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Decoding Complex Cardiac Arrhythmia using Mathematical Optimization

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Sebastian Sager, Florian Kehrlé, Eberhard Scholz

Decoding complex cardiac arrhythmia using mathematical optimization

June 26, 2014 — NETCO2014, Tours



Klaus Tschira Stiftung
gemeinnützige GmbH



UniversitätsKlinikum Heidelberg



Issues in mixed-integer optimal control

DAE Constraints

Gerdts&Sager, 2012

PDE Constraints

Hante&Sager, 2013

Vanishing Constraints

Jung, Kirches, Sager, 2013

Real-time optimization

Kirches et al., 2010

Combinatorial Constraints

Jung, Kirches, Sager, 2011

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

Uncertainty

Huschto et al., 2011

Decomposition

Engelhart et al., 2013

Experimental Design

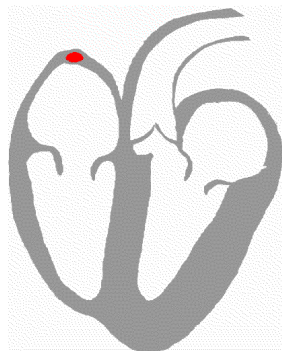
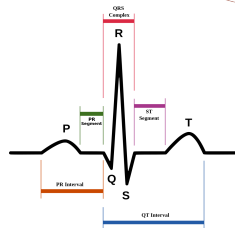
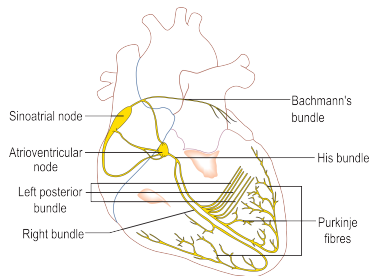
Sager, 2013



Outline

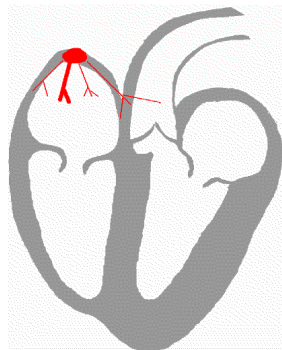
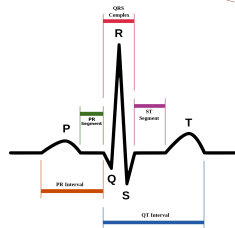
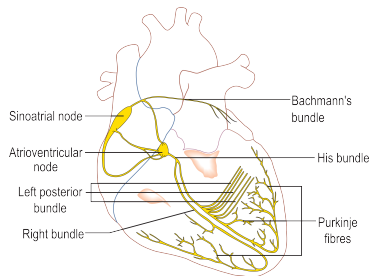
- ① Medical Problem
- ② Mathematical Approaches
- ③ Inverse Simulation of Multilevel AV block
- ④ Algorithmic Approaches
- ⑤ Modeling of the Optimization Problem
- ⑥ Numerical Results and Summary

Reminder: the human heart [Images: Wikipedia]



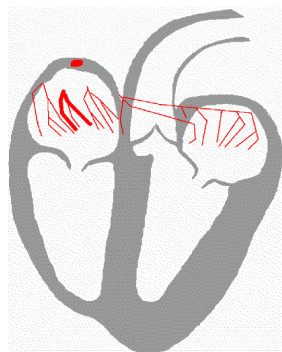
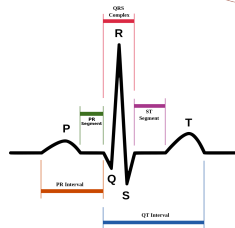
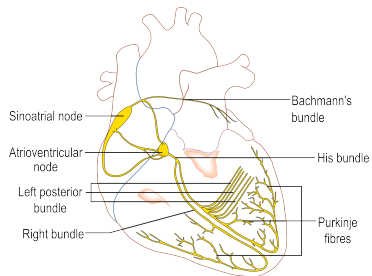
Pacemaker signal in sinoatrial node

Reminder: the human heart [Images: Wikipedia]



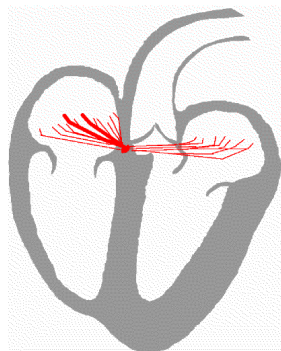
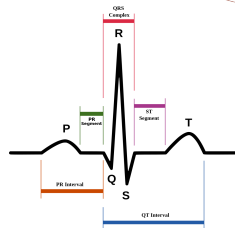
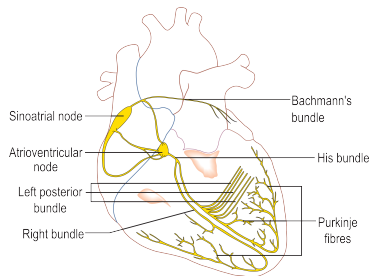
Atrial chambers

Reminder: the human heart [Images: Wikipedia]



P Atrial depolarization → atrial contraction

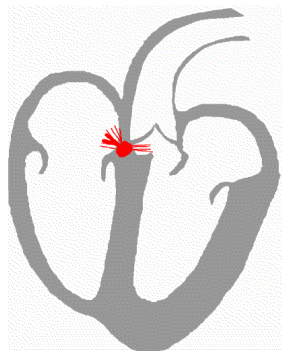
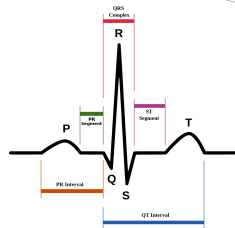
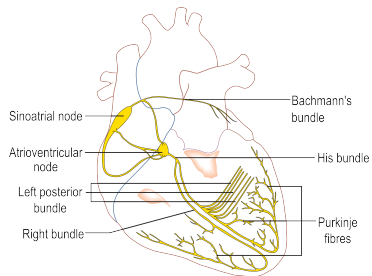
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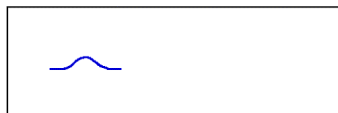
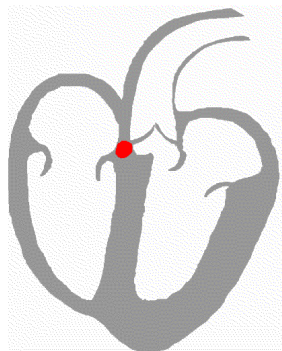
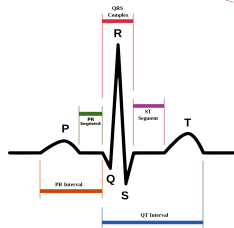
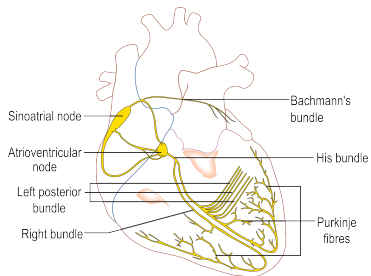


Reminder: the human heart [Images: Wikipedia]



