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Decoding complex cardiac arrhythmia using mathematical optimization

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Klaus Tschira Stiftung gemeinnützige GmbH
KTS
UniversitätsKlinikum Heidelberg
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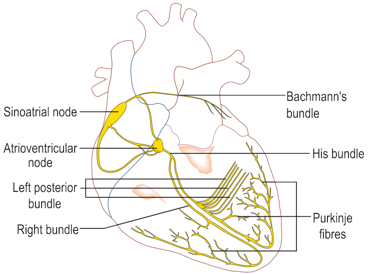
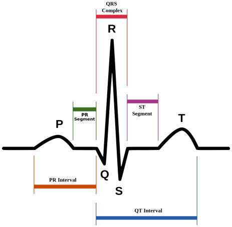
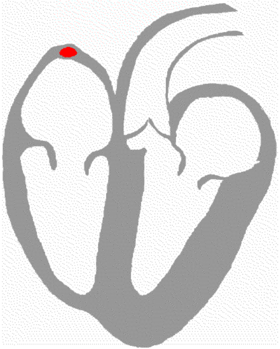
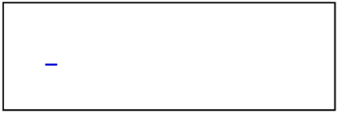
Outline

Reminder: the human heart [Images: Wikipedia]



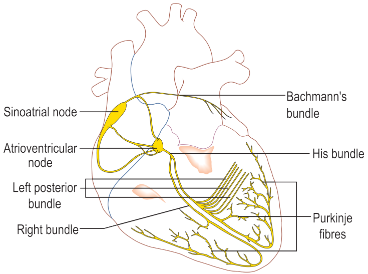


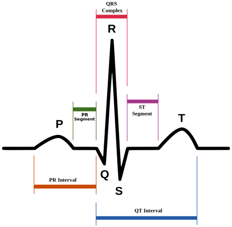


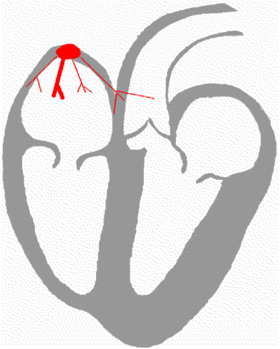


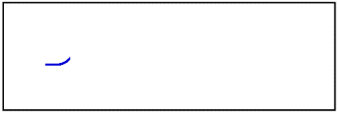
Pacemaker signal in sinoatrial node

Reminder: the human heart [Images: Wikipedia]









Atrial chambers

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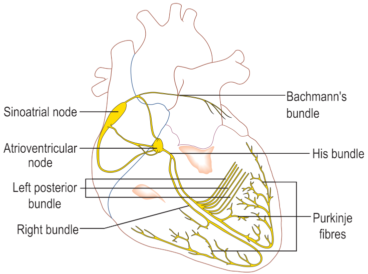

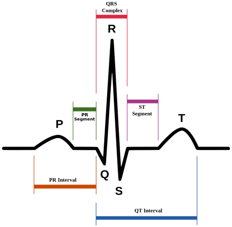

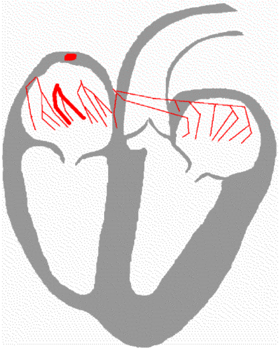

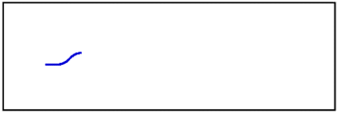

P Atrial depolarization → atrial contraction

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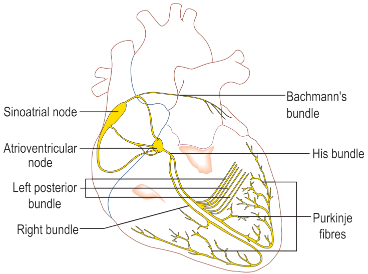

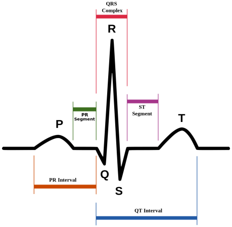

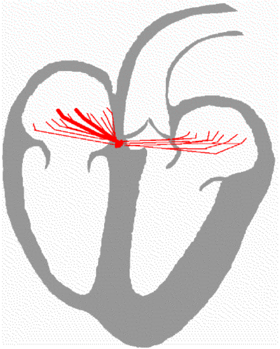

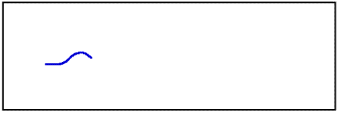

P Atrial depolarization → atrial contraction

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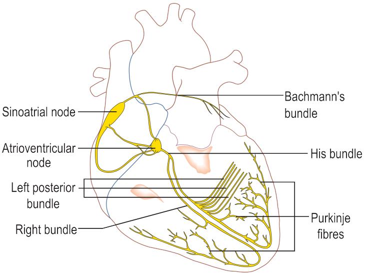

