The bound receptor activates the enzymes catalyzing the steroidogenesis
- Clément et al., 2001

Biosynthesis of the Steroids

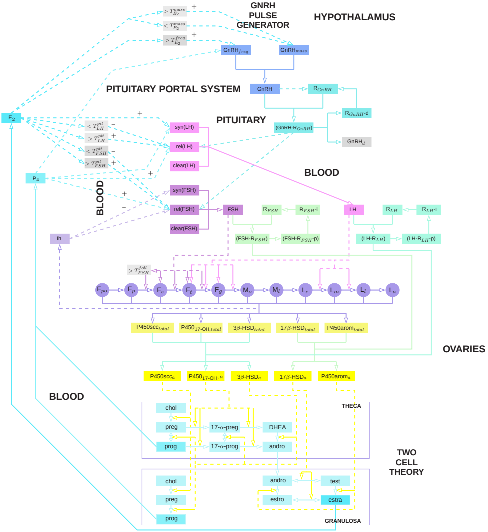




(KEGG PATHWAY Database)

Model Scheme

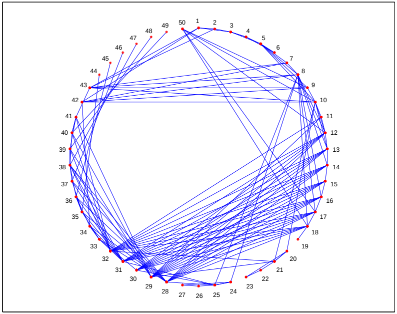
- # DDEs: 43
- # Further components: 6
- # Parameters: 191



I. Reinecke, P. Deuflhard, 2007

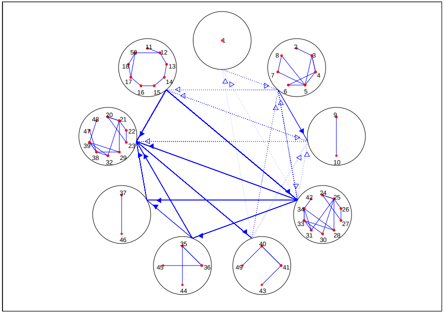
Model Decomposition

- Formulation of the model as graph
- Edge: right hand side of model equation dependent
- Numbers: components of the model
- Examples:
  8: LH
  10: FSH
  42: P_4
  43: E_2
  50: Inhibin



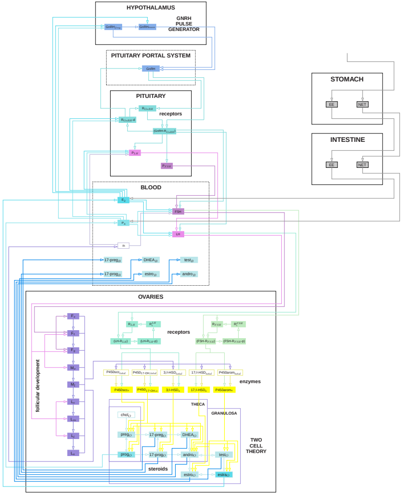
A6: Endocrinological Network

- In circles: model parts
- Solid arc: input from other model parts
- Dotted arc: input can be replaced by approximations of experimental data



Model Scheme Including Birth Control Pill

- # DDEs: 49
- # Further components: 6
- # Parameters: 208



Basis of chemistry: The N-electron Schrödinger equation,

$$\Big\{ -\frac{1}{2}\sum_{i=1}^{N}\Delta_i - \sum_{i=1}^{N}\sum_{\nu=1}^{K}\frac{Z_\nu}{|x_i - a_\nu|} + \frac{1}{2}\sum_{i\neq j}\frac{1}{|x_i - x_j|}\Big\}\psi \;=\; E\psi,$$

for electrons at $x_1, \ldots, x_N$ in $\mathbb{R}^3$ and fixed nuclei.

The problem: the solutions ψ depend on $3N$ variables!

The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble.

P.A.M. Dirac, 1929

Chemists and physicists

Simplified model with approximations: HF, DFT, MCHF, etc.

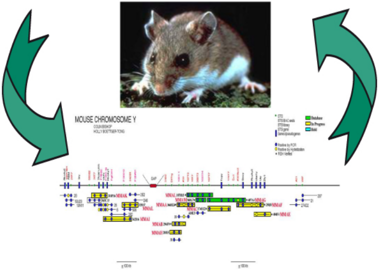
MATHEON A7

Develop the mathematical underpinnings for a direct approach:

- new regularity theory for high-order mixed derivatives,
- recent advances in high-dimensional approximation theory
- computational complexity independent of N !

