Mathematical Optimization for Clinical Decision Support and Training

Sebastian Sager

Institute for Mathematical Optimization

Otto-von-Guericke-Universität Magdeburg

Będlewo, June 10, 2015

Outline

1 Introduction to MODEST

2 Decoding complex cardiac arrhythmia

3 Optimal control for leukemia treatment

4 Possible other clinical applications

5 Training
- Complex Problem Solving
- Optimization Approach to CPS
- Optimization-based Feedback
- Results of a Web-based Feedback Study

6 Summary

Clinical decision making

- Clinical practice $\mapsto$ ubiquitous decision making for physicians
- Difficult! Patient- and situation-dependent, non-intuitive, high work load, time constraints, knowledge transfer, ...

- We want to develop mathematical tools (modeling, simulation, and optimization) to support and train clinical decision making

CLINICAL PRACTICE

ALGORITHMS

Clinical decision training

Simulation: what would happen if... ?
Optimization: what would be best?

CLINICAL PRACTICE

ALGORITHMS

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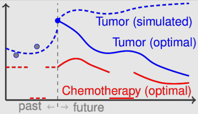

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Mathematical Optimization for clinical DEcision Support and Training

ERC Consolidator Grant MODEST-647573

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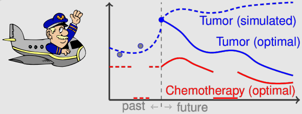

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Optimization: what would be best?

Physician training

Relevant scenarios

Personalized medicine via optimization

Simulation:
warnings and alerts
what would happen if...?

Optimization:
fit models to patient data
get patient-specific treatment
get patient-specific diagnosis

e.g., for cardiac arrhythmia

Probability for Atrial Fibrillation: 85%

Probability for Atrial Flutter: 93%

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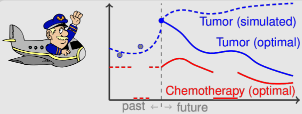

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Solution methodology

Challenges for optimization

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Challenges for optimization

ALGORITHMS

Mixed-integer nonlinear optimal control

Uncertainties, e.g.,
  model-plant mismatch
  patient-specific parameters
Integrality, e.g.,
  which combination of drugs?
  Wenckebach or Mobitz block?
Global optima needed

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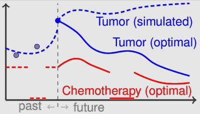

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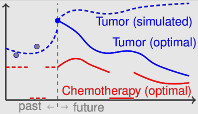
CLINICAL PRACTICE

Clinical decision training



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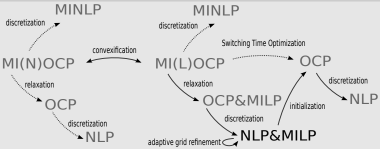

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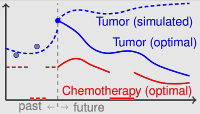
CLINICAL PRACTICE

Simulators for diseases

Decision support systems

Clinical decision training



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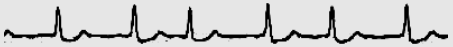

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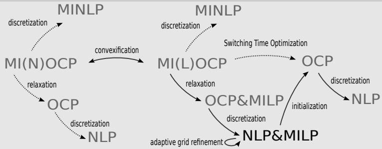

Theoretical advances

New & better algorithms

Open source software

Interdisciplinary team effort

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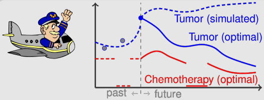

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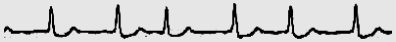
Cardiac arrhythmia:



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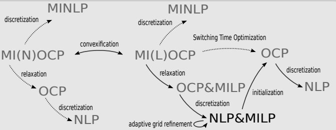

OTTO VON GUERICKE
UNIVERSITÄT
MAGDEBURG

So how can optimization help?

Fundamental assumption: relevant variables and equations are known!

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A) Getting the right set of equations and parameters

- Parameter estimation

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C) Individual medicine

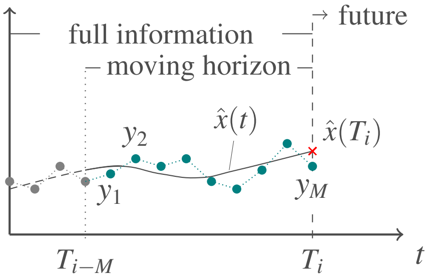
- Closed-loop online state and parameter estimation and control

Same schedule for everyone?

The future: Individualized medicine

Online Optimization

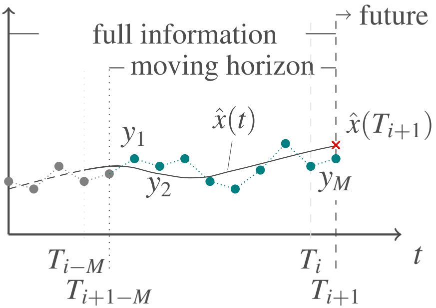
Moving Horizon Estimation



Estimate parameters and states

Online Optimization

Moving Horizon Estimation



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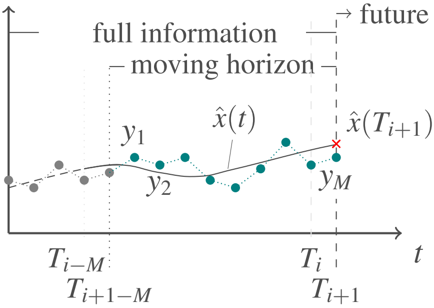
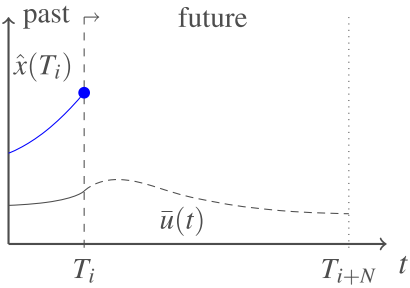


Estimate parameters and states

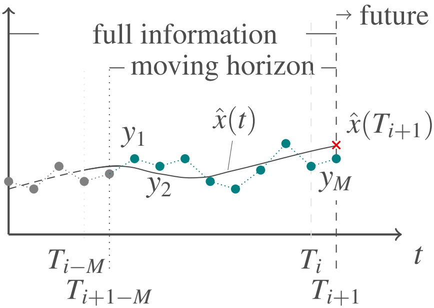
Model Predictive Control



Drug choice, dosage, timing

Online Optimization

Moving Horizon Estimation



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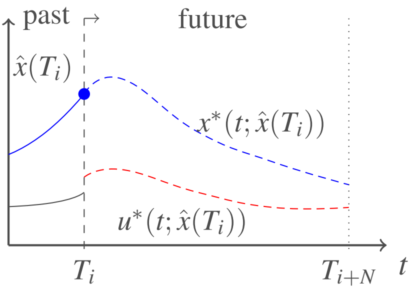

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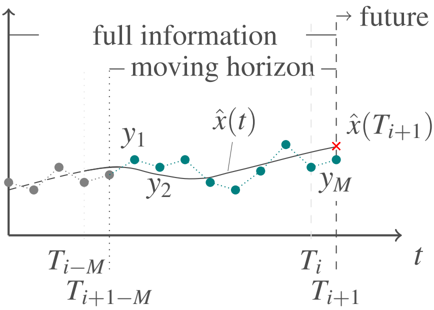

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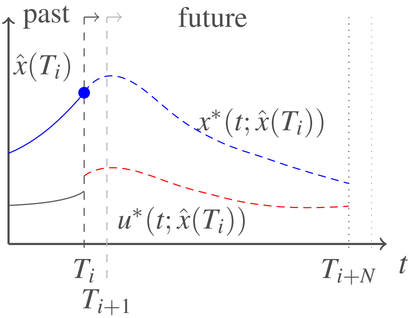

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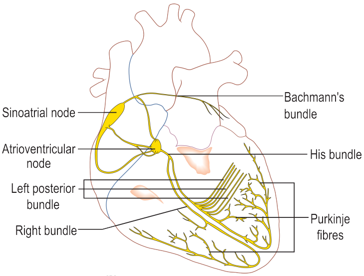
Decoding complex cardiac arrhythmia using mathematical optimization

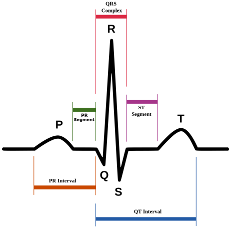
Sebastian Sager, Florian Kehrle, Eberhard Scholz

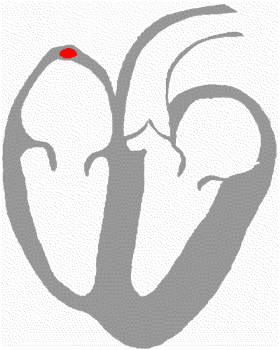
Otto-von-Guericke Universität Magdeburg,
Uniklink Heidelberg

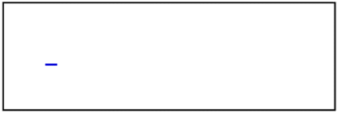
Będlewo, June 10, 2015

Reminder: the human heart [Images: Wikipedia]









Pacemaker signal in sinoatrial node

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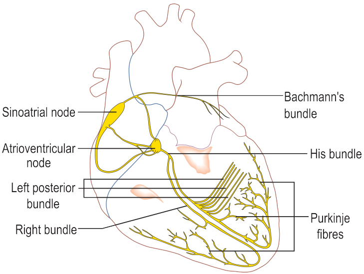
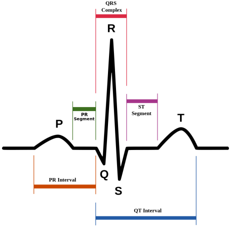
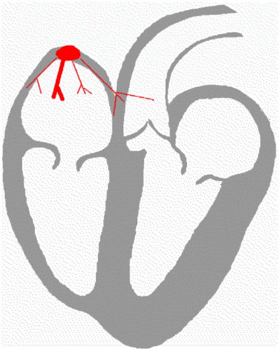
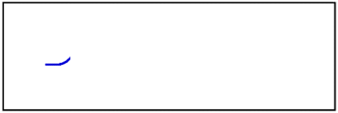


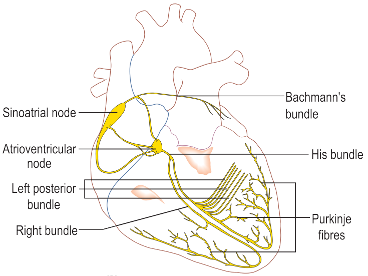


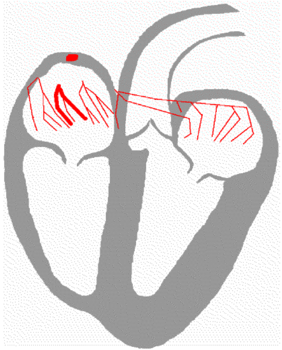


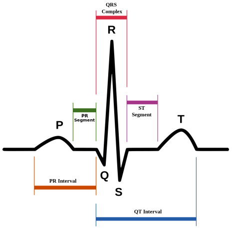


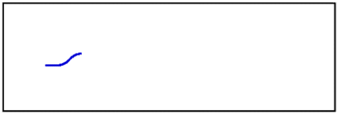
Atrial chambers

Reminder: the human heart [Images: Wikipedia]









P Atrial depolarization $\rightarrow$ atrial contraction

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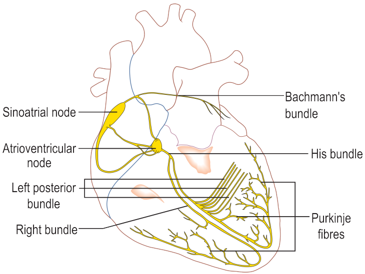

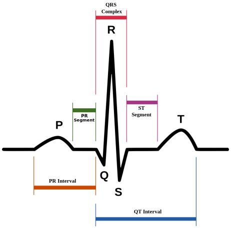

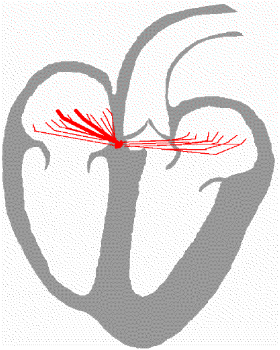

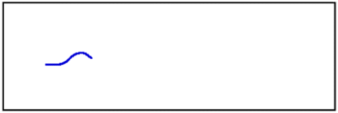

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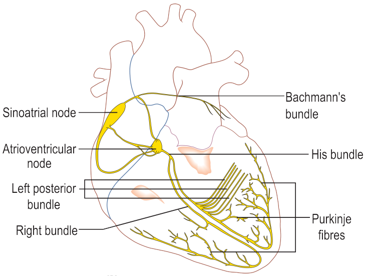

