Estimation and verification of hybrid heart models for personalised medical and wearable devices

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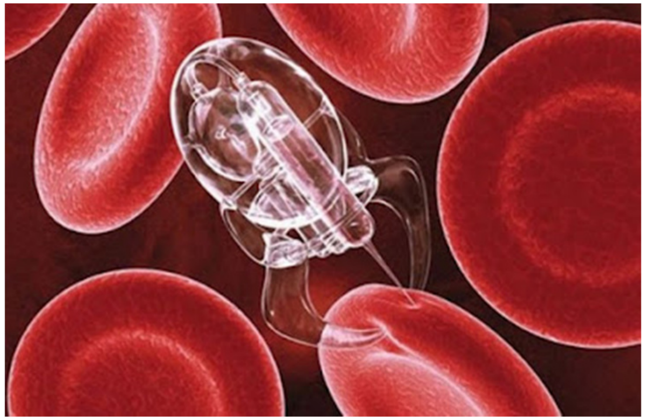
Ubiquitous computing

- Smartphones, tablets…
- Intelligent spaces
- Intelligent vehicles
  - self-driving cars
- Wearables
  - sports monitoring
  - fashion gadgets
- Implantable devices
  - insulin pumps
  - cardiac pacemakers
- Patient monitoring and drug delivery
  - doctor in the cell

Ubiquitous computing

- Computing without computers

- Populations of sensor-enabled computing devices that are
  - embedded in the environment, or even in our body
  - sensor enabled
  - software controlled
  - operate autonomously, unattended
  - devices are mobile
  - miniature size, even nanoscale
  - limited resources



- Unstoppable technological progress
  - smaller and smaller devices, more and more complex scenarios, increasing take up…

Perspectives on ubiquitous computing

- Technological: calm technology [Weiser 1993]
  - “The most profound technologies are those that disappear. They weave themselves into everyday life until they are indistinguishable from it.”

- Usability: ‘everyware’ [Greenfield 2008]
  - Hardware/software evolved into ‘everyware’: household appliances that do computing

- Scientific: “Ubicomp can empower us, if we can understand it” [Milner 2008]
  - “What concepts, theories and tools are needed to specify and describe ubiquitous systems, their subsystems and their interaction?”
- “Ubiquitous Computing, by 2020”
  - much progress since 2008 Royal Society Discussion Meeting!

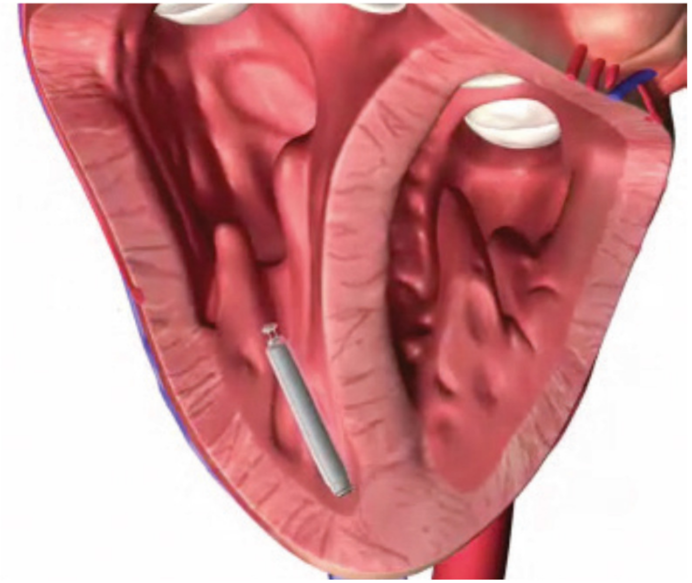
Wearable gadgets

UP3 by Jawbone fitness band

- Activity tracking
  - counts steps
- Advanced sleep
  - track your sleep stages
- Food logging
  - track calories with UP® barcode scanner
- Smart coach
  - motivation
- Heart health
  - tracking your heart rate

Implantable medical devices

- Nanostim™ leadless pacemaker
  - smaller than a AAA battery
  - resides entirely in the right ventricle
  - inserted through catherer
  - no leads
  - no reduced mobility
  - no chest incision
  - no scar
  - no lump under the skin
- First implanted 2014
- New designs being developed

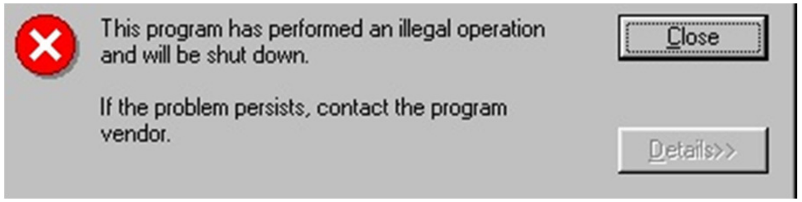


Wearable authentication devices

- Nymi band
  - ECG (Electrocardiogram) used as a biometric identifier
  - first creates biometric template
  - compares with real ECG signal when required
  - difficult to copy
- Can be paired with devices
  - with an app companion
- Proposed uses
  - for access into buildings and restricted spaces
  - for payment, etc

Are we safe?

- Embedded software at the heart of the device
- Need to monitor and control complex physiological processes



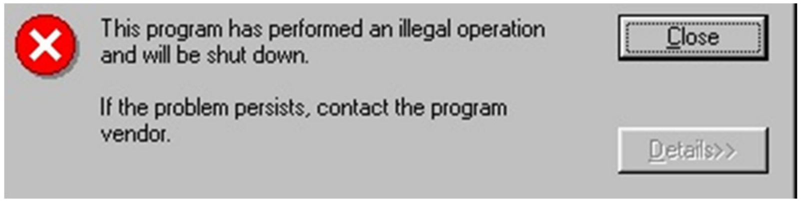
This program has performed an illegal operation and will be shut down.

If the problem persists, contact the program vendor.

- What if…
  - infusion pump software delivers wrong dosage
  - pacemaker software fails

Are we safe?

- Embedded software at the heart of the device
- Need to monitor and control complex physiological processes



This program has performed an illegal operation and will be shut down.

If the problem persists, contact the program vendor.

- What if…
  - infusion pump software delivers wrong dosage
  - pacemaker software fails
- Imagined or real?
  - May 2010 and each year since: FDA recalls programmable infusion pumps, over 710 patient deaths in five years, some because the device’s software malfunctioned
  - Jan-June 2010 Killed by code: FDA recalls 23 defective pacemaker devices because they can cause adverse health consequences or death, six likely caused by software defects

Software reliability challenge

- Software is an integral component
  - performs critical, lifesaving functions and basic daily tasks
  - software failure costly and life endangering
- Need quality assurance methodologies
  - model-based development
  - rigorous software engineering
- Use formal techniques to produce guarantees for:
  - safety, reliability, performance, resource usage, trust, …
  - (safety) "heart rate never drops below 30 BPM"
  - (energy) "energy usage is below 2000 mA per minute"
- Focus on automated, tool-supported methodologies
  - automated verification via model checking
  - quantitative/probabilistic verification
  - automated synthesis from specifications

Personalisation challenge

- Device must adapt to the physiology of the human wearer
  - achieved through model parameterisation
  - parameter estimation
  - optimal parameter synthesis
- Multiple uses
  - delivery of medical intervention
  - device safety assurance, for testing
  - reproduce the unique characteristics for authentication
- Personalisation: key enabler of personalised healthcare
  - automation of intervention strategies
  - uniquely adapted to the individual
- Focus on
  - overview progress and challenges of personalisation of ECG based devices

Focus on…

Modelling

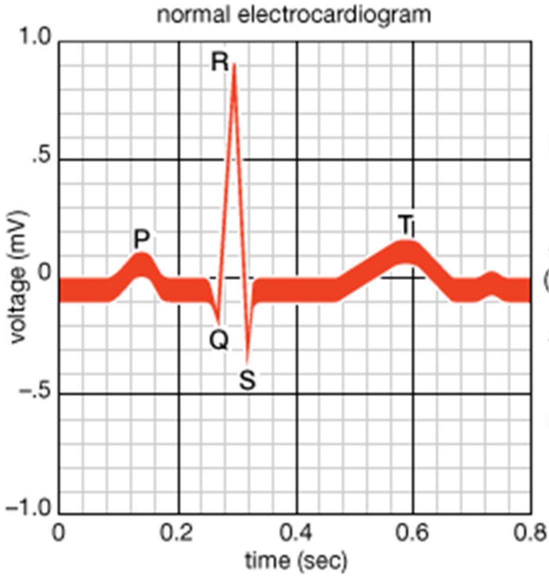
Verification

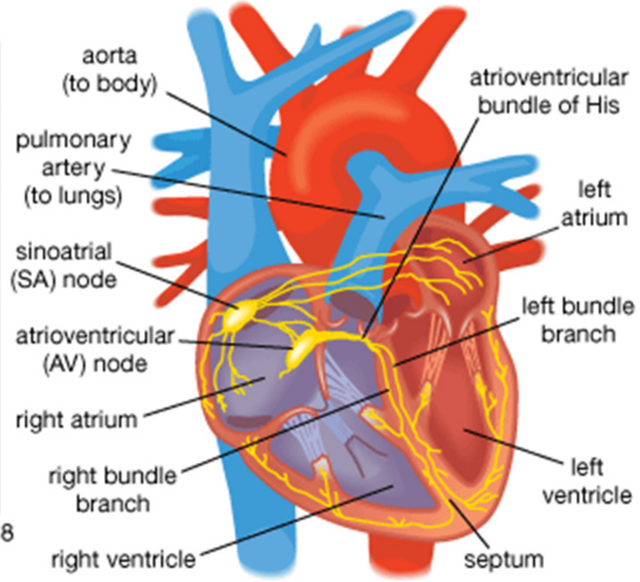
Personalisation

Modelling of the heart

- The heart maintains blood circulation by contracting the atria and ventricles
  - spontaneously generates electrical signal (action potential)
  - conducted through cellular pathways into atrium, causing contraction of atria then ventricles
  - repeats, maintaining 60-100 beats per minute

- Abnormalities in electrical conduction
  - missed/slow heart beat (Bradycardia)
  - treatable with pacemakers





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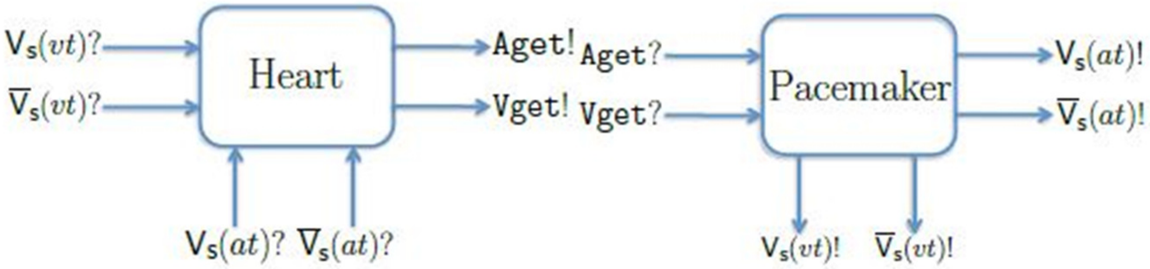
Model-based framework

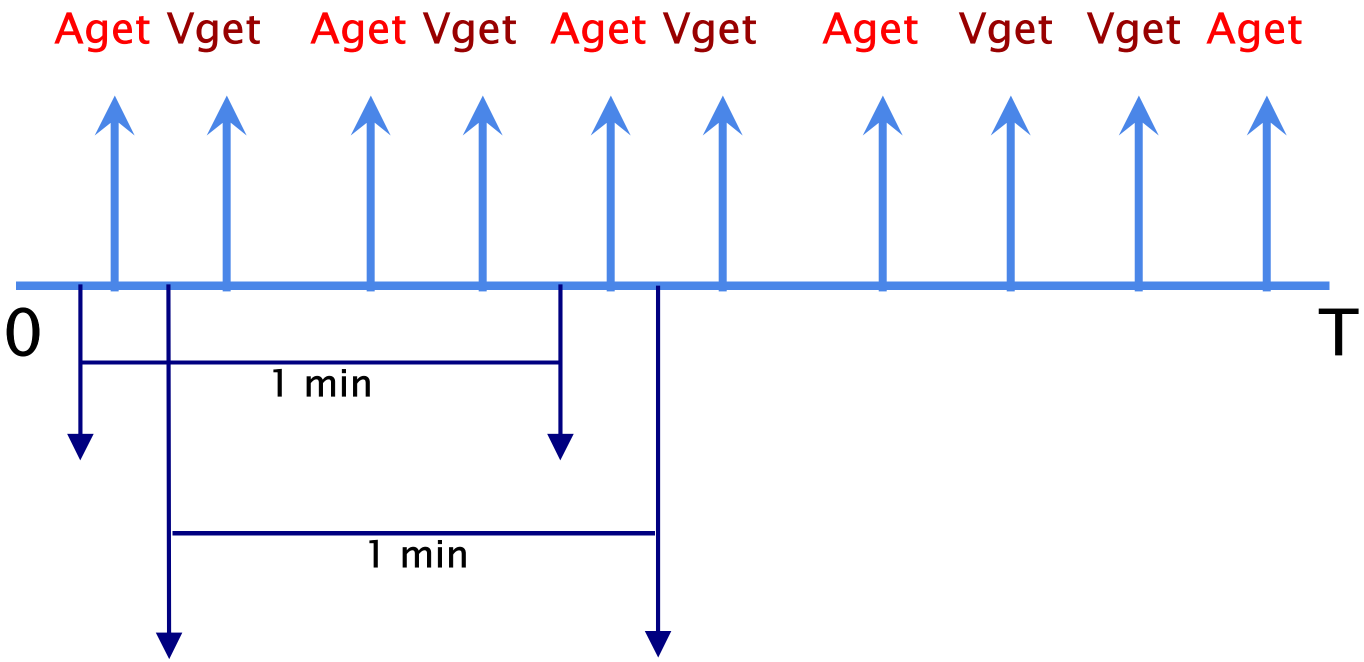
- We advocate a model-based framework
  - models are networks of communicating hybrid I/O automata, realised in Matlab Simulink
    - discrete mode switching and continuous flows: electrical conduction system
    - quantitative: energy usage and battery models
    - patient-specific parameterisation
  - framework supports plug-and-play composition of
    - **heart models** (timed/hybrid automata, some stochasticity)
    - **pacemaker models** (timed automata)