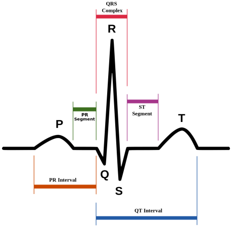

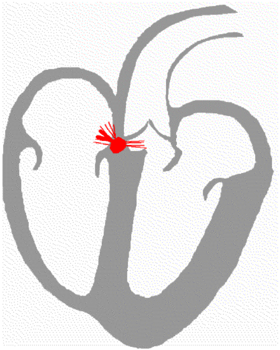

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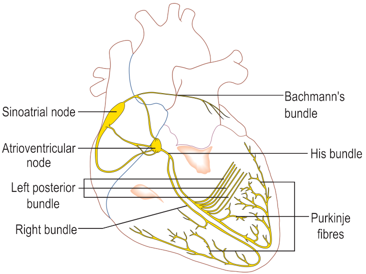
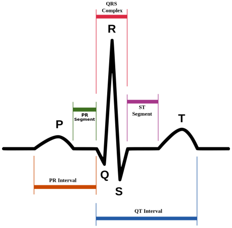
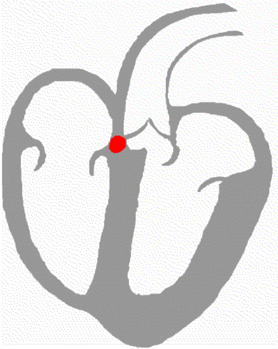
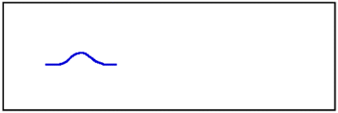


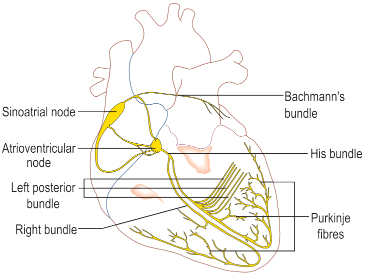


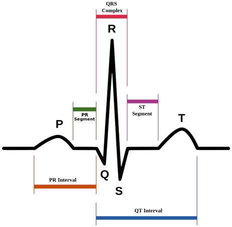


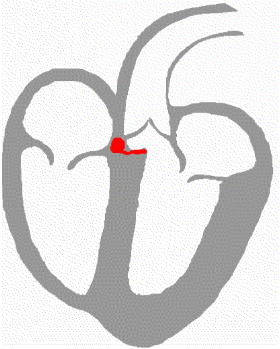


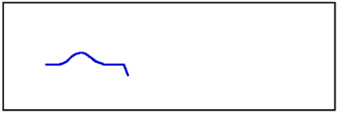
PR Atrioventricular node

Reminder: the human heart [Images: Wikipedia]



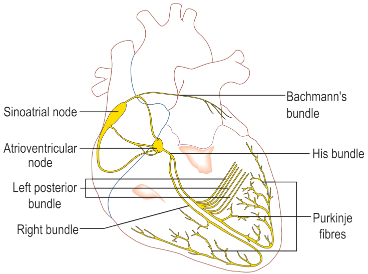


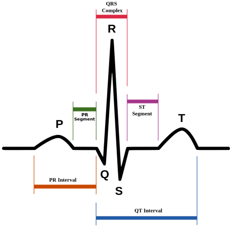


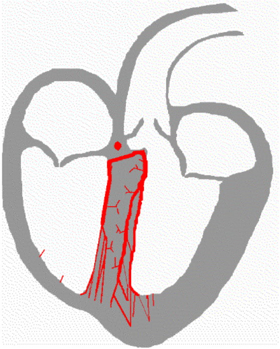


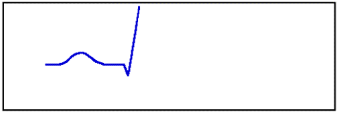
Q Depolarization of the interventricular septum

Reminder: the human heart [Images: Wikipedia]



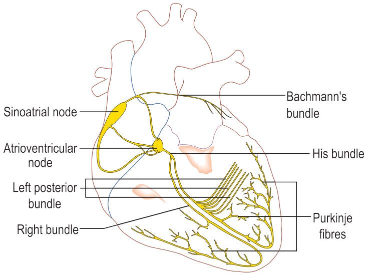


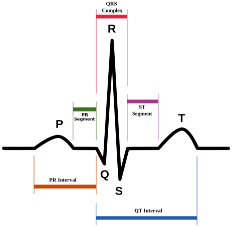


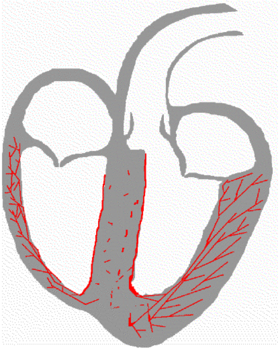


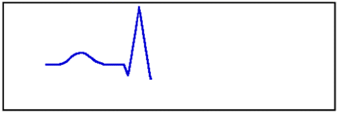
R Polarization of the ventricles

Reminder: the human heart [Images: Wikipedia]



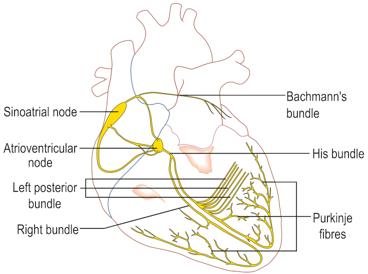


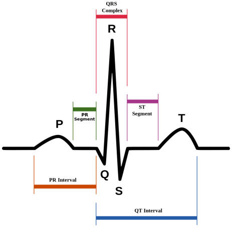


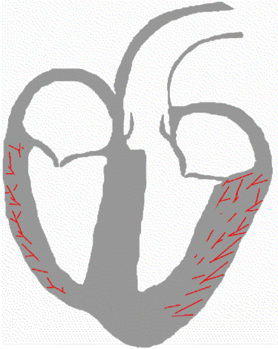


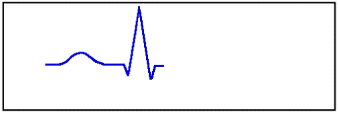
S (De)polarization

Reminder: the human heart [Images: Wikipedia]