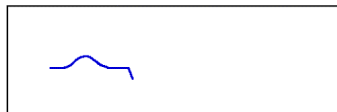
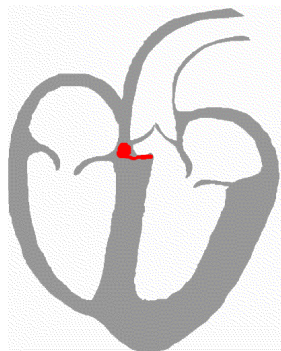
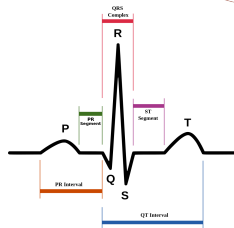
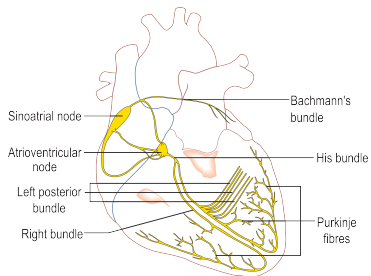
P Atrial depolarization → atrial contraction

Reminder: the human heart [Images: Wikipedia]



PR Atrioventricular node

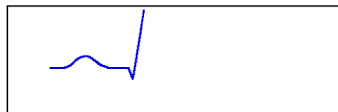
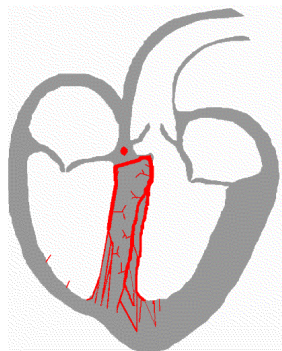
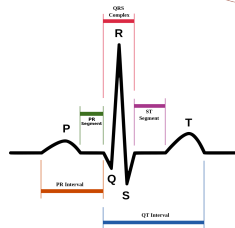
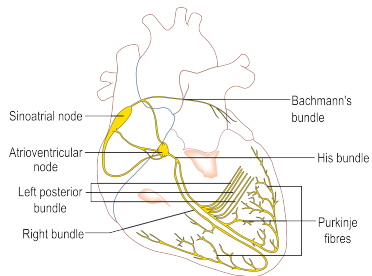
Reminder: the human heart [Images: Wikipedia]



Q Depolarization of the interventricular septum

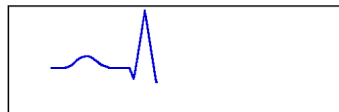
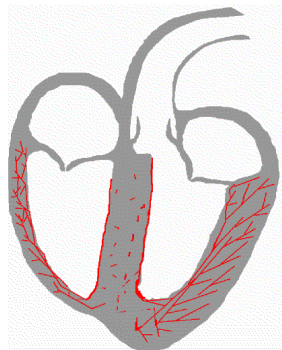
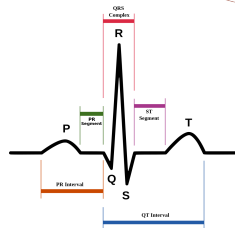
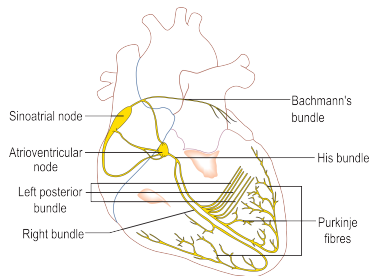


Reminder: the human heart [Images: Wikipedia]



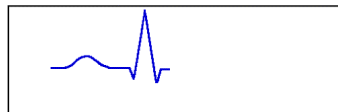
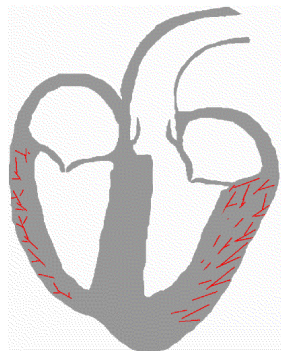
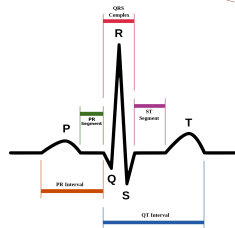
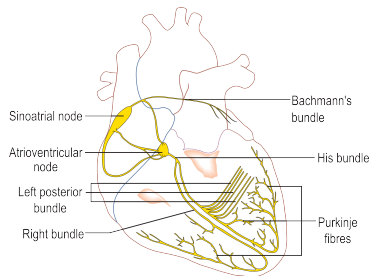
R Polarization of the ventricles

Reminder: the human heart [Images: Wikipedia]



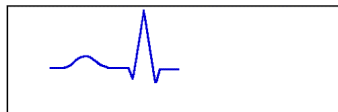
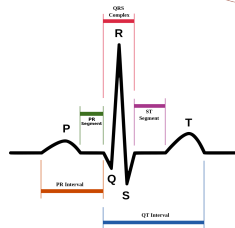
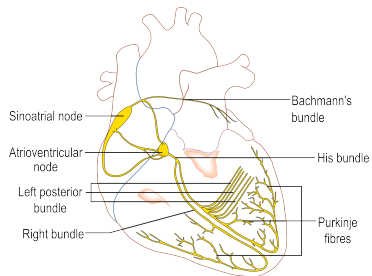
S (De)polarization

Reminder: the human heart [Images: Wikipedia]



S Depolarization, contraction

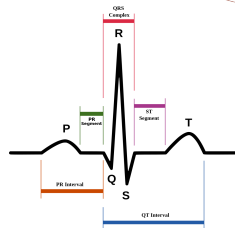
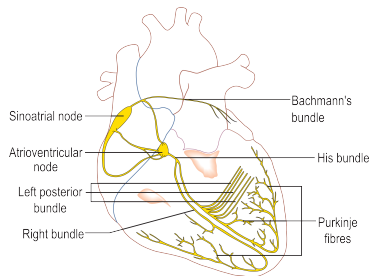
Reminder: the human heart [Images: Wikipedia]



ST Depolarization, contraction

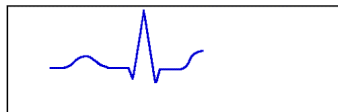
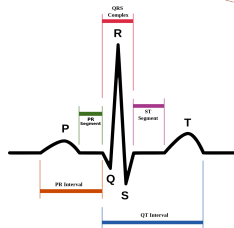
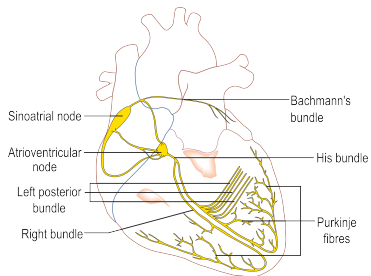


Reminder: the human heart [Images: Wikipedia]



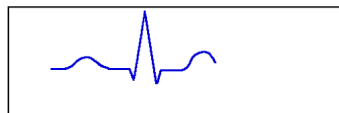
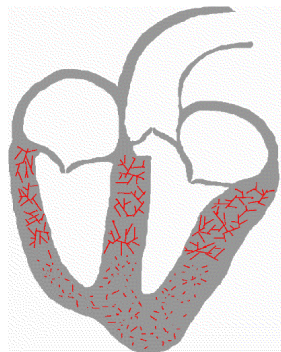
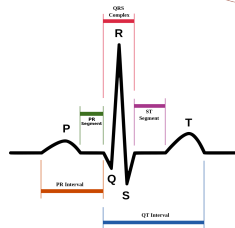
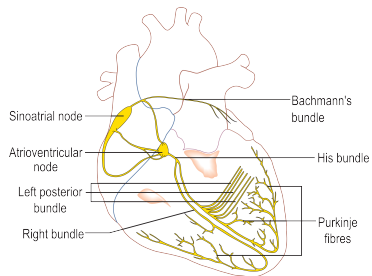
ST Depolarization, contraction