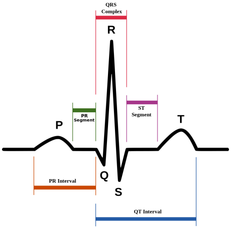

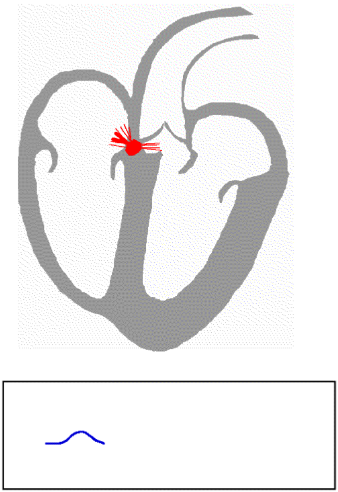

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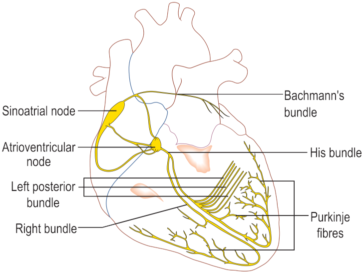
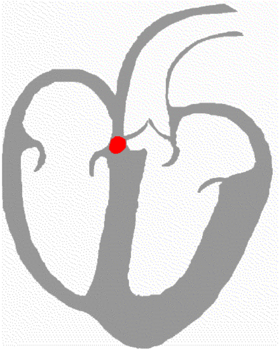
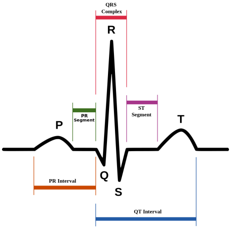
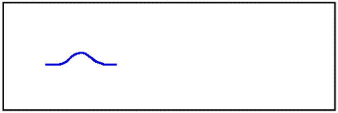


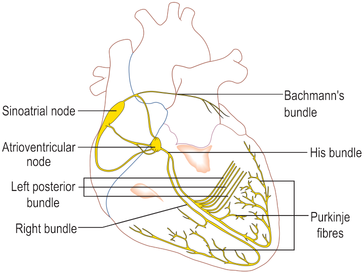


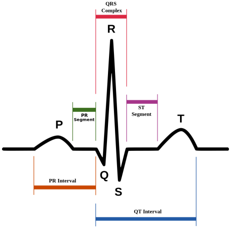


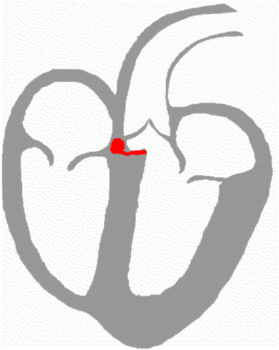


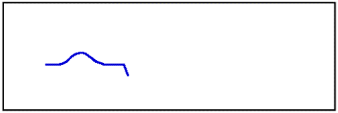
PR Atrioventricular node

Reminder: the human heart [Images: Wikipedia]



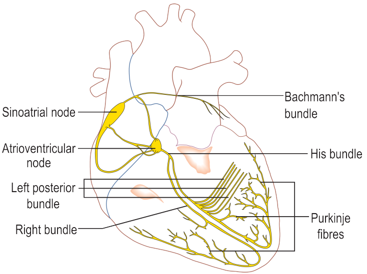


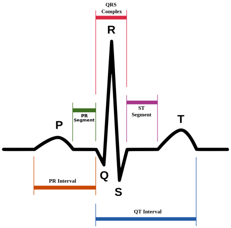


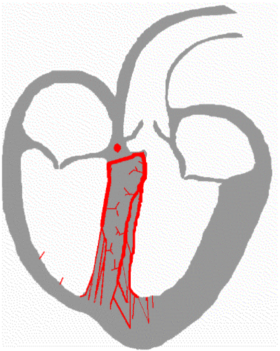


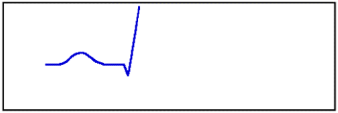
Q Depolarization of the interventricular septum

Reminder: the human heart [Images: Wikipedia]



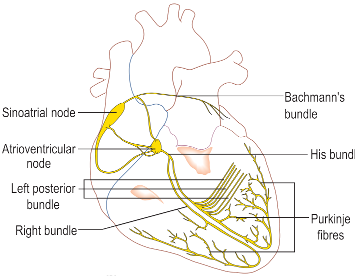


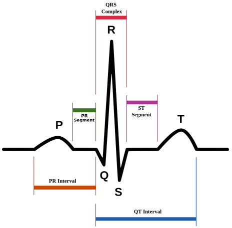


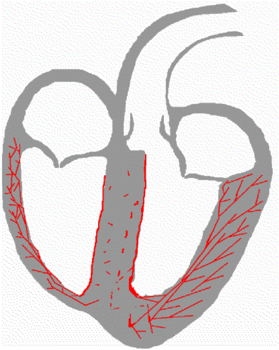


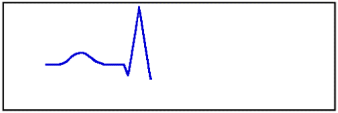
R Polarization of the ventricles

Reminder: the human heart [Images: Wikipedia]



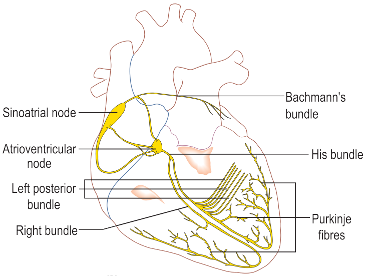


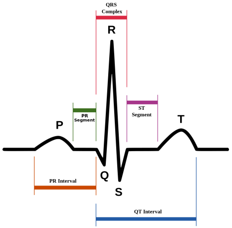


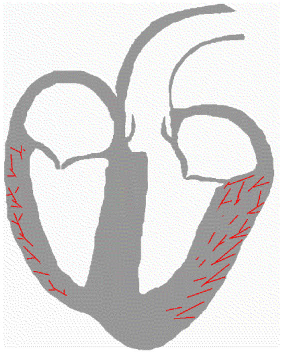


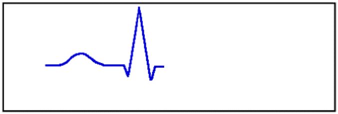
S (De)polarization

Reminder: the human heart [Images: Wikipedia]



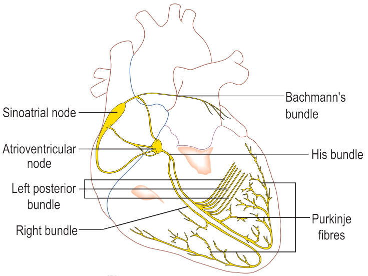


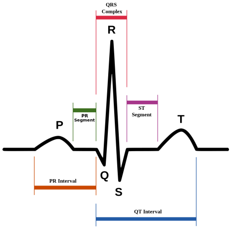




S Depolarization, contraction

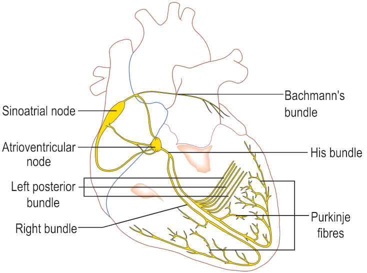
Reminder: the human heart [Images: Wikipedia]

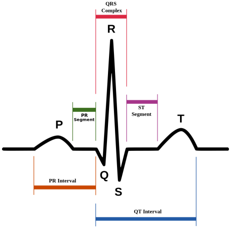




ST Depolarization, contraction

Reminder: the human heart [Images: Wikipedia]





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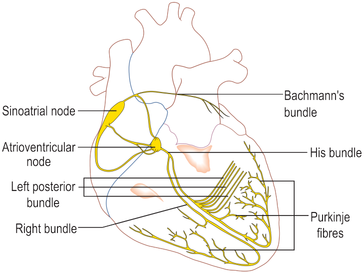

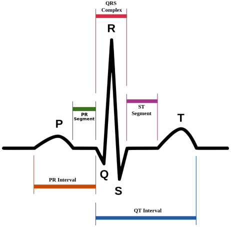

T Secondary excitation

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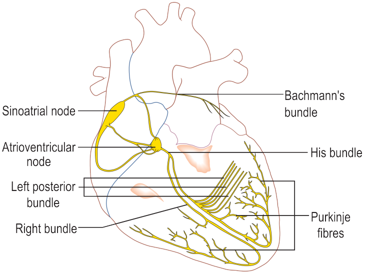

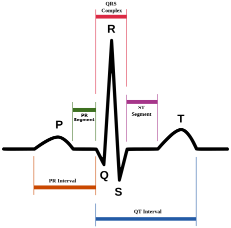

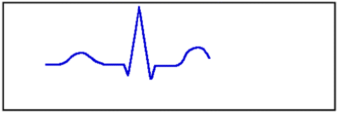

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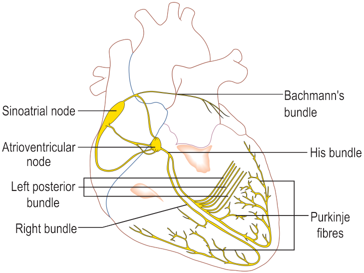

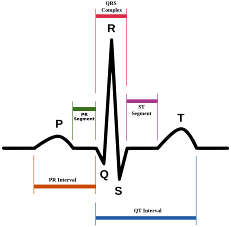

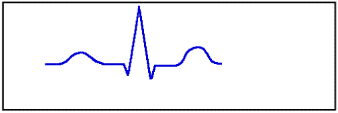

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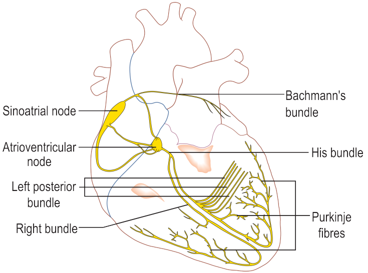

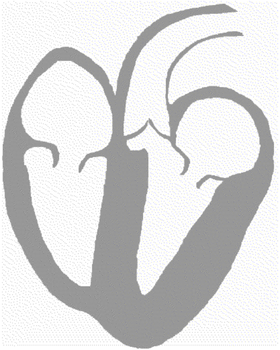

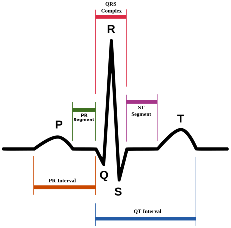

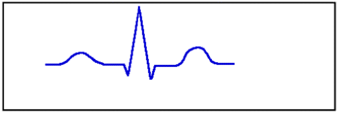

Rest

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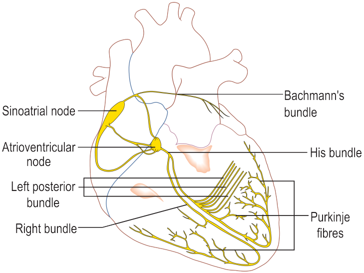
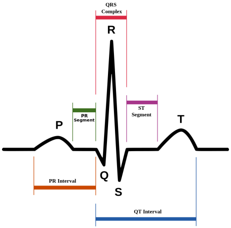
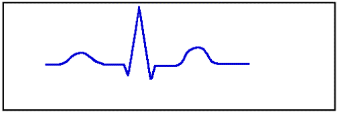
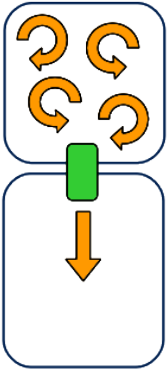




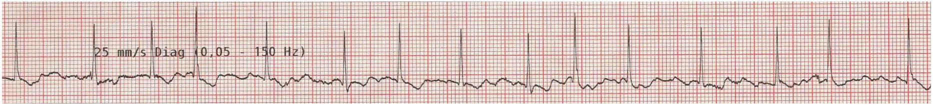


Rest

Atrial Fibrillation

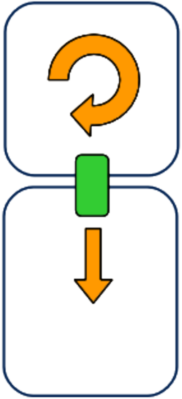


- Regular electric impulses are overwhelmed by disorganized ones (non-constant frequency)



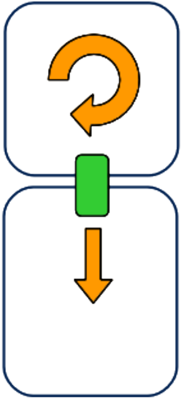
Atrial Flutter

- Regular electric impulses (constant frequency) in the atria, may be filtered
- Makes sense: pumping inefficient if too fast



Atypical Atrial Flutter

- But: filter may also result in irregular signal!
- Something happening in the AV node?!?