S Depolarization, contraction

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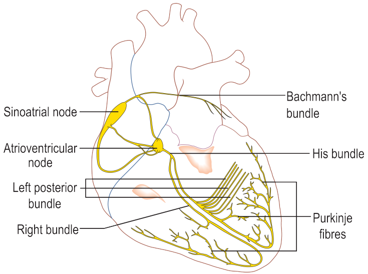
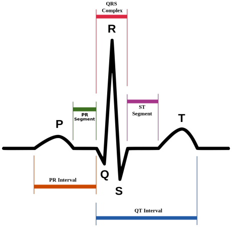
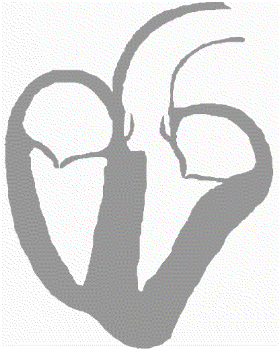
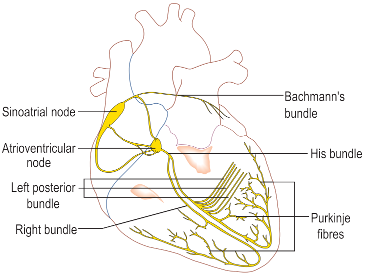


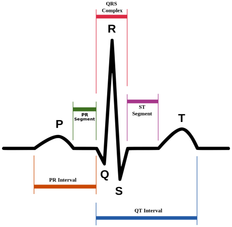




ST Depolarization, contraction

Reminder: the human heart [Images: Wikipedia]





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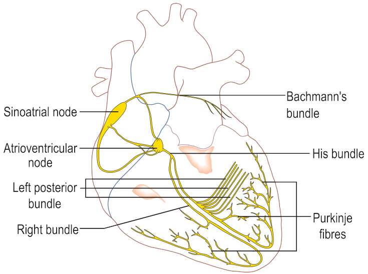

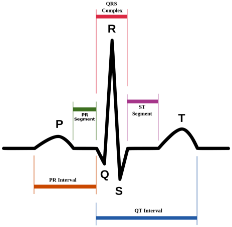

T Secondary excitation

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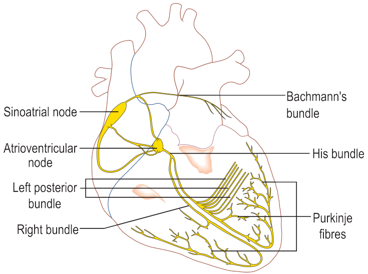

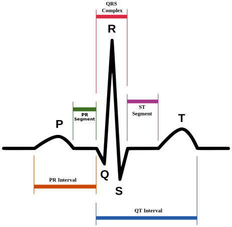

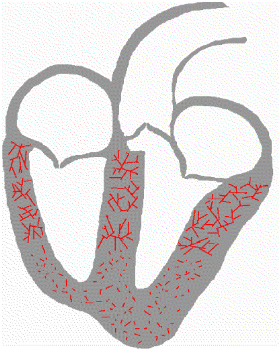

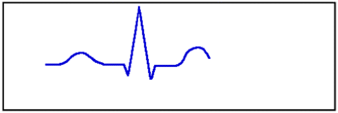

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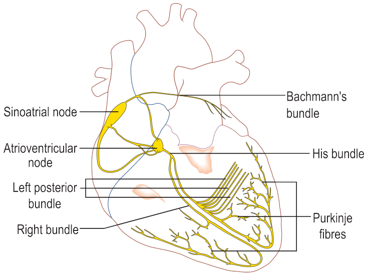

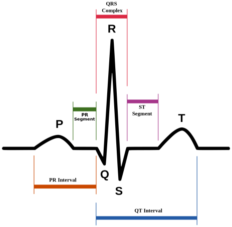

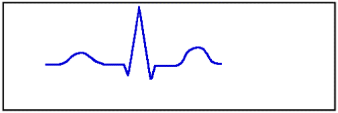

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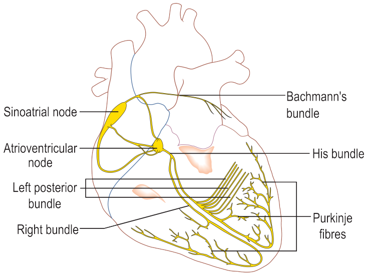

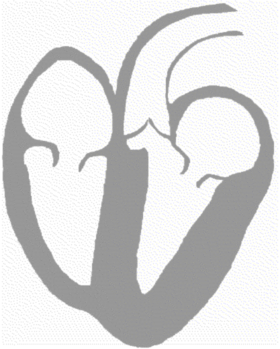

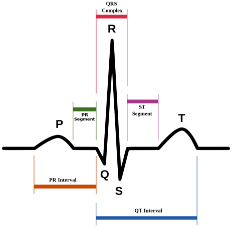

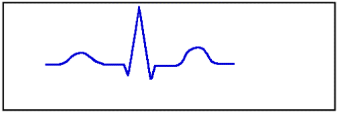

Rest

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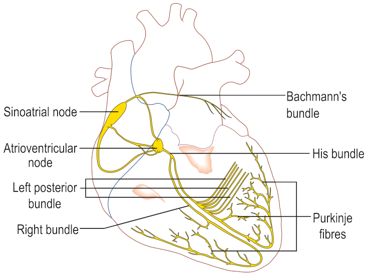