(a) Heart model (b) Pacemaker model

Quantitative Verification of Implantable Cardiac Pacemakers over Hybrid Heart Models. Chen *et al*, *Information and Computation*, 2014

Property specification: Counting MTL



$$\Box^{[0,\tau]}(\#_0^\tau \mathrm{Vget} \geqslant B_1 \wedge \#_0^\tau \mathrm{Vget} \leqslant B_2)$$

Safety "for any 1 minute window, heart rate is in the interval [60,100]"

Event counting not expressible in MTL (Metric Temporal Logic)

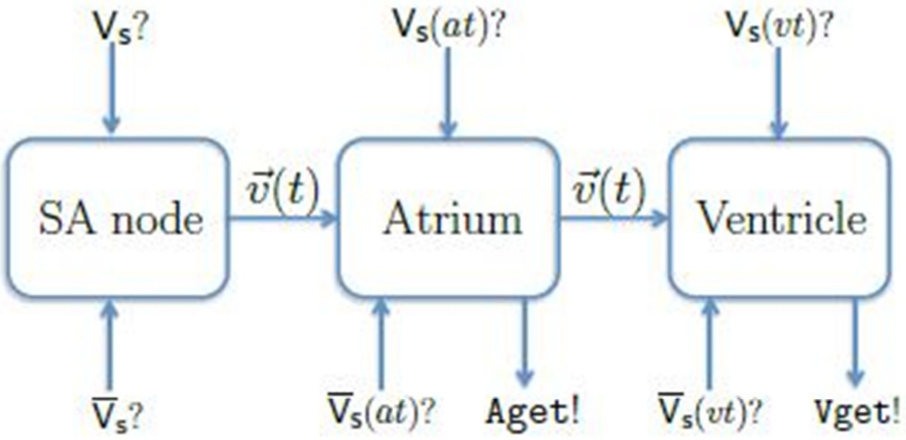
Framework functionality

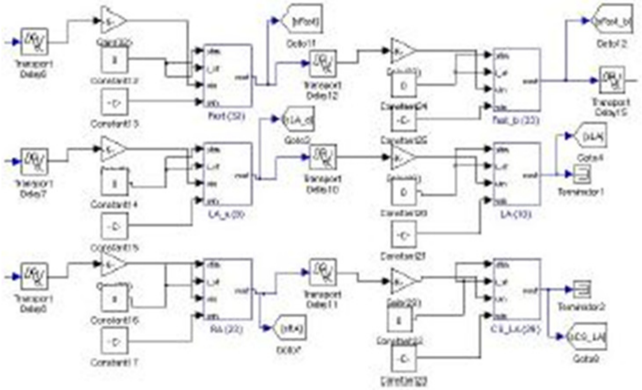
- Broad range of techniques
  - Monte-Carlo simulation of composed models
    - with (confidence level) guarantees for non-linear flows
  - (approximate) quantitative verification against variants of MTL
    - to ensure property is satisfied
  - parametric analysis
    - for in silico evaluation, to reduce need for testing on patients
  - automated synthesis of optimal timing parameters
    - to determine delays between paces so that energy usage is optimised for a given patient
  - patient-specific parameterisation
  - hardware-in-the-loop simulation
    - parameter optimisation with respect to real energy measurements

- See http://www.veriware.org/pacemaker.php

Cardiac cell heart model

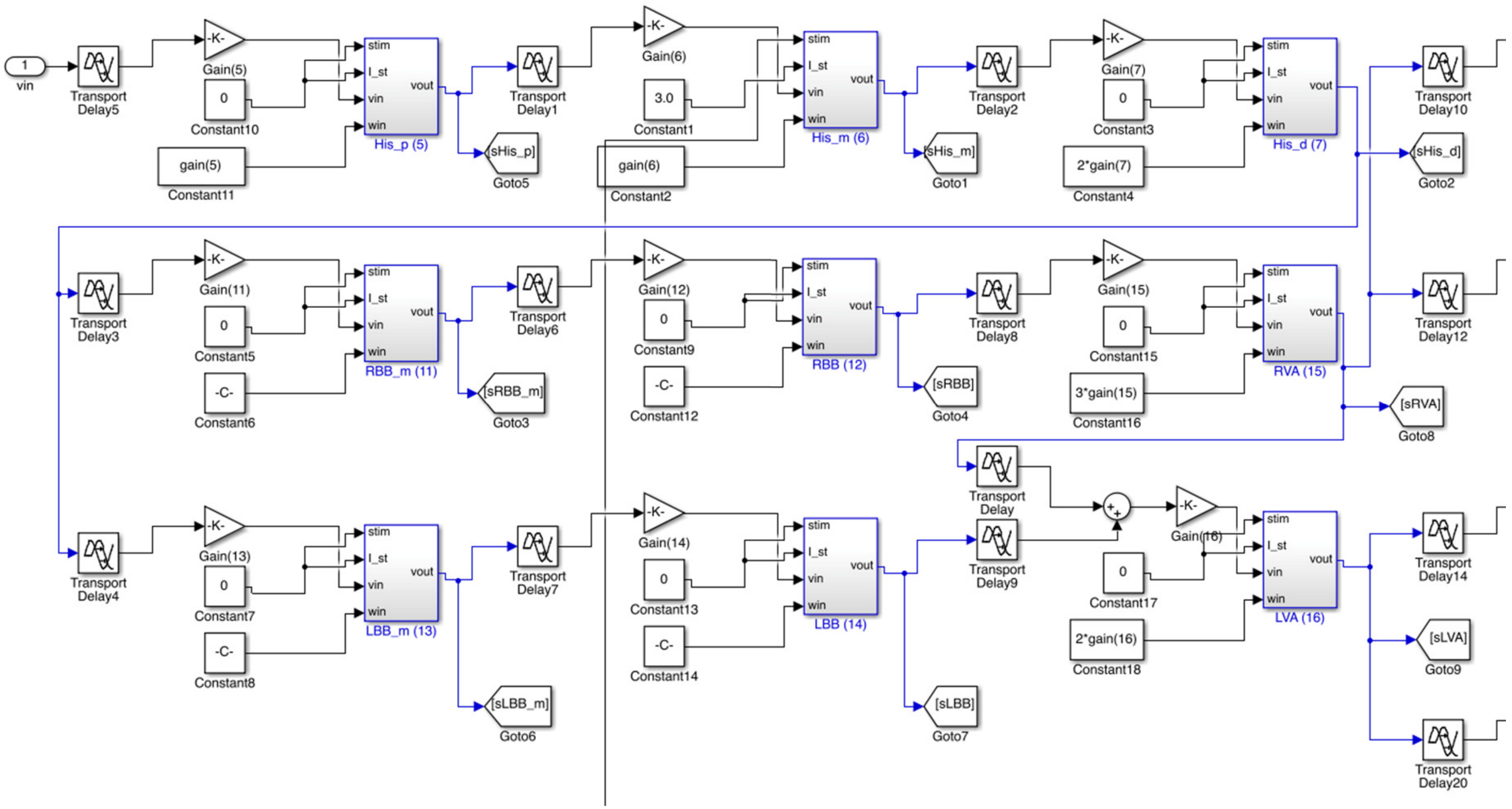
- Based on model of electrical conduction [Grosu et al]
  - abstracted as a network of cardiac cells that conduct voltage





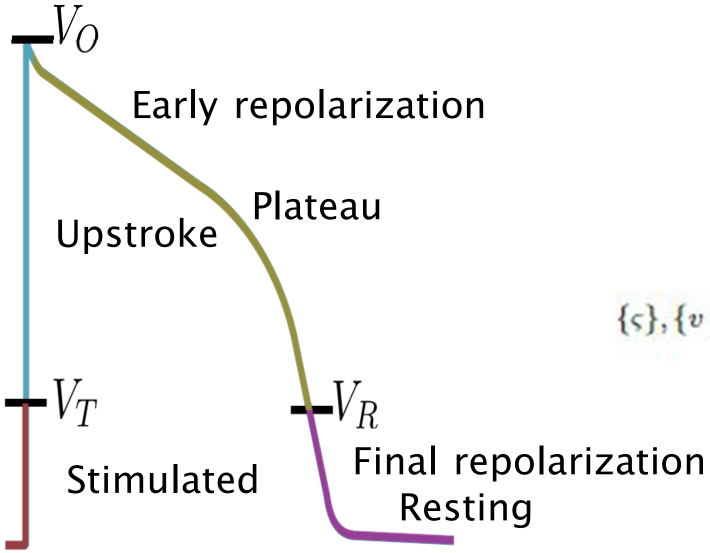
  - cells connected by pathways, modelled using Simulink delay and gain components
  - SA node is the natural pacemaker

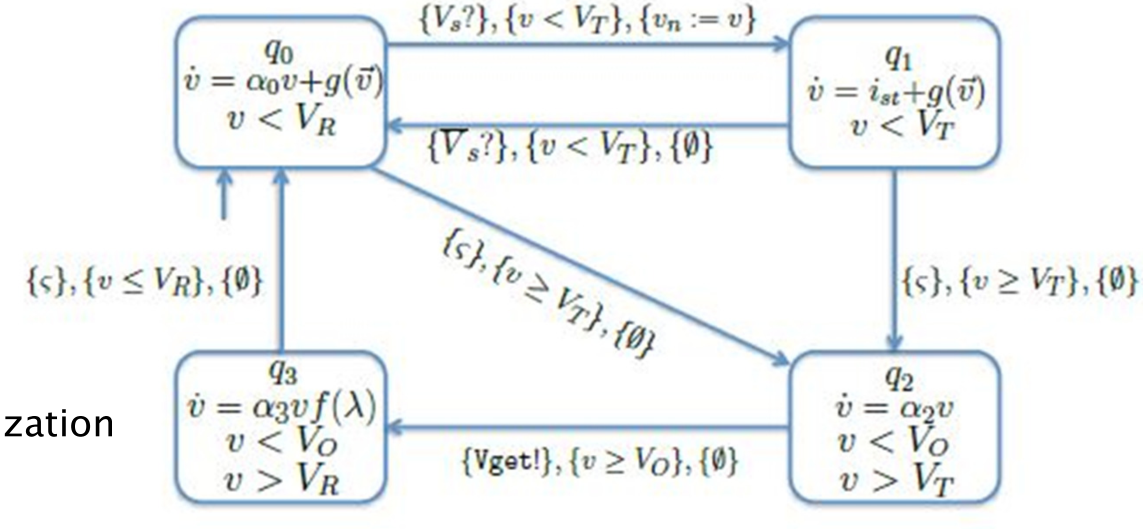
Cardiac cell network in Simulink



Cardiac cell heart model: single cell

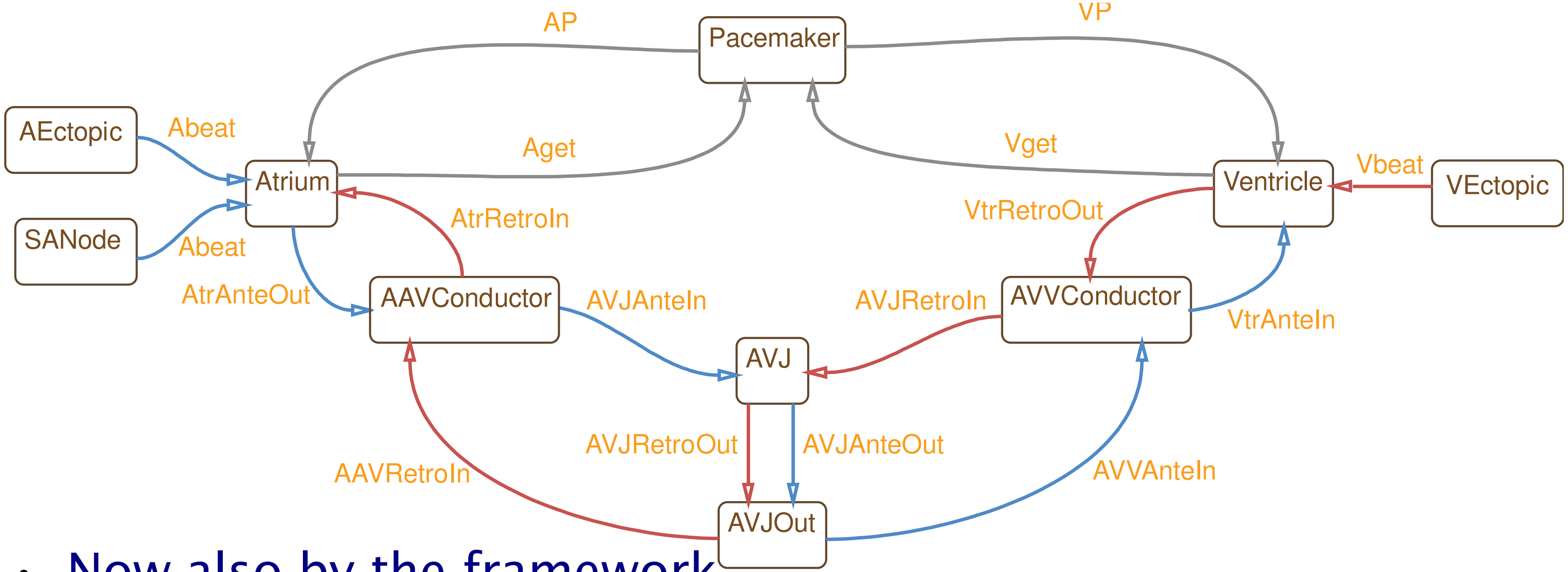
- Single ventricular cell [Grosu et al]
  - four modes: resting and final repolarisation (q_0), stimulated (q_1), upstroke (q_2) and plateau and early repolarisation (q_3)





