



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

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Joint work with Benoit Barbot and Nicola Paoletti

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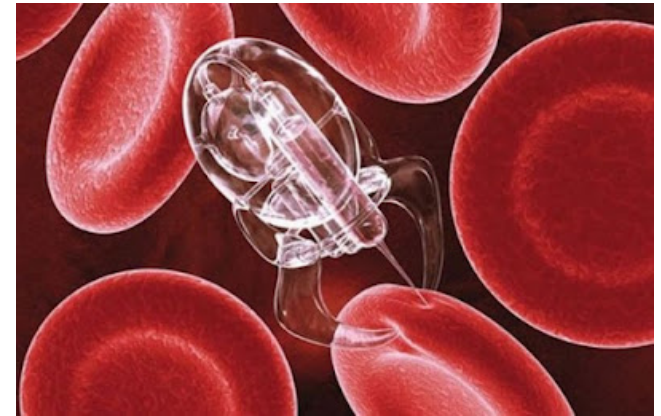
Ubiquitous computing

- 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 catheter
 - no leads
 - no reduced mobility
 - no chest incision
 - no scar
 - no lump under the skin
- First implanted 2014
- New designs being developed



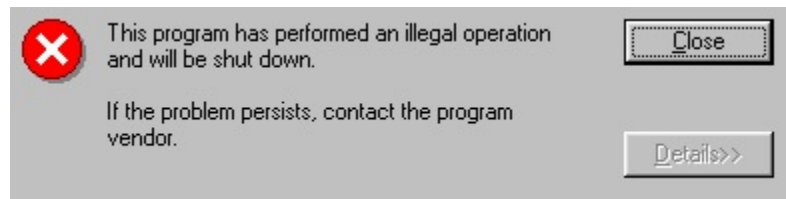
Wearable authentication devices

- **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?

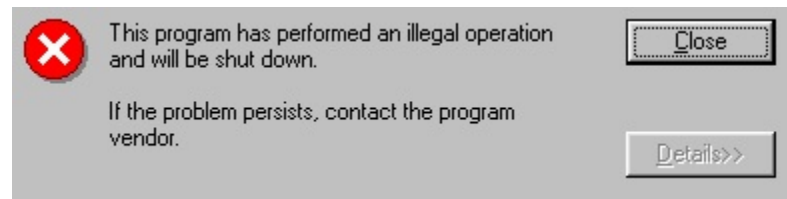
- Embedded software at the heart of the device
- Need to monitor and control complex physiological processes



- 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



- 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 **ECC** **based** devices

Focus on...



Modelling

Verification



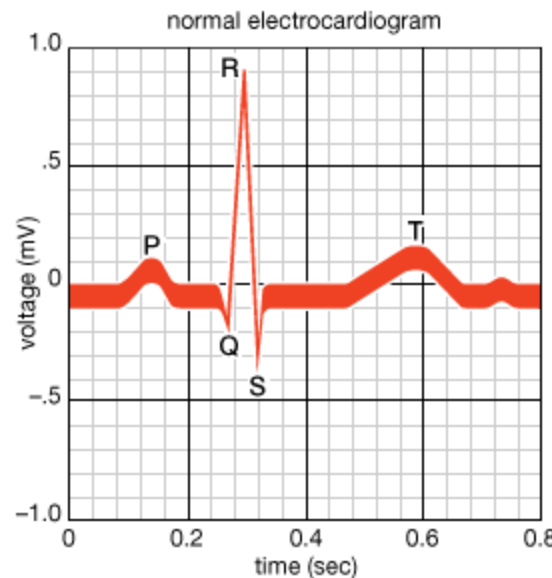
Personalisation

Modelling of the heart

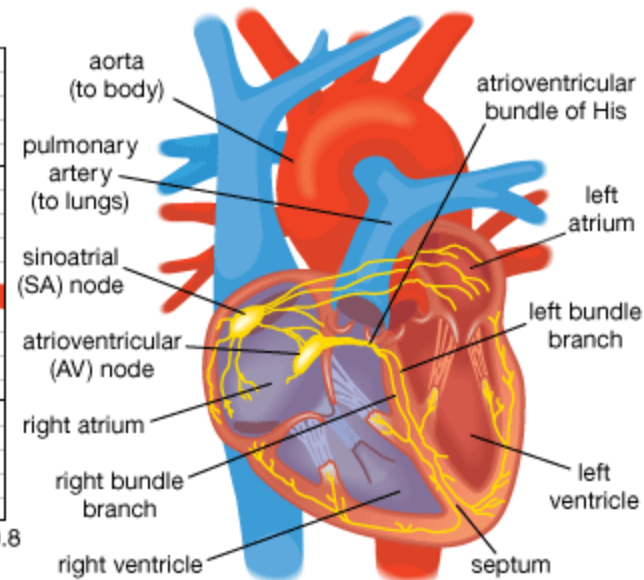
- The heart maintains blood circulation by contracting the atria and ventricles
 - spontaneously generates electrical signal (action potential)
 - conducted through cellular pathways into atrium, causing contraction of atria then ventricles
 - repeats, maintaining 60–100 beats per minute

- Abnormalities in electrical conduction

- missed/slow heart beat (Bradycardia)
- treatable with pacemakers

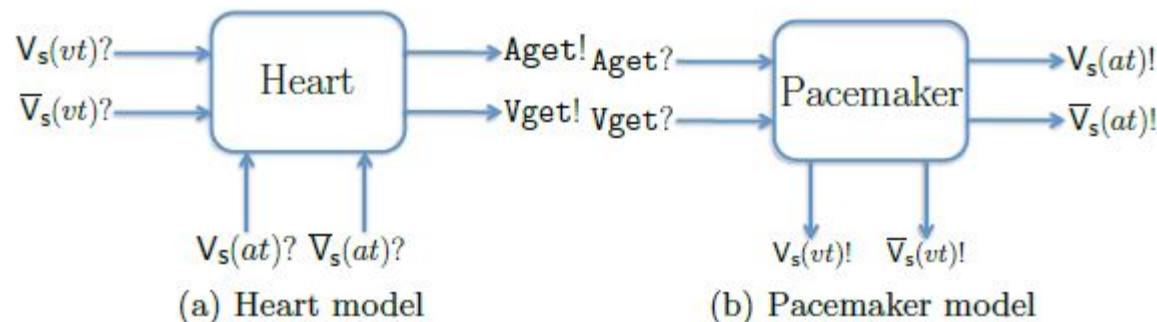


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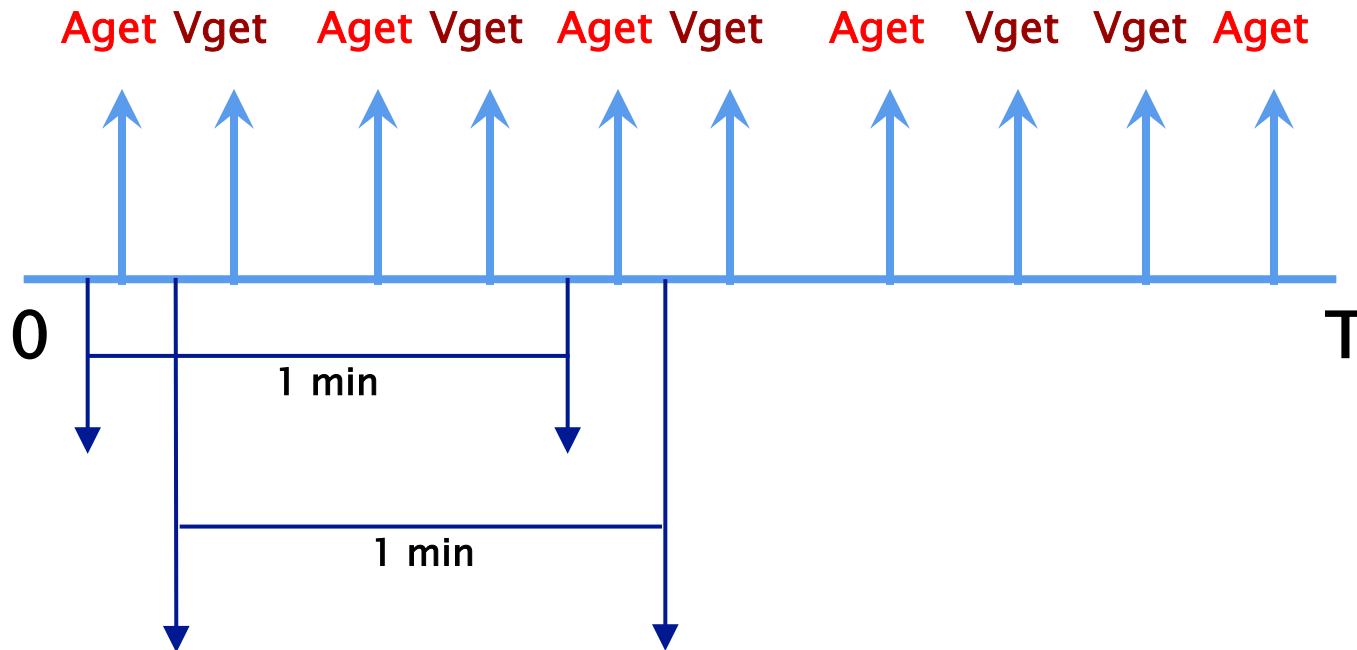


Model-based framework

- 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)



Property specification: Counting MTL



$$\Box^{[0,\tau]} (\#_0^\tau Vget \geq B_1 \wedge \#_0^\tau Vget \leq B_2)$$

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

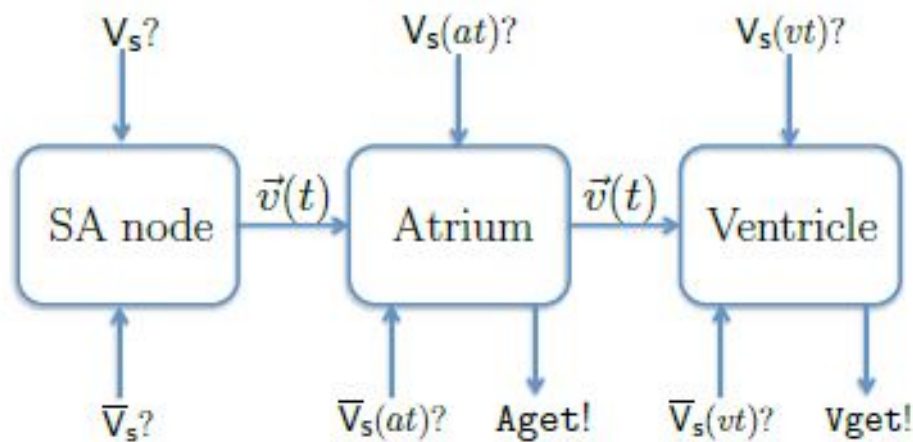
Event counting not expressible in MTL (Metric Temporal Logic)