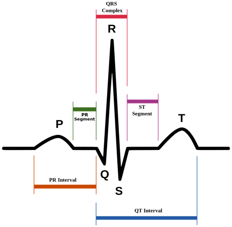

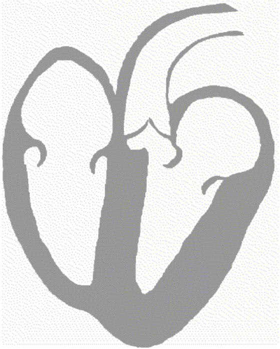

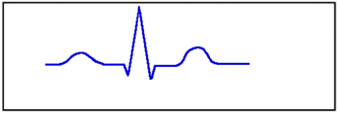

Rest

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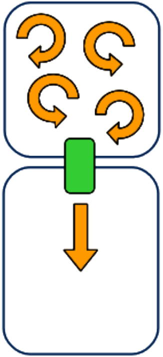
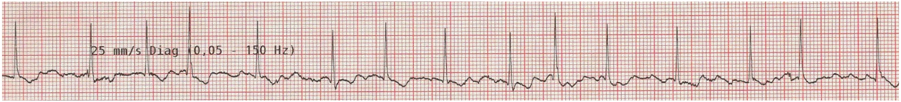
Atrial Fibrillation

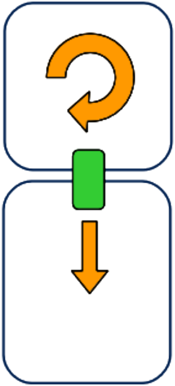
- Regular electric impulses are overwhelmed by disorganized ones (non-constant frequency)





Atrial Flutter

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



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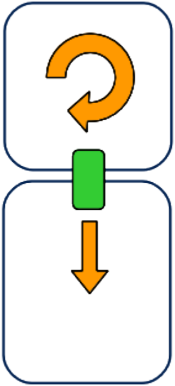
Atrial Flutter

- But: filter may also result in irregular signal!



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?

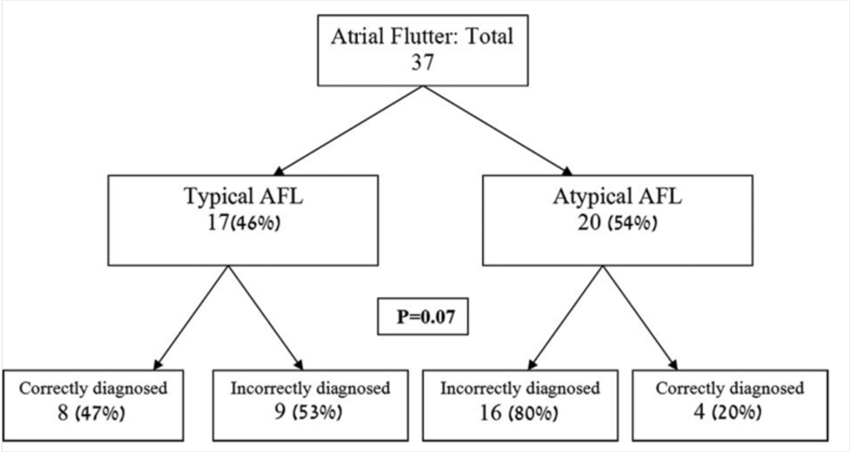
So, what do you think?

Flutter, Flutter, Fibrillation

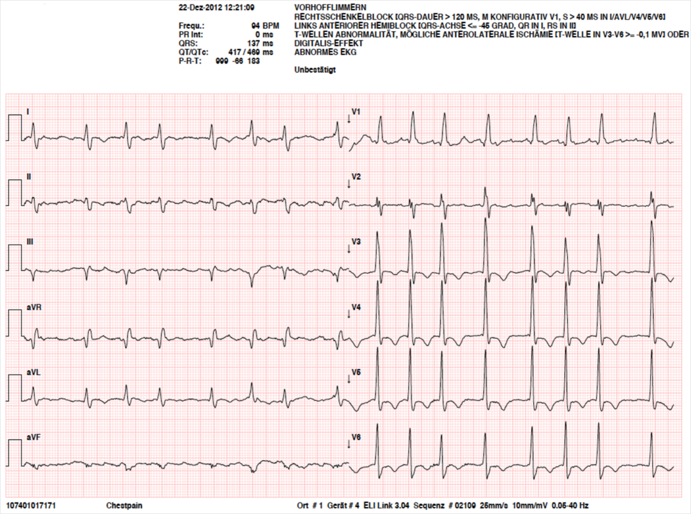
So, what do you think?

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?



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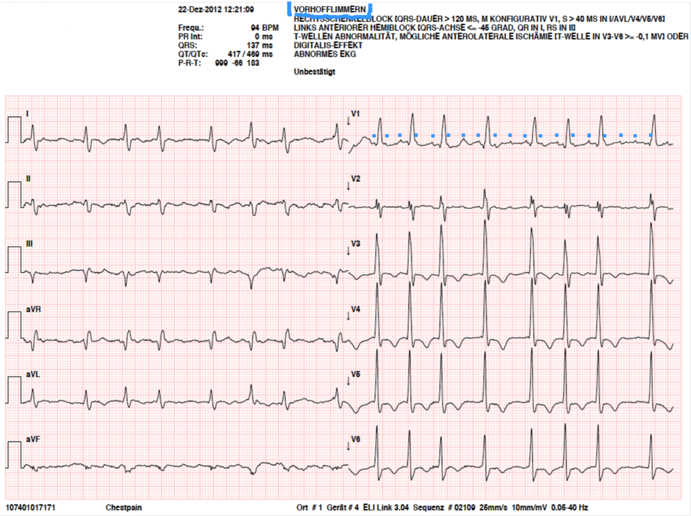

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Outline

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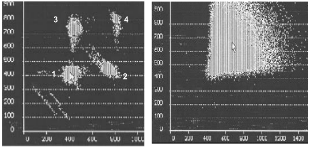
Large variety of different approaches possible