  - variables: v – membrane voltage, i_{st} – stimulus current
  - constants: V_R – repolarisation voltage, V_T – threshold, V_O – overshoot voltage

New heart model



- Now also by the framework
  - structurally simpler, yet more powerful [Lian et al 2010]
  - antegrade and retrograde conduction paths
  - models AV conduction delay
  - allows Cardiac Output (CO) estimation
  - supports personalisation from ECG

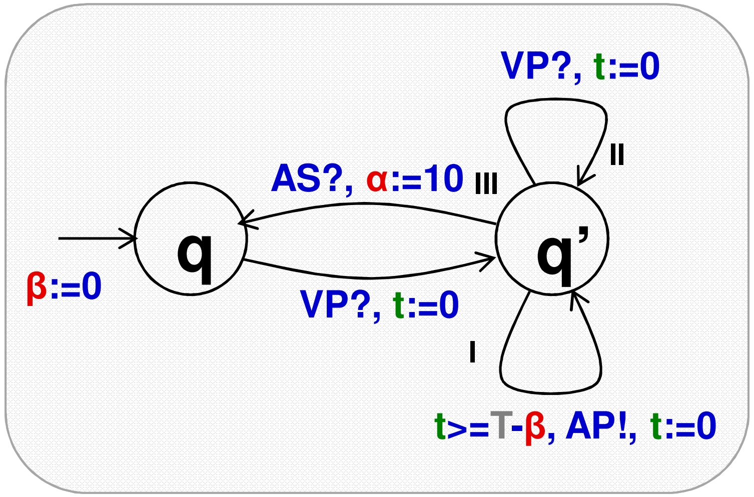
Open source modelling of heart rhythm and cardiac pacing, Lian et al., *Open Pacing Electrophysiol Ther J*, 3:4, 2010

Heart model of Lian et al

- Hybrid dynamics of electrical conduction relatively simple
  - can be modelled using parametric timed automata with data and priorities
  - priorities define a total ordering of the edges
  - enables Cardiac Output estimation (heart’s efficiency measure)
  - no continuous flows
- To model conduction
  - use data variables in the guards
  - each time edge taken, update the data variables using reset
- Expressed in a subset of Simulink/Stateflow language
- Additionally allow
  - non-linear guards and resets
  - probabilistic resets, physiologically more realistic

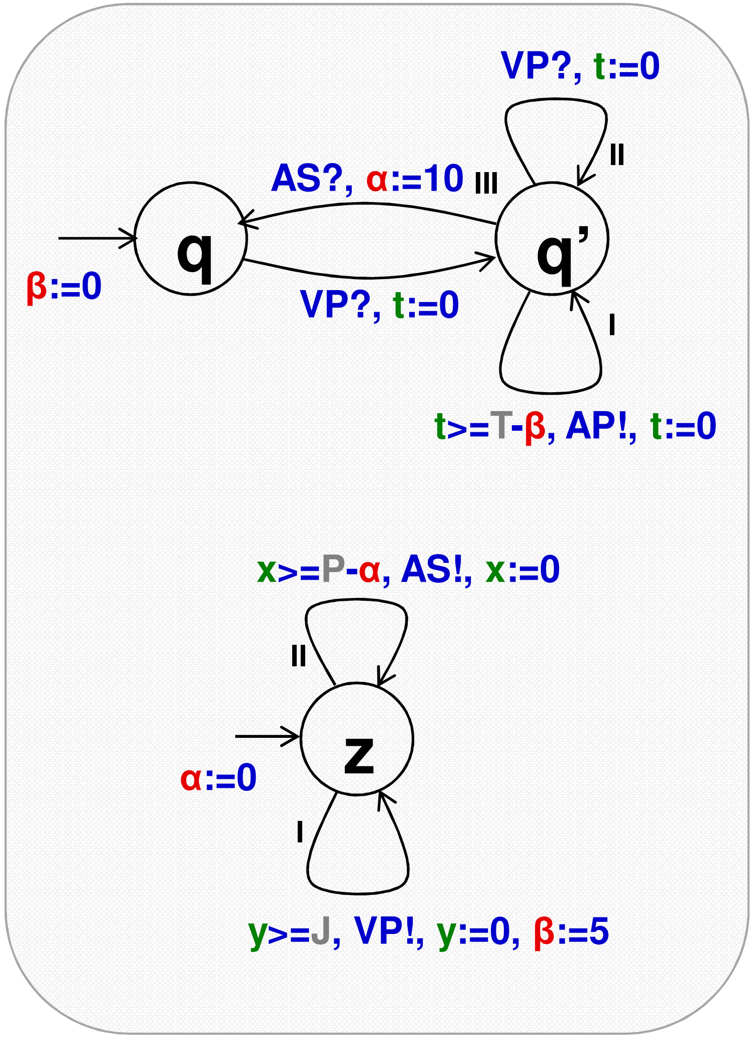
Timed I/O automata with data (TIOAs)

- Finite set of locations
- Real-valued variables
  - clocks and data
  - parameters
- Edges labelled with actions
  - input AS?, output AP!
- Guards may be non-linear
- Resets of variables similar to clock resets
- Priorities ensure determinism
- No continuous flows
- Extend with probabilistic rests

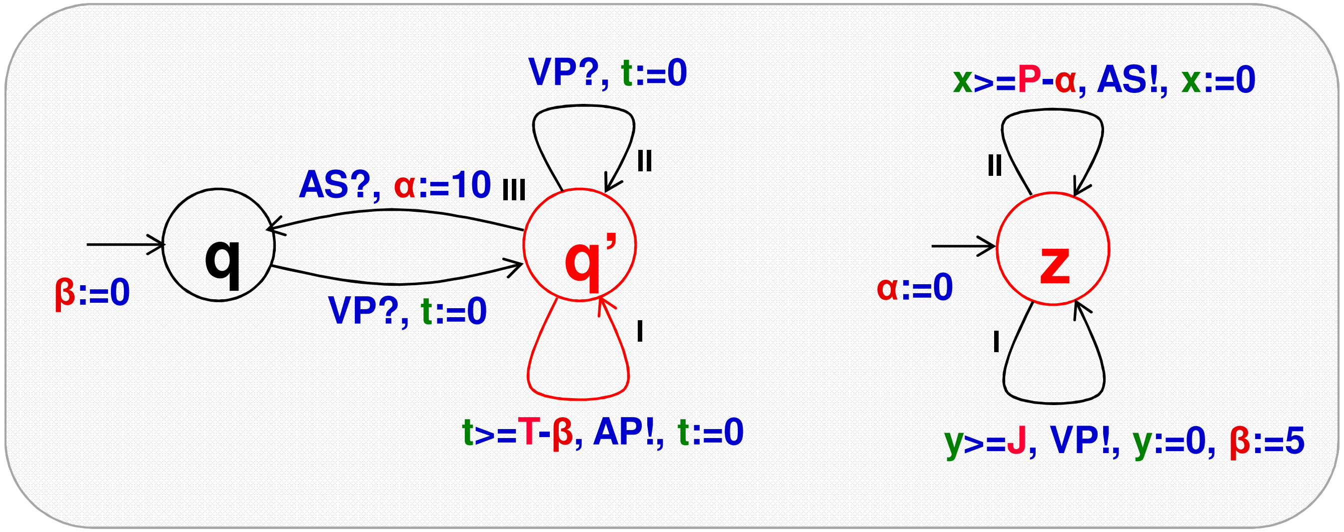


Networks of TIOAs

- Multiple TIOA components synchronise on input and output actions
- Semantics given as timed paths
- Enabled edges are urgent (performed as soon as they become enabled)
- Among the enabled edges, we pick the one with highest priority
- Deterministic evolution



Network example

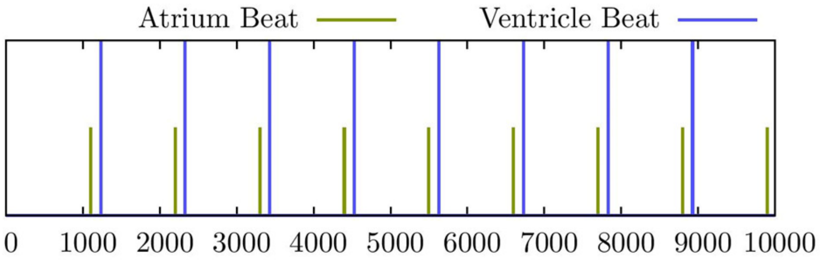


Timed Path

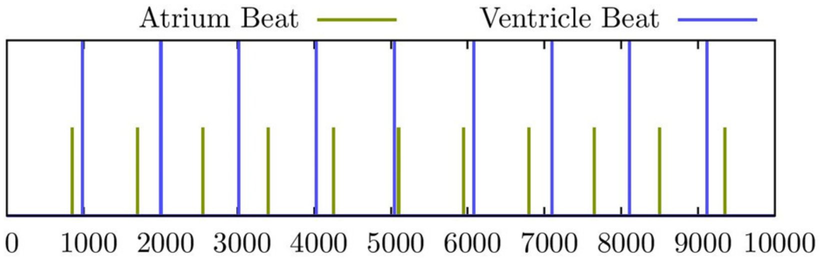
$$((q,z),(\alpha=0,\beta=0,t=0,x=0,y=0))$$
$$\downarrow J, \text{VP}$$
$$((q',z),(\alpha=0,\beta=5,t=0,x=J,y=0))$$
$$\downarrow T{-}5, \text{AP}$$
$$((q',z),(\alpha=0,\beta=5,t=0,x=J{+}T{-}5,y=T{-}5))$$

Examples of heart dynamics

- Model reproduces range of healthy and diseased behaviours, including Bradycardia



- Wenckebach AV Block (shown), etc



Focus on...

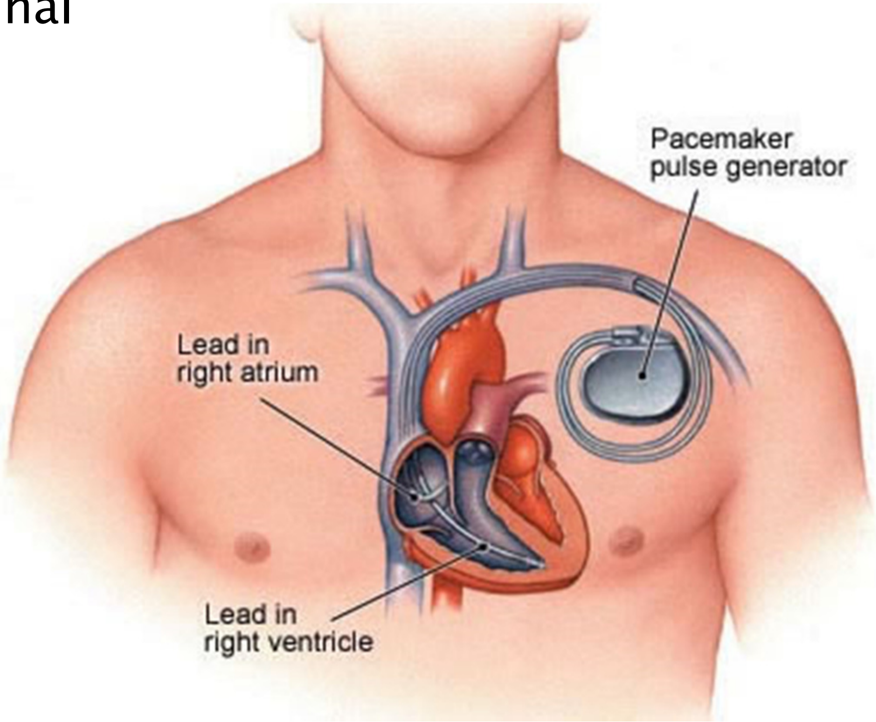
Modelling

Verification

Personalisation

Implantable pacemaker

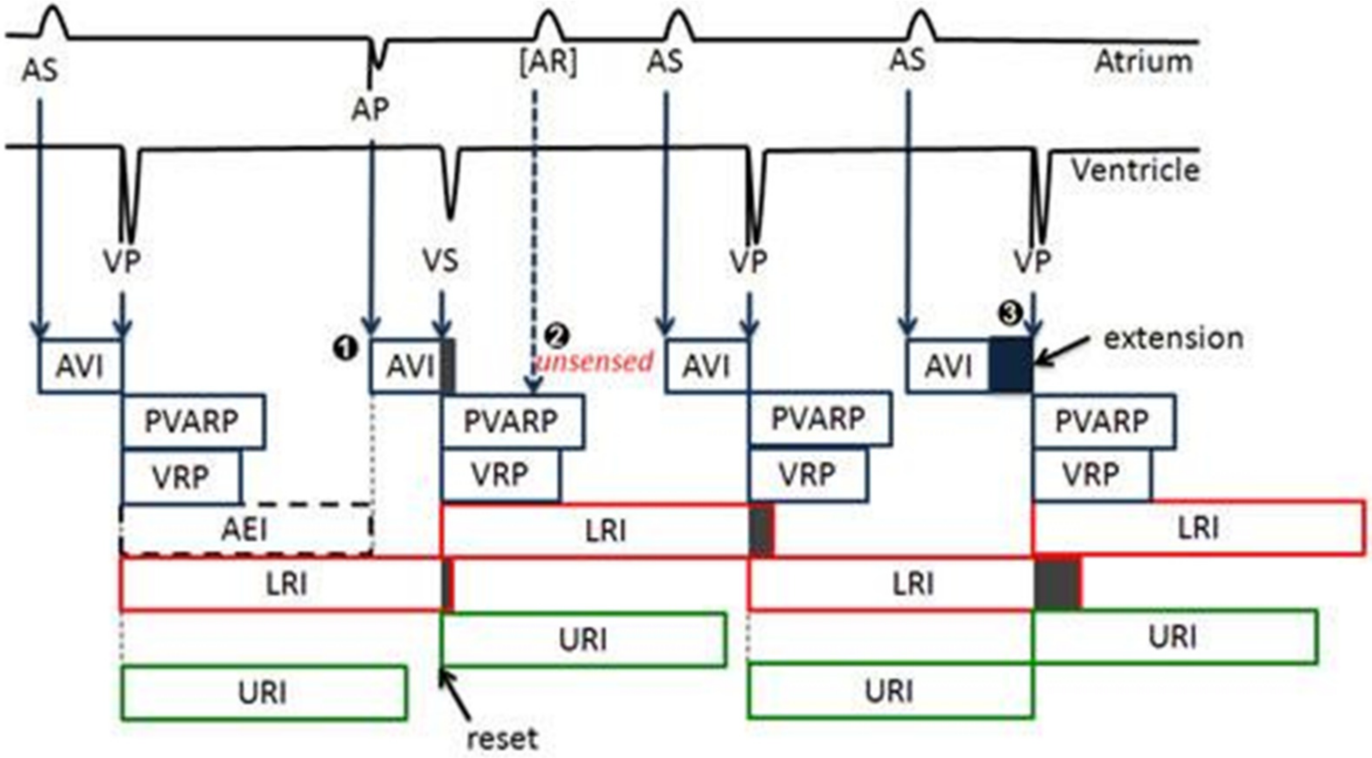
- How it works
  - reads electrical (action potential) signals through sensors placed in the right atrium and right ventricle
  - monitors the timing of heart beats and local electrical activity
  - generates artificial pacing signal as necessary
- Real-time system!