Framework functionality

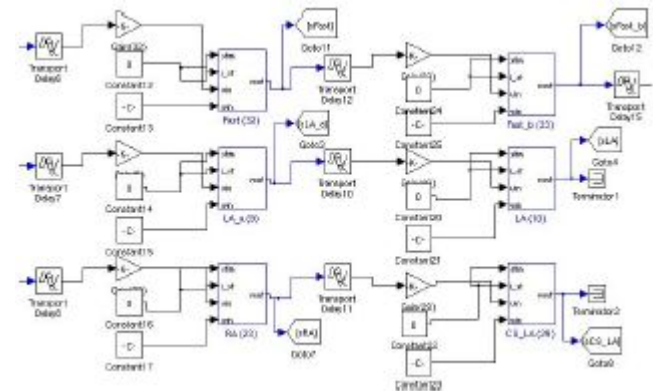
- Broad range of techniques
 - Monte-Carlo **simulation** of composed models
 - with (confidence level) guarantees for non-linear flows
 - (approximate) **quantitative verification** against variants of MTL
 - to ensure property is satisfied
 - **parametric** analysis
 - for **in silico** evaluation, 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

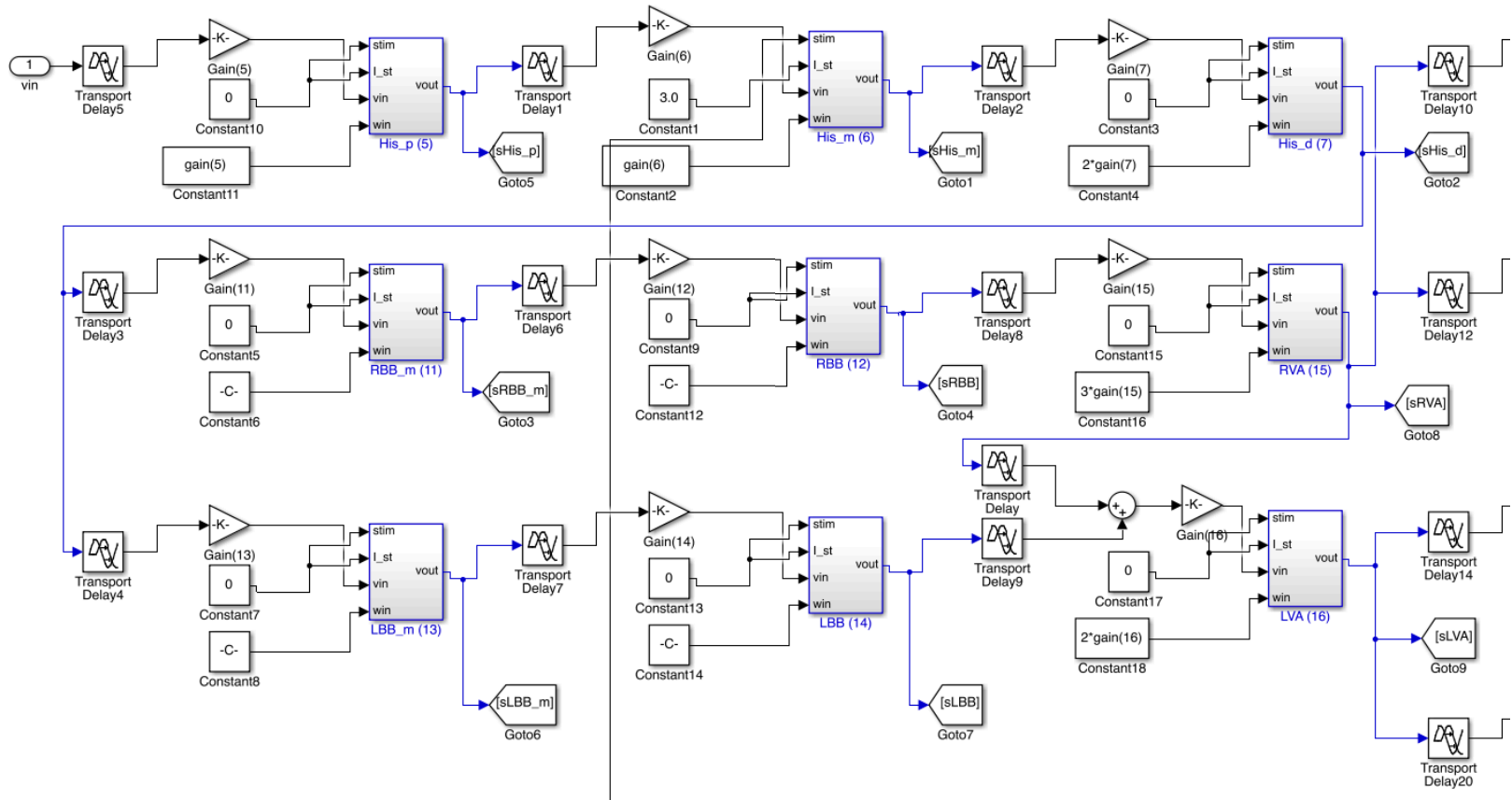
- Based on model of electrical conduction [Grosu et al]
 - abstracted as a **network** of **cardiac cells** that conduct voltage



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



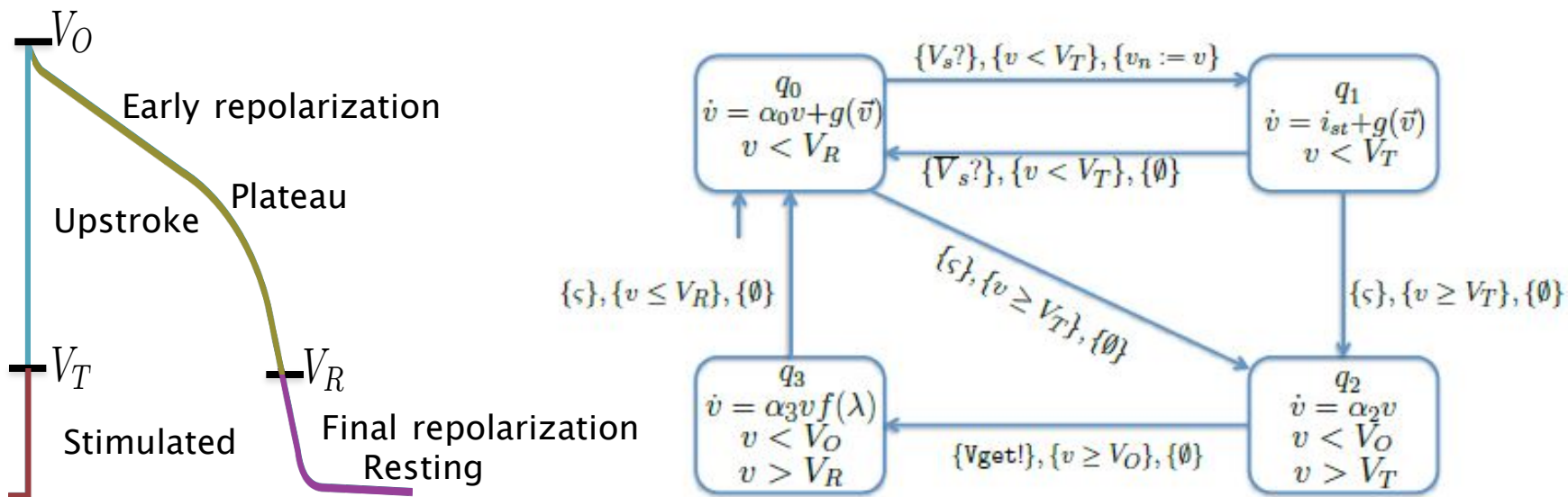
Cardiac cell network in Simulink



Cardiac cell heart model: single cell

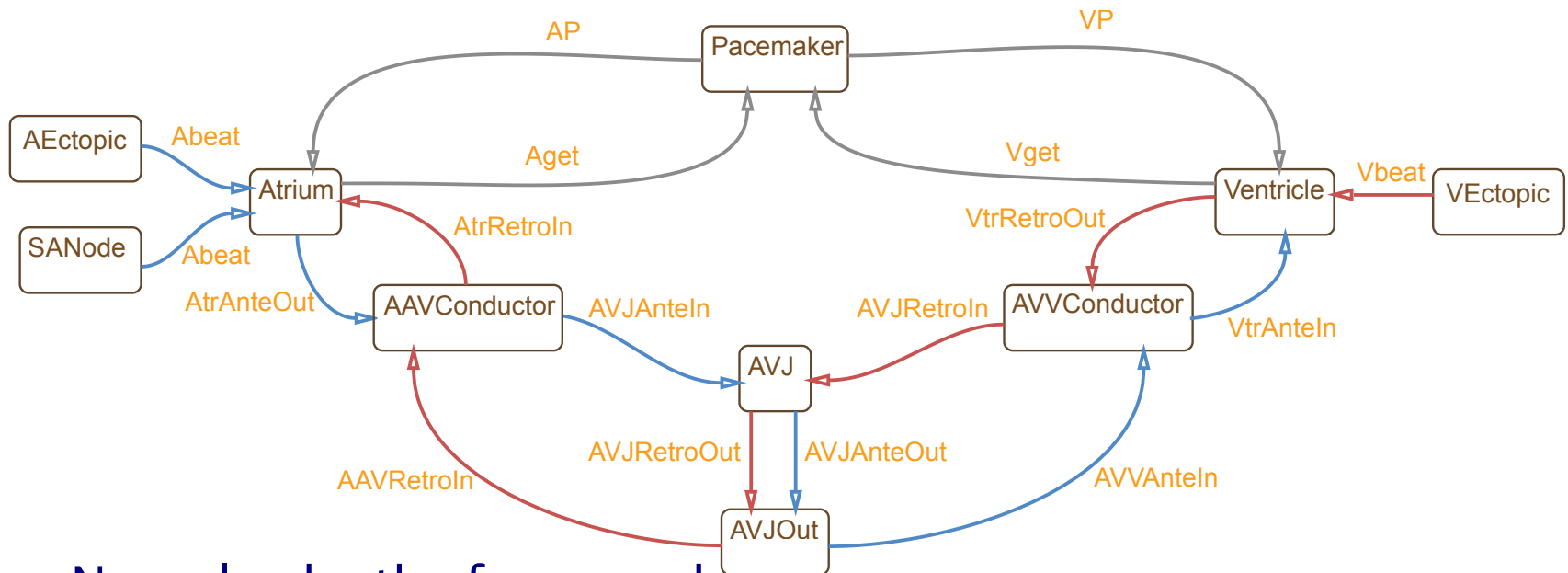
- Single ventricular cell [Grosu et al]