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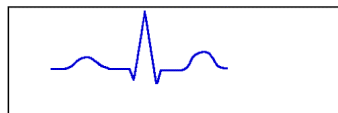
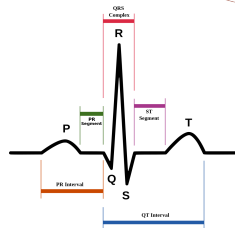
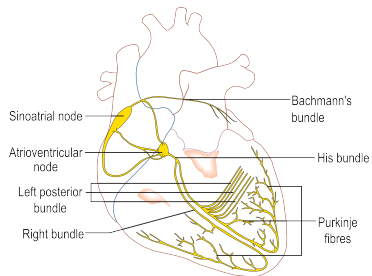
T Secondary excitation

Reminder: the human heart [Images: Wikipedia]



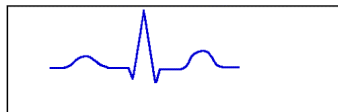
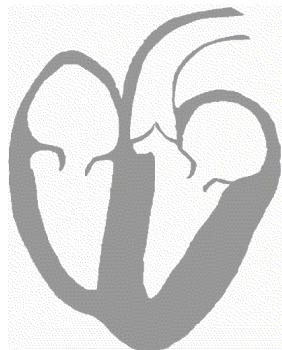
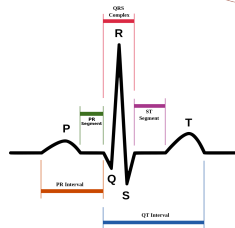
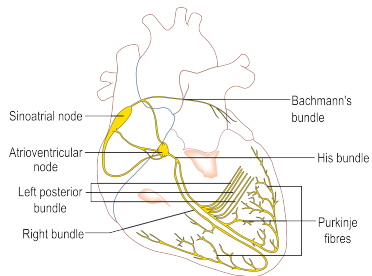
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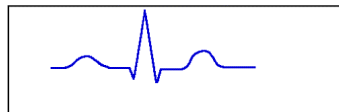
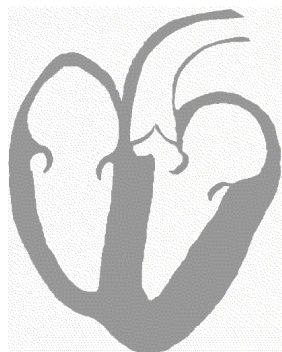
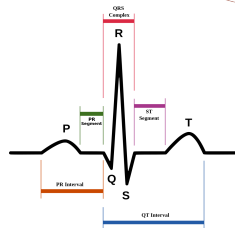
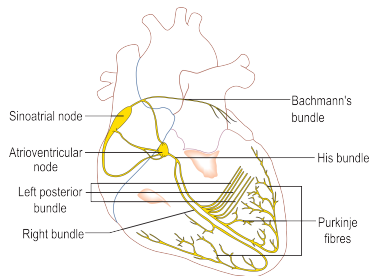
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Rest

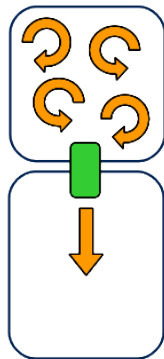
Reminder: the human heart [Images: Wikipedia]



Rest

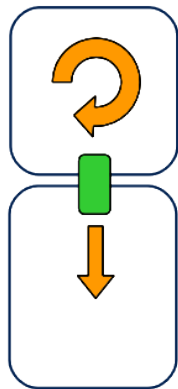
Atrial Fibrillation

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



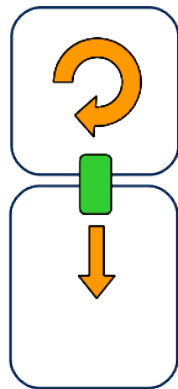
Atrial Flutter

- 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?!?

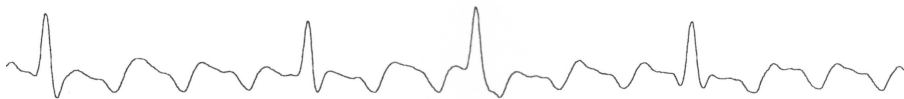
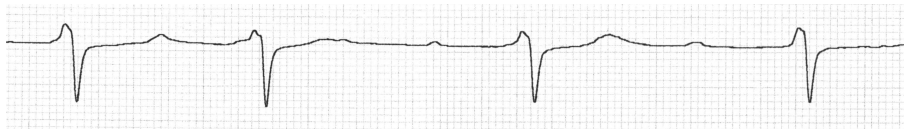


Summary of the decision problem

- 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?

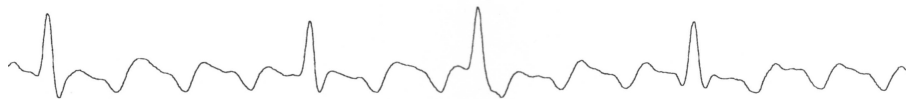
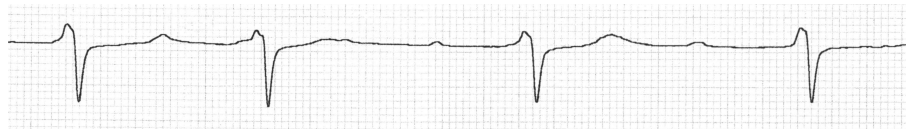


So, what do you think?



Fibrillation or Flutter?

So, what do you think?

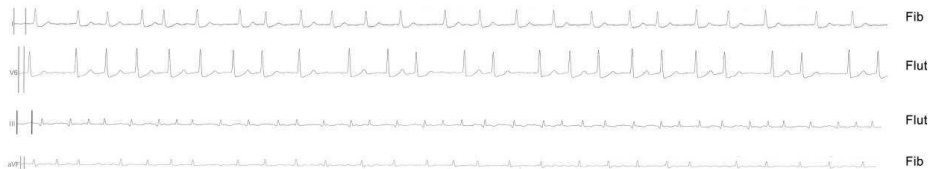


Flutter, Flutter, Fibrillation

So, what do you think?

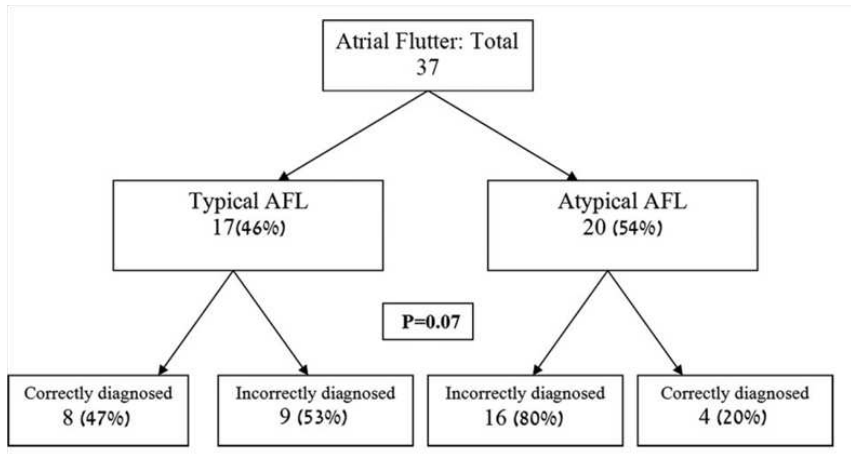


So, what do you think?