Summary of the decision problem

- Two possible reasons for chaotic ECG data (R waves):
  1. Atrial fibrillation – irregular atrial signal
  2. Secondary tachycardia – regular atrial signal

- Also different treatments!!
  1. Mainly drug treatments
  2. Mainly ablation

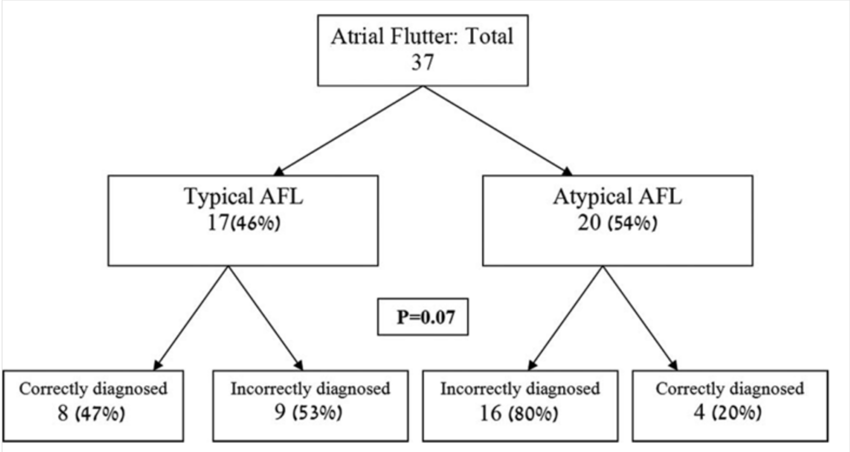
- More and more appearances of irregular flutter as secondary tachycardia after ablation

- Why should it be difficult to distinguish them from the ECG?

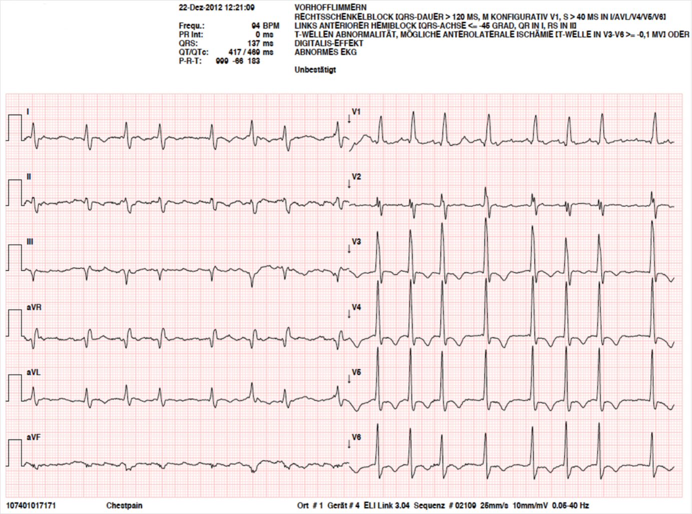
So, what do you think?

So, what do you think?

So, what do experts think? [Shiyovich et al. 2010 Am J Med Sci]



So, what do (current) expert systems think?



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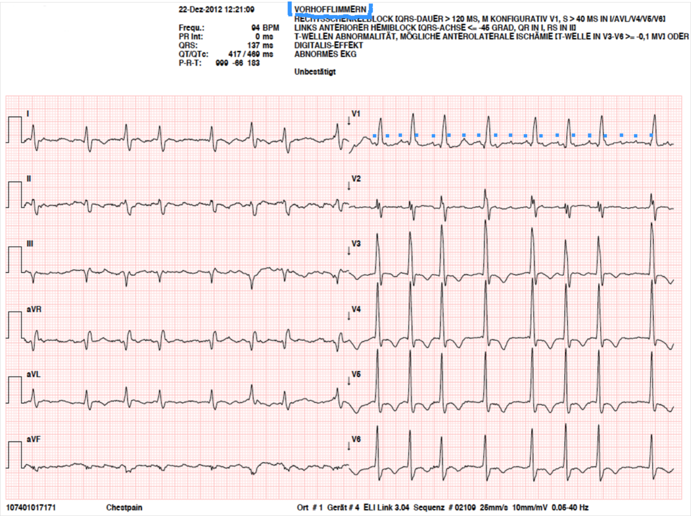

Large variety of different approaches possible

Mostly based on statistical approaches of RR-intervals:

- Fourier transforms
- Wavelets
- Machine learning
- Bayesian logic
- Nonlinear time series analysis

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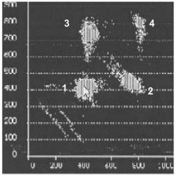
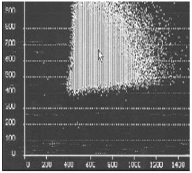


AFlu



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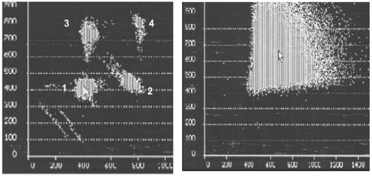

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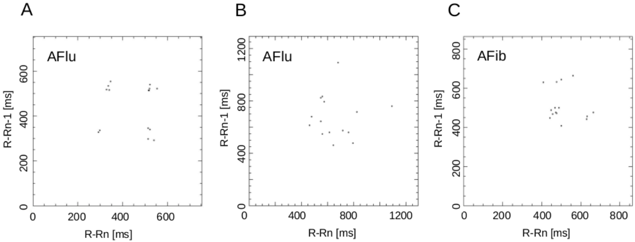
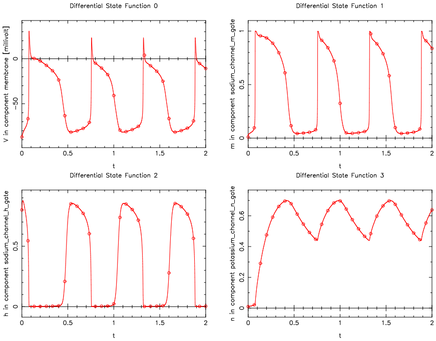


The Noble model [Noble, D. 1962 Journal of Physiology]

- ODEs model action potential based on Hodgkin-Huxley equations [Nobel Prize 1963]
- The electrical potential V across the membrane changes due to ionic currents
- Sodium current in channels m and h, potassium current n

$$
\begin{aligned}
\frac{\mathrm{d}V}{\mathrm{d}t} &= -\frac{i_{Na} + i_K + i_{Leak}}{Cm} \quad = -\frac{(4 \cdot 10^5 m^3 h + 140)(V - E_{Na})}{Cm} \\
&\quad -\frac{(1200 e^{\frac{-V-90}{50}} + 15 e^{\frac{V+90}{60}}(V - E_K) + 1200 n^4 (V - E_K) + 75(V - E_{An})}{Cm} \\
\frac{\mathrm{d}m}{\mathrm{d}t} &= \frac{100(-V-48)}{\exp((-V-48)/15) - 1}(1-m) - \frac{120(V+8)}{\exp((V+8)/5) - 1} m \\
\frac{\mathrm{d}h}{\mathrm{d}t} &= 170 \exp(\frac{-V-90}{20})(1-h) - \frac{1000}{1 + \exp((-V-42)/10)} h \\
\frac{\mathrm{d}n}{\mathrm{d}t} &= \frac{0.1(-V-50)}{exp((-V-50)/10) - 1}(1-n) - \exp(\frac{-V-90}{80}) n
\end{aligned}
$$

Simulation of Noble model [Noble, D. 1962 Journal of Physiology]



- Successfully predicted several (unknown) phenomena
- Many extensions, models with ≈ 100 states or PDEs [D. Noble, 2012]
- One extension: calcium ion channels
- Tough optimization problems [Lebiedz & Sager, Physical Review Letters, 2005]

Phenomenological approach

- Important & difficult to distinguish between fibrillation and flutter
- Exiting approaches have shortcomings, not real-time feasible

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- Exiting approaches have shortcomings, not real-time feasible

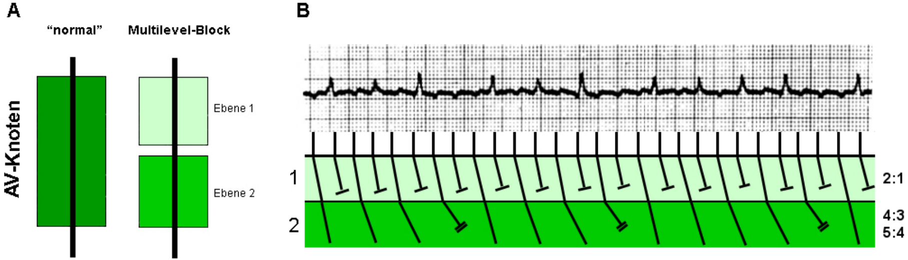
- Idea: let us look at simpler phenomenological models
- Well known in medicine: different kinds of AV blocks

Type Mobitz I

Type Mobitz II (Wenckebach)
Linear prolongation of intervals

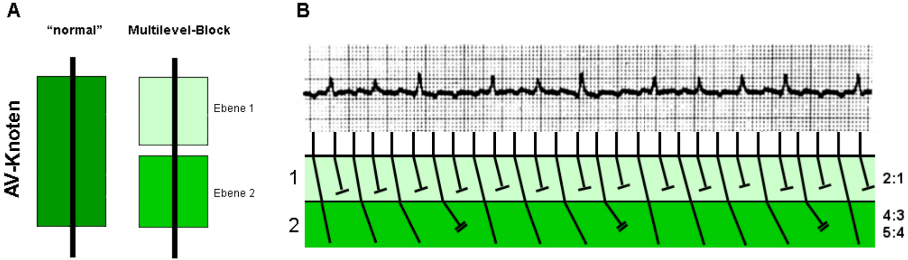
Multilevel approach

- Idea: consider sequential filters of this simple type!



Multilevel approach

- Idea: consider sequential filters of this simple type!



- 1912: Detection of ventricular arrhythmia for atrial flutter
- 1950: Implication of two block levels
- 1975: first EPU indicating localisation of block (= AV node!)
- 1976: Called "Multilevel AV-Block" [Kosowsky et al. 1976 Circulation]
- 1982: last high-impact paper on this topic

Simulation of Mobitz block

Input : n_α incoming time points α_i, transit data τ_{con}
Output: n_β time points β_j after Mobitz–type block
begin
    $j := 1, r := 0$;
    for $i = 1 \ldots n_\alpha$ **do**
        `/* Signal can be processed */`
        if $\alpha_i + \tau_{con} \geq r$ **then**
            $\beta_j = \alpha_i + \tau_{\text{con}}$;
            $r = \beta_j + \tau_{\text{ref}}$;
            $j = j + 1$;
    $n_\beta = j - 1$;

Basic idea of our approach

- Published in [Scholz, E.P., Kehrle, F., Vossel, S., Hess, A., Zitron, E., Katus, H.A., Sager, S., *Discriminating atrial flutter from atrial fibrillation using a multilevel model of atrioventricular conduction*, Heart Rhythm, 2014, 11(5), 877–884]

- Regard the inputs to simulation as optimization variables
  - Regular signal $\Delta\alpha_i = \Delta\alpha$ in atrium
  - Number n_{lvl} and type π^j of levels
  - Transit data $\tau^j_{\text{con}}, \tau^j_{\text{inc}}$ and refrac time τ^j_{ref} for all levels
- Minimize deviation of forward simulation from ventricular data

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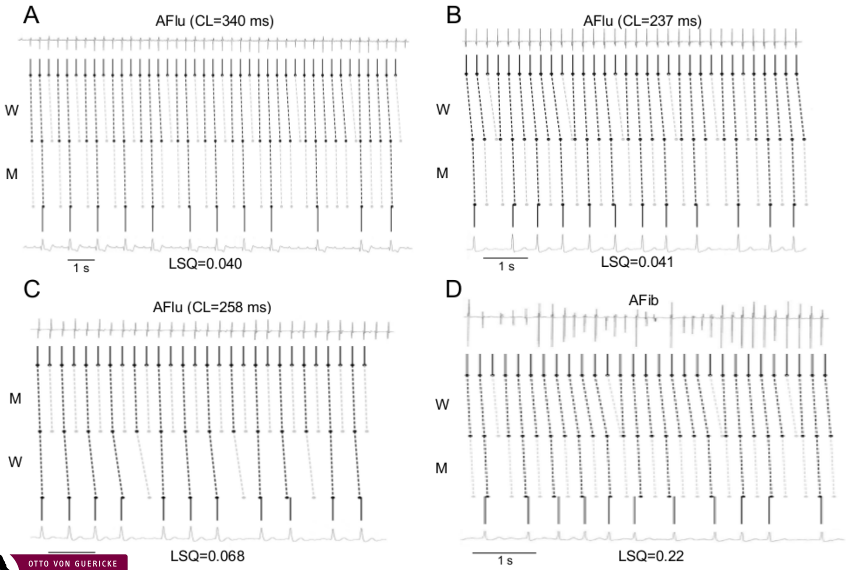
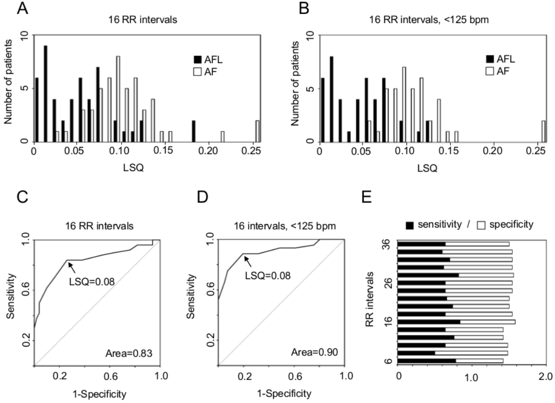
- Verify / falsify hypothesis “atrial flutter”:
  - Objective small $\Rightarrow$ indication for atrial flutter
  - Objective high $\Rightarrow$ indication for atrial fibrillation

Discrimination Examples [Scholz et al., Heart Rhythm, 2014]



Discrimination Results [Scholz et al., Heart Rhythm, 2014]

- Based on ECG data of ≈ 100 patients in Heidelberg
- Comparison to intracardiac measurements, verified by two experts
- Sensitivity 79%, specificity 100%. RR statistics only 58% / 24%!