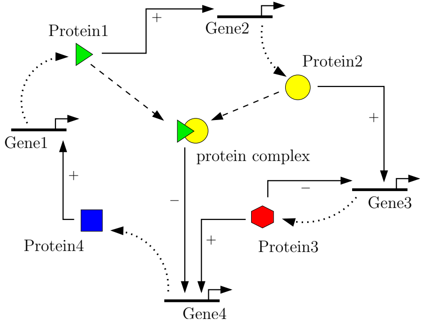
A8: Systems Biology

Molecular biology: study components of a biological system in isolation

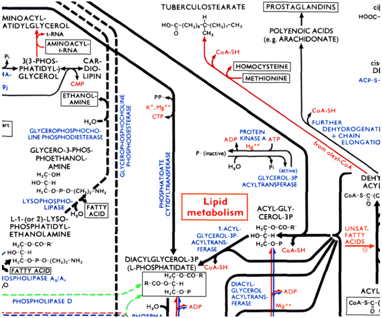


Systems biology: understand how the components interact to perform biological function

- Discrete modeling approach: discrete variables and parameters
- Logical analysis of the network dynamics ⇝ model checking
- Incorporating time constraints ⇝ hybrid discrete/continuous modeling
- Relating topology and dynamics of the network



- Metabolic networks at steady state
- New constraint-based description of the steady flux cone
  - minimal
  - unique
- Applications
  - characterize metabolic behaviors
  - identify reaction dependencies
  - study effect of gene deletion



http://expasy.org/tools/pathways/

We consider positive descriptor systems:

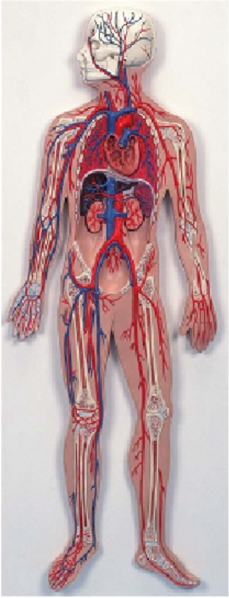
$$\begin{aligned} F(t,x,\dot{x},u) &= 0,\ x(t_0) = x_0, \\ y &= G(x,u). \end{aligned}$$

Linearization along constant trajectories leads to:

$$\begin{aligned} E\dot{x} &= Ax + Bu,\ x(t_0) = x_0, \\ y &= Cx. \end{aligned}$$

Positivity

Non-negative state x, input u, output y for all t.



A9: Applications and Results

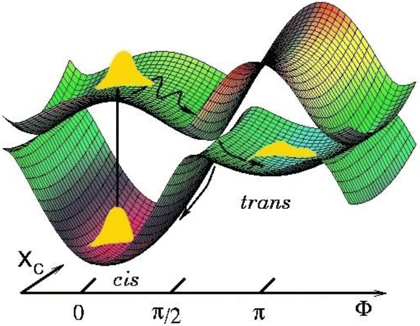
Applications

- Pollutant transport, chemo-taxis
- Pharmacokinetics
- Input-output models (Leontief)
- Population models
- Compartmental systems

Aims

- Theoretical insight
- Positivity preserving numerical methods for simulation and control

Aim: Numerical integrators for nucleonic quantum evolution



(First step of vision: isomerisation of retinal in rhodopsin)

Mathematical model: time-dependent Schrödinger systems with avoided and conical eigenvalue crossings,

$$i\hbar\partial_t\psi = -\frac{\hbar^2}{2m}\Delta_x\psi + \begin{pmatrix} v_{11} & v_{12} \\ v_{21} & v_{22} \end{pmatrix}\psi, \qquad \psi(0) = \psi_0.$$

Open Problems:

- sampling of highly oscillatory data,
- resolution of interference effects.

Outline

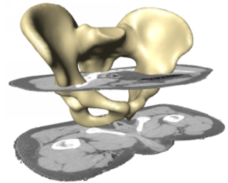
Scientists in charge:
K. Polthier, J. Sullivan, G. M. Ziegler

Topics:

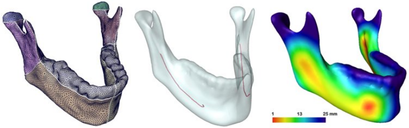
- discrete differential geometry
- geometry processing
- image processing
- virtual reality PORTAL

F2: Atlas-based 3D Image Segmentation

Applications

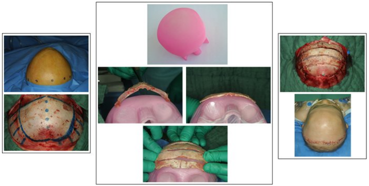


Geometry Reconstruction
from 2D and 3D image data.



Analysis of Shape Variability
based on statistical shape models.

Clinical Therapy and Surgery Planning



Outreach

Visualization Laboratory "Studio DaVinci"
public events, student groups,
industrial and academic collaborators

Cooperations

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN	neurosurgery, hyperthermia, liver oncology, biomechanics
MERCURY Computer Systems, Inc.	amira software, segmentation
PHILIPS sense and simplicity	3D reconstruction from x-ray images
SYNTHES	surgical toolkit for craniosynostosis
AO Foundation	reconstruction of orbital defects