- Core specification by Boston Scientific
- Basic pacemaker can be modelled as a network of timed automata [Zhang et al]

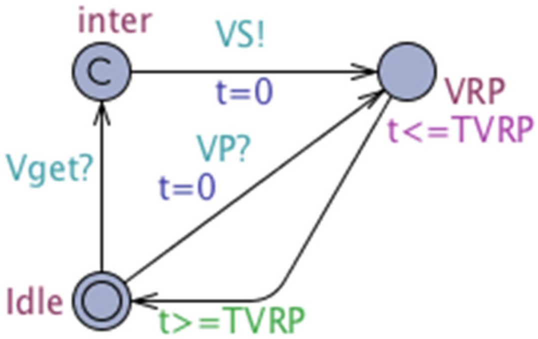
Pacemaker timing cycle

- Atrial and ventricular events



Pacemaker modelling

- Modelled as networks of TIOAs
  - extend with parameters
  - synchronise on input-output
  - add priority and urgency of output



- Properties: Counting Metric Temporal Logic (CMTL)
  - linear-time, real-valued time bounds
  - event counting in an interval of time

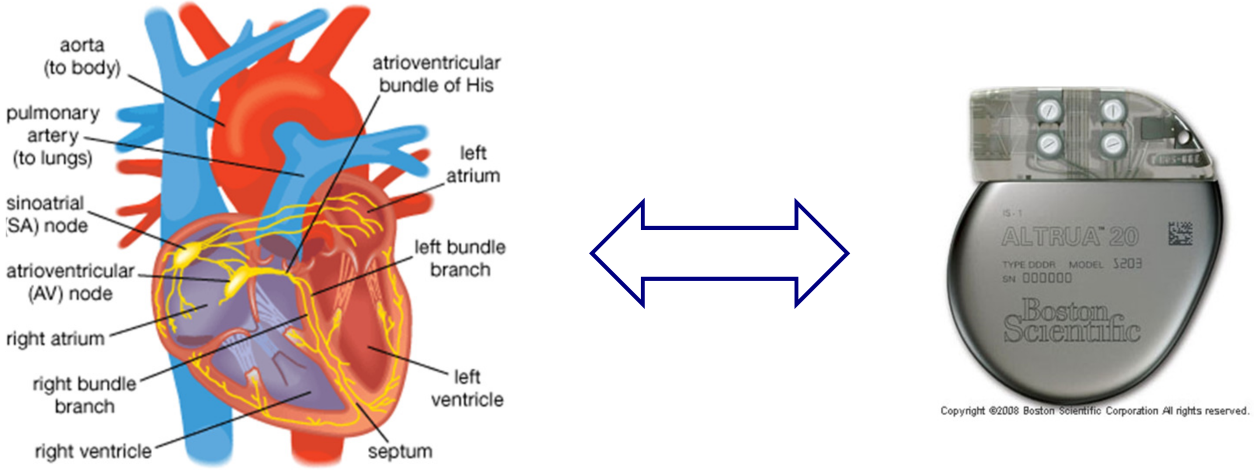
$$\Box^{[0,\tau]}(\#_0^\tau \mathtt{Vget} \geqslant B_1 \wedge \#_0^\tau \mathtt{Vget} \leqslant B_2)$$

  - reward weighting, e.g. energy consumption

$$1 \cdot \#_0^\tau \mathtt{AP} + 2 \cdot \#_0^\tau \mathtt{VP} \leqslant \mathsf{E}$$

Quantitative verification for pacemakers

- Model the pacemaker and the heart as timed I/O automata
- Compose and verify



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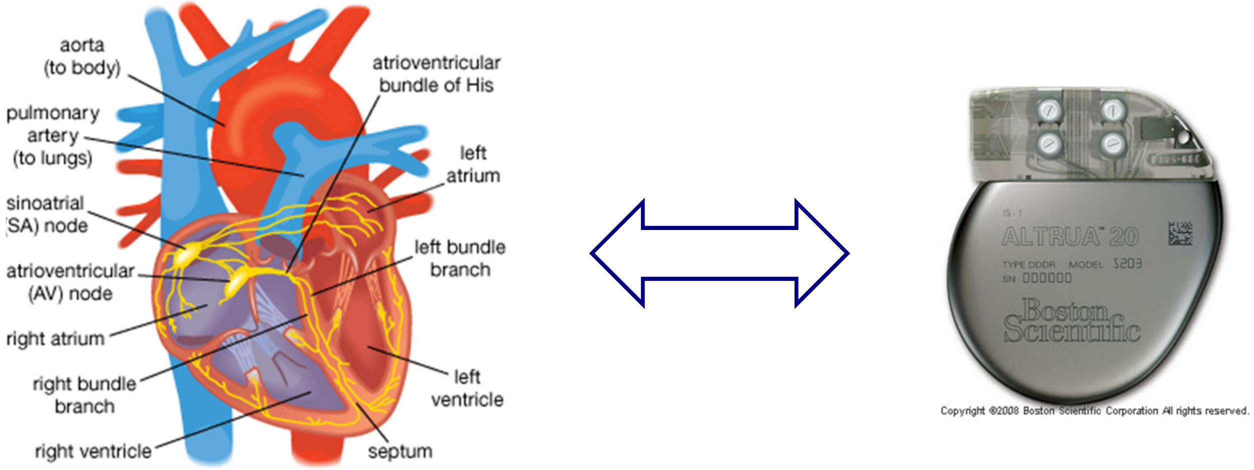

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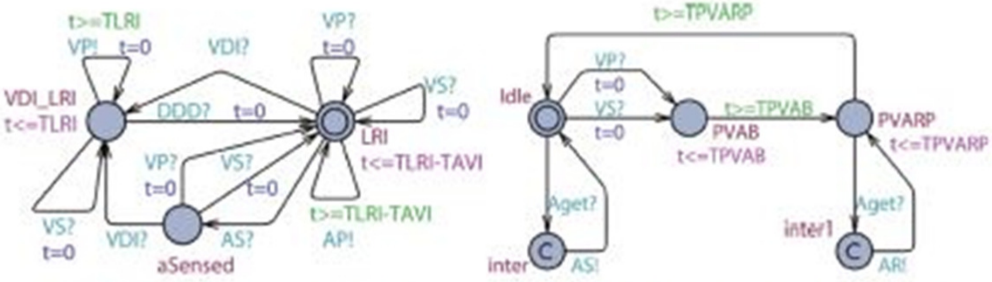
- Can we synthesise (controllable) timing delays to minimise energy, without compromising safety?

Basic pacemaker

- Consists of five communicating timed I/O automata components [Jiang et al]



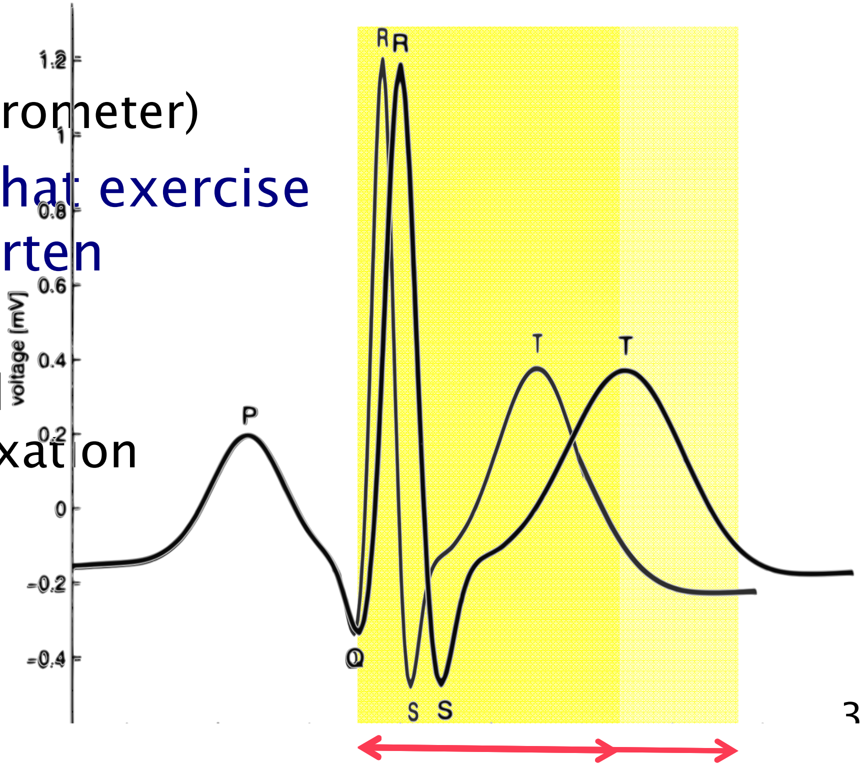
(a) LRI component (b) PVARP component

  - LRI keeps the heart rate above a given minimum value
  - PVARP notifies all other components that an atrial event has occurred

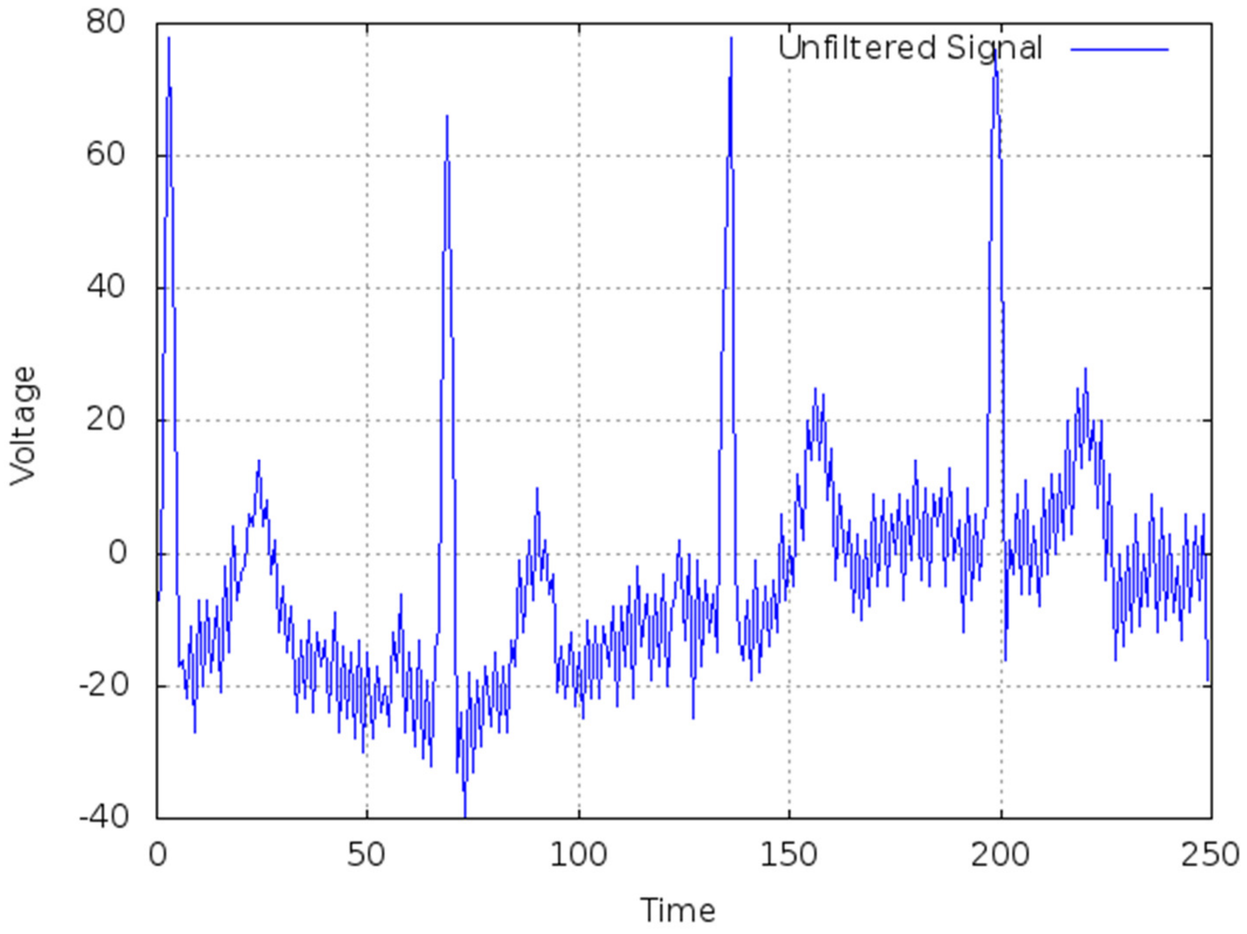
- Can be enhanced with noise and probabilistic switching between healthy and diseased heart (for personalisation)