- Based on statistics (of RR-intervals)
  - Bayesian logic
  - Fourier transforms
  - Wavelets
  - Clustering of RR times [Esperer et al. 2008 ANE]
  - Machine learning
  - Nonlinear time series analysis
  - …



- Based on cellular automata
  - Shows wave propagation patterns depending on probabilities of excitation by neighboring cells [M. Small, Dynamics of Biological Systems, CRC, 2012]
- Based on first-principle models
  - PDEs, SDEs, DDEs, ODEs, …
  - Survey [D. Noble, 2012]: ≈ 100 models with significant contributions

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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

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{i_{Na}+i_K+i_{Leak}}{Cm} = -\frac{(4\cdot 10^5 m^3 h + 140)(V-E_{Na})}{Cm}$$

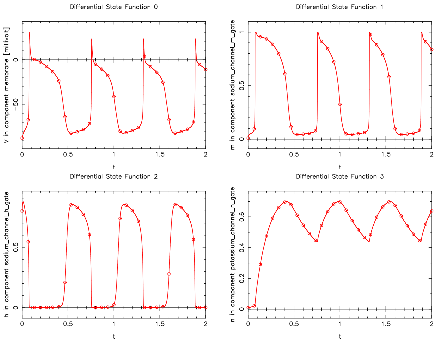
$$-\frac{(1200 e^{\frac{-V-90}{50}} + 15 e^{\frac{V+90}{60}}(V-E_K) + 1200 n^4 (V-E_K) + 75(V-E_{An})}{Cm}$$

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

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

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

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



- Successfully predicted several (unknown) phenomena
- Many extensions, models with ≈ 100 states or PDEs
- Very tough optimization problems [Lebiedz & Sager, Physical Review Letters 2005]

Outline

Phenomenological approach

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

Phenomenological approach

- Important & difficult to distinguish between fibrillation and flutter
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- 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

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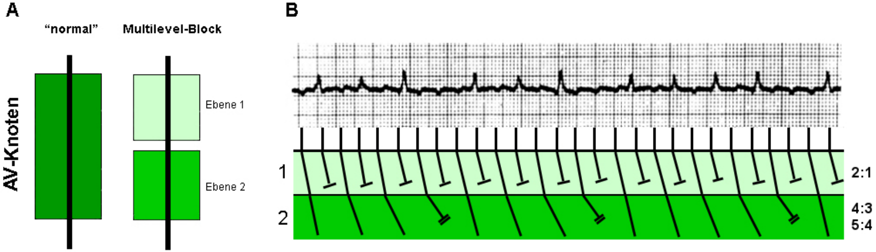
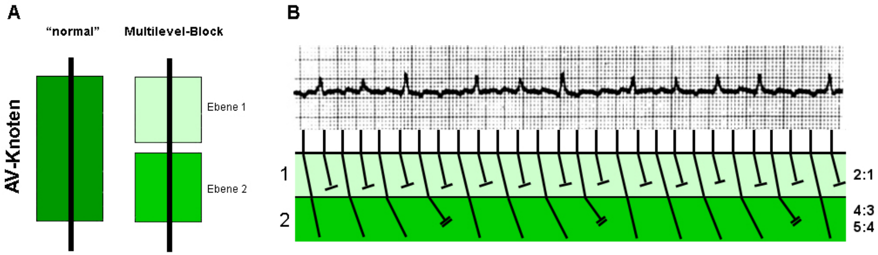
Multilevel approach