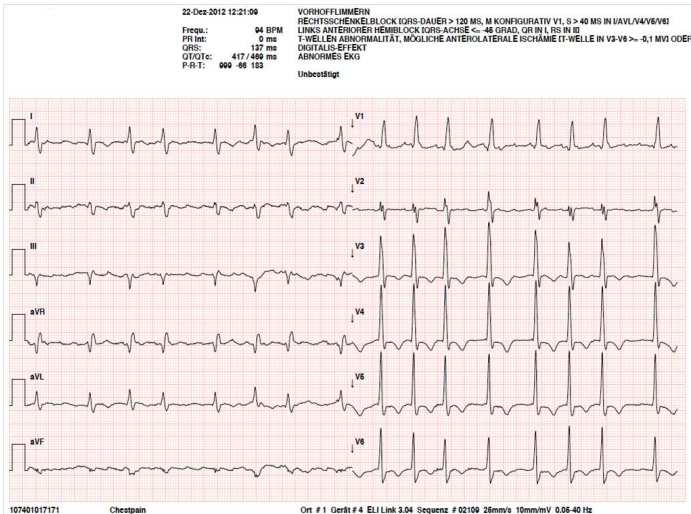


So, what do experts think?

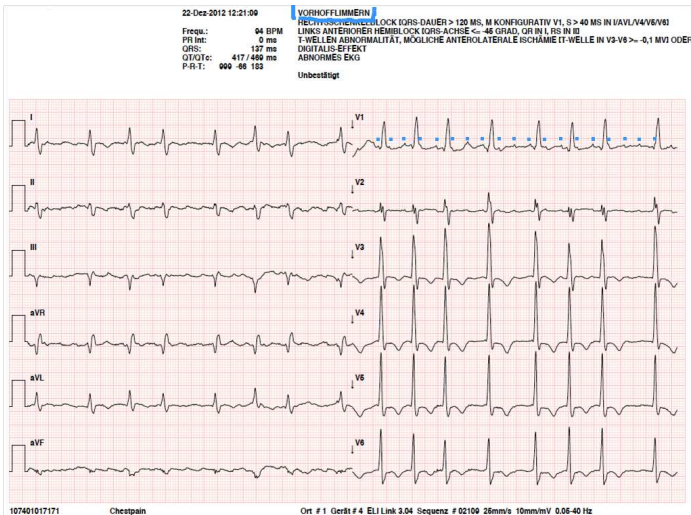
[Shiyovich et al. 2010 Am J Med Sci]



So, what do (current) expert systems think?



So, what do (current) expert systems think?



Inverse Simulation

I never guess. It is a shocking habit — destructive to the logical faculty.

[Arthur Conan Doyle, The Sign of the Four, 1890]

How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?

[Arthur Conan Doyle, The Sign of the Four, 1890]



Outline

- ① Medical Problem
- ② Mathematical Approaches**
- ③ Inverse Simulation of Multilevel AV block
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Large variety of different approaches possible

Mostly based on statistical approaches of RR-intervals:

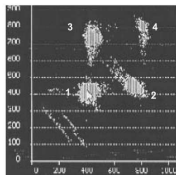
- Fourier transforms
- Wavelets
- Machine learning
- Bayesian logic
- Nonlinear time series analysis



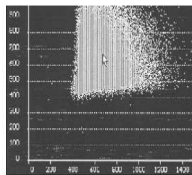
Large variety of different approaches possible

Mostly based on statistical approaches of RR-intervals:

- Fourier transforms
- Wavelets
- Machine learning
- Bayesian logic
- Nonlinear time series analysis
- Clustering of RR times [Esperer et al. 2008 ANE]



AFlu

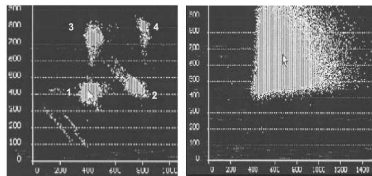


AFib

Large variety of different approaches possible

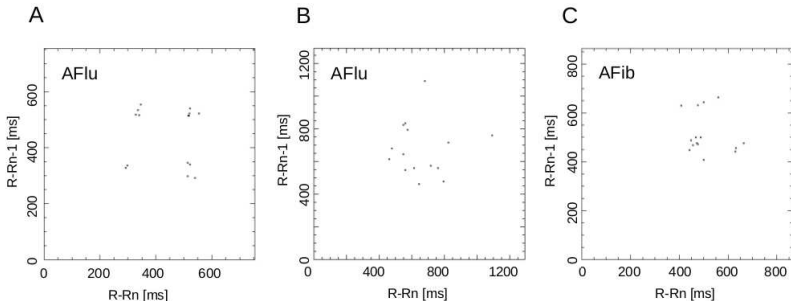
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AFlu

AFib



Understand what is going on

- Statistical approaches don't work for short ECGs
- Statistical approaches don't give insight
- Alternative?

Understand what is going on

- Statistical approaches don't work for short ECGs
- Statistical approaches don't give insight
- Alternative?

- ECG measures electrical potential
- Can we model this on a single cell level?

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

$$\frac{dV}{dt} = -\frac{i_{Na} + i_K + i_{Leak}}{Cm} = -\frac{(4 \cdot 10^5 m^3 h + 140)(V - E_{Na})}{Cm} - \frac{(1200e^{\frac{-V-90}{50}} + 15e^{\frac{V+90}{60}})(V - E_K) + 1200n^4(V - E_K) + 75(V - E_{An})}{Cm}$$

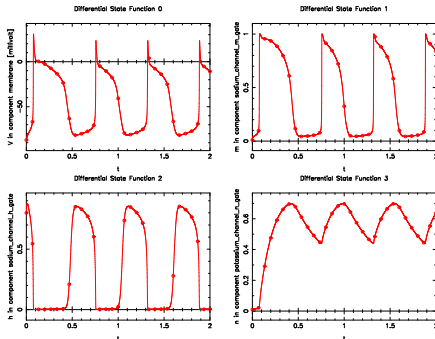
$$\frac{dm}{dt} = \frac{100(-V - 48)}{\exp((-V - 48)/15) - 1}(1 - m) - \frac{120(V + 8)}{\exp((V + 8)/5) - 1}m$$

$$\frac{dh}{dt} = 170 \exp\left(\frac{-V - 90}{20}\right)(1 - h) - \frac{1000}{1 + \exp((-V - 42)/10)}h$$

$$\frac{dn}{dt} = \frac{0.1(-V - 50)}{\exp((-V - 50)/10) - 1}(1 - n) - \exp\left(\frac{-V - 90}{80}\right)n$$