Mathematical algorithms in clinical practice

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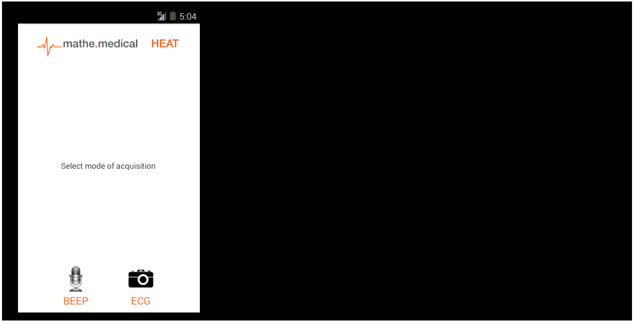

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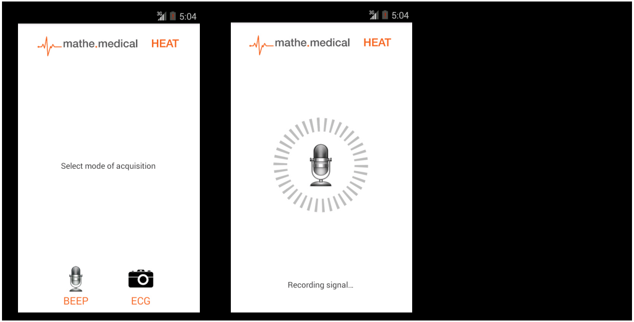

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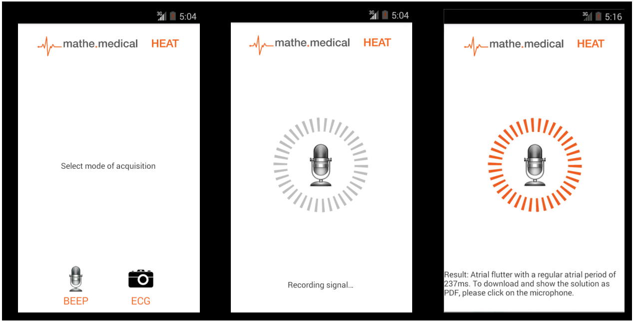
- GmbH founded in Heidelberg 2014
- Dissemination: App is 1 possibility



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6 Summary

K. RINKE · R. BARTSCH · R. FINDEISEN · T. FISCHER · K. RINKE · E. SCHALK · S. SAGER

Mathematical modelling and simulation of Acute Myeloid Leukemia

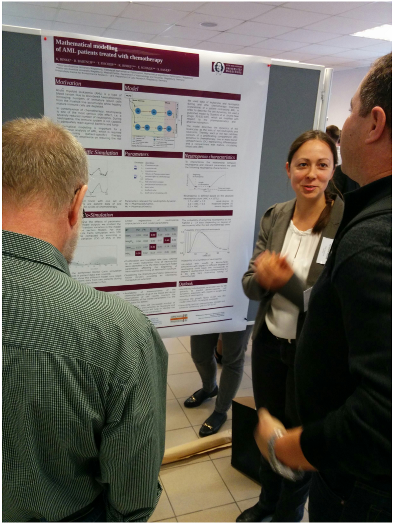
IMPRS ProEng
International Max Planck Research School for Advanced Methods in Process and Systems Engineering
Magdeburg

Klinik für Hämatologie und Onkologie
Otto-von-Guericke Universität Magdeburg

Mathematical Algorithmic Optimization Group
Faculty of Mathematics
Otto-von-Guericke University Magdeburg

Otto von Guericke Universität Magdeburg

Poster session yesterday



General remarks: chemotherapy planning

Obviously cancer growth is a complex dynamic process:

- Dynamic
- Nonlinear
- Delays
- High-dimensional
- Conflicting objectives
- Hard constraints
- Interaction with angiogenesis, immune-system, cell survival, . . .

Intuition: optimal control should be able to help giving decision support for oncologists!

First steps [Engelhart, Lebiedz, Sager, Mathematical Biosciences 2011]

- Literature survey: how useful are models?
- Until today mathematical models far away from reality!

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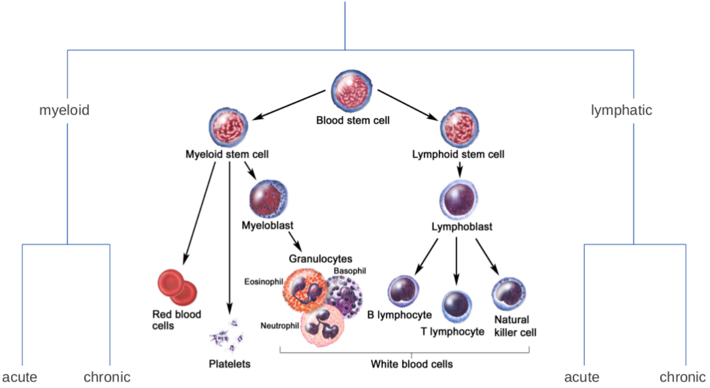
Idea:

- Maximize tumor size at the end with same amount of drugs?
- Allows comparison with minimization $\rightarrow$ potential of timing!

Showed: very dependent on mathematical model, but worth the effort!

Acute myeloid leukemia

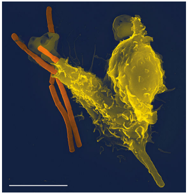
Leukemia: abnormal increase of immature white blood cells called “blasts”
Myeloid: relates to granulocyte precursor (blood-forming) cells in bone marrow
Acute: characterized by rapid increase; bone marrow is unable to produce healthy blood cells and an immediate treatment is required



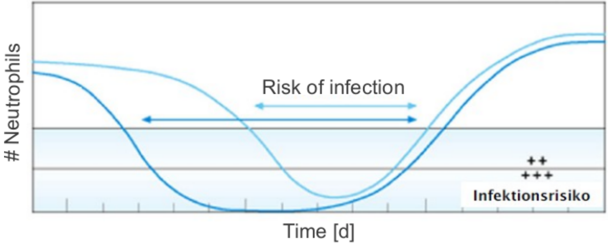
Neutropenia in AML

Neutrophils

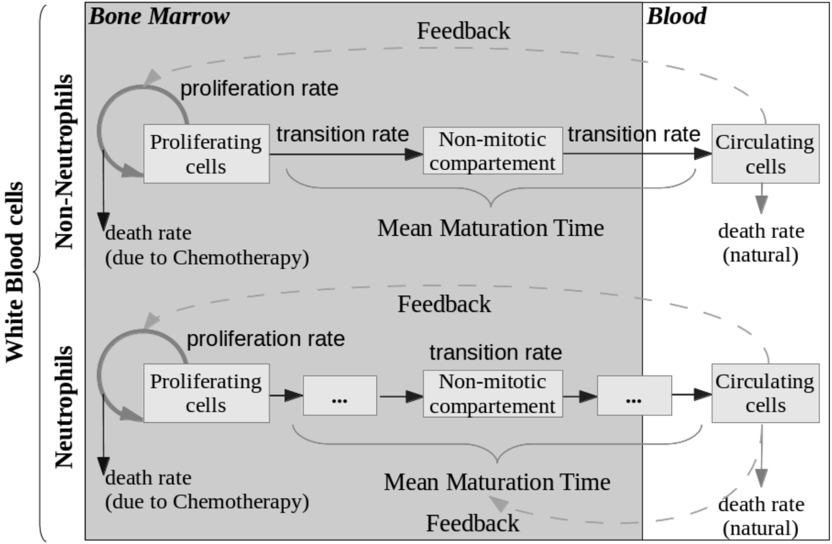
- form an essential part of the innate immune system
- can ingest other cells (e.g. invasive bacteria)



During AML Therapy:



Schematic Mathematical Model [based on Quartino2012, Pefani2013]



Modeling neutropenia during chemotherapy

Pharmacokinetic model

$$\dot{x}_0 = -k_{10}\cdot x_0 - k_{12}\cdot x_0 + k_{21}\cdot x_1 + \text{Chemotherapy}$$
$$\dot{x}_1 = k_{12}\cdot x_0 - k_{21}\cdot x_1$$

Pharmacodynamic model

$$E = \frac{E_{max}\cdot x_0^{hill}}{EC_{50}^{hill} + x_0^{hill}}$$

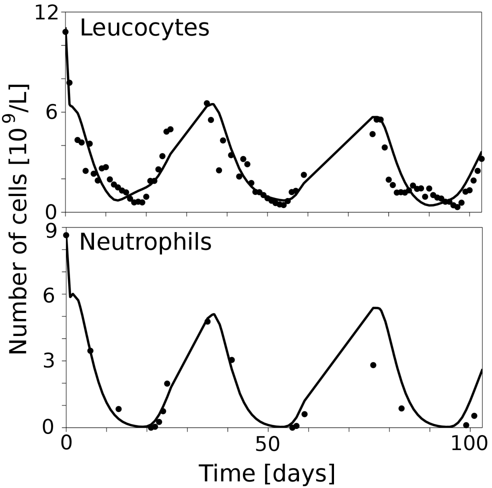
Cell dynamic model

Non-Neutrophils
$$\begin{cases} \dot{x}_2 = k_{NN}\cdot x_2\left(\left(1 - E\right)\left(B_{NN}/x_4\right)^{\gamma_{NN}} - 1\right) \\ \dot{x}_3 = k_{NN}\left(x_2 - x_3\right) \\ \dot{x}_4 = k_{NN}\cdot x_3 - ke_{NN}\cdot x_4 \end{cases}$$

Neutrophils
$$\begin{cases} \dot{x}_5 = k_N\cdot x_5\left(\left(1 - E\right)\left(B_N/x_{n+1}\right)^{\gamma_N} - 1\right) \\ \dot{x}_6 = k_N\left(x_5 - x_6\right) \\ \quad\vdots \\ \dot{x}_n = k_N\left(x_{n-1} - x_n\right) \\ \dot{x}_{n+1} = k_N\cdot x_n - ke_N\cdot x_{n+1} \end{cases}$$

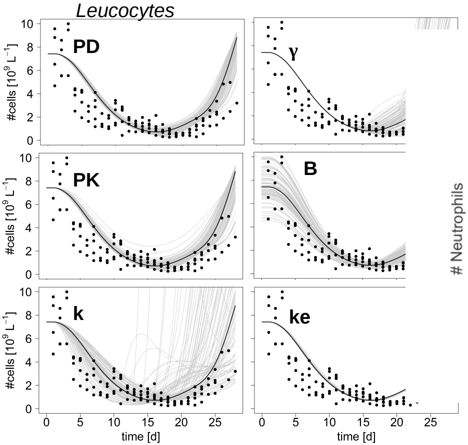
	Parameter	Description
PD	k_{10}	*Elemination rate*
	k_{12}	*transition rate*
	k_{21}	*transition rate*
PK	E_{max}	*maximal effect of chemotherapy*
	$hill$	*hill factor*
	EC_{50}	*half saturation constant*
	k_{NN}	*proliferation/transition rate*
	B_{NN}	*basic value*
	γ_{NN}	*feedback value*
	ke_{NN}	*death rate of circulating cells*
	k_N	*proliferation/transition rate*
	B_N	*basic value*
	γ_N	*feedback value*
	ke_N	*death rate of circulating cells*

Parameter estimation

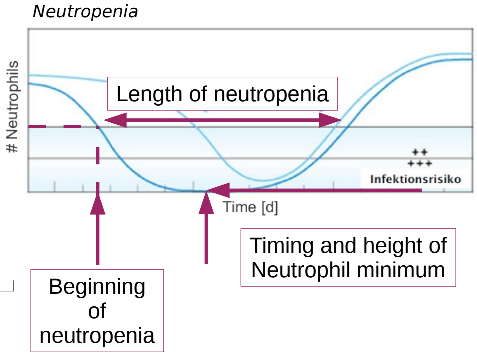


Sensitivity analysis

- Monte Carlo (100 realisations per parameter, CV 25%)



Cardinal events:



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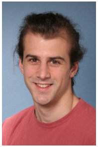
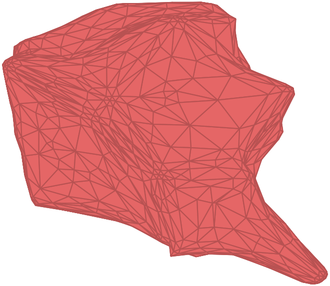
Source detection for extrasystoles



- Certain heart area needs ablation to avoid extrasystoles
- Common practice: measure time delay of wave at several points
- Search (based on experience and trial-and-error) source area

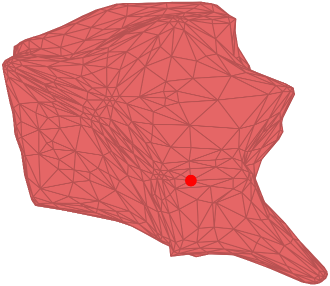
- Idea: can we minimize the number of measurements?