- 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_0 – overshoot voltage

New heart model



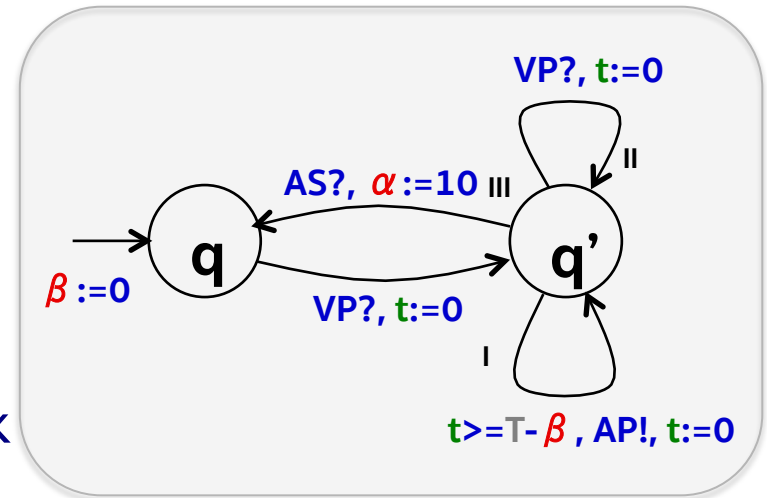
- Now also by the framework
 - structurally simpler, yet more powerful [Lian et al 2010]
 - antegrade and retrograde conduction paths
 - models AV conduction delay
 - allows Cardiac Output (CO) estimation
 - supports **personalisation** from ECG

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

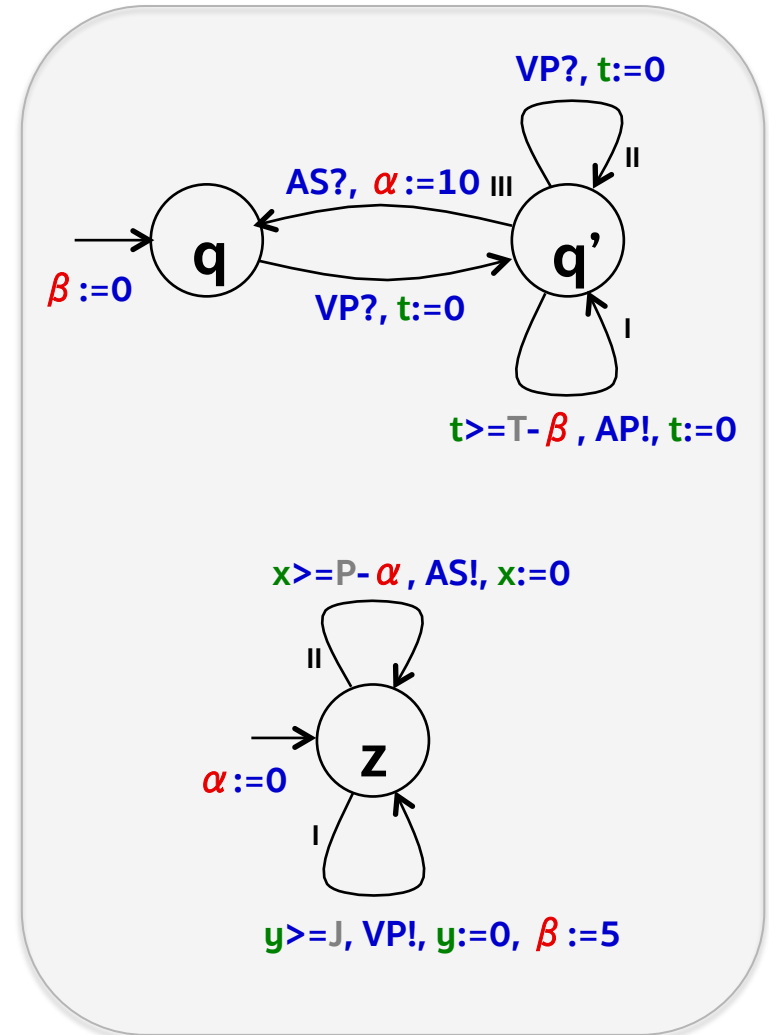
Timed I/O automata with data (TIOAs)

- 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

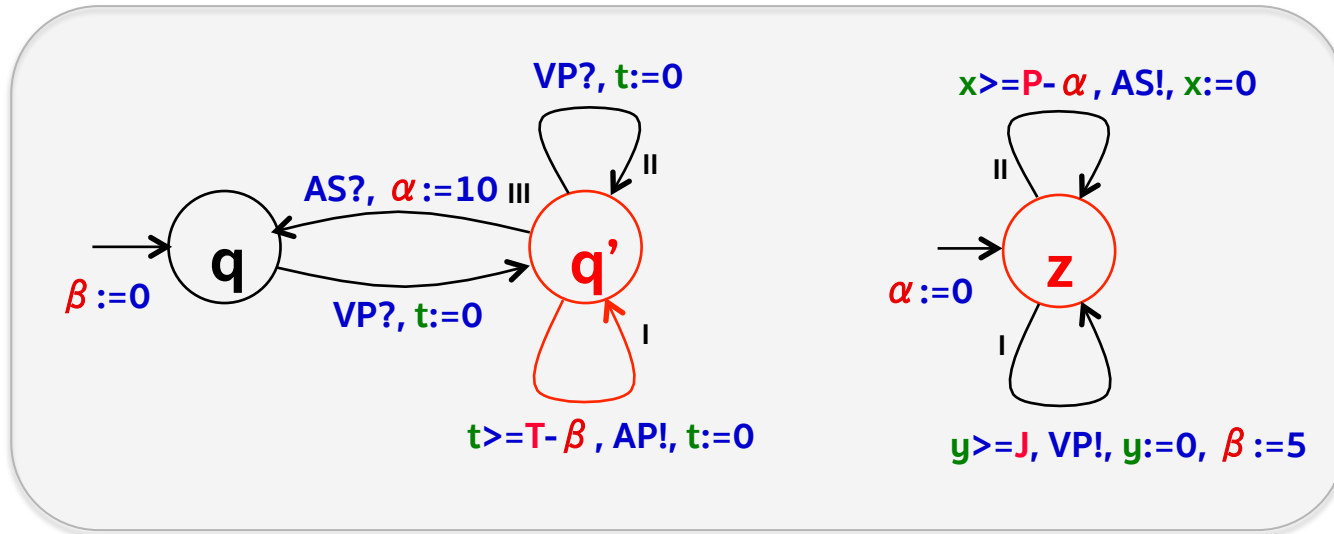


Networks of TIOAs

- 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

$((q, z), (\alpha = 0, \beta = 0, t = 0, x = 0, y = 0))$

$\downarrow J, VP$

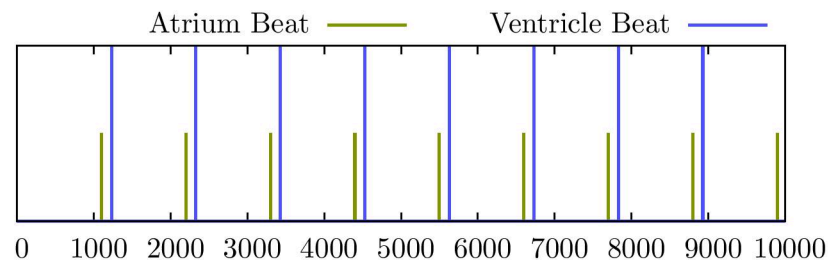
$((q', z), (\alpha = 0, \beta = 5, t = 0, x = J, y = 0))$

$\downarrow T-5, AP$

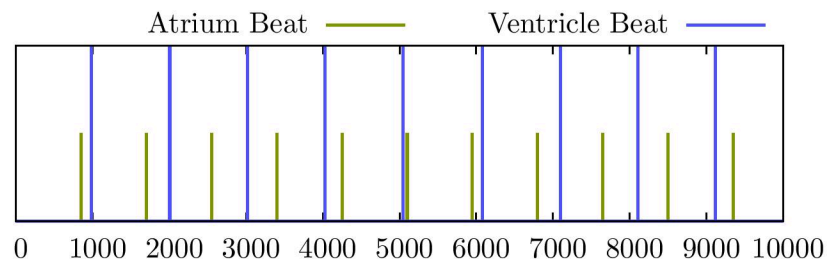
$((q', z), (\alpha = 0, \beta = 5, t = 0, x = J+T-5, y = T-5))$

Examples of heart dynamics

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



- Wenckebach AV Block (shown), etc



Focus on...