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 [Lebediez & Sager, Physical Review Letters, 2005]



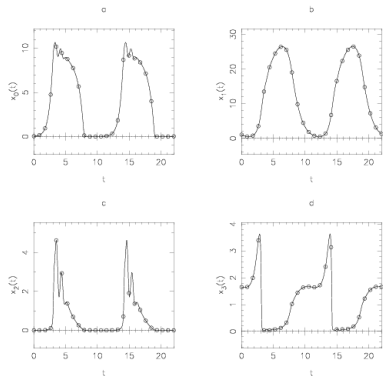
Calcium concentration in cells, [U. Kummer et al., 2002]

- State: a activated G-proteins
- State: b active phospholipase C
- State: c intracellular calcium
- State: d intra-ER calcium
- Control: timing of inhibitors [Lebiedz, S. et. al., Physical Review Letters, 2005]

$$\min_{y, w, w_{\max}} \int_{t_0}^{t_f} \|y(t) - \hat{y}\|^2 dt \quad \text{subject to}$$
$$\begin{aligned}\dot{a} &= k_1 + k_2 a - k_3 \frac{a b}{a+K_4} - k_5 \frac{a c}{a+K_6} \\ \dot{b} &= k_7 a - k_8 \frac{b}{b+K_9} \\ \dot{c} &= k_{10} \frac{b c d}{d+K_{11}} + k_{12} b + k_{13} a - k_{14} \frac{c}{w c+K_{15}} - k_{16} \frac{c}{c+K_{17}} + \frac{d}{10} \\ \dot{d} &= -k_{10} \frac{b c d}{d+K_{11}} + k_{16} \frac{c}{c+K_{17}} - \frac{d}{10} \\ y(t_0) &= y_0, \quad w(t) \in \{1, w_{\max}\}, \quad y(t) = (a, b, c, d)^T\end{aligned}$$

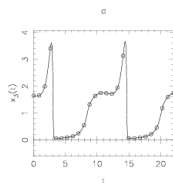
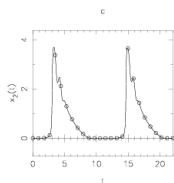
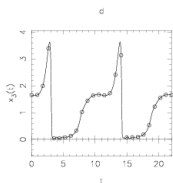
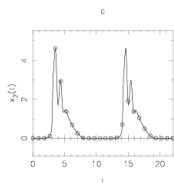
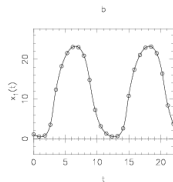
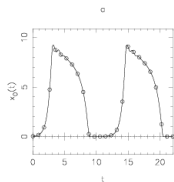
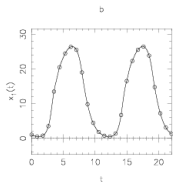
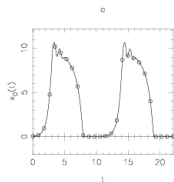


Simulation



$$w(t) = 1$$

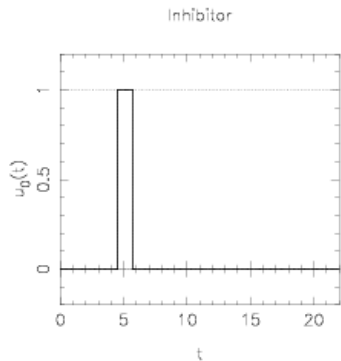
Simulation



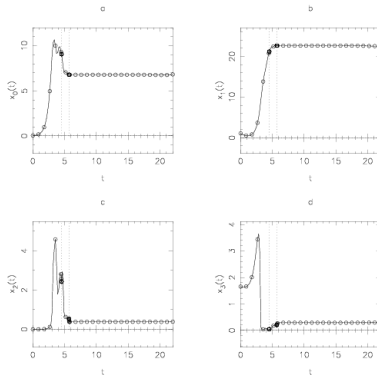
$$w(t) = 1$$

$$w(t) = W_{\max}$$

Integer solution

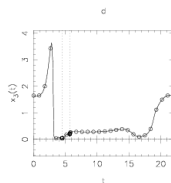
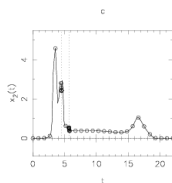
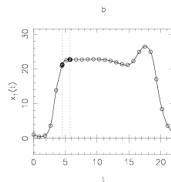
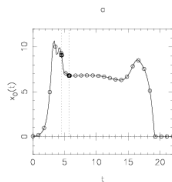
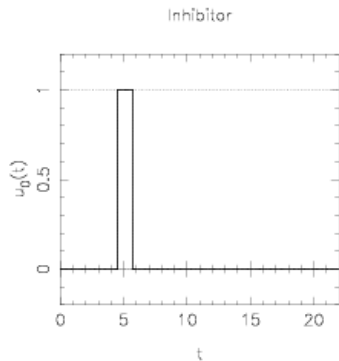


Control



States

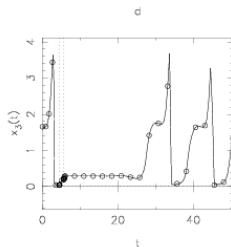
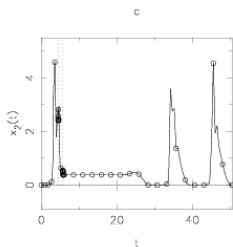
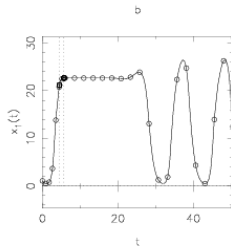
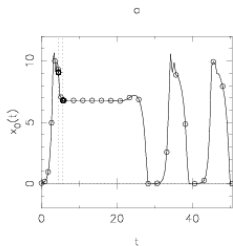
Integer solution - after small change