Illustration: the heart chamber



- Cardiac tissue
- Rhythmic heart beat
- Cardiac Excitation

Illustration: the heart chamber



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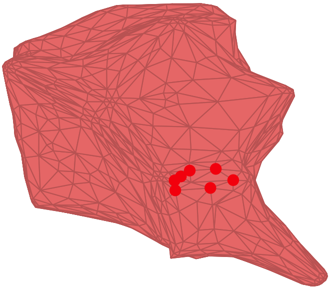

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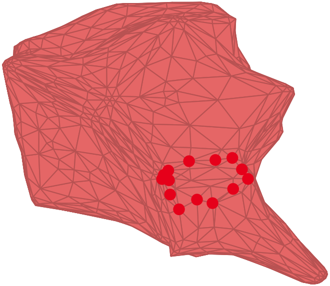

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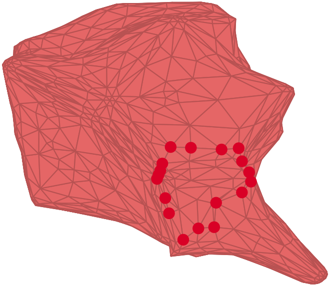

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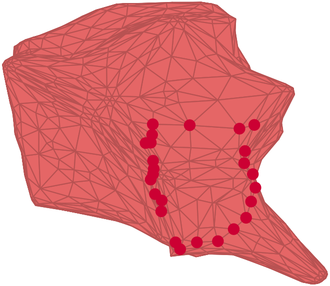

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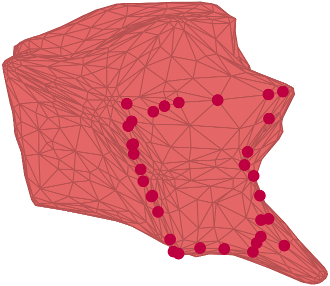

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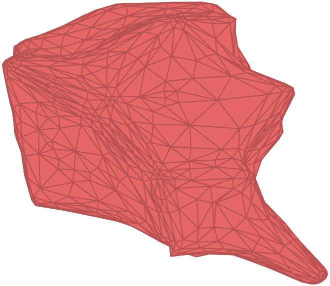

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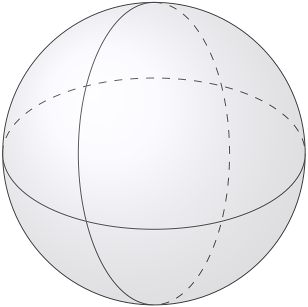

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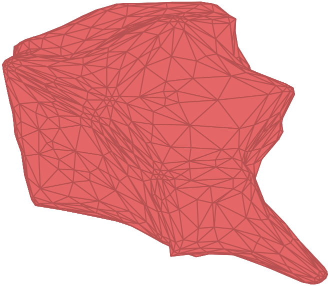

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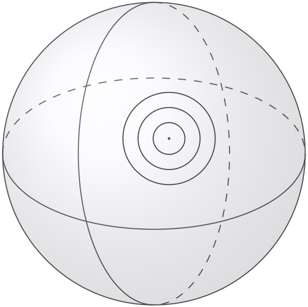
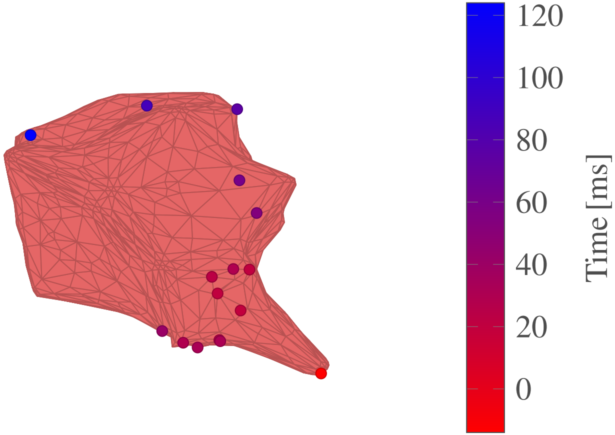
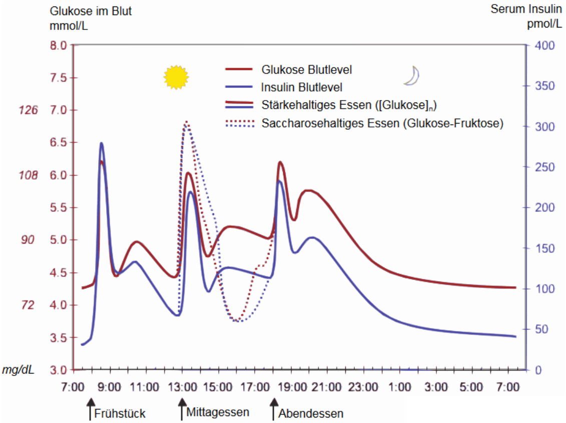


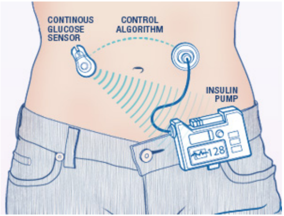
Measurement data



Optimal control of insulin pumps

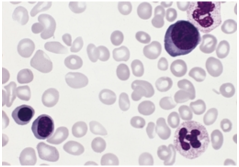
- Automatic control already used in practice
- Do this adaptively / optimally?





Modeling and simulation of Polycythaemia Vera

- neoplasm in which the bone marrow makes too many red blood cells
- only cure: “breathing a vein” (blood-letting)
- difficult scheduling of appointments!



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UNIVERSITÄT
HEIDELBERG
Zukunft. Seit 1386.

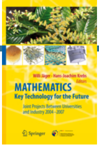
Analysis and Training of Human Decision Making

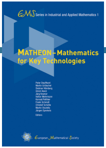
Michael Engelhart, Joachim Funke, Sebastian Sager

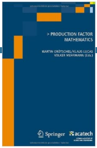
Otto-von-Guericke Universität Magdeburg,
Uni Heidelberg

Będlewo, June 10, 2015

Questions



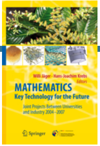


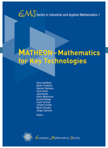


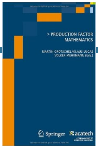
Optimization in practice . . .

- a key technology for 21st century, enabling progress&prosperity

Questions







Optimization in practice …

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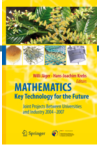
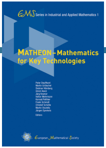
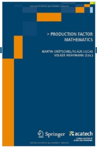
- risks to increase the gap compared to human decision making

Questions







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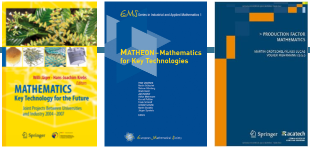
Question: can optimization also be used to train humans?

Questions



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Question: can optimization also be used to train humans?

Questions to you:

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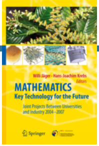
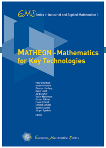
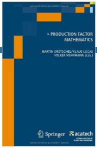
Questions







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- Who thinks to perform better (without algorithms) in finding a good solution to a random optimization problem “within your area of expertise” compared to an average citizen?
- Who thinks this has to do with having seen optimal solutions and sensitivities of similar optimization problems?

Complex Problem Solving

- Humans are asked to solve a given complex problem
- Interest of psychologists: correlation to emotion regulation etc.
- Gets more attention: included in future PISA evaluations

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- Developped in the 1980s (Dörner et al.)

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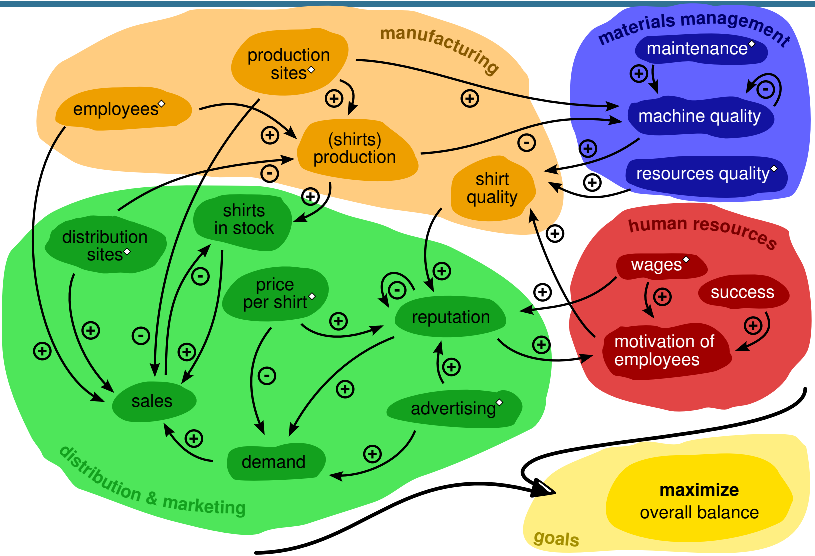
- Participant has to run shirt company
- Round-based scenario
- Aim: maximize overall capital of company

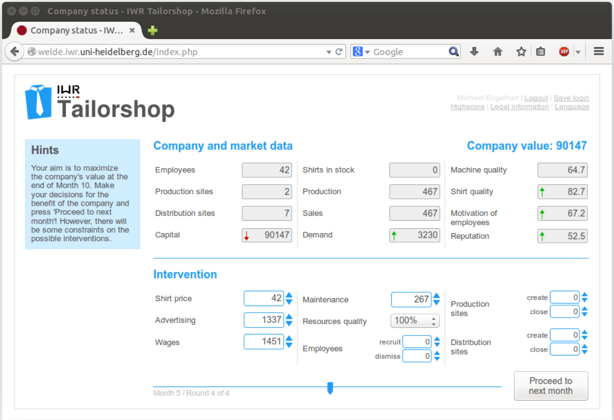
The *IWR Tailorshop*

[Engelhart, Funke, S., Journal of Computational Science, 2013]



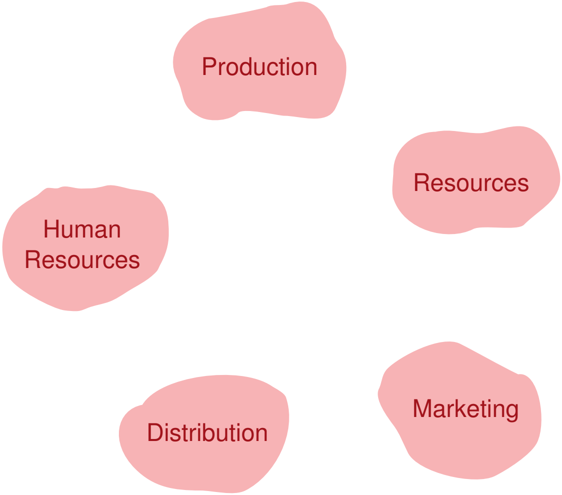
Diamonds indicate influence of participant's decisions.