Rate-adaptive pacemakers

- Can regulate the pacing rate according to patient’s needs (exercise, stress, …)
  - needed when the heart cannot adapt its rate to increasing demand (chronotopic incompentence)
- Use implantable sensors to detect activity level and metabolic need
  - e.g. body movement (accelerometer)
- QT sensors exploit the fact that exercise and increased heart rate shorten QT interval (QTI)
  - QT in the ECG is the interval from the contraction to relaxation of ventricles
  - can be measured from ECG (method implemented)



QT detection



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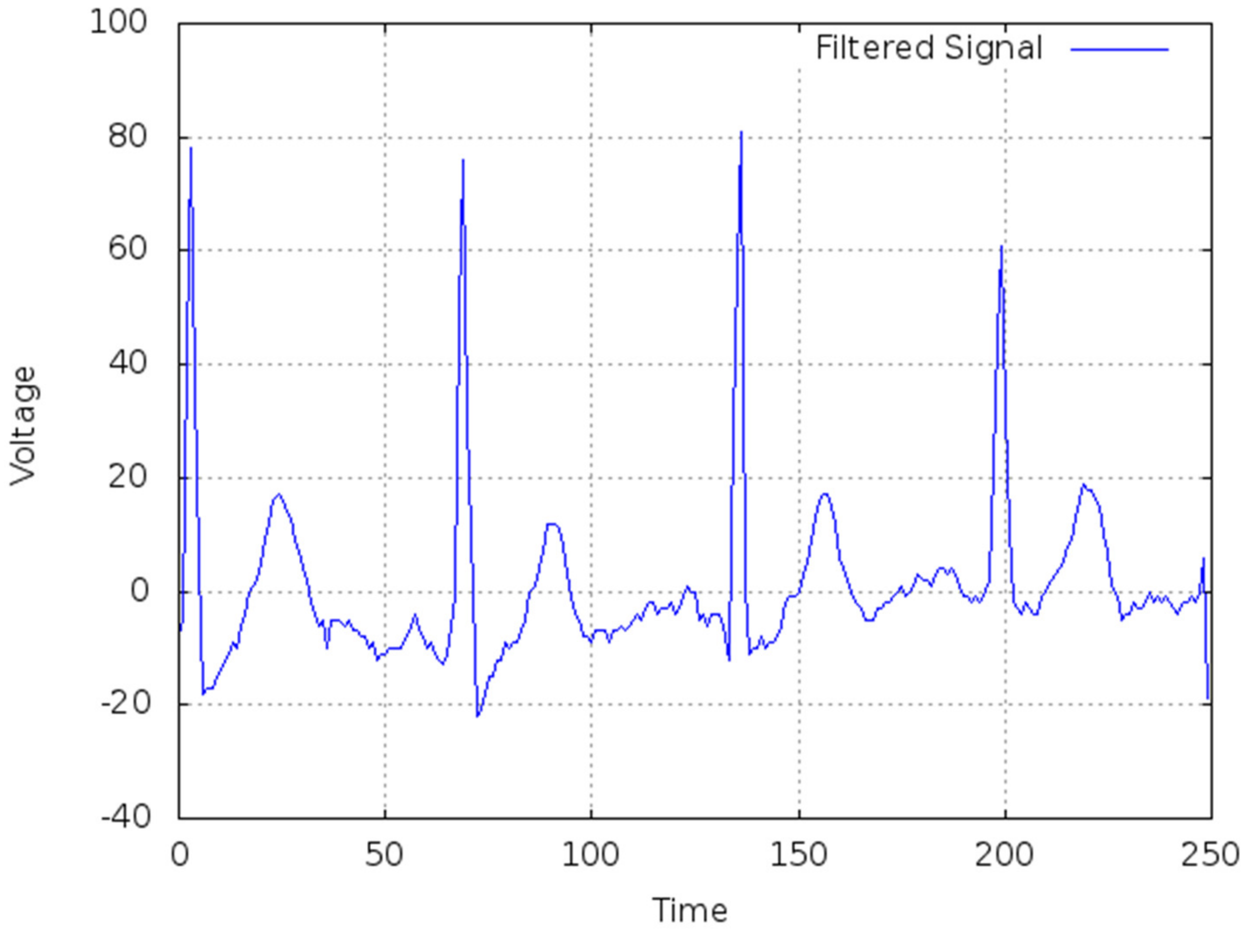

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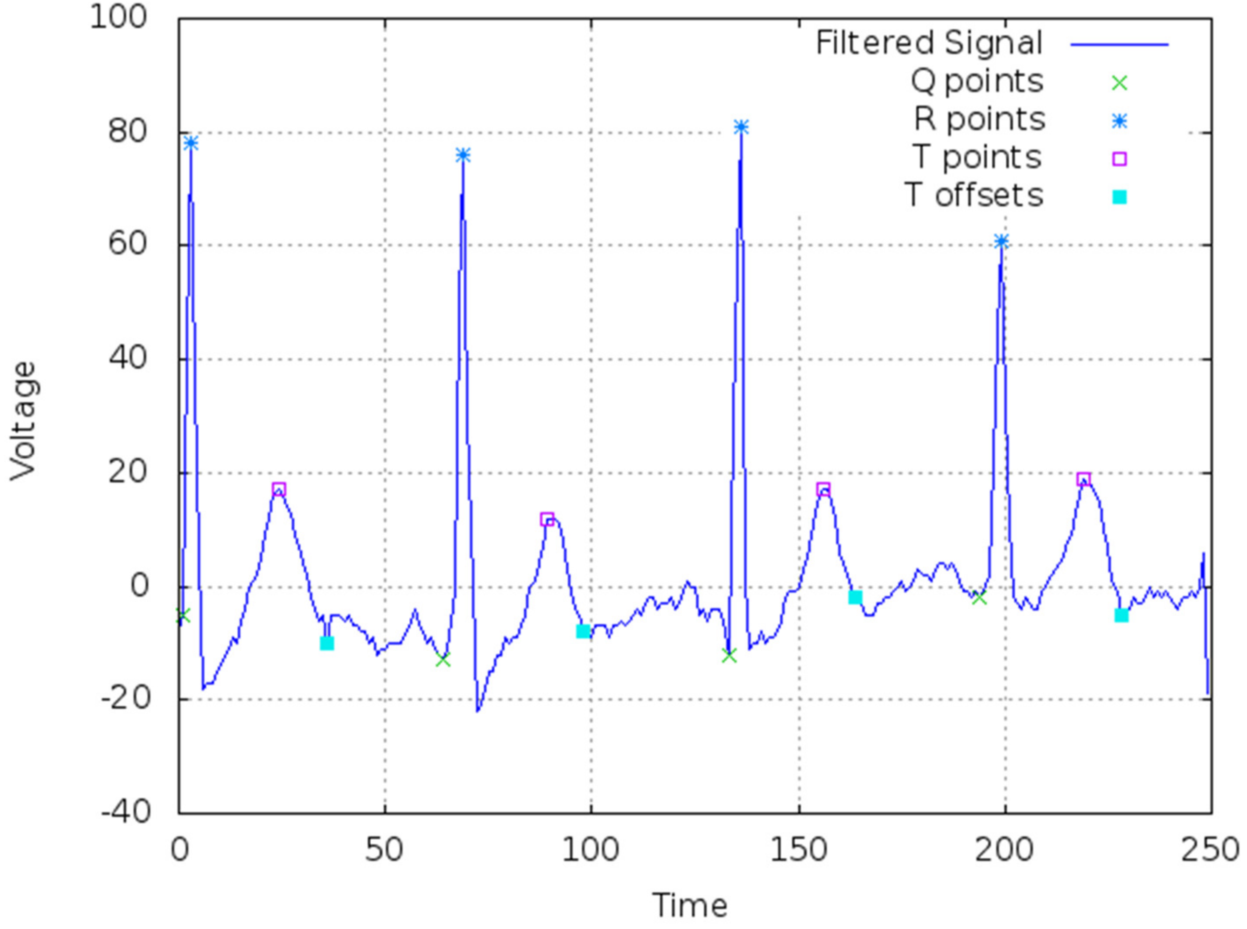
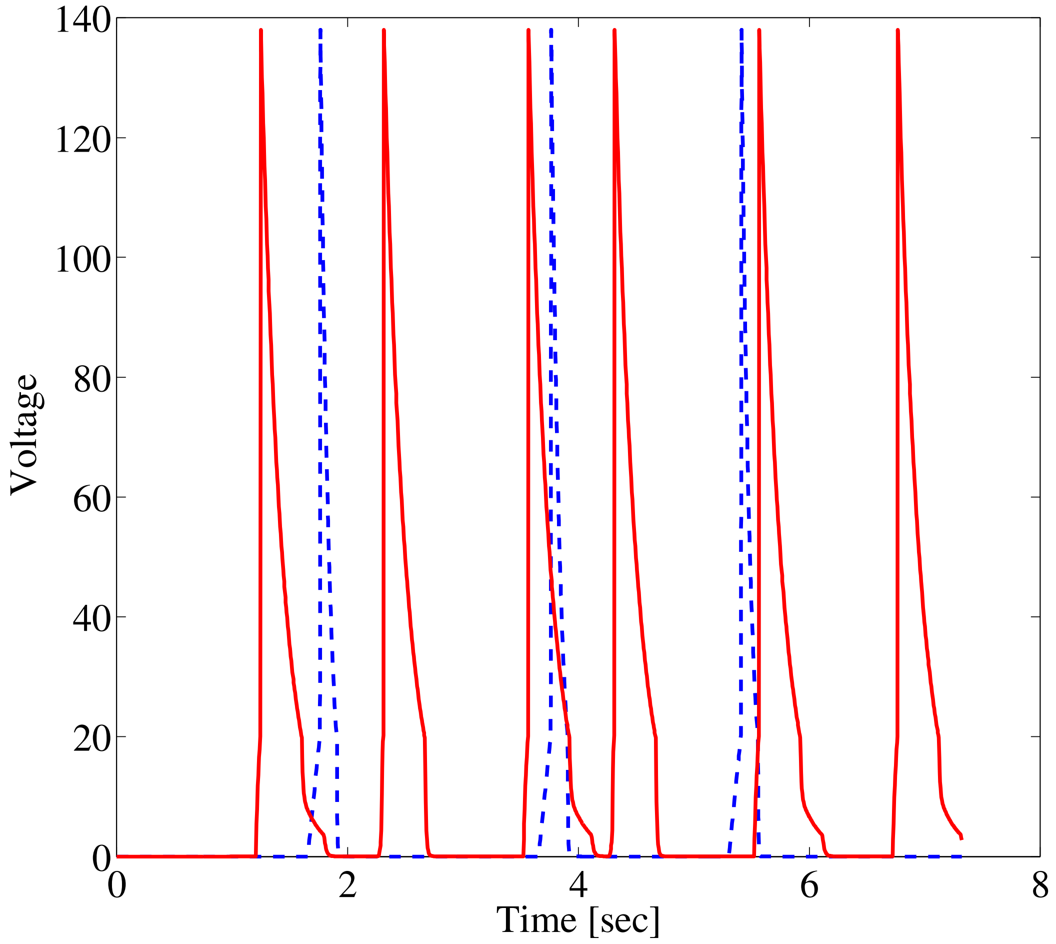
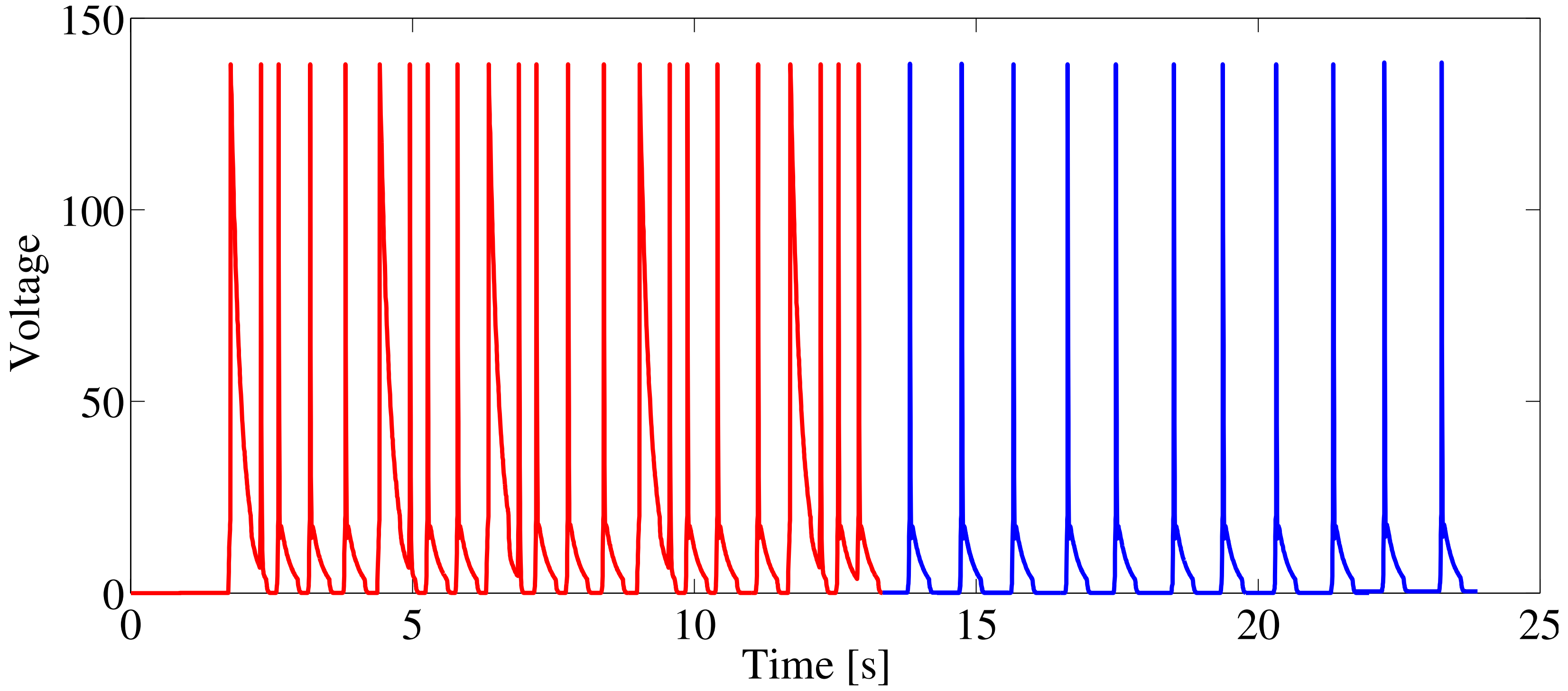