Modelling

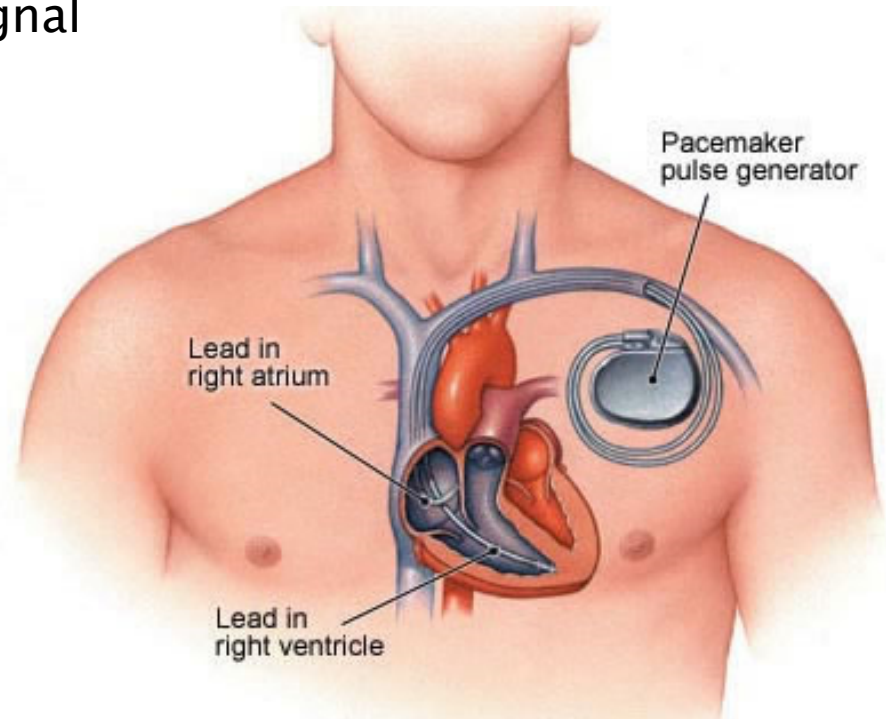
Verification



Personalisation

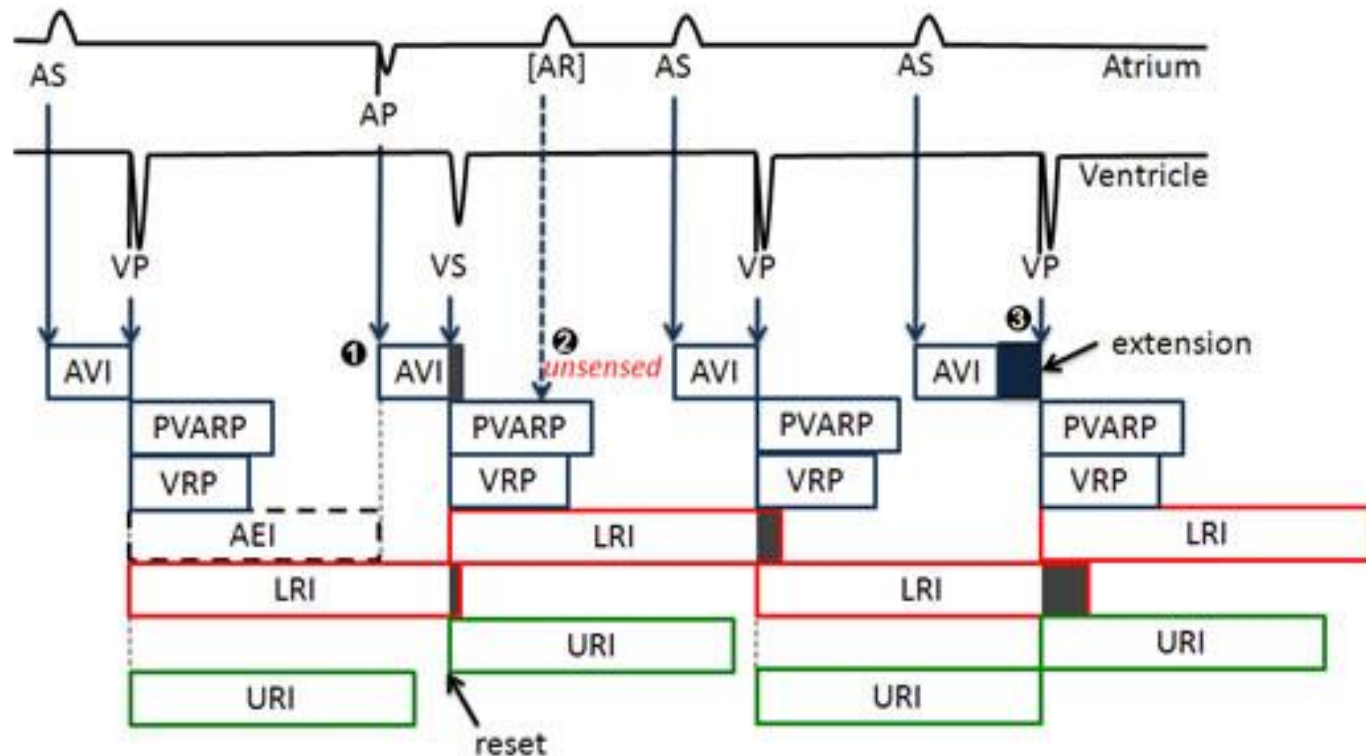
Implantable pacemaker

- 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]



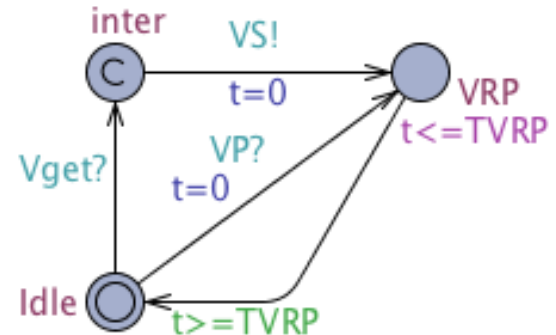
Pacemaker timing cycle

- 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

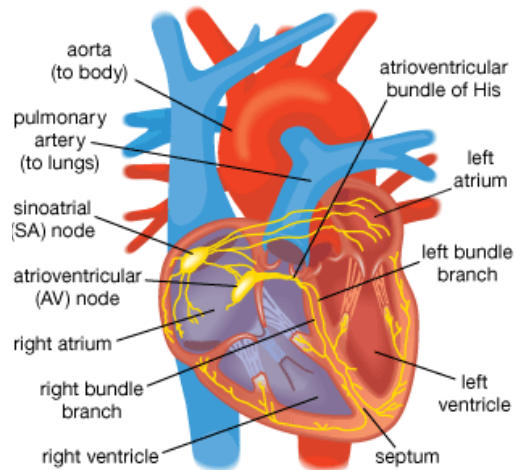
$$\Box^{[0,\tau]}(\#_0^\tau \text{Vget} \geq B_1 \wedge \#_0^\tau \text{Vget} \leq B_2)$$

- reward weighting, e.g. energy consumption

$$1 \cdot \#_0^\tau \text{AP} + 2 \cdot \#_0^\tau \text{VP} \leq E$$

Quantitative verification for pacemakers

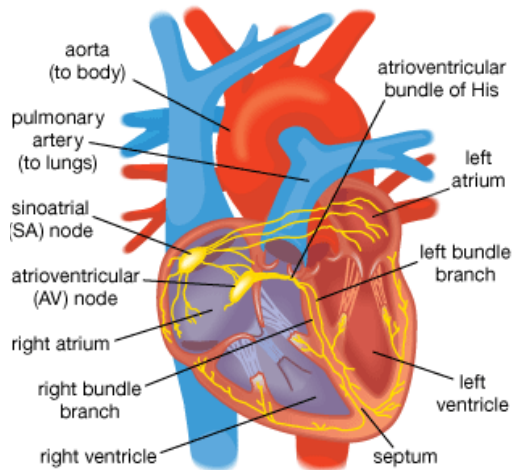
- Model the pacemaker and the heart as timed I/O automata
- Compose and **verify**



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Quantitative verification for pacemakers

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

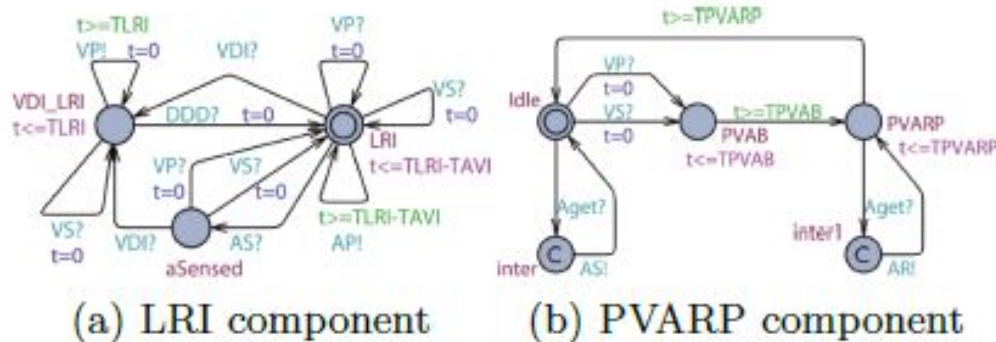


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- Can we **synthesise** (controllable) timing delays to minimise energy, without compromising **safety**?

Basic pacemaker

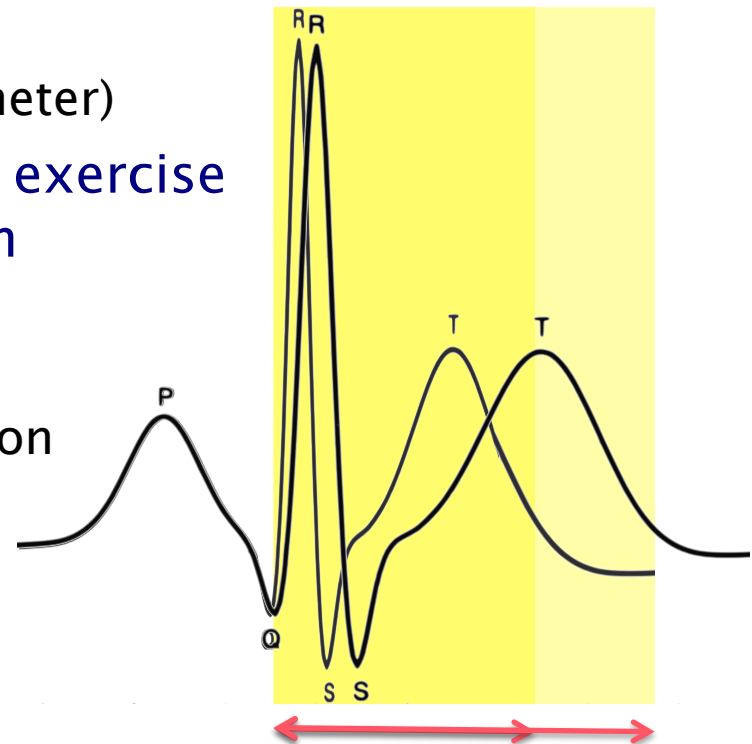
- Consists of five communicating timed I/O automata components [Jiang et al]