IWR Tailorshop web interface

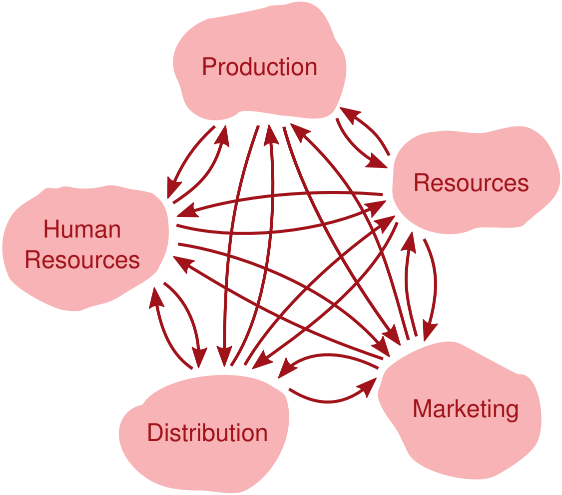


- implementation with AJAX, PHP using a MySQL database
- adaptive interface for mobile devices

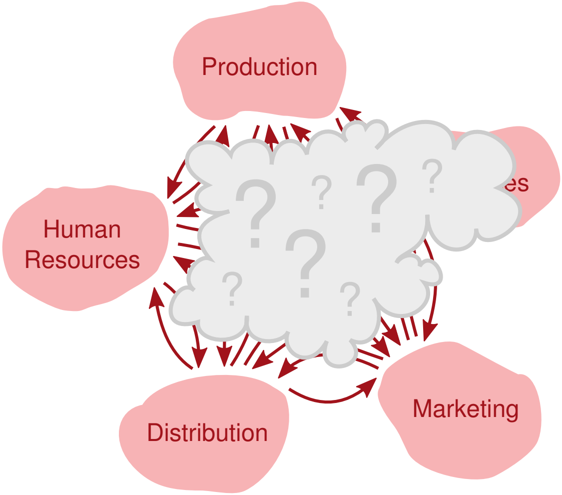
Complex Problems: Complexity



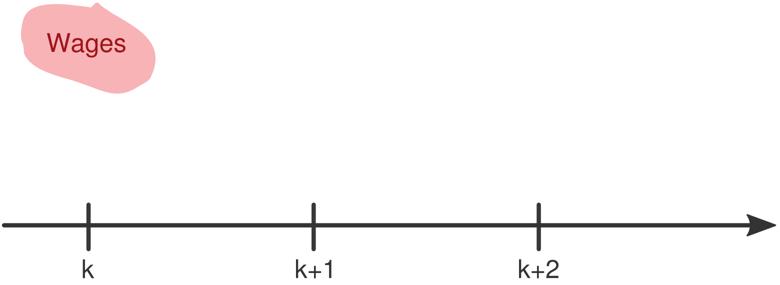
Complex Problems: Interdependence



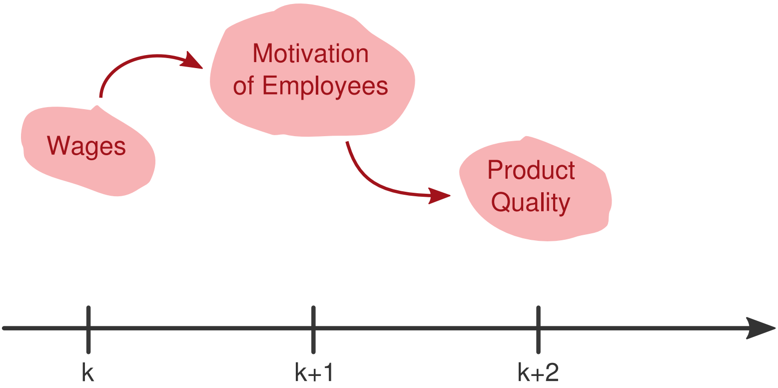
Complex Problems: Intransparency



Complex Problems: Dynamics



Complex Problems: Dynamics



Complex Problems: mixed-integer decisions

- Continuous decisions, e.g., wages
- Discrete decisions, e.g., open/close a distribution site

Optimization and Complex Problem Solving

- First: use optimization to define interesting microworld
- Bounded solution, multiple local maxima, important / unimportant decisions, …

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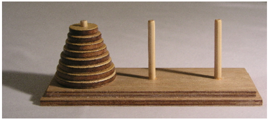
  optimal solution as performance indicator!

Optimization and Complex Problem Solving

- First: use optimization to define interesting microworld
- Bounded solution, multiple local maxima, important / unimportant decisions, ...

- Second:
  optimal solution as performance indicator!
- Simple test-scenarios (e.g. Tower of Hanoi):
  optimal solution known
- Complex test-scenarios:
  optimal solution **unknown**



- Third: can optimal solutions be used for training?

Formulate abstract optimization problem

- Same mathematical model (equations) for all tasks
- Dynamic model with discrete time $k = 0 \dots N$
- Decisions $u_k = u(k)$ and states $x_k = x(k)$
- Scenario specified by initial values x_0 and parameters p

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- First: use optimization to define interesting microworld:

$\rightarrow$ determine initial values x_0 and parameters p

- Second and Third: analysis and training

$\rightarrow$ find decisions u_k to maximize objective function

$\rightarrow$ Compare participant's performance to optimal solution

$\rightarrow$ Provide feedback on better choice for learning

IWR Tailorshop states

States	Variable	Unit
employees	x^{EM}	person(s)
production sites	x^{PS}	site(s)
distribution sites	x^{DS}	site(s)
shirts in stock	x^{SH}	shirt(s)
production	x^{PR}	shirt(s)
sales	x^{SA}	shirt(s)
demand	x^{DE}	shirt(s)
reputation	x^{RE}	—
shirts quality	x^{SQ}	—
machine quality	x^{MQ}	—
motivation of employees	x^{MO}	—
capital	x^{CA}	M.U.

M.U. means monetary units.

IWR Tailorshop controls

Controls	Variable	Unit
shirt price	u^{SP}	M.U./shirt
advertising	u^{AD}	M.U.
wages	u^{WA}	M.U./person
maintenance	u^{MA}	M.U.
resources quality	u^{RQ}	—
recruit/dismiss employees	u^{dEM}/u^{DEM}	person(s)
create/close production site	u^{dPS}/u^{DPS}	site(s)
create/close distribution site	u^{dDS}/u^{DDS}	site(s)

M.U. means monetary units.

IWR Tailorshop example model equations

State equations: $x_{k+1} = G(x_k, x_{k+1}, u_k, p)$

$$x_{k+1}^{EM} = x_k^{EM} - u_k^{dEM} + u_k^{DEM}$$

$$x_{k+1}^{DE} = p^{DE,0} \cdot \exp\left(-p^{DE,1} \cdot u_k^{SP}\right) \cdot \log\left(p^{DE,2} \cdot u_k^{AD} + 1\right) \cdot \left(x_k^{RE} + p^{DE,3}\right)$$

$$x_{k+1}^{SA} = \min\left\{p^{SA,0} \cdot x_{k+1}^{DS} \cdot \log\left(\frac{p^{SA,1} \cdot x_{k+1}^{EM}}{x_{k+1}^{PS} + x_{k+1}^{DS} + p^{SA,2}} + 1\right); x_k^{SH} + x_{k+1}^{PR}; p^{SA,3} \cdot x_{k+1}^{DE}\right\}$$

$$\ldots$$

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Second and Third: Optimization problem

$$
\begin{array}{llcll}
\max\limits_{x,u} & F(x_N) & & & \\
\text{s.t.} & x_{k+1} & = & G(x_k, u_k, p), & k = n_s \dots N-1, \\
 & 0 & \leq & H(x_k, u_k, p), & k = n_s \dots N-1, \\
 & u_k & \in & \Omega, & k = n_s \dots N-1, \\
 & x_{n_s} & = & x_{n_s}^p. &
\end{array}
$$

- Dynamic model with discrete time $k = 0 \dots N$
- Nonconvex mixed-integer nonlinear program

Second and Third: Optimization problem

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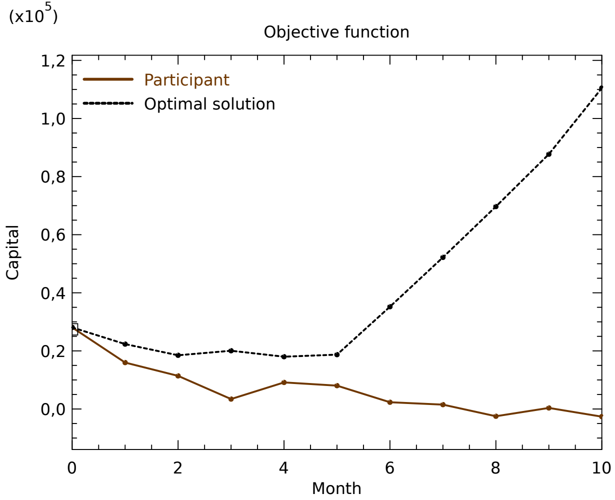
 & x_{n_s} & = & x^p_{n_s}. &
\end{array}
$$

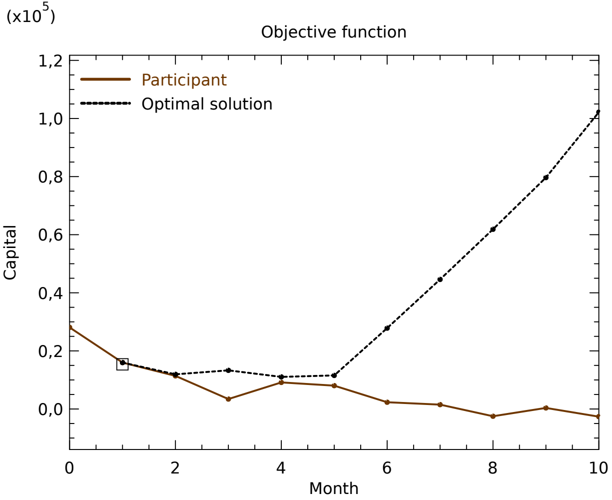
- Dynamic model with discrete time $k = 0 \dots N$
- Nonconvex mixed-integer nonlinear program

- Starting at month n_s with same data $x^p_{n_s}$ as participant
- Need to solve $N-1$ optimization problems per participant

Optimal Solutions



Optimal Solutions



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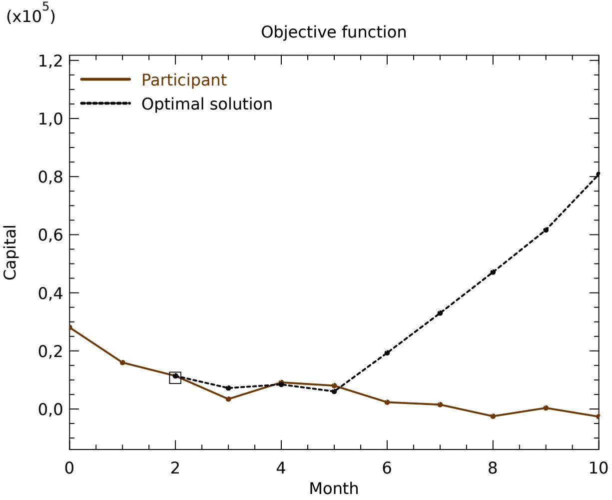

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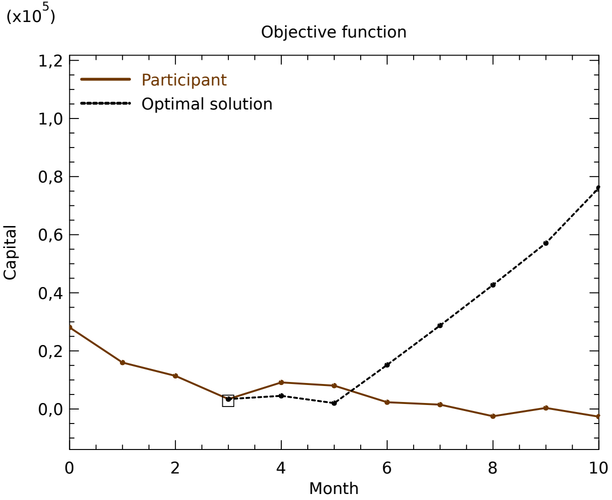
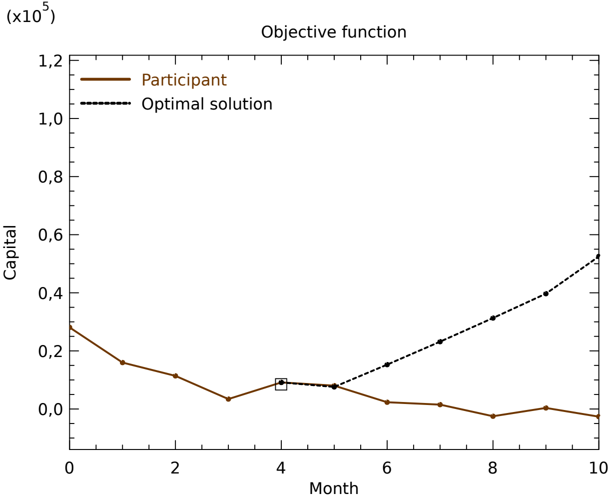
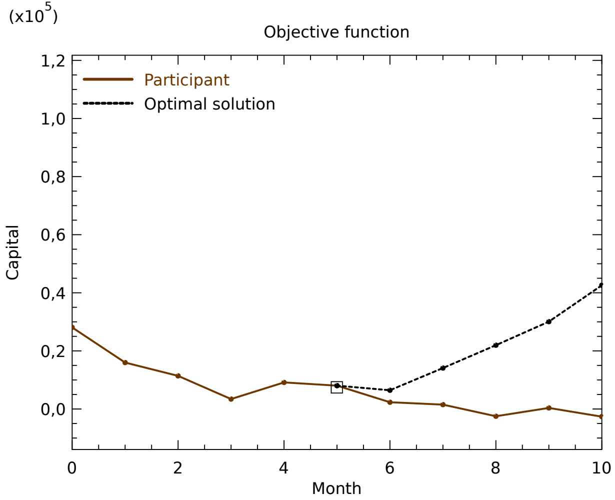