Correction of Bradycardia



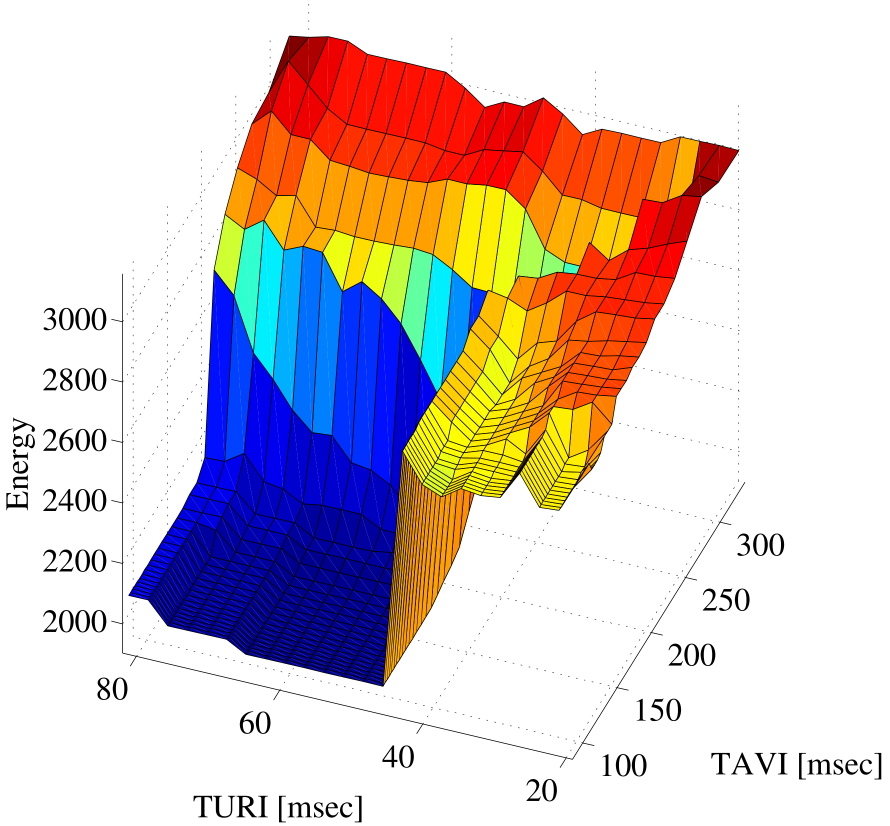
Blue lines original (slow) heart beat, red are induced (correcting)

Correction of PMT



Red lines original (PMT) heart beat, blue are induced (correcting)

Energy consumption



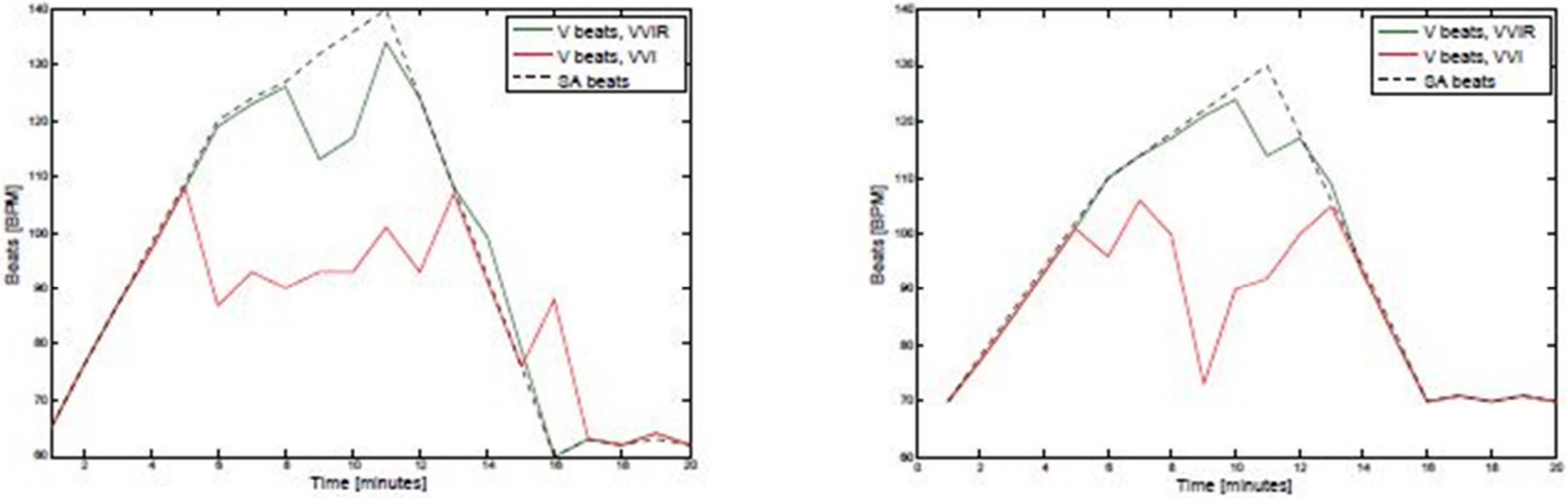
Efficiency “energy consumed must be below some fixed level”

Battery charge in 1 min under Bradycardia, varying timing parameters

Based on real power measurements

Hardware-in-the-loop simulation and energy optimization of cardiac pacemakers.
Barker *et al*, In *Proc EMBC*, 2015

Modulation during physical activity

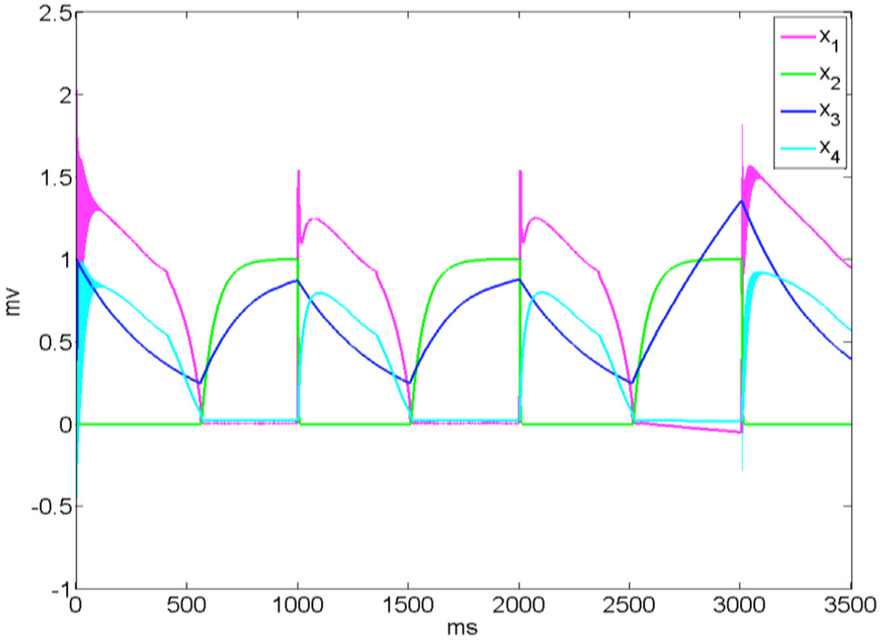


(a) Young patient (b) Old patient

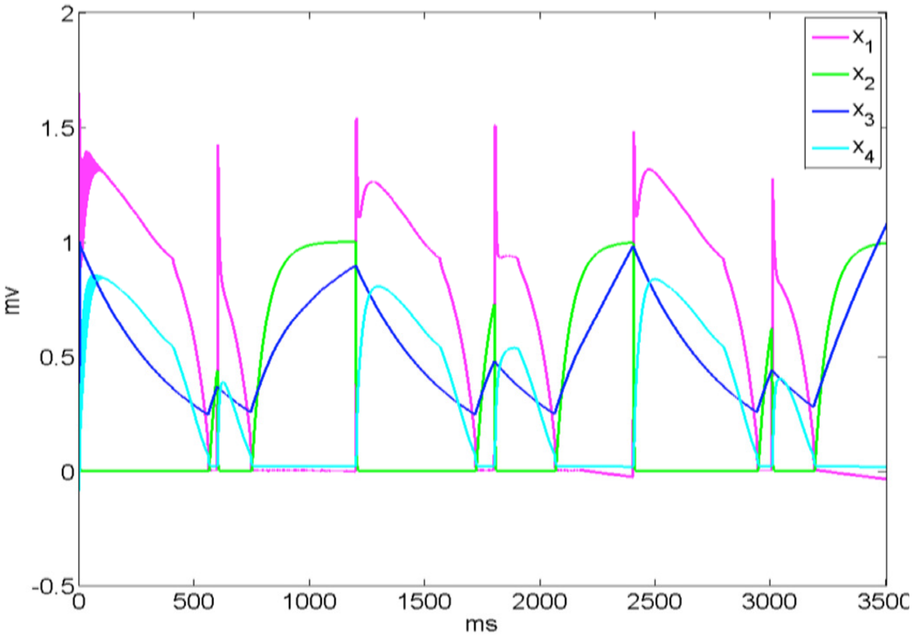
Rate modulation during exercise. Black dashed line indicates metabolic demand, and the green and red curves show rate-adaptive VVIR and fixed-rate VVI pacemakers.

Formal Modelling and Validation of Rate-Adaptive Pacemakers, Kwiatkowska *et al*. In *IEEE International Conference on Healthcare Informatics*, ACM. 2014

Alternans in the heart



Pacing rate: 1s



Pacing rate: 0.6s

We plot the reach set from a set of initial states observe whether the AP durations alternate

Invariant Verification of Nonlinear Hybrid Automata Networks of Cardiac Cells. Huang *et al*
In *CAV*, volume 8559 of LNCS, pages 373-390, Springer, 2014.

From verification to synthesis…

- Automated verification aims to establish if a property holds for a given model
- Can we find a model so that a property is satisfied?
  - difficult…
- The parameter synthesis problem is
  - given a parametric network of timed I/O automata, set of controllable and uncontrollable parameters, CMTL property ϕ and length of path n
  - find the optimal controllable parameter values, for any uncontrollable parameter values, with respect to an objective function O, such that the property ϕ is satisfied on paths of length n, if such values exist
- Objective function
  - maximise volume, or ensure robustness

Synthesising Optimal Timing Delays for Timed I/O Automata. Diciolla et al. In *14th International Conference on Embedded Software (EMSOFT'14)*, ACM. To appear. 2014

Optimal timing delays

- Bi-level optimisation problem
- Safe heart rhythm CMTL property (inner problem)

$$\phi = \square^{[0,T]} \left(vPeriod \in [500, 1000] \right)$$

  - at any time in [0,T] any two consecutive ventricular beats are between 500 and 1000 ms, i.e. heart rate of 60 and 120 BPM
- Cost function (outer problem)

$$2 \cdot \#_0^{60000} \left(act = AP \right) + 3 \cdot \#_0^{60000} \left(act = VP \right)$$

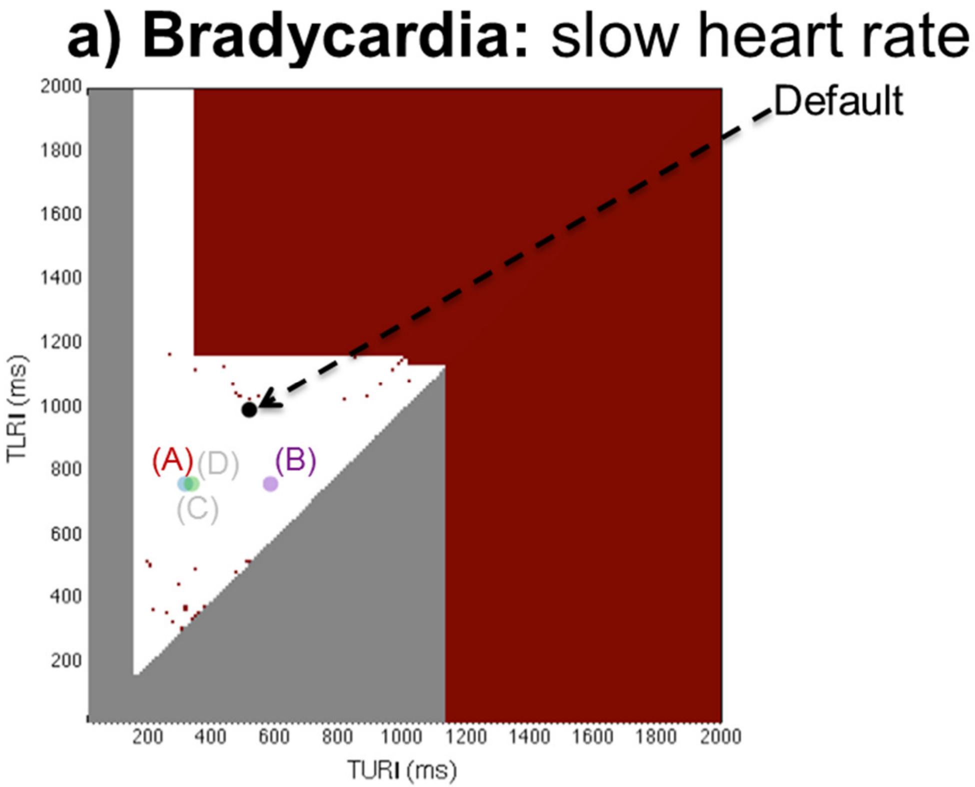
  - energy consumption in 1 minute

$$\frac{\sum_{(\mathbf{q},\eta)\in Vbeat(\rho')} |\eta(CO) - \overline{CO}|}{|Vbeat(\rho')|}$$