- 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 ... n_α do
        /* Signal can be processed */
        if α_i + τ_con ≥ r then
            β_j = α_i + τ_con
            r = β_j + τ_ref
            j = j + 1
    n_β = 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 ... n_α do
        /* Signal can be processed                  */
        if τ_con + c · τ_inc ≤ τ_ref then
            β_j = α_i + τ_con + c · τ_inc
            j = j + 1, c = c + 1
        /* Signal can not be processed              */
        else
            c = 0
    n_β = j − 1
end
```

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]

  (*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 τ^j_{con}, τ^j_{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

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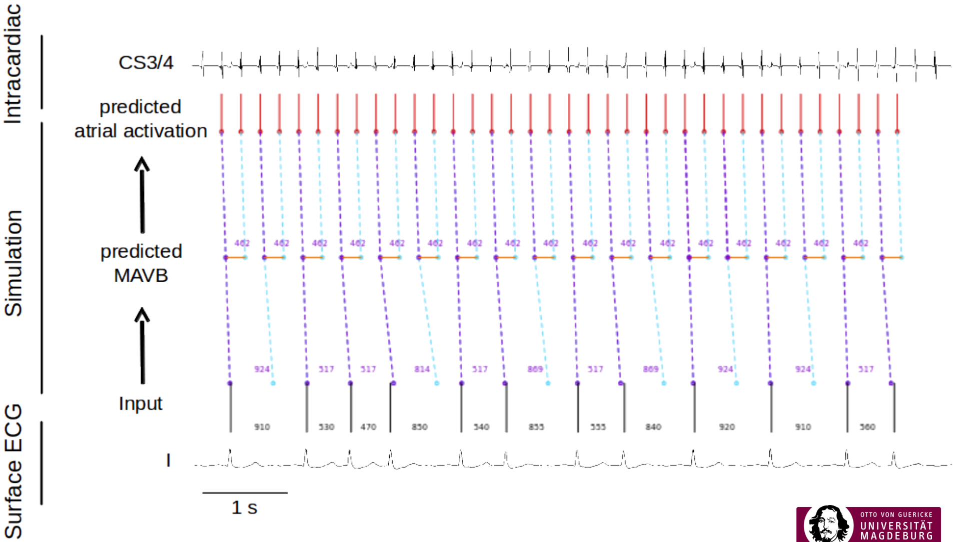
Visualizing example of our approach



Outline

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Challenges in MINLP modeling

- What are the (state) variables? Dimensions? Depend on $\Delta\alpha$!

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- How to model inner `for` loop with unknown length?

---

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

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

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

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

  else

    $c = 0$

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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?

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Variables

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

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MINLP formulation

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

subject to

- Bounds and integrality
- $x_{i+1}^0 = x_i^0 + \Delta\alpha, \quad i \in \{1, \ldots, n_\alpha - 1\}$
- Permutation matrix $\phi_{k,i}$ makes sense
- Signal $x_i^{n_{\text{lvl}}}$ 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

$$\begin{aligned} \delta_i^0 &= 1, \quad i \in I \\ \delta_i^{j-1} &\geq \delta_i^j, \quad i \in I, j \in J \end{aligned}$$

Connection permutation matrix and block. Upper triangular

$$\begin{aligned} \sum_{k \in V} \phi_{k,i} &= \delta_i^{n_{\text{lvl}}}, \quad i \in I \\ \phi_{k,i} &= 0, \quad k \in V, i \in I \text{ with } k > i \end{aligned}$$

Only 1 signal, no overtaking

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

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