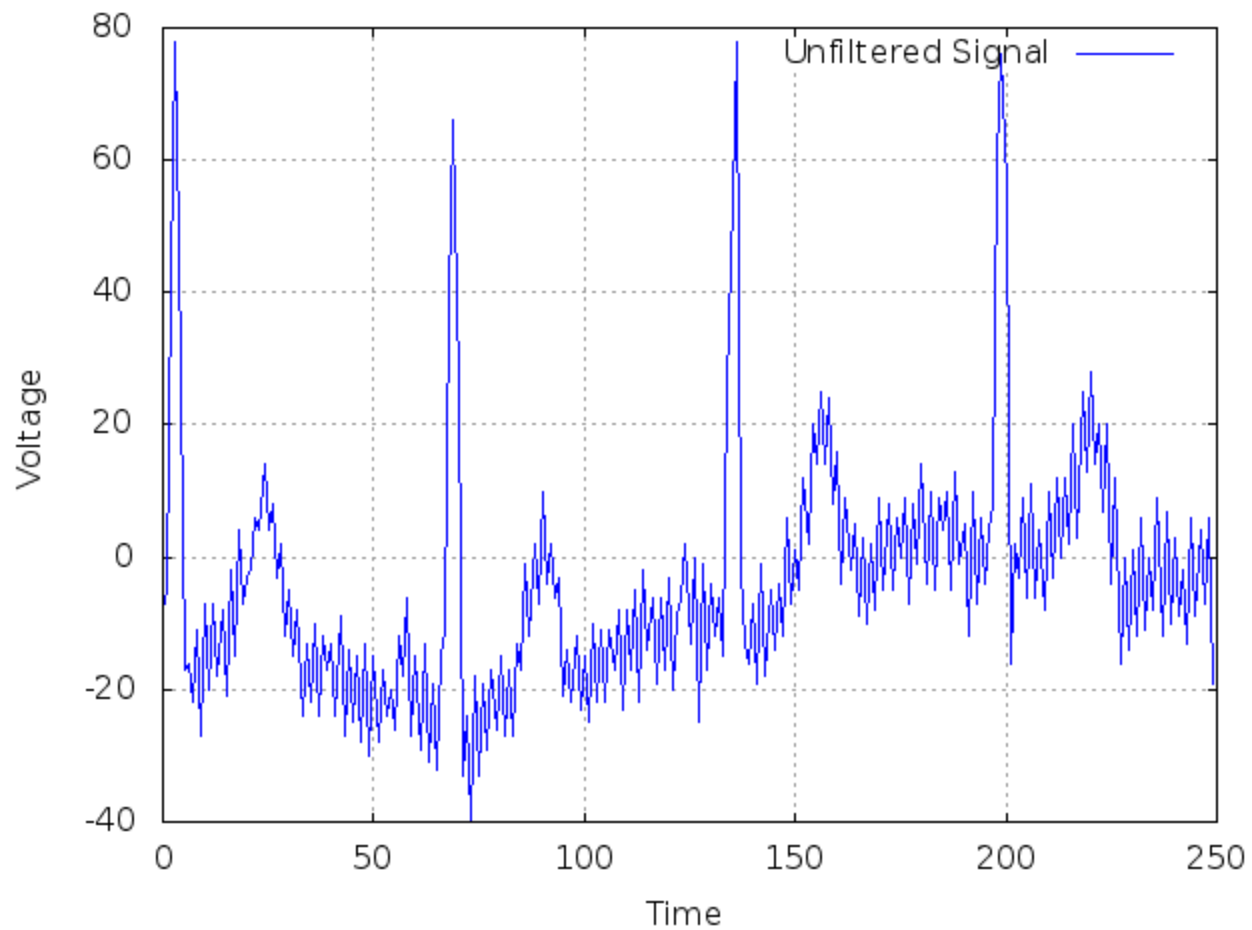
- LRI keeps the heart rate above a given minimum value
- PVARP notifies all other components that an atrial event has occurred
- Can be enhanced with **noise** and **probabilistic switching** between healthy and diseased heart (for personalisation)

Rate-adaptive pacemakers

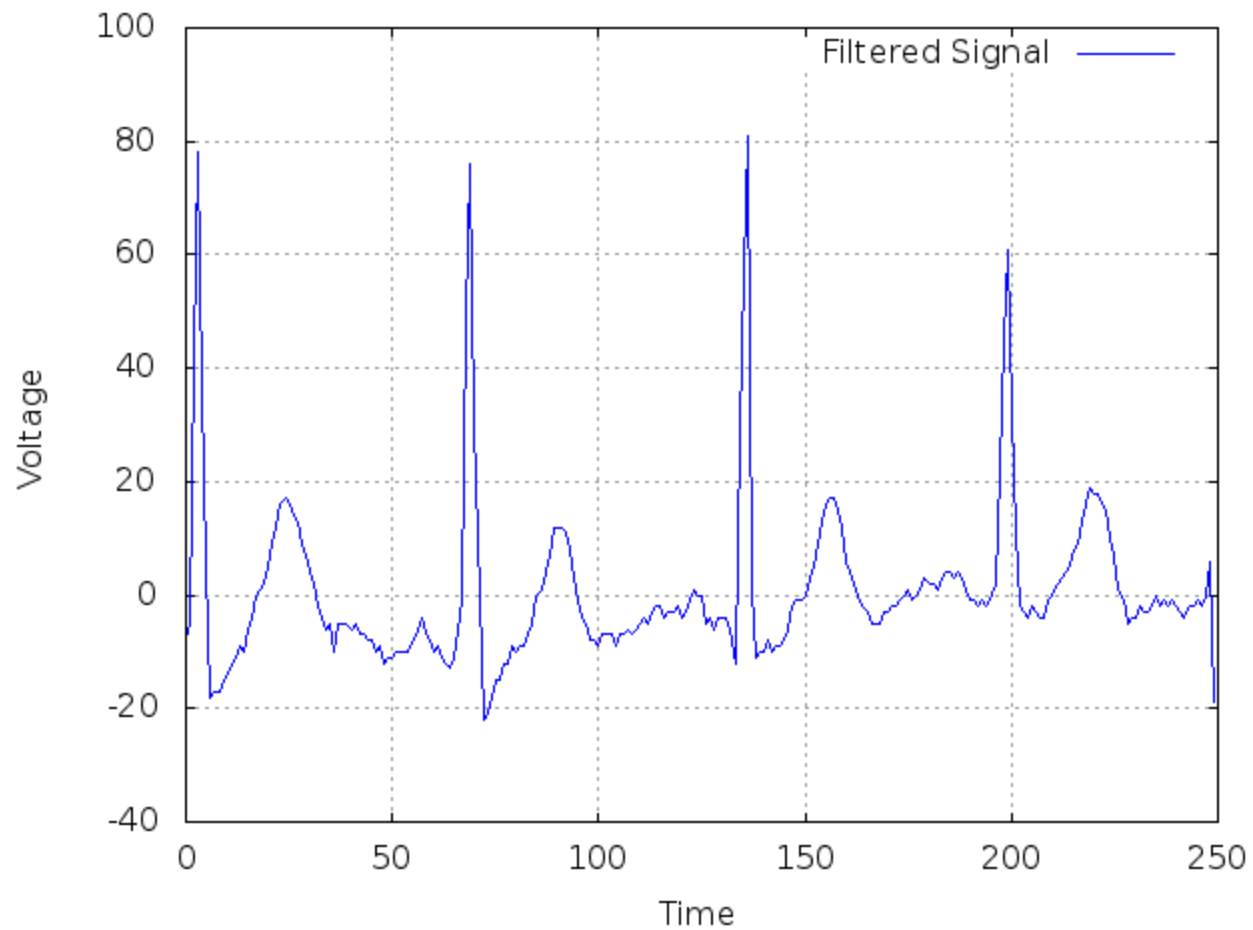
- Can **regulate** the pacing rate according to patient's needs (exercise, stress, ...)
 - needed when the heart cannot adapt its rate to increasing demand (chronotropic incompetence)
- Use implantable **sensors** to detect activity level and metabolic need
 - e.g. body movement (accelerometer)
- **QT 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)