  - mean difference between cardiac output and reference value

Synthesis results

- Solved through SMT encoding (inner problem) combined with evolutionary computation (outer problem)
- Pacemaker parameters:
  - TLRI: time the PM waits before pacing atrium
  - TURI: time before pacing ventricle after atrial event
- Significant improvement (>50%) over default values
  - path 20
- A (exact),B (evo) energy
- C (exact),D (evo) CO
  - evo faster, less precise



Synthesising robust and optimal parameters for cardiac pacemakers using symbolic and evolutionary computation techniques, Kwiatkowska et al.,In *Proc* HSB 2015

Focus on…

Modelling

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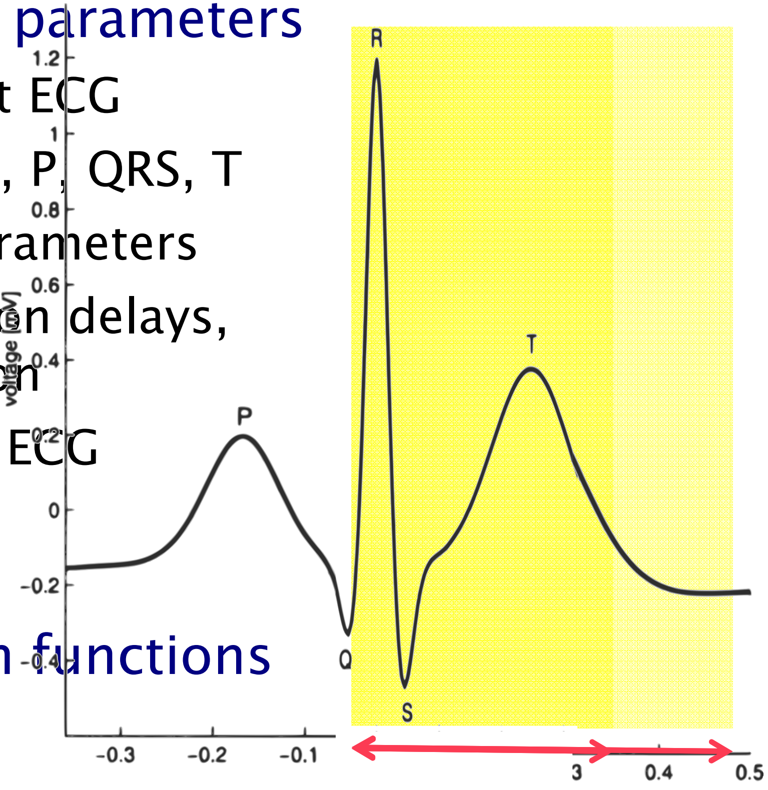
Estimation from ECG data



- Steps towards personalisation of parameters
  - filtering and analysis of the input ECG
  - detection of characteristic waves, P, QRS, T
  - mapping of intervals: explicit parameters
  - implicit parameters, eg conduction delays, use Gaussian Process optimisation
  - compare synthetic ECG with real ECG using statistical distance

- Synthetic ECG = sum of Gaussian functions centred at each wave l_i

$$\text{synthECG}(t) = \sum_{i \in \{P,Q,R,S,T\}} \sum_{l_i \in \text{Peaks}_i} a_i \cdot \exp\left(-\frac{(t-l_i)^2}{2c_i^2}\right).$$

Statistical distance

- Computed between the filtered and synthetic ECG
- How similar are two signals?
  - returns value between 0 (identical) and 1
- Works by phase assignment
  - discretise the wave forms into discrete distributions,
  - then compute total variation distance

$$d(\mu_{i,p}, \mu_{j,p}) = \frac{1}{2} \sum_{x \in X} |\mu_{i,p} - \mu_{j,p}|.$$

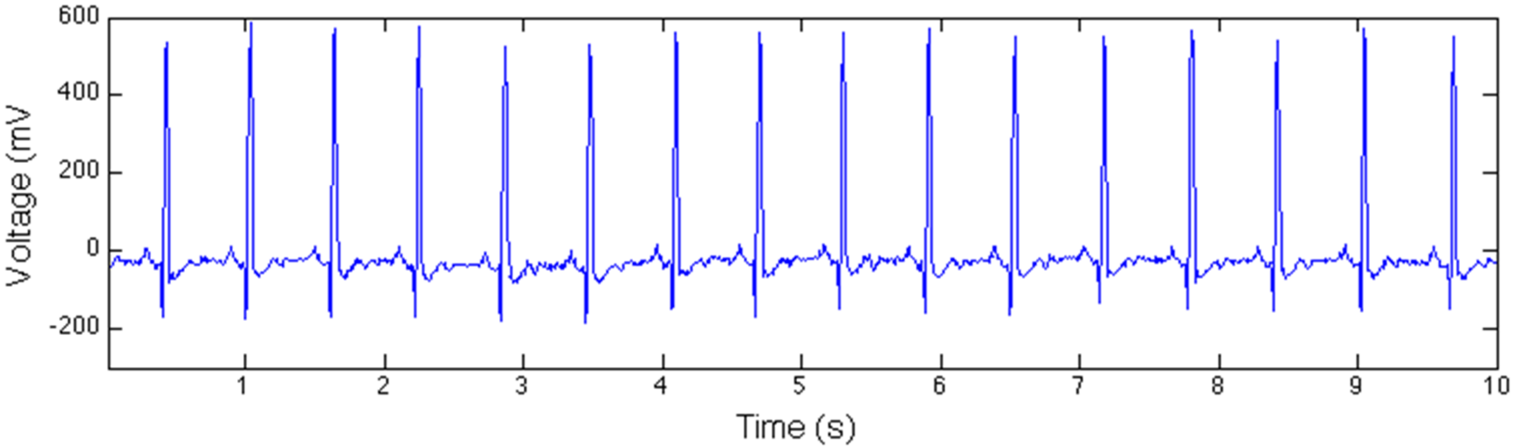
  - finally compute the mean of the distances for each point