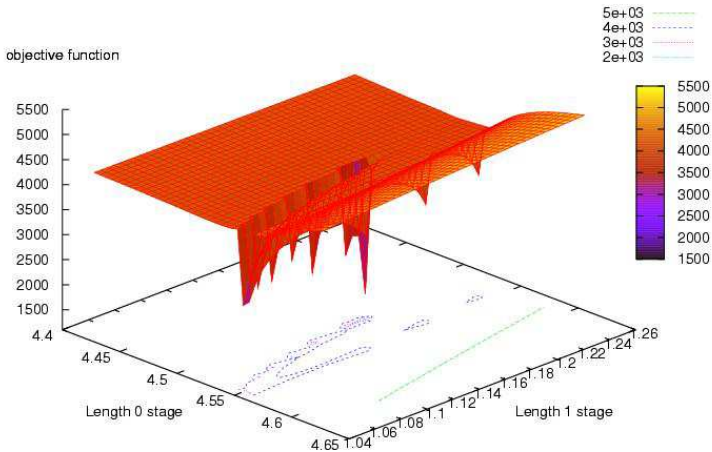
Control - 10^{-3} too early

States

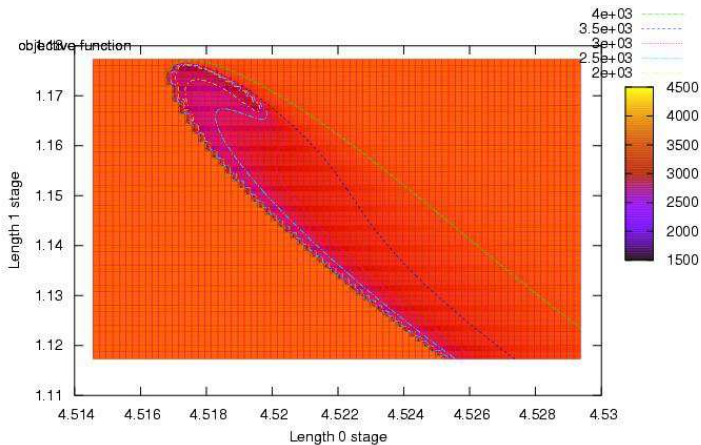
State is instable



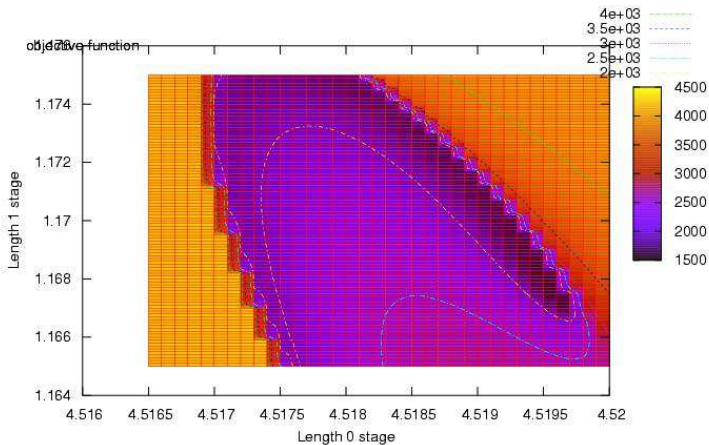
Objective function - scale 10^{-1}



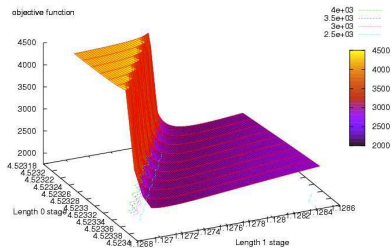
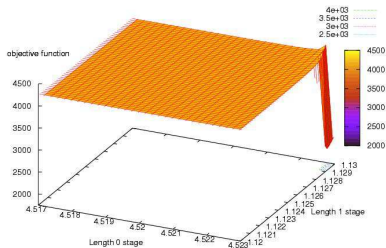
Objective function - scale 10^{-2}



Objective function - optimum



Objective function - border



Understand what is going on

- Single cell level
 - Survey [D. Noble, 2012]: ≈ 100 models with significant contributions
 - Electrical action potential well understood

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 - Can use cellular automata: very simple setting (2d, homogeneous cells) show wave propagation patterns depending on probabilities of excitation by neighboring cells [M. Small, Dynamics of Biological Systems, CRC, 2012]

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- But: personalized medicine impossible (geometry etc.)!!



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- ① Medical Problem
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- ⑥ Numerical Results and Summary

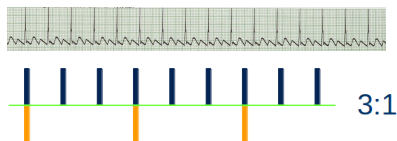
Phenomenological approach

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Phenomenological approach

- Important & difficult to distinguish between **fibrillation** and **flutter**
- Existing 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



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 $i = 1 \dots n_\alpha$ **do**

 /* Signal can be processed */

if $\alpha_i + \tau_{con} \geq r$ **then**

$\beta_j = \alpha_i + \tau_{con}$

$r = \beta_j + \tau_{ref}$

$j = j + 1$

$n_\beta = j - 1$

end

Simulation of Wenckebach block

Input : n_α incoming signal α_i , transit data τ_{con} , τ_{inc} , refrac time τ_{ref}

Output: n_β time points β_j after Wenckebach-type block

begin

```
   $j := 1, c := 0$ 
```

```
  for  $i = 1 \dots n_\alpha$  do
```

```
    /* Signal can be processed                               */
```

```
    */
```

```
    if  $\tau_{con} + c \cdot \tau_{inc} \leq \tau_{ref}$  then
```

```
       $\beta_j = \alpha_i + \tau_{con} + c \cdot \tau_{inc}$ 
```

```
       $j = j + 1, c = c + 1$ 
```

```
    /* Signal can not be processed                           */
```

```
    */
```

```
    else
```

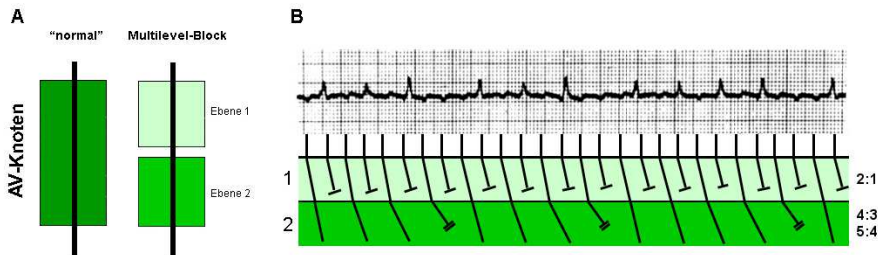
```
       $c = 0$ 
```

```
   $n_\beta = j - 1$ 
```

end

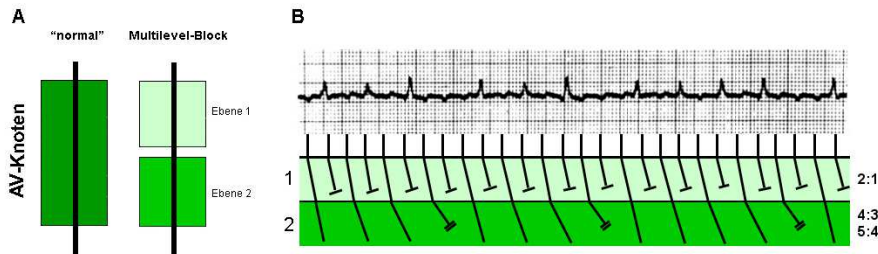
Multilevel approach

- Idea: consider **sequential filters** of this simple type!



Multilevel approach

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- 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



Basic idea of our approach

- Published in [Scholz, E.P., Kehrlé, 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]

(*Heart Rhythm* has impact factor 5.2)

- 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 $\tau_{con}^j, \tau_{inc}^j$ and refrac time τ_{ref}^j for all levels
- Minimize deviation of forward simulation from ventricular data