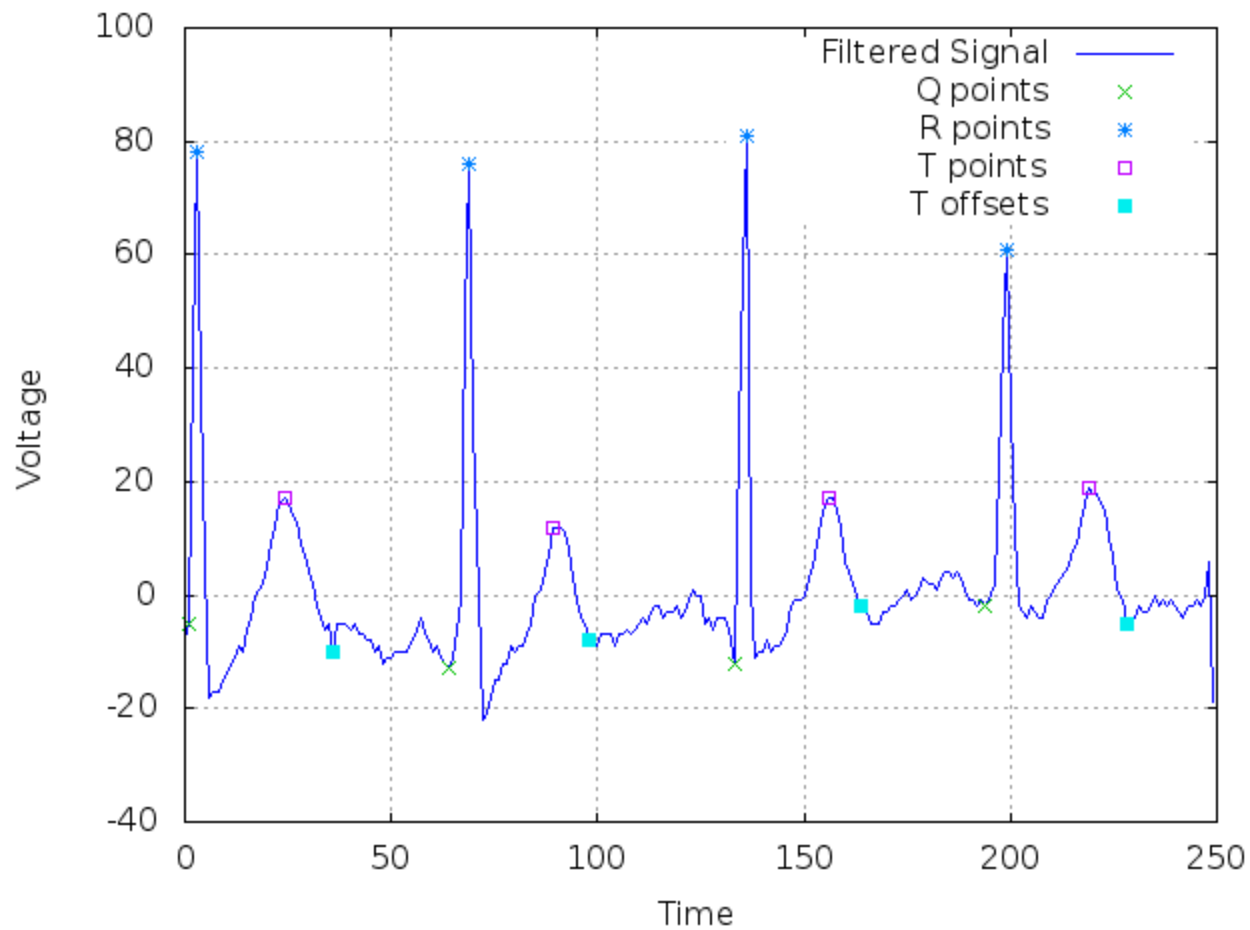
QT detection



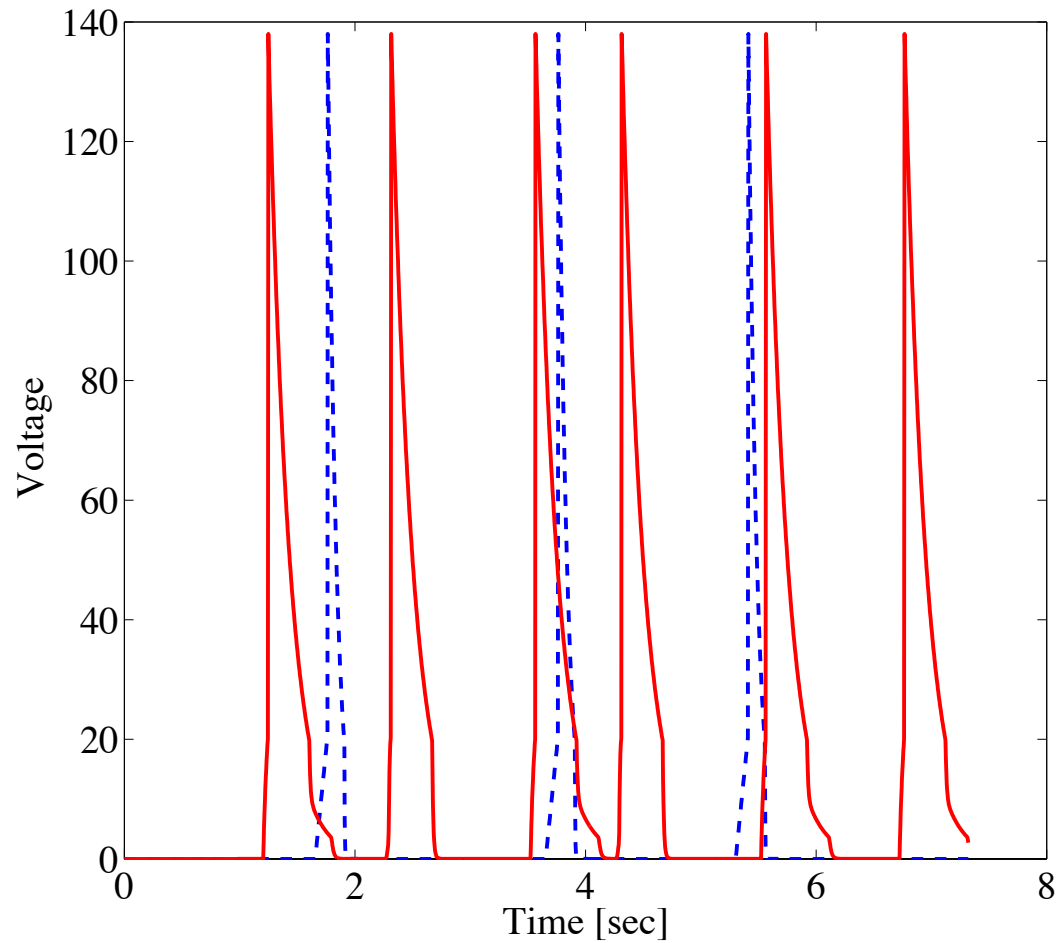
QT detection



QT detection

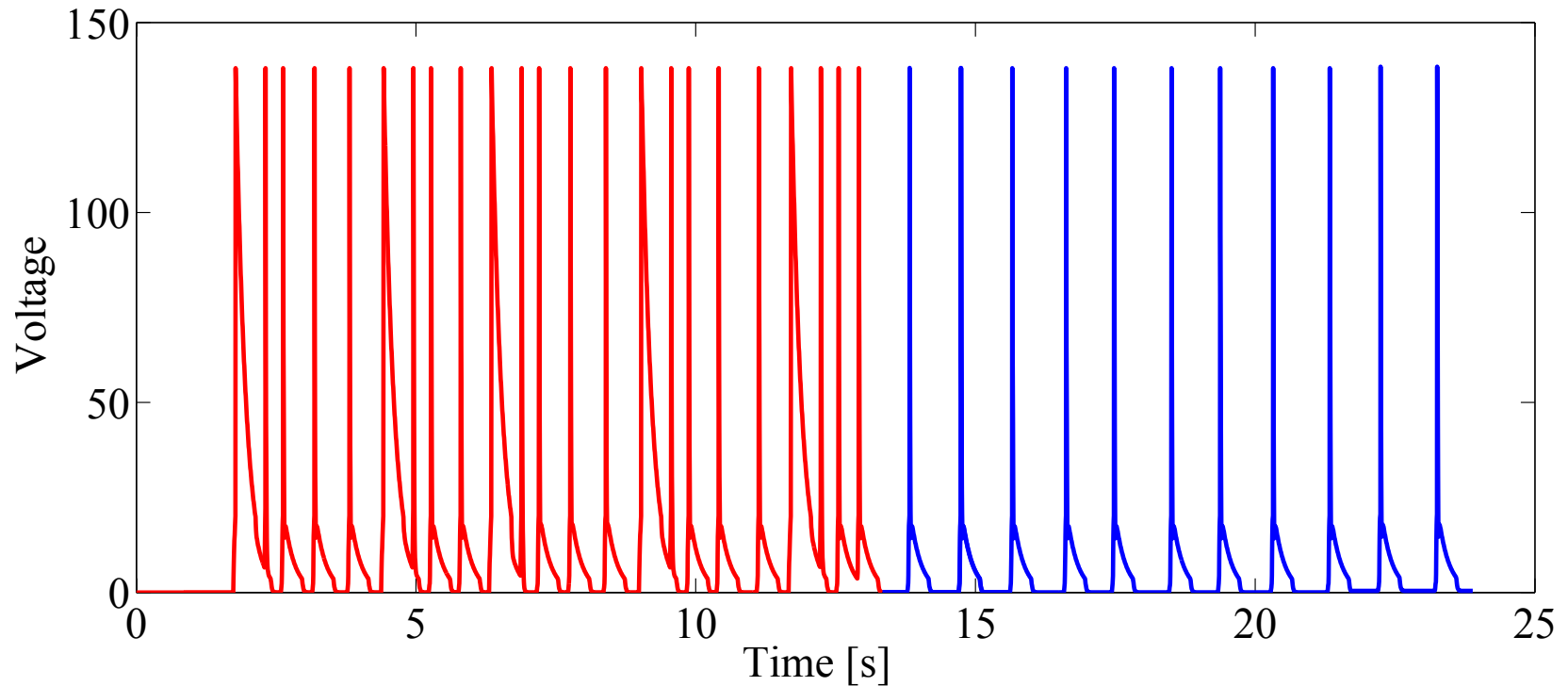


Correction of Bradycardia



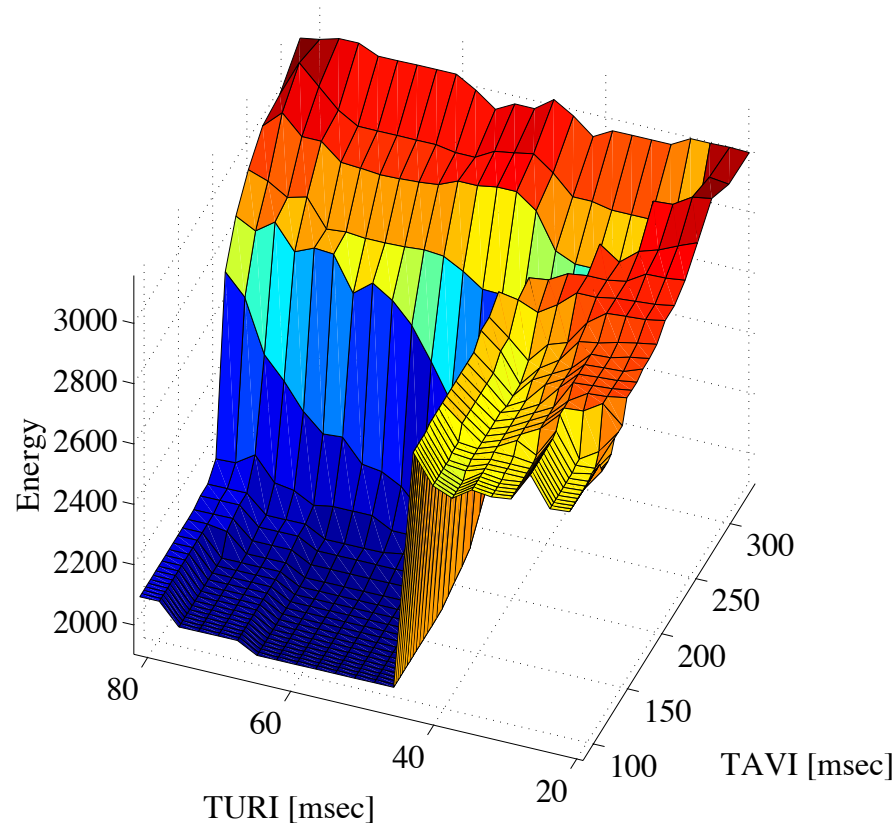
Blue lines original (slow) heart beat, red are induced (correcting)

Correction of PMT



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

Energy consumption



Efficiency “energy consumed must be below some fixed level”

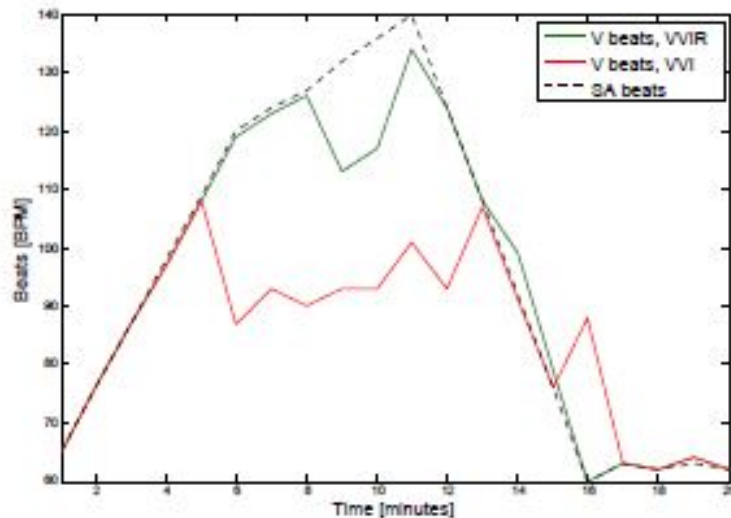
Battery charge in 1 min under Bradycardia, varying timing parameters