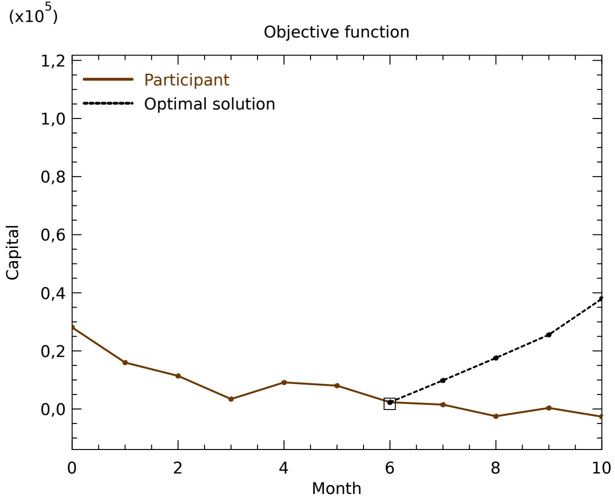
Optimal Solutions



Optimal Solutions



Optimal Solutions



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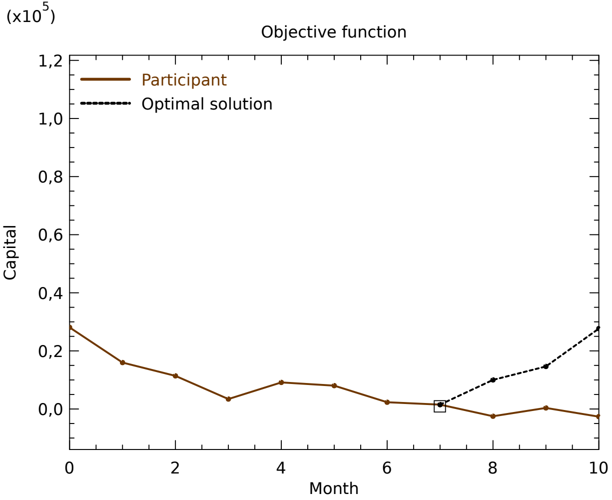

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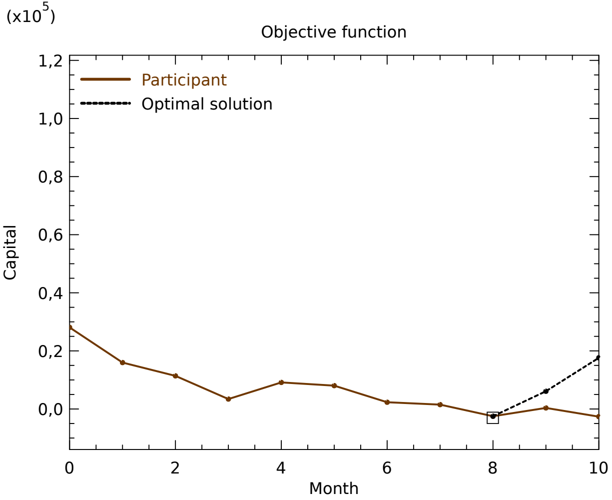

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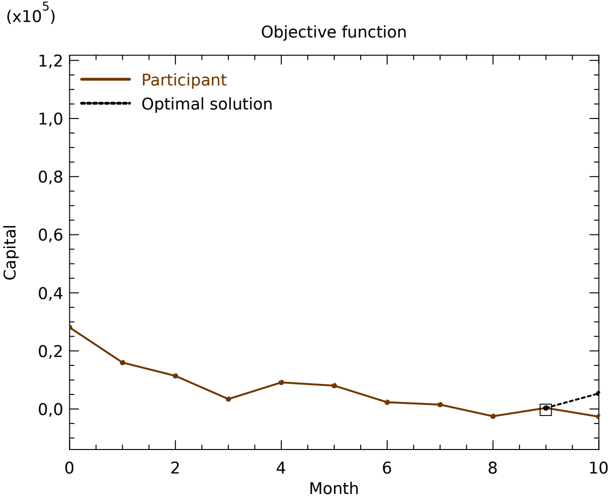
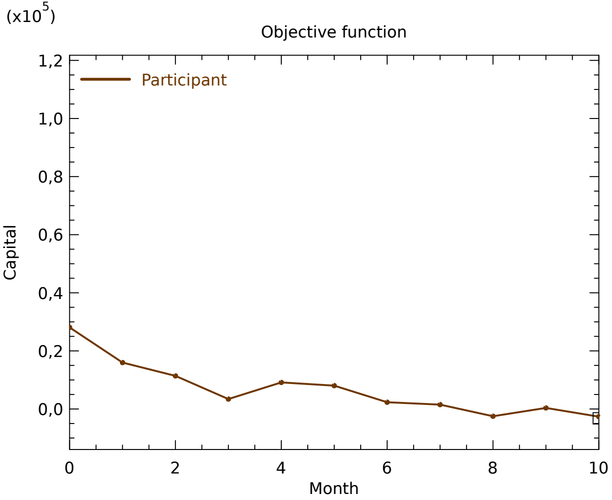


Optimal Solutions



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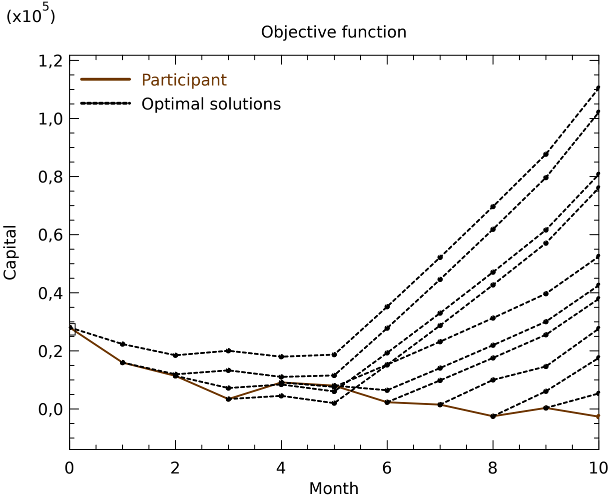
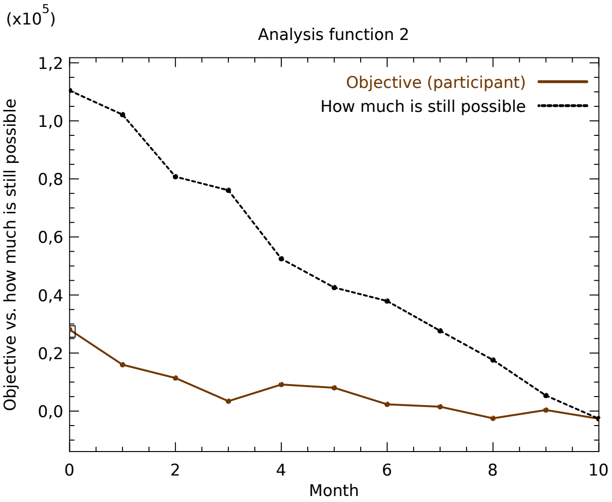


How Much Is Still Possible



Second use of optimization: analysis

Have to work a little (N optimization problems) to get it. But:

- provides objective performance measure
- allows time– and decision–specific analysis of what went wrong

- Details in [S., Barth, Diedam, Engelhart, Funke, *Optimization as an analysis tool for human complex problem solving*, SIAM Journal of Optimization, 2011]

Third use: Optimization-based Feedback

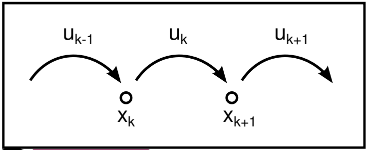
OPTIMIZATION | **FEEDBACK**

A Start optimization in x_{k+1}

Identical to the start values, the participant will have for next decisions u_{k+1}

B Start optimization in x_k, fix decisions u_k with constraints

Artificial constraints for u_k yield sensitivities



1 Highlight variables

55

2 Show arrows

↑ 55

↑ 55

3 Toggle values

55

38

4 Bar chart

Web-based feedback study

- study conducted Nov/Dec 2013
- *IWR Tailorshop* web interface
- **participants** recruited in lectures and social networks
- 100 complete datasets

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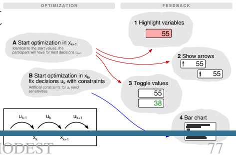
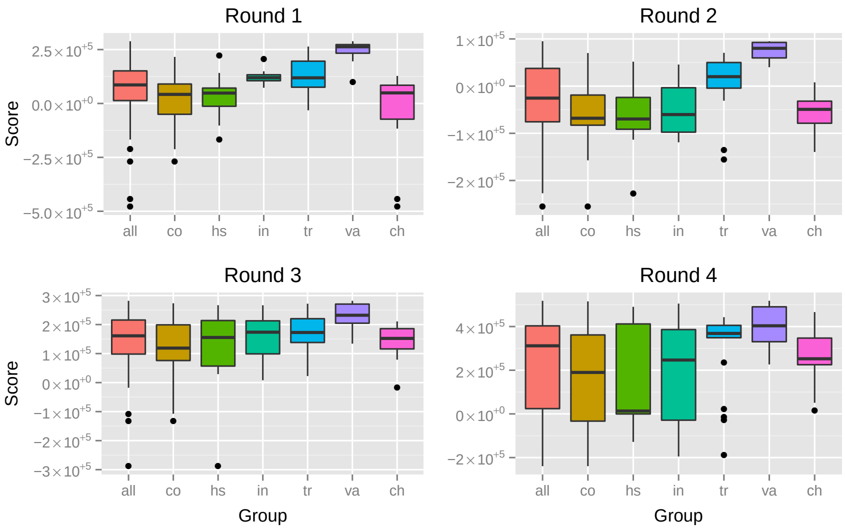
  - **2 rounds** (= 20 months) **without** (goal: performance)

- Feedback in 6 **randomized groups**:
  control, highscore, highlight, arrows, value, chart



Study results: feedback groups



ontrol, hi=highscore, in=highlight variable, tr=show arrows, va=show values, ch=sensitivity chart)

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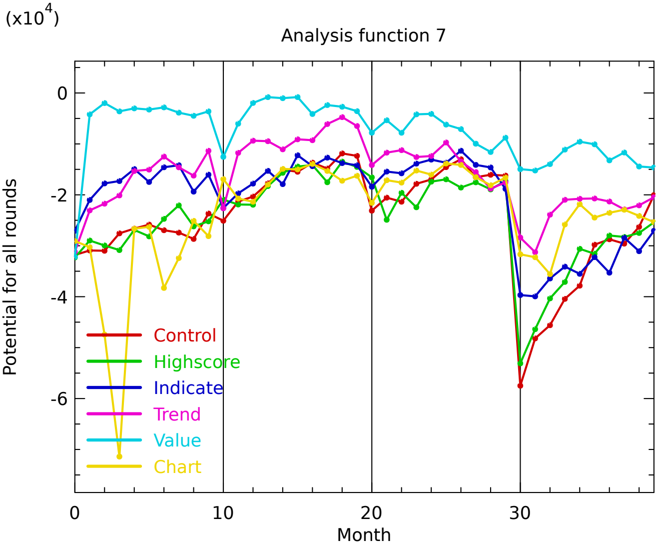
Study results: use of potential



Hypothesis		Proved
(A)	participants with opt.-based feedback perform better overall	✓
(B)	participants with opt.-based feedback perform better in feedback rounds	✓
(C)	participants with opt.-based feedback perform better in performance rounds	✓
(D)	control group performs worst	—
(E)	control group performs worse than opt.-based groups in performance rounds	✓
(F)	trend group performs best overall	—
(G)	trend group performs best in performance rounds	—
(H)	value group performs best in feedback rounds	✓

Hypothesis		Proved
(I)	value group performs better in feedback rounds, worse in performance rounds	(✓)
(J)	participants with high BFI-10 values perform worse/better	—
(K)	participants who play computer games regularly perform better	✓
(L)	participants interested in economics perform better	✓
(M)	participants who solve problems systematically perform better	✓
(N)	control group needs more time than opt.-based feedback groups	—
(O)	well-performers know more about the model	✓

	Hypothesis	Proved
(P)	participants who know much about the model, perform well	✓
(Q)	value group knows less, trend group knows most about the model	—/✓
(1)	participants learn to control the model	✓
(2)	learning function is approximately logarithmic	—
(3)	optimization-based feedback groups learn faster	(✓)
(4)	*value* group does almost not learn in feedback rounds	✓
(5)	*trend* group learns fastest	✓

Hypothesis		Proved
(6)	participants who learn much, perform well	?
(7)	participants who perform well, learned much	?
(8)	participants with high model knowledge learned more	✓
(9)	initial performance is not important for final performance	✓
(10)	chart group suffered from feedback	(✓)

IWR Tailorshop: global solutions?