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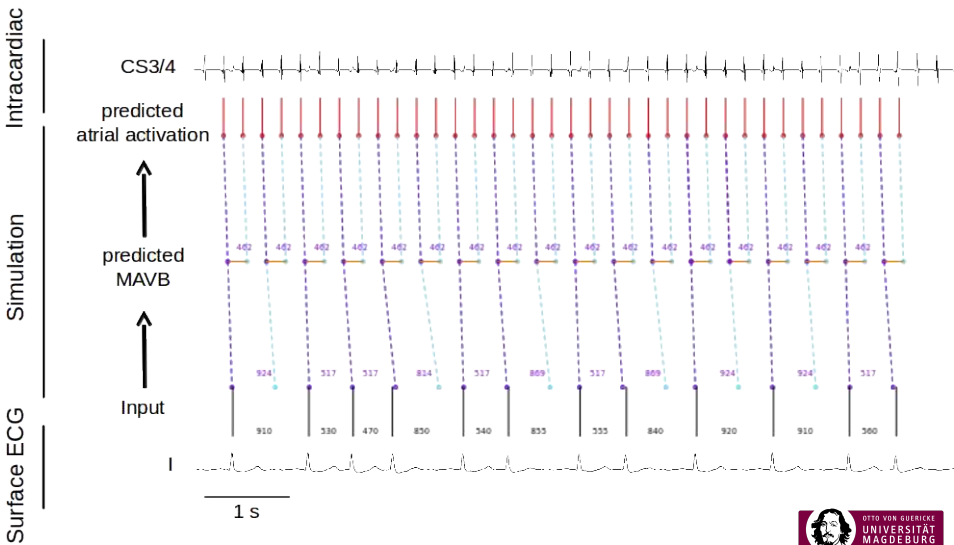
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- Minimize deviation of forward simulation from ventricular data
- Verify / falsify hypothesis “atrial flutter”:
 - Objective small \Rightarrow indication for **atrial flutter**
 - Objective high \Rightarrow indication for **atrial fibrillation**



Visualizing example of our approach



Outline

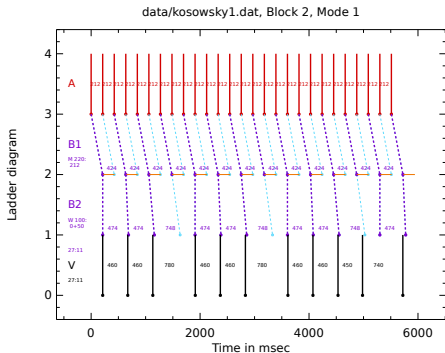
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Optimization-driven simulation

How to find the best values for τ_{con}^j , τ_{inc}^j , τ_{ref}^j , $\Delta\alpha$, π^j ? We implemented

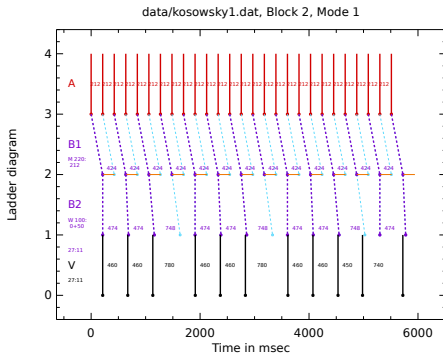
- 1 Enumeration on discrete grid
- 2 Derivative-free optimization
 - Pattern search [Hooke, Jeeves]
 - NEWUOA [Powell]
 - Particle Swarm [Vaz, Vicente]
- 3 Dynamic Programming
- 4 Tailored **MINLP** branching algorithm
- 5 Solution of the **MINLP** with Couenne and SCIP

Dynamic Programming



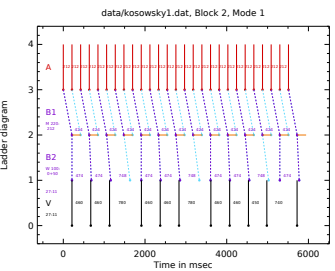
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Dynamic Programming



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 - “Controls” $\Delta\alpha$, π^j , τ_{con}^j , τ_{inc}^j , τ_{ref}^j independent of i . **Enumeration!**

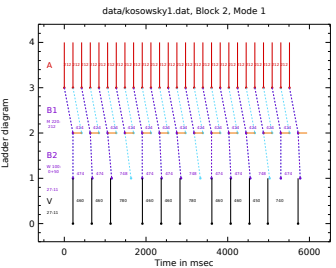
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- Maybe rotate problem? Now dependent on j !

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 - “Controls” $\Delta\alpha$, π^j , τ_{con}^j , τ_{inc}^j , τ_{ref}^j independent of i . **Enumeration!**
- Maybe rotate problem? Now dependent on j !
 - But few levels compared to signals, **curse of dimensionality**



Tailored branching algorithm [Florian Kehrle]



- Work on (adaptive) grid as in enumeration
- Intelligent tree search, forward in time, like in [Jung, Reinelt, Sager, 2014 OMS]
- Remove subtrees with unphysical behavior
- Remove subtrees which lead to “missing” ventricular signal



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- Remove subtrees which lead to “missing” ventricular signal
- evaluate simulations on nodes
- thus not really “all-at-once” (simulation and optimization) so far
- “Merge upper and lower Mobitz block” into neighbor level by clever modification of variables



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```
for  $i = 1 \dots n_\alpha$  do
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```

- How to model **objective function**? Least-squares? l^1 ? Huber?
- How to penalize wrong number of signals compared to data?
- How to make sure signal i is compared to correct data j ?



Variables

Symbol	Range	Set
J	$1 \dots n_{lv1}$	Block levels (0 =atrium, $n_{lv1} + 1$ =ventricle)
I	$1 \dots n_{\alpha}$	Time signals atrium (output)
V	$1 \dots n_{\beta}$	Time signals ventricle (input)

Symbol	Range	Meaning
x_k^V	$k \in V$	Impulse times ventricle
x_i^0	$i \in I$	Impulse times atrium
x_i^j	$i \in I, j \in J$	Impulse times passing level j
r_i^j	$i \in I, j \in J$	Cells are quiescent (excitation possible)
τ_{ref}^j	$j \in J$	Refractory time τ_{ref}^j
τ_{con}^j	$j \in J$	Transition constant τ_{con}^j
τ_{inc}^j	$j \in J$	Transition increment τ_{inc}^j
$\Delta\alpha$		Regular atrium signal
$\pi^j \in \{0, 1\}$	$j \in J$	Mobitz or Wenckebach?
$y_i^j \in \mathbb{N}$	$i \in I, j \in J$	Wenckebach Counter
$\delta_i^j \in \{0, 1\}$	$i \in I, j \in J$	Signal i arriving at level j ?
$\phi_{k,i} \in \{0, 1\}$	$k \in V, i \in I$	Permutation matrix



MINLP formulation

$$\min_{x_i^0, x_i^j, r_i^j, \tau_{\text{ref}}^j, \tau_{\text{con}}^j, \tau_{\text{inc}}^j, \Delta\alpha, \pi^j, y_i^j, \delta_i^j, \phi_{k,i}} \sum_{k \in V} \left(\sum_{i \in I} \phi_{k,i} x_i^{\text{nlvl}} - x_k^v \right)^2$$

subject to

- Bounds and integrality
- $x_{i+1}^0 = x_i^0 + \Delta\alpha, \quad i \in \{1, \dots, n_\alpha - 1\}$
- Permutation matrix $\phi_{k,i}$ makes sense
- Signal x_i^{nlvl} is result of forward simulation

Permutation matrix e.g., 2:1 Mobitz $\phi = \begin{pmatrix} 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \end{pmatrix}$