Based on **real** power measurements

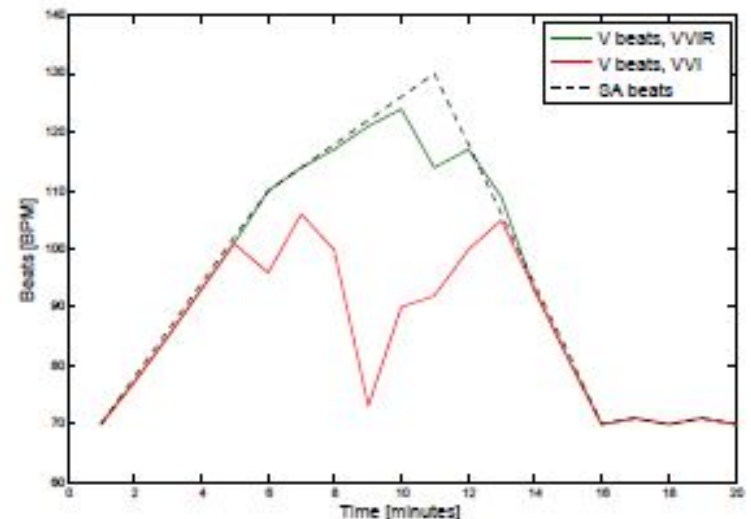
Hardware-in-the-loop simulation and energy optimization of cardiac pacemakers.

Barker *et al*, In *Proc EMBC*, 2015

Modulation during physical activity



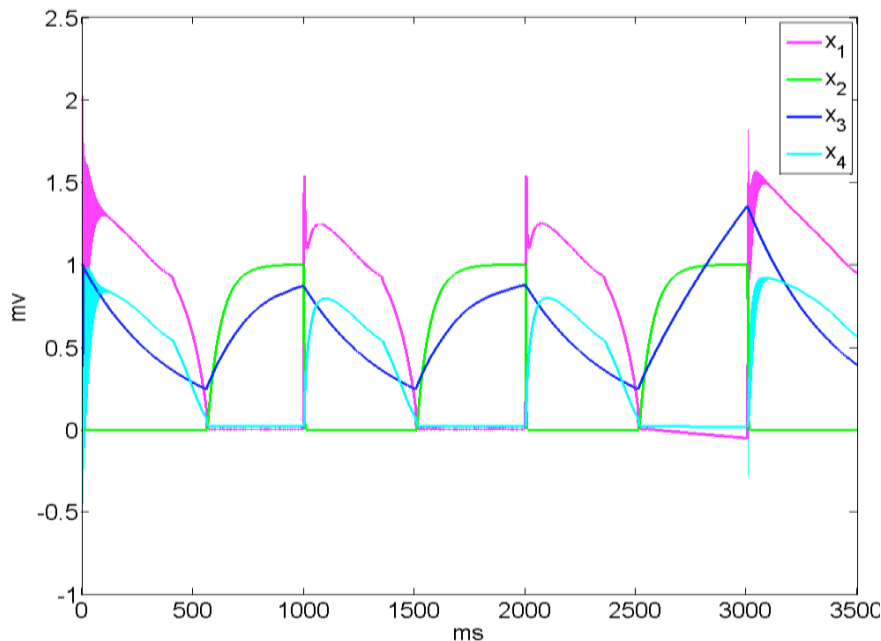
(a) Young patient



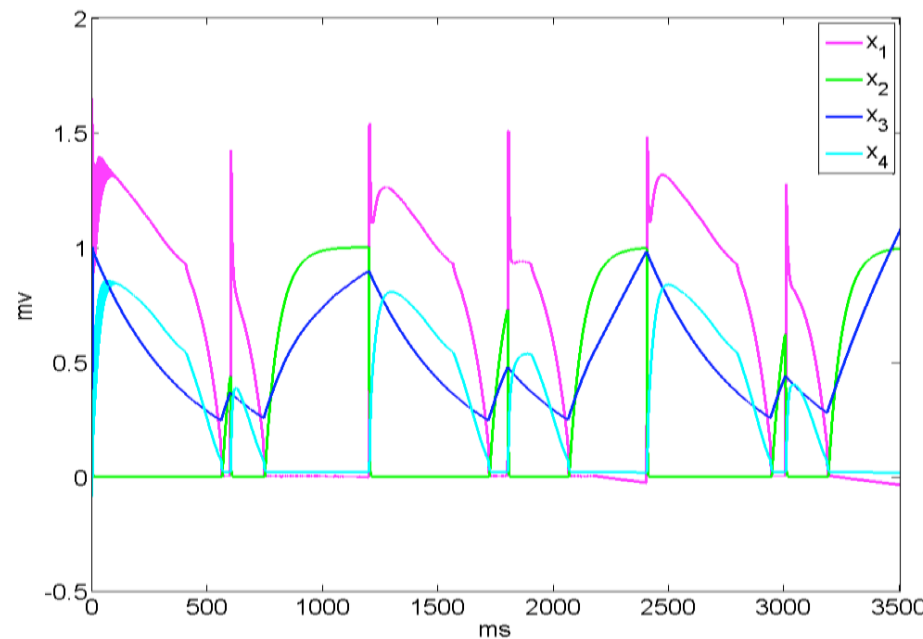
(b) Old patient

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.

Alternans in the heart



Pacing rate: 1 s



Pacing rate: 0.6 s

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*⁴¹
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

Optimal timing delays

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

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

- 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)

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

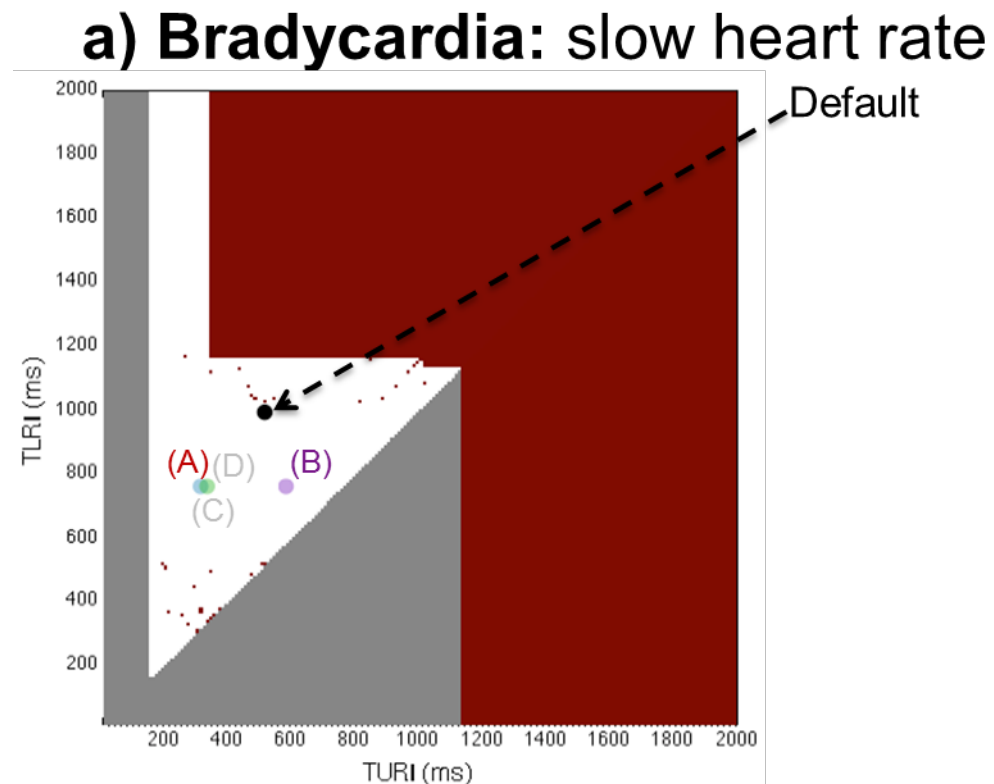
- energy consumption in 1 minute

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

- 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



Focus on...