$$d(w_i, w_j) = \frac{\sum_{p \in P} d(\mu_{i,p}, \mu_{j,p})}{|P|}$$

- Method not affected by the heart rate

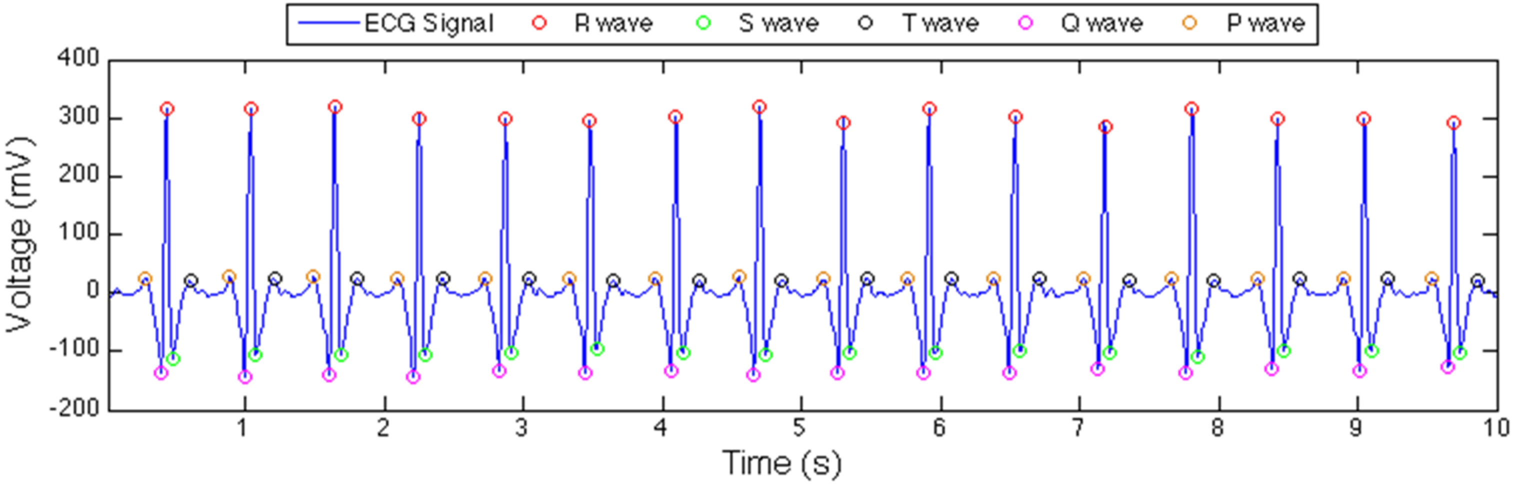
Raw ECG signal

- Real data



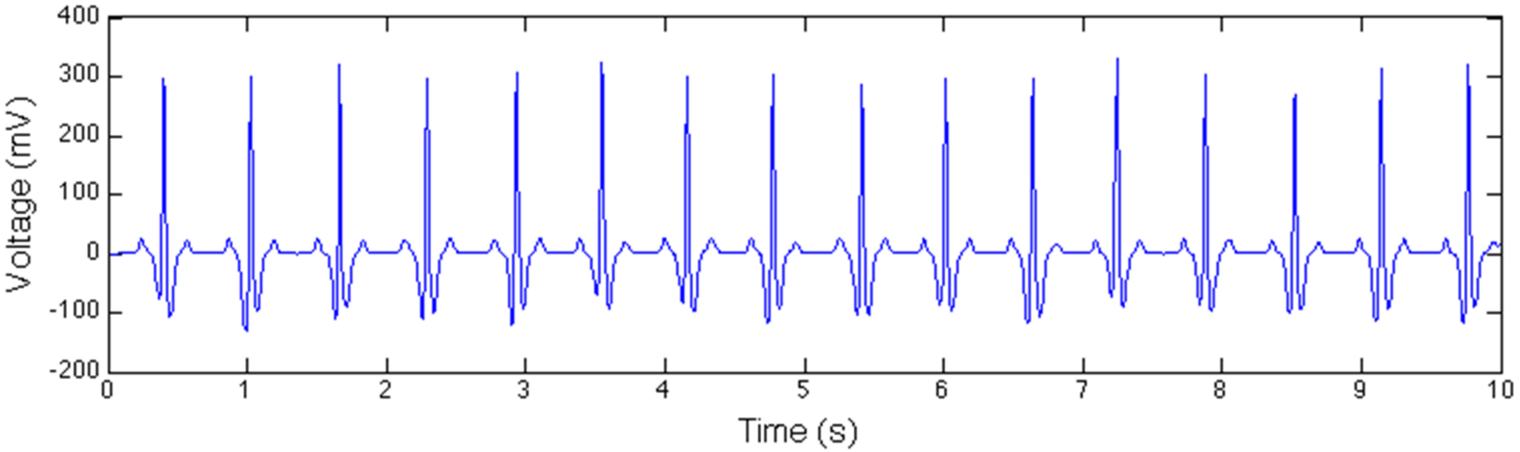
Filtered signal

- P,Q,R,S,T waves identified

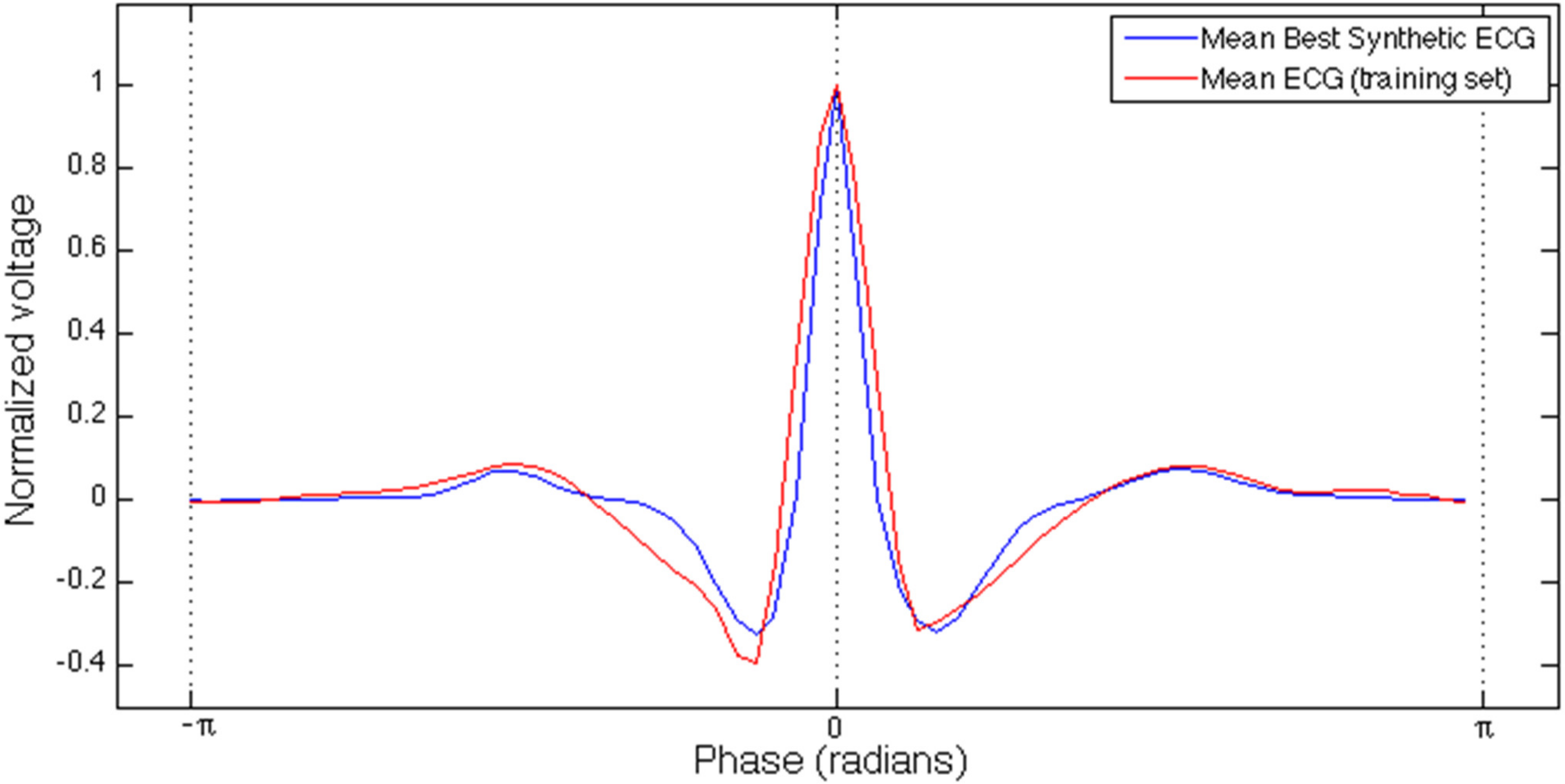


Synthetic ECG

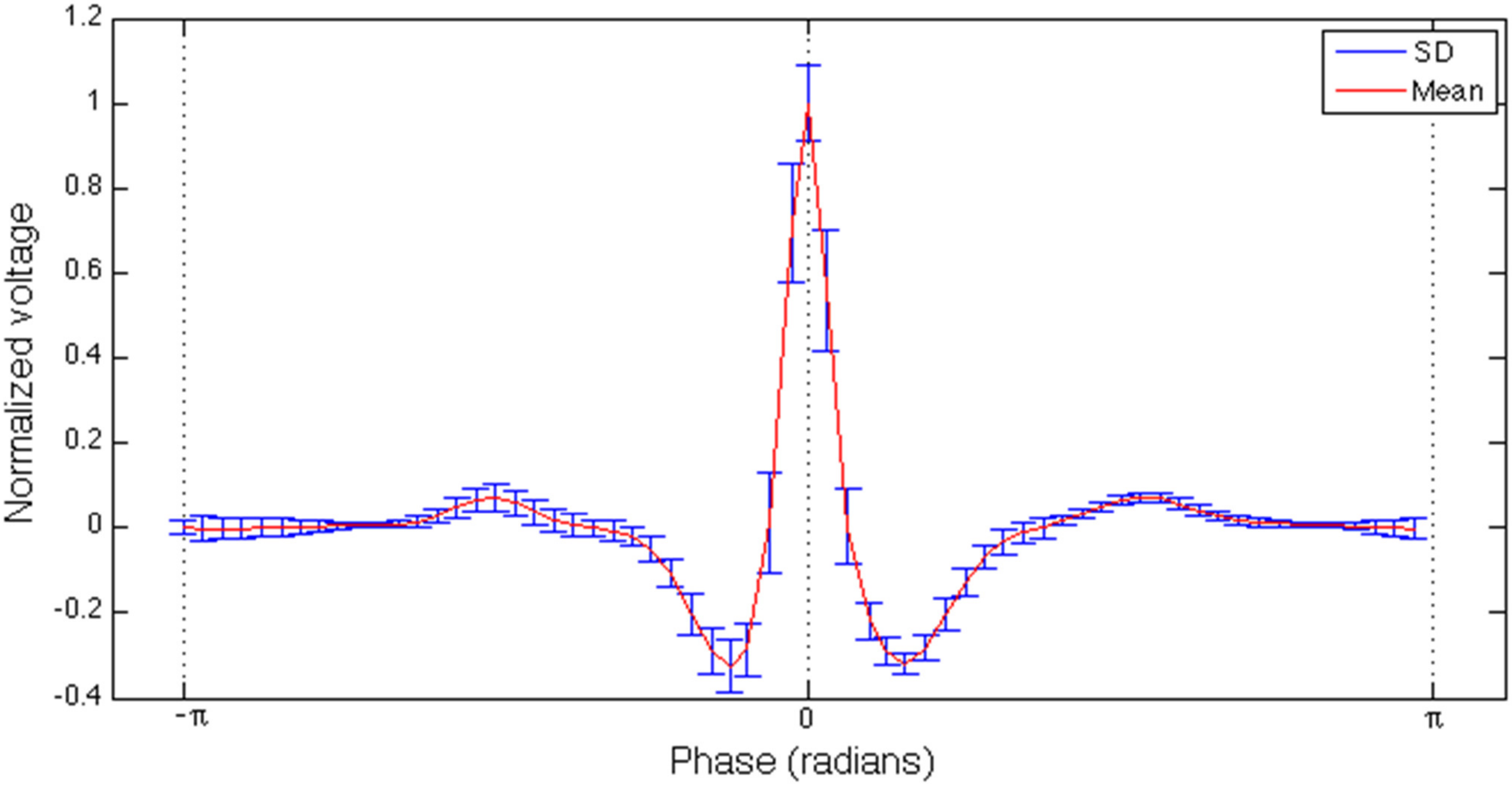
- Produced by the personalised model



Training set ECG



Best synthetic ECG



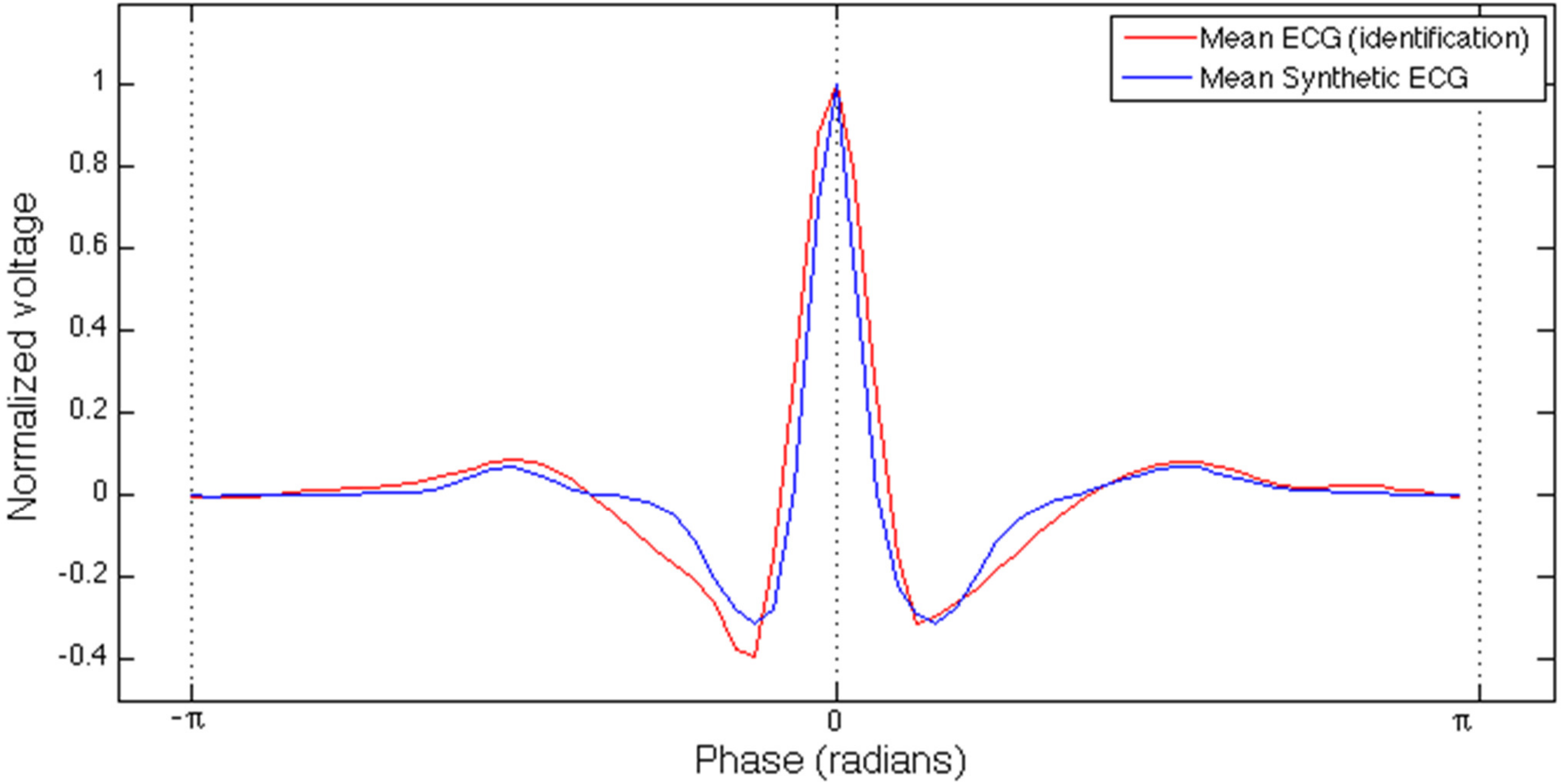
What good are personalised models?

- Variety of uses!
- Train the model for testing purposes
  - e.g. new pacemaker designs
- Evaluation of effectiveness of therapy
  - CO measure
  - energy efficiency, etc
- Authentication
  - ECG biometric signal

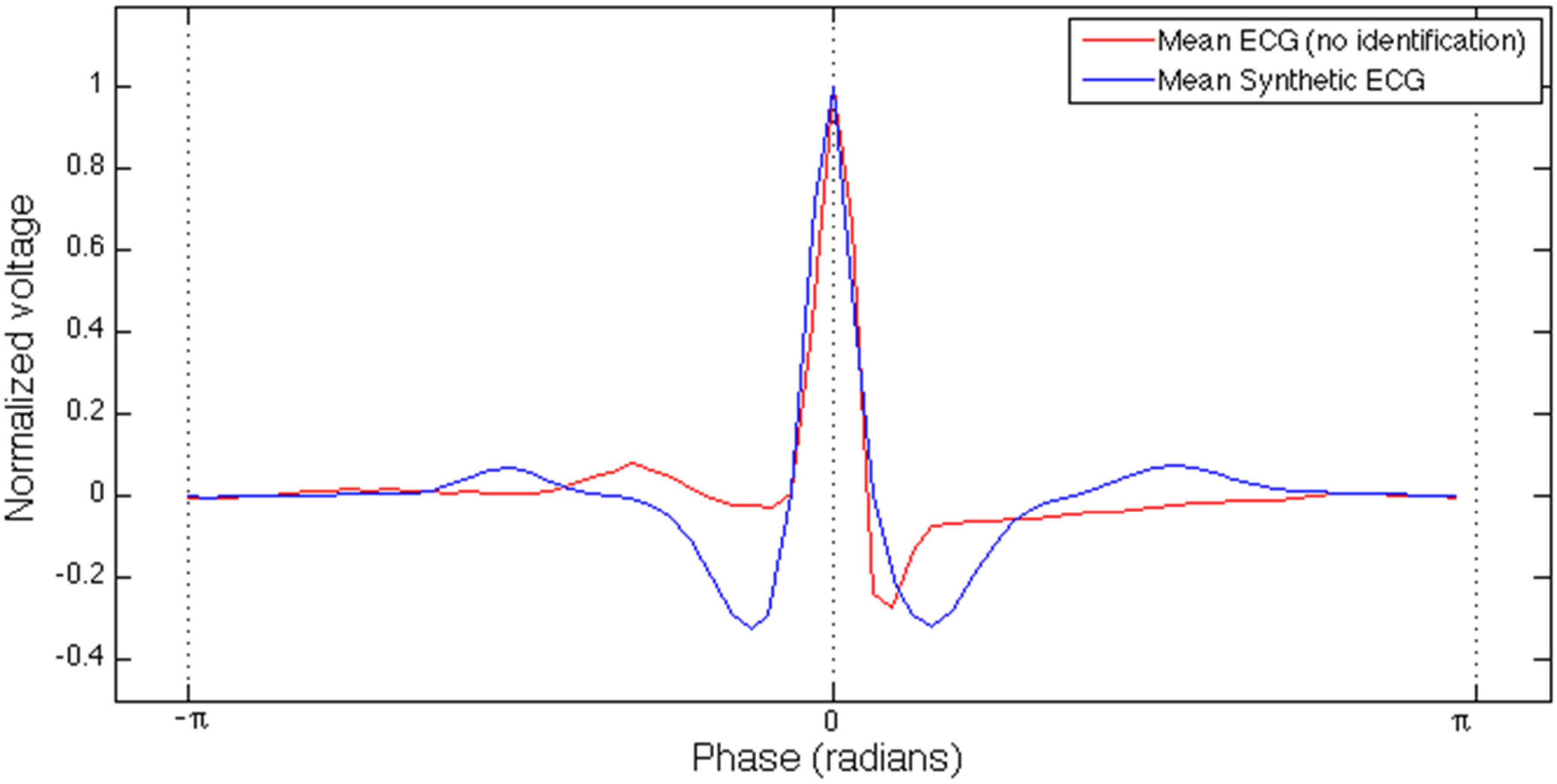
ECG-based authentication

- Growing interest in biometrics based on ECG
  - good level of accuracy
  - can be continuously monitored
  - difficult to falsify
    - unlike fingerprints
  - typically used in conjunction with other methods
- Enrolment
  - capture and processing of ECG
  - generation of the biometric template
- Authentication
  - capture recognition ECG
  - match with biometric template
- Variety of ECG authentication methods exist
  - here statistical distance

Same individual



Different individuals



Conclusion

- Demonstrated techniques for personalisation of heart models
  - other physiological processes?
  - suitable data widely available and easily collectable
  - how best to utilise?
- Multiple uses of personalisation
  - testing and product evaluation
  - authentication
  - personalised medicine, or electronic life?
- Model-based frameworks offer
  - rigour, unambiguous specifications
  - reusability
  - safety assurance
  - energy optimisation
  - code generation

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Summing up…

- Medical applications of ubiquitous computing fast increasing
  - Implantable, closed-loop and wearable devices
  - Need to monitor and adapt to physiological signals
  - Software an integrated and critical component
  - 24/7 health performance expectation
  - Safety-critical context, software failures on the increase

- Many scientific and technological challenges remain
  - Huge and complex models!
  - Scalability of quantitative verification
  - Accuracy of approximate verification
  - Efficiency of parameter synthesis
  - Efficiency of personalisation
  - Model synthesis from quantitative requirements

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- See also
  - VERIWARE www.veriware.org
  - PRISM www.prismmodelchecker.org