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Signal conducted? Only possible if at parent level

$$\delta_i^0 = 1, \quad i \in I$$

$$\delta_i^{j-1} \geq \delta_i^j, \quad i \in I, j \in J$$

Connection permutation matrix and block. Upper triangular

$$\sum_{k \in V} \phi_{k,i} = \delta_i^{n_{lv}}, \quad i \in I$$

$$\phi_{k,i} = 0, \quad k \in V, i \in I \text{ with } k > i$$

Only 1 signal, no overtaking

$$\sum_{i \in I} \phi_{k,i} \leq 1, \quad k \in V$$

$$\phi_{k+1,n} - \sum_{i=1}^{n-1} \phi_{k,i} \leq 0, \quad k \in \{1, \dots, n_\beta - 1\}, n \in I$$



subject to Mobitz block: $\pi^j = 1$

Conducted? $x_i^j + \tau_{\text{con}}^j \geq r_{i-1}^j \Leftrightarrow \delta_i^j = 1$

$$\pi^j \delta_i^j (x_i^j + \tau_{\text{con}}^j - r_{i-1}^j) \geq 0, \quad i \in I, j \in J$$

$$\pi^j (1 - \delta_i^j) (x_i^j + \tau_{\text{con}}^j - r_{i-1}^j + \varepsilon) \leq 0, \quad i \in I, j \in J$$

Quiescent? r_i^j changes $\Leftrightarrow \delta_i^j = 1$

$$r_0^j = 0, \quad j \in J$$

$$(1 - \delta_i^j) (r_{i-1}^j - r_i^j) = 0, \quad i \in V, j \in J$$

$$\pi^j \delta_i^j (x_i^{j+1} + \tau_{\text{ref}}^j - r_i^j) = 0, \quad i \in V, j \in J$$

Set time x_i^j

$$\pi^j (\delta_i^j (x_i^j + \tau_{\text{con}}^j) - x_i^{j+1}) = 0, \quad i \in I, j \in J$$

subject to Wenckebach block $\pi^j = 0$

$$\text{Conducted? } \tau_{\text{con}}^j + y_{i-1}^j \tau_{\text{inc}}^j \leq \tau_{\text{ref}}^j \Leftrightarrow \delta_i^j = 1$$

$$(1 - \pi^j) \delta_i^j (\tau_{\text{con}}^j + y_{i-1}^j \tau_{\text{inc}}^j - \tau_{\text{ref}}^j) \leq 0, \quad i \in I, j \in J$$

$$(1 - \pi^j)(1 - \delta_i^j)(\tau_{\text{con}}^j + y_{i-1}^j \tau_{\text{inc}}^j - \tau_{\text{ref}}^j - \varepsilon) \geq 0, \quad i \in I, j \in J$$

$$\text{Increase Wenckebach counter } y_i^j \Leftrightarrow \delta_i^j = 1$$

$$y_0^j = 0, \quad j \in J$$

$$\delta_i^j (y_i^j - (y_{i-1}^j + 1)) = 0, \quad i \in V, j \in J$$

$$(1 - \delta_i^j) y_i^j = 0, \quad i \in V, j \in J$$

Avoid overtaking of signals

$$\delta_i^j (x_k^{j+1} - x_i^{j+1} + \varepsilon) \leq 0, \quad k > i \in I, j \in J$$

Set time x_i^j

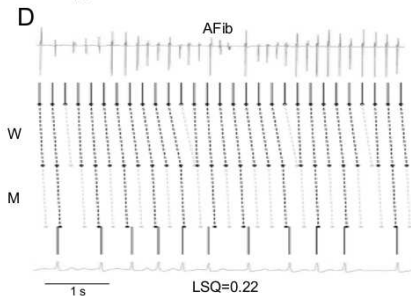
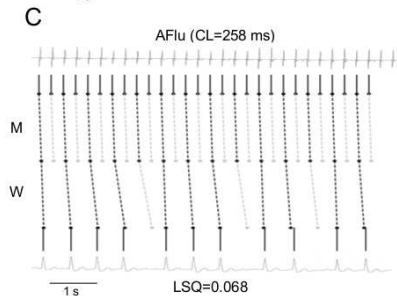
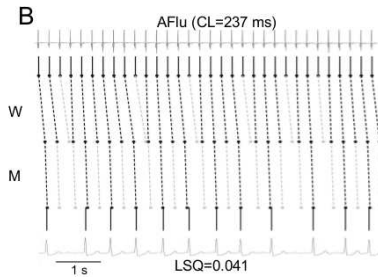
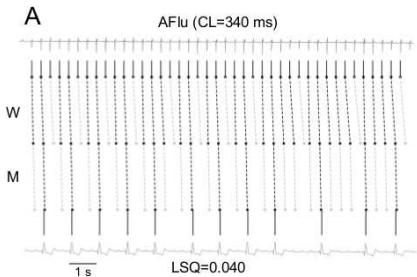
$$(1 - \pi^j)(\delta_i^j (x_i^j + \tau_{\text{con}}^j + y_{i-1}^j \tau_{\text{inc}}^j) - x_i^{j+1}) = 0, \quad i \in I, j \in J$$



Outline

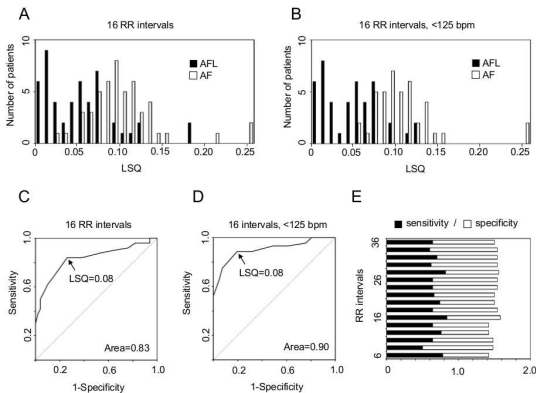
- ① Medical Problem
- ② Mathematical Approaches
- ③ Inverse Simulation of Multilevel AV block
- ④ Algorithmic Approaches
- ⑤ Modeling of the Optimization Problem
- ⑥ Numerical Results and Summary

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



mathe.medical HEAT

Select mode of acquisition



BEEP



ECG



Mathematical algorithms in clinical practice



mathe.medical HEAT

Select mode of acquisition



mathe.medical HEAT



Recording signal...

Mathematical algorithms in clinical practice



mathe.medical HEAT

Select mode of acquisition



mathe.medical HEAT



Recording signal...



mathe.medical HEAT



Result: Atrial flutter with a regular atrial period of 237ms. To download and show the solution as PDF, please click on the microphone.

Mathematical algorithms in clinical practice

5:04

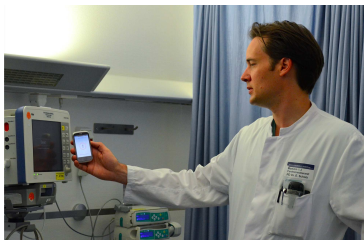
mathe.medical HEAT

Select mode of acquisition



5:04

mathe.medical HEAT



5:16

mathe.medical HEAT



Result: Atrial flutter with a regular atrial period of 237ms. To download and show the solution as PDF, please click on the microphone.



Summary

- Challenging and important medical problem
- Innovative optimization-driven inverse simulation approach
- Already $\approx 80 - 90\%$ specificity / sensitivity
- Patent granted

- Challenging MI(N)LP formulation with open questions
- Structure-exploiting branching best algorithm so far

- Future: extend models to include rare events
- Future: remove symmetry
- Future: include uncertainty / stochastics
- Future: link to differential equations / automata

Thank you for your attention and comments!