- Nonconvex mixed-integer nonlinear program
- Need global solutions! Can we use `Couenne` or `Baron`?

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- **But:** for $N = 1$: 0.9 sec,
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  for $N = 3$: $\gg$ 10 min …
- Interesting effects (investment paying off) for $N \geq 5$.

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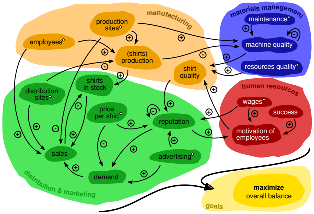
  for $N = 2$: 12 sec,
  for $N = 3$: $\gg$ 10 min …
- Interesting effects (investment paying off) for $N \geq 5$.

- Developed tailored decomposition approach for tight bounds (fast)
- [Engelhart, Funke, S., *A Decomposition Approach for a New Test-Scenario in Complex Problem Solving*, **Journal of Computational Science**, 2013]

Summary: optimization-based training



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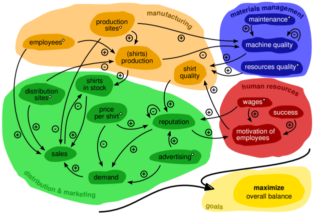

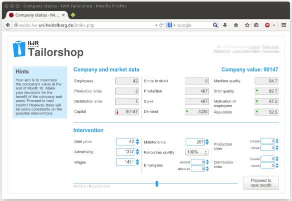

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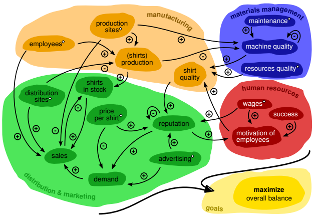
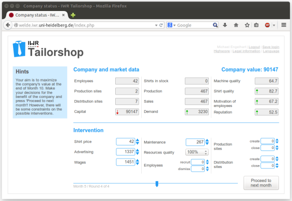
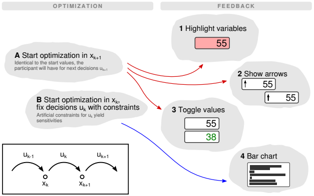
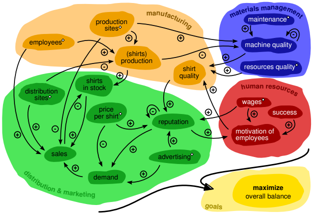
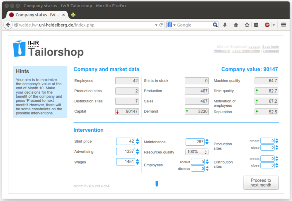


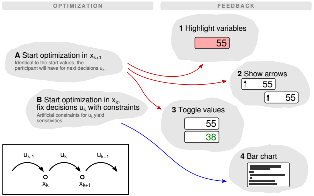




Summary: optimization-based training







- Optimization 1) to design microworld 2) to analyze 3) to train
- Online study with 100 participants:
  - Participants **with optimization feedback** in training rounds **perform better** and **have more model knowledge**!
  - But depends on type of feedback! General effect? → future work!
- Goal: use same approach for analysis and training of medical decision making

Summary

- Systematic & synergetic modeling and optimization approach
- Three uses: get good microworld, analysis, and training

Summary

- Systematic & synergetic modeling and optimization approach
- Three uses: get good microworld, analysis, and training
- Challenging MINLPs solved by tailored decomposition
- Web-based study with 100 complete datasets:
  optimization-based feedback can make a significant difference

- Details can be found in:

- [Engelhart, Funke, S., *A Decomposition Approach for a New Test-Scenario in Complex Problem Solving*, **Journal of Computational Science**, 2013]
- [S., Barth, Diedam, Engelhart, Funke, *Optimization as an analysis tool for human complex problem solving*, **SIAM Journal of Optimization**, 2011]
- [Engelhart, PhD thesis, University of Heidelberg, 2015]

Outline

1 Introduction to MODEST

2 Decoding complex cardiac arrhythmia

3 Optimal control for leukemia treatment

4 Possible other clinical applications

5 Training
- Complex Problem Solving
- Optimization Approach to CPS
- Optimization-based Feedback
- Results of a Web-based Feedback Study

6 Summary

Summary

- Interested in dynamic processes
- Approach:
  - Find mathematical model (variables, equations, constraints)
  - Calibrate parameters to fit measurements (patient-specific)
  - Optimize over degrees of freedom
  - Interact with medical doctor

Issues in mixed-integer optimal control

DAE Constraints
Gerdts&Sager, 2012

PDE Constraints
Hante&Sager, 2013

Vanishing Constraints
Jung, Kirches, Sager, 2013

Combinatorial Constraints
Jung, Kirches, Sager, 2011

Real-time optimization
Kirches et al., 2010

Mixed-integer optimal control
based on Outer Convexification

Global Optimization
Sager, Claeys, Messine, 2014

Multi-objective
Logist et al., 2010

MINLPs
Belotti, Kirches et al., 2013

Decomposition
Engelhart et al., 2013

Uncertainty
Huschto et al., 2011

Experimental Design
Sager, 2013

IWR Tailorshop objective function

$$x_{k+1}^{CA} = p^{CA,0} \cdot \Bigg(x_k^{CA} + \left(x_{k+1}^{SA} \cdot u_k^{SP}\right) - \left(x_{k+1}^{EM} \cdot u_k^{WA}\right) - u_k^{AD} - \left(x_{k+1}^{SH} \cdot p^{CA,6}\right)$$

$$- \left(x_{k+1}^{PR} \cdot u_k^{RQ} \cdot p^{CA,3}\right) - u_k^{MA} \qquad - \left(x_k^{PS} \cdot p^{CA,4}\right) - \left(x_k^{DS} \cdot p^{CA,5}\right)$$

$$+ \left(u_k^{dPS} \cdot p^{CA,1}\right) + \left(u_k^{dDS} \cdot p^{CA,2}\right) - \left(u^{DPS} \cdot p^{CA,7}\right) - \left(u^{DDS} \cdot p^{CA,8}\right) \Bigg)$$

Objective function:

$$F(x_N) = x_N^{CA}$$

IWR Tailorshop objective function

$$\tilde{x}_{k+1}^{CA} = p^{CA,0} \cdot \Bigg(x_k^{CA} + \left(x_{k+1}^{SA} \cdot u_k^{SP}\right) - \left(x_{k+1}^{EM} \cdot u_k^{WA}\right) - u_k^{AD} - \left(x_{k+1}^{SH} \cdot p^{CA,6}\right)$$

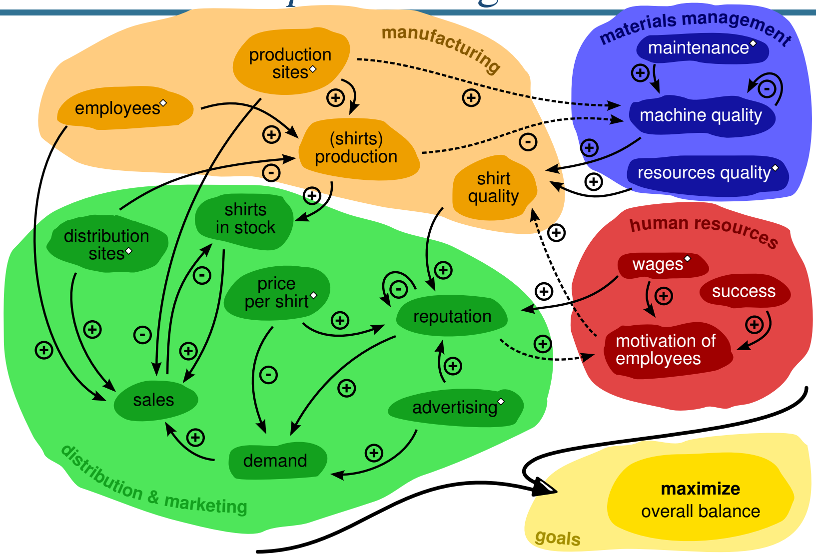
$$+ f_1\left(x_{k+1}^{PR}, u_k^{SQ}\right) \qquad + f_2\left(x_k^{PS}, x_k^{DS}, x_{k+1}^{PR}, x_{k+1}^{EM}\right)$$

$$+ \left(u_k^{dPS} \cdot p^{CA,1}\right) + \left(u_k^{dDS} \cdot p^{CA,2}\right) - \left(u^{DPS} \cdot p^{CA,7}\right) - \left(u^{DDS} \cdot p^{CA,8}\right) \Bigg)$$

Objective function:

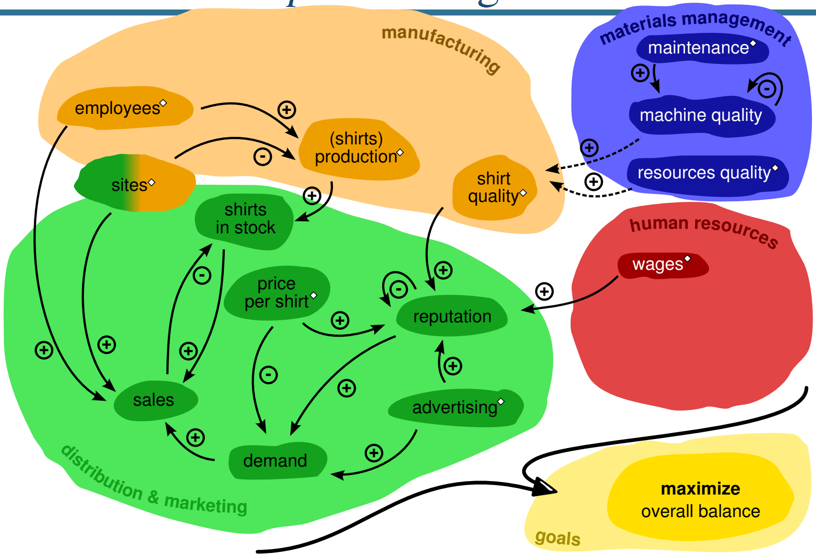
$$\tilde{F}(x_N) = \tilde{x}_N^{CA}$$

The *IWR Tailorshop*: reducing the model



Diamonds indicate (influence of) free variables.

The *IWR Tailorshop*: reducing the model



Diamonds indicate (influence of) free variables.

Decomposition approach

- **Idea:** split problem up to get (at least) good upper bound
- Comparable to Lagrangian Relaxation approaches

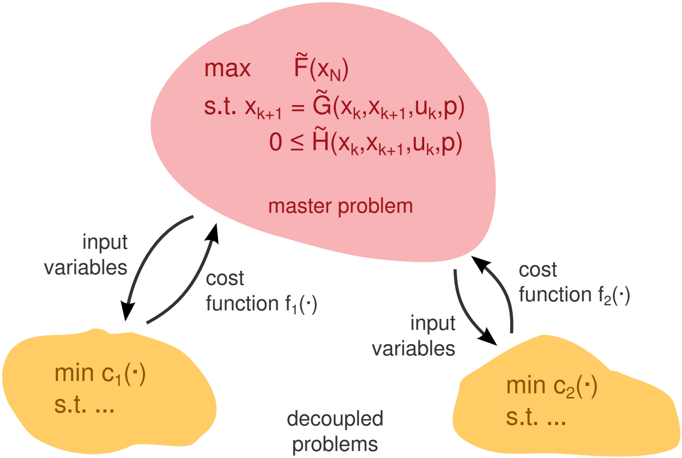
- One master problem, several decoupled problems
- Coupled via the newly introduced cost functions f_1 and f_2 for the decoupled problems

Decomposition approach

$$\begin{aligned} \max \quad & F(x_N) \\ \text{s.t. } x_{k+1} &= G(x_k, x_{k+1}, u_k, p) \\ 0 &\le H(x_k, x_{k+1}, u_k, p) \end{aligned}$$

original problem

Decomposition approach



Decomposition approach

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$$0 \leq H(x_k, x_{k+1}, u_k, p)$$

$$\leq$$

decomposition

$$\max \quad \tilde{F}(x_N)$$
$$\text{s.t. } x_{k+1} = \tilde{G}(x_k, x_{k+1}, u_k, p)$$
$$0 \leq \tilde{H}(x_k, x_{k+1}, u_k, p)$$

min $c_1(\cdot)$
s.t. ...

min $c_2(\cdot)$
s.t. ...

Original problem vs. decomposition

n_x	Original*	Decomposition*	Gap in %
1	189750.1	198795.0	4.5 %
2	195925.0	208899.3	6.2 %
3	202285.2	219306.8	7.8 %
4	208836.2	230026.5	9.2 %
5	215583.8	241067.7	10.6 %
6	222533.7	252440.2	11.8 %
7	229692.2	264153.9	13.0 %
8	237065.4	276219.0	14.2 %
9	244659.8	288646.0	15.2 %
10	252482.0	301445.9	16.2 %

* Using *Bonmin* (local solver) for original, *Couenne* (global solver) for decomposition.

Computation times similar ($\ll$1 min).