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

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

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

$$
\begin{aligned}
r_0^j &= 0, \quad j \in J \\
(1 - \delta_i^j)(r_{i-1}^j - r_i^j) &= 0, \quad i \in V, j \in J \\
\pi^j \delta_i^j (x_i^{j+1} + \tau_{\text{ref}}^j - r_i^j) &= 0, \quad i \in V, j \in J
\end{aligned}
$$

Set time x_i^j

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

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

Conducted? $\tau^j_{\text{con}} + y^j_{i-1}\tau^j_{\text{inc}} \leq \tau^j_{\text{ref}} \Leftrightarrow \delta^j_i = 1$

$$(1-\pi^j)\delta^j_i(\tau^j_{\text{con}} + y^j_{i-1}\tau^j_{\text{inc}} - \tau^j_{\text{ref}}) \leq 0, \quad i \in I, j \in J$$

$$(1-\pi^j)(1-\delta^j_i)(\tau^j_{\text{con}} + y^j_{i-1}\tau^j_{\text{inc}} - \tau^j_{\text{ref}} - \varepsilon) \geq 0, \quad i \in I, j \in J$$

Increase Wenckebach counter $y^j_i \Leftrightarrow \delta^j_i = 1$

$$y^j_0 = 0, \quad j \in J$$

$$\delta^j_i(y^j_i - (y^j_{i-1} + 1)) = 0, \quad i \in V, j \in J$$

$$(1-\delta^j_i)y^j_i = 0, \quad i \in V, j \in J$$

Avoid overtaking of signals

$$\delta^j_i(x^{j+1}_k - x^{j+1}_i + \varepsilon) \leq 0, \quad k > i \in I, j \in J$$

Set time x^j_i

$$(1-\pi^j)(\delta^j_i(x^j_i + \tau^j_{\text{con}} + y^j_{i-1}\tau^j_{\text{inc}}) - x^{j+1}_i) = 0, \quad i \in I, j \in J$$

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Outline

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. Solution of the MINLP with `Couenne` and `SCIP`
   - 2 levels and 10 signals in $\approx$ 30 seconds
5. Tailored branching algorithm

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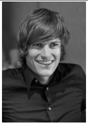
Tailored branching algorithm [Florian Kehrle]



- Work on (adaptive) grid as in enumeration

- Intelligent tree search, forward in time, like in [Jung, Reinelt, Sager, 2014 OMS]
- Remove subtrees with with unphysical behavior
- Remove subtrees which lead to “missing” ventricular signal

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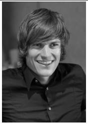

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- evaluate simulations on nodes
- thus not really “all-at-once” (simulation and optimization) so far

- “Merge upper and lower Mobitz block” into neighbor level by clever modification of variables

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Outline

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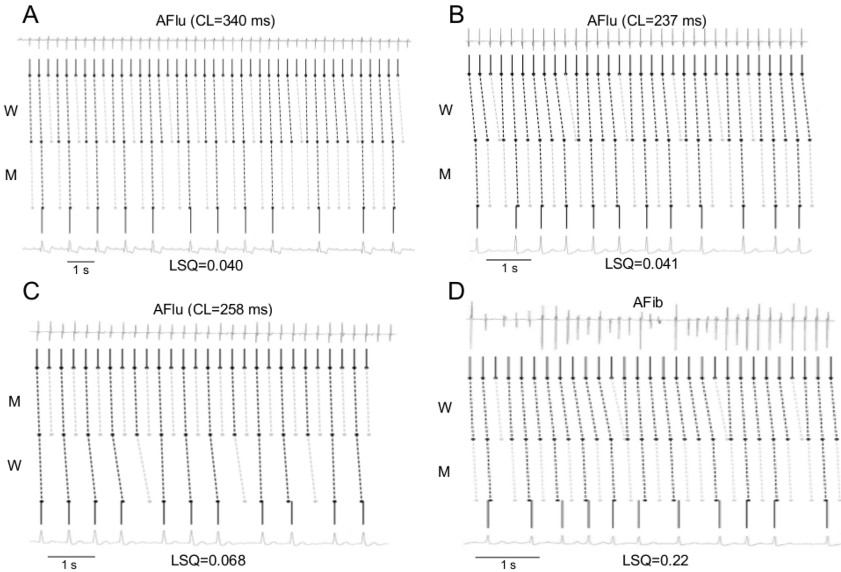
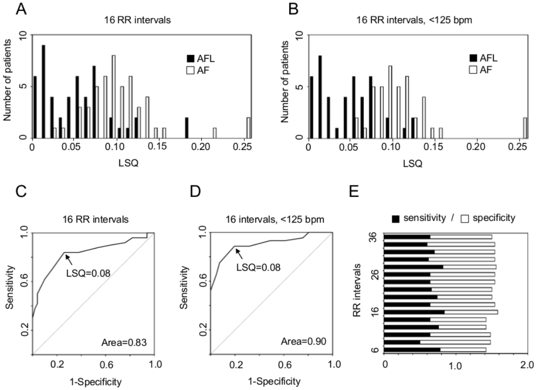
Discrimination Examples [Scholz et al., Heart Rhythm, 2014]



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%!



Summary

- Challenging and important medical problem
- Innovative optimization-driven inverse simulation approach
- already $\approx 80 - 90\%$ specificity / sensitivity
- Company `mathe.medical` founded for dissemination

- 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!

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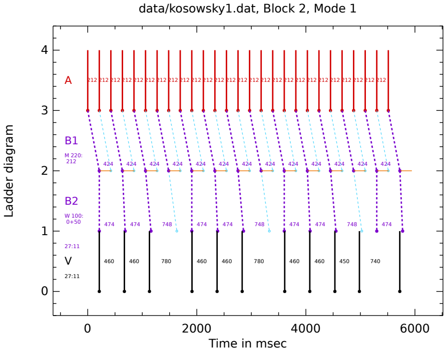
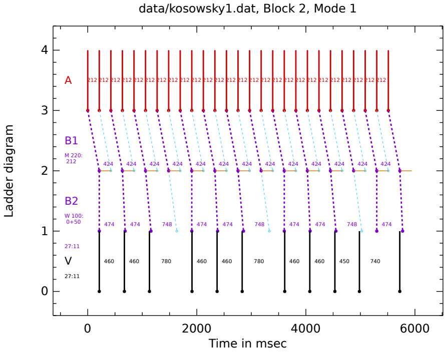
Outline

Dynamic Programming



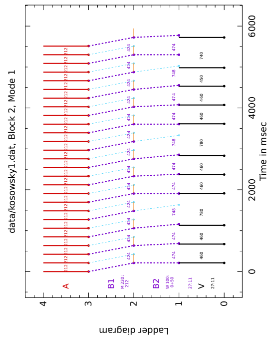
- Dynamic Programming looks promising?

Dynamic Programming



- Dynamic Programming looks promising?
  - "Controls" $\Delta\alpha$, π^j, τ^j_{con}, τ^j_{inc}, τ^j_{ref} independent of i. Enumeration!

Dynamic Programming



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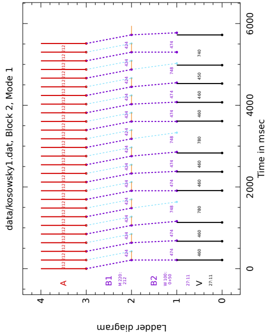
- Maybe rotate problem? Now dependent on j!

Dynamic Programming



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

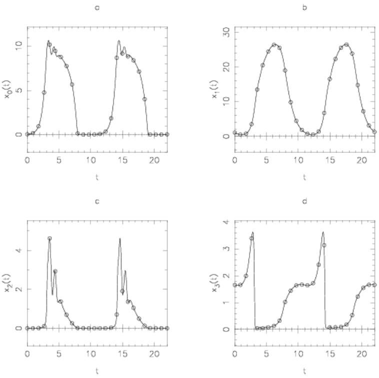
Calcium concentration in cells, [U. Kummer et al., 2002]

- 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]

$$\min_{y,w,w_{\max}} \int_{t_0}^{t_f} ||y(t) - \hat{y}||^2 \, \mathrm{d}t \qquad \text{subject to}$$

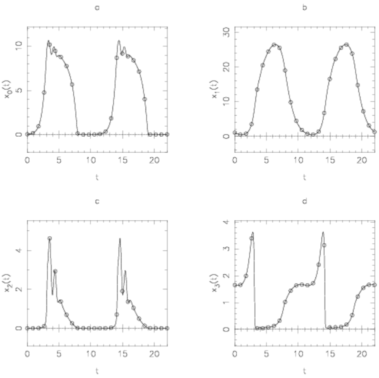
$$\begin{aligned}
\dot{a} &= k_1 + k_2\, a - k_3 \frac{a\, b}{a+K_4} - k_5 \frac{a\, c}{a+K_6} \\
\dot{b} &= k_7\, a - k_8 \frac{b}{b+K_9} \\
\dot{c} &= k_{10} \frac{b\, c\, d}{d+K_{11}} + k_{12}\, b + k_{13}\, a - k_{14} \frac{c}{w\, c+K_{15}} - k_{16} \frac{c}{c+K_{17}} + \frac{d}{10} \\
\dot{d} &=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

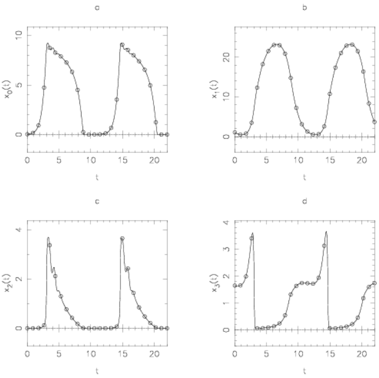
Simulation



$$w(t) = 1$$

Simulation

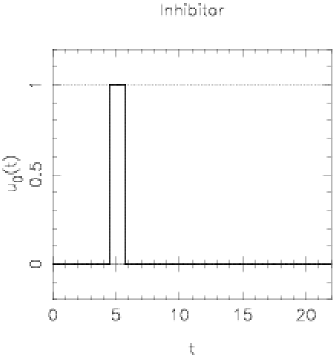


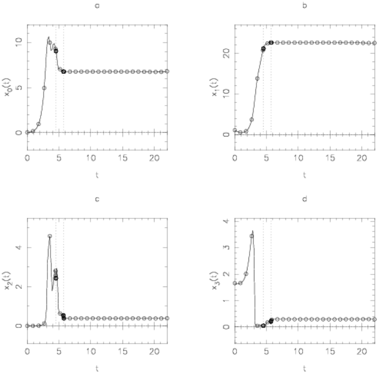


$w(t) = 1$

$w(t) = w_{\text{max}}$

Integer solution

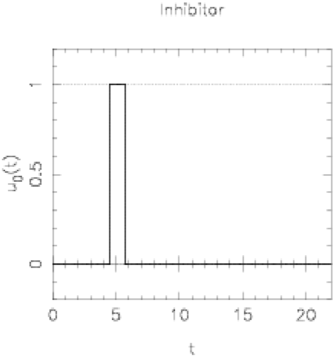




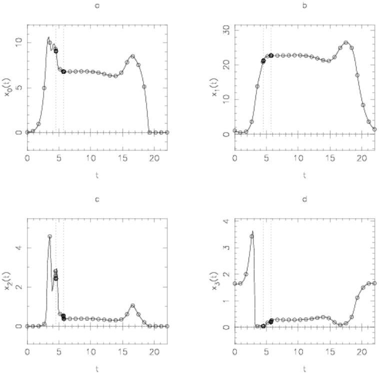
Control

States

Integer solution - after small change

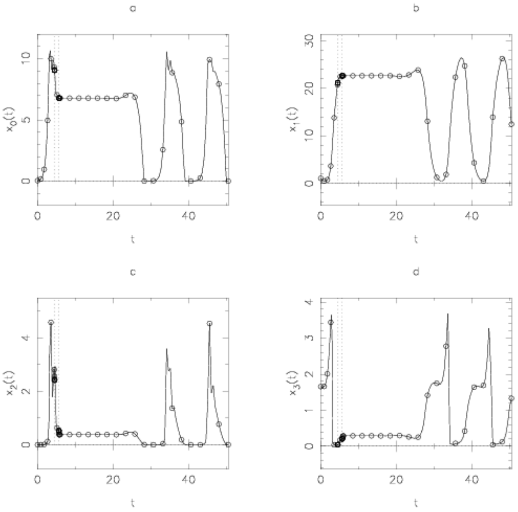


Control - 10^{-3} too early

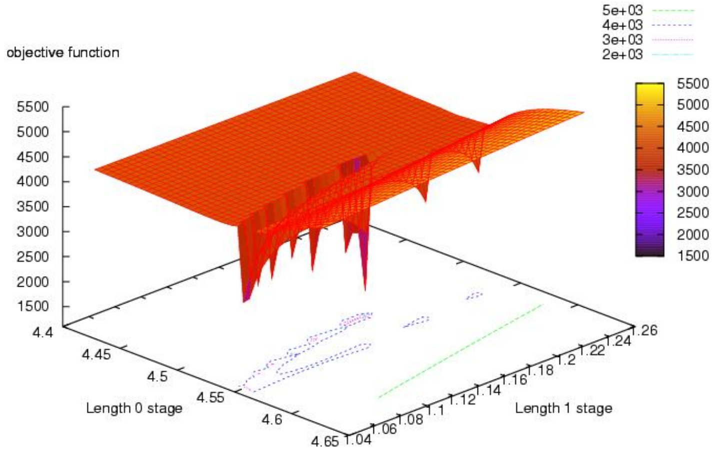


States

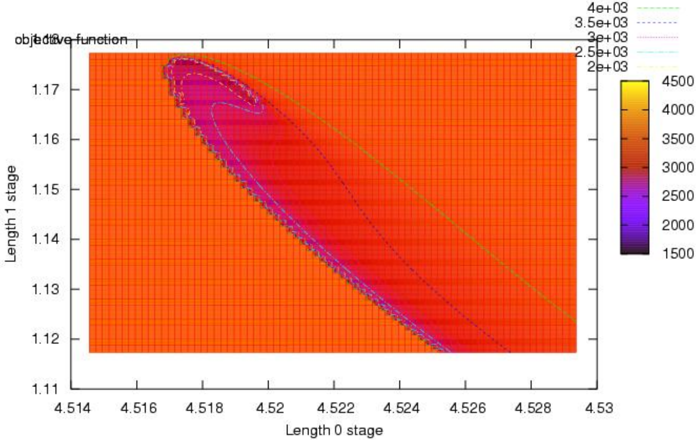
State is instable



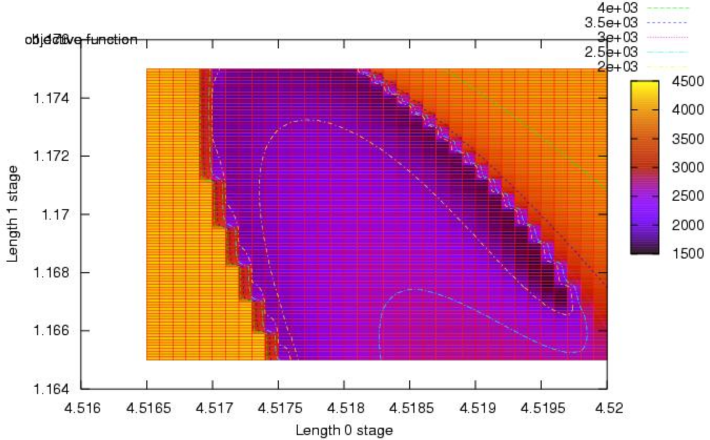
Objective function - scale 10^{-1}



Objective function - scale 10^{-2}



Objective function - optimum



Objective function - border