Modelling

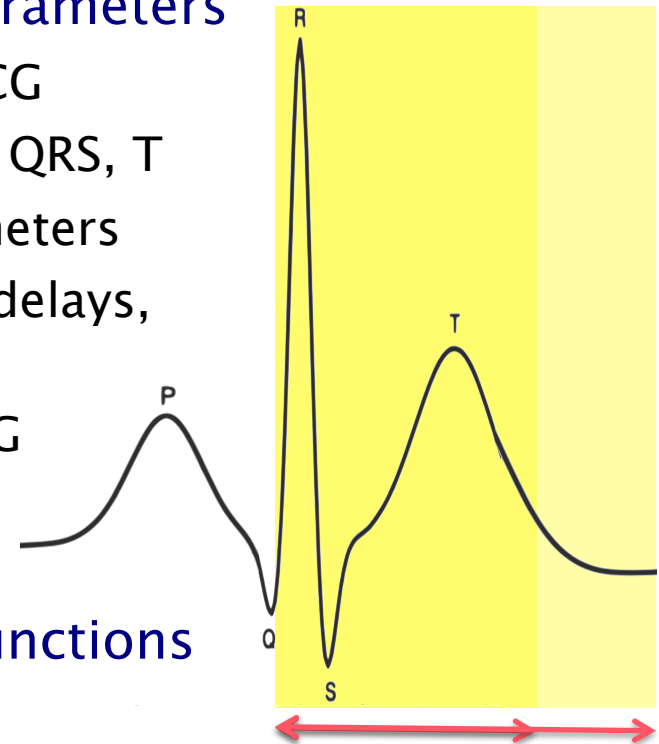
Verification



Personalisation

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

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

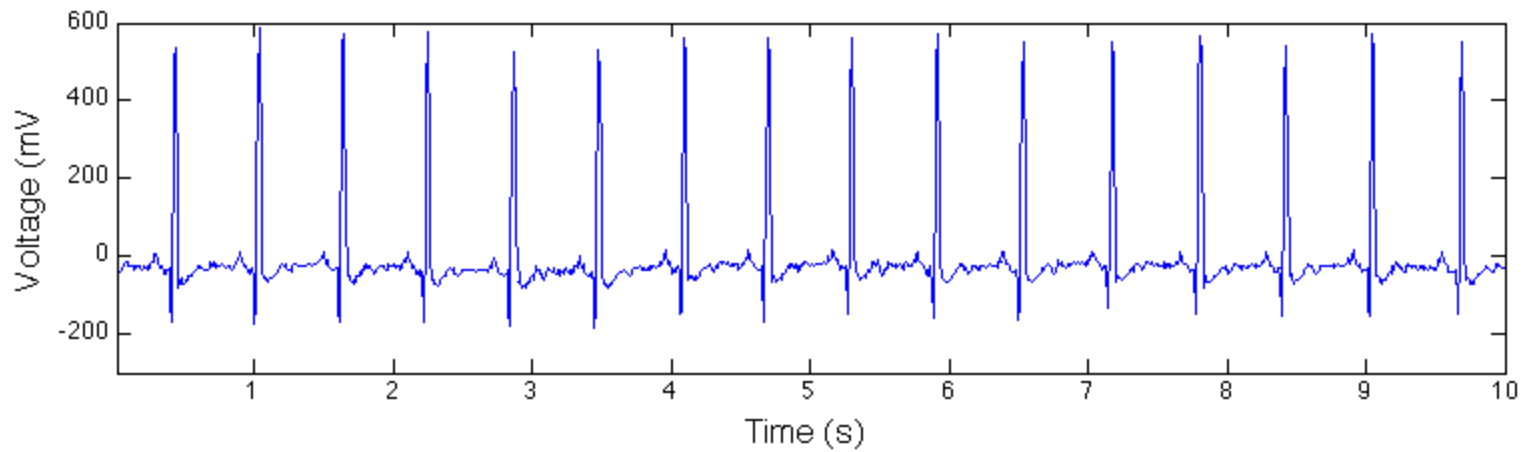
- finally compute the mean of the distances for each point

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

- Method **not** affected by the heart rate

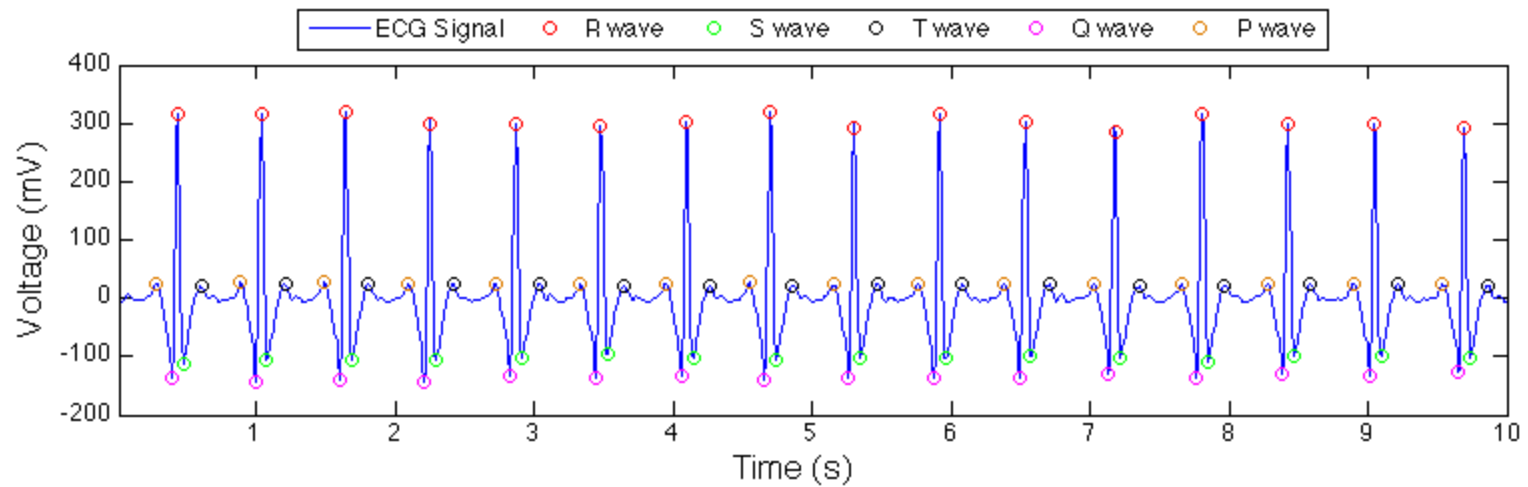
Raw ECG signal

- Real data



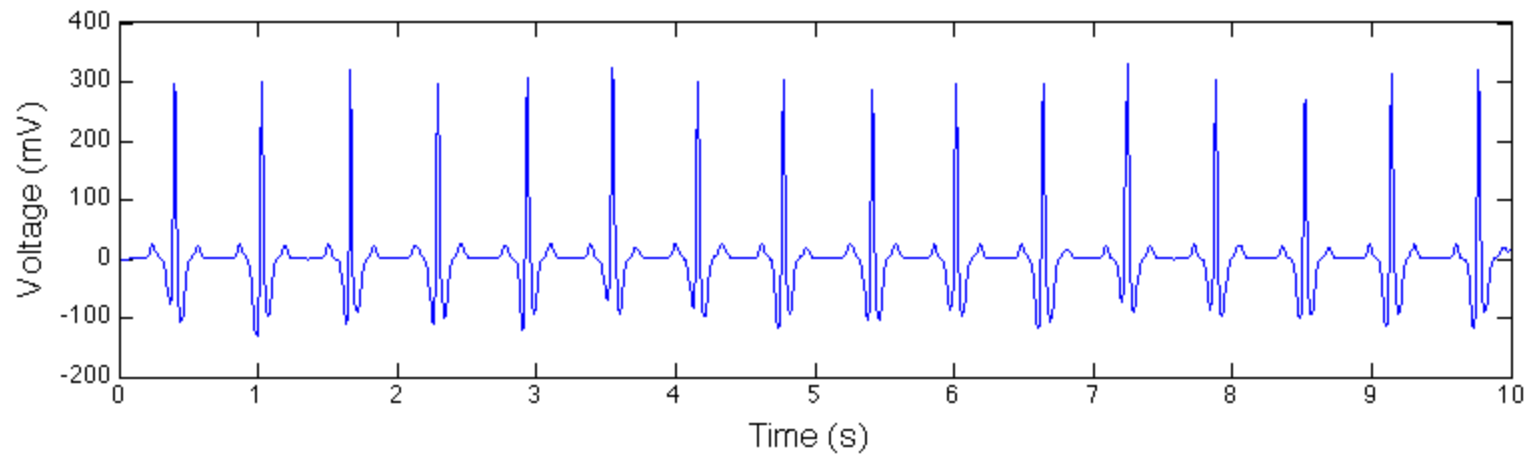
Filtered signal

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

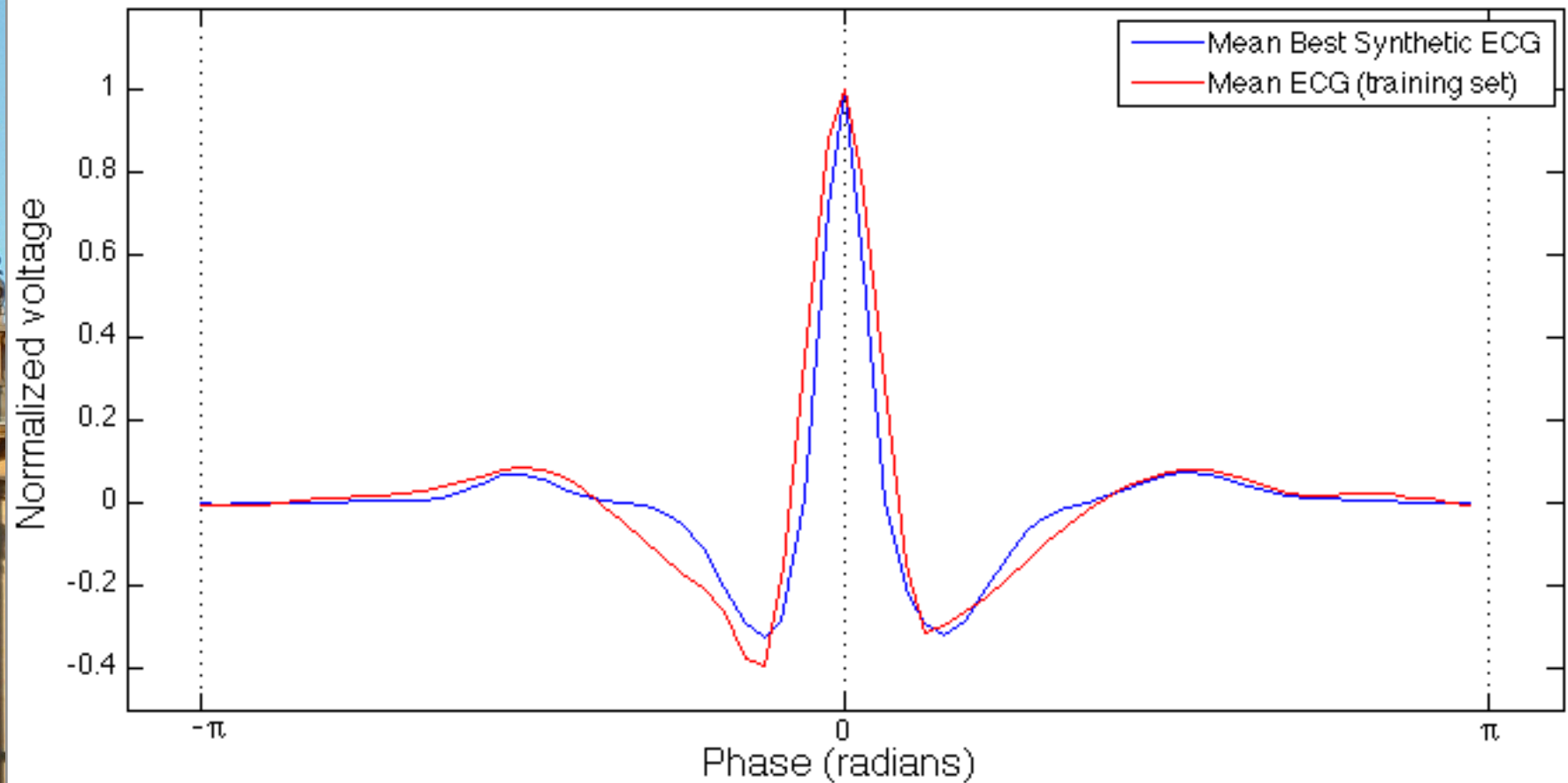


Synthetic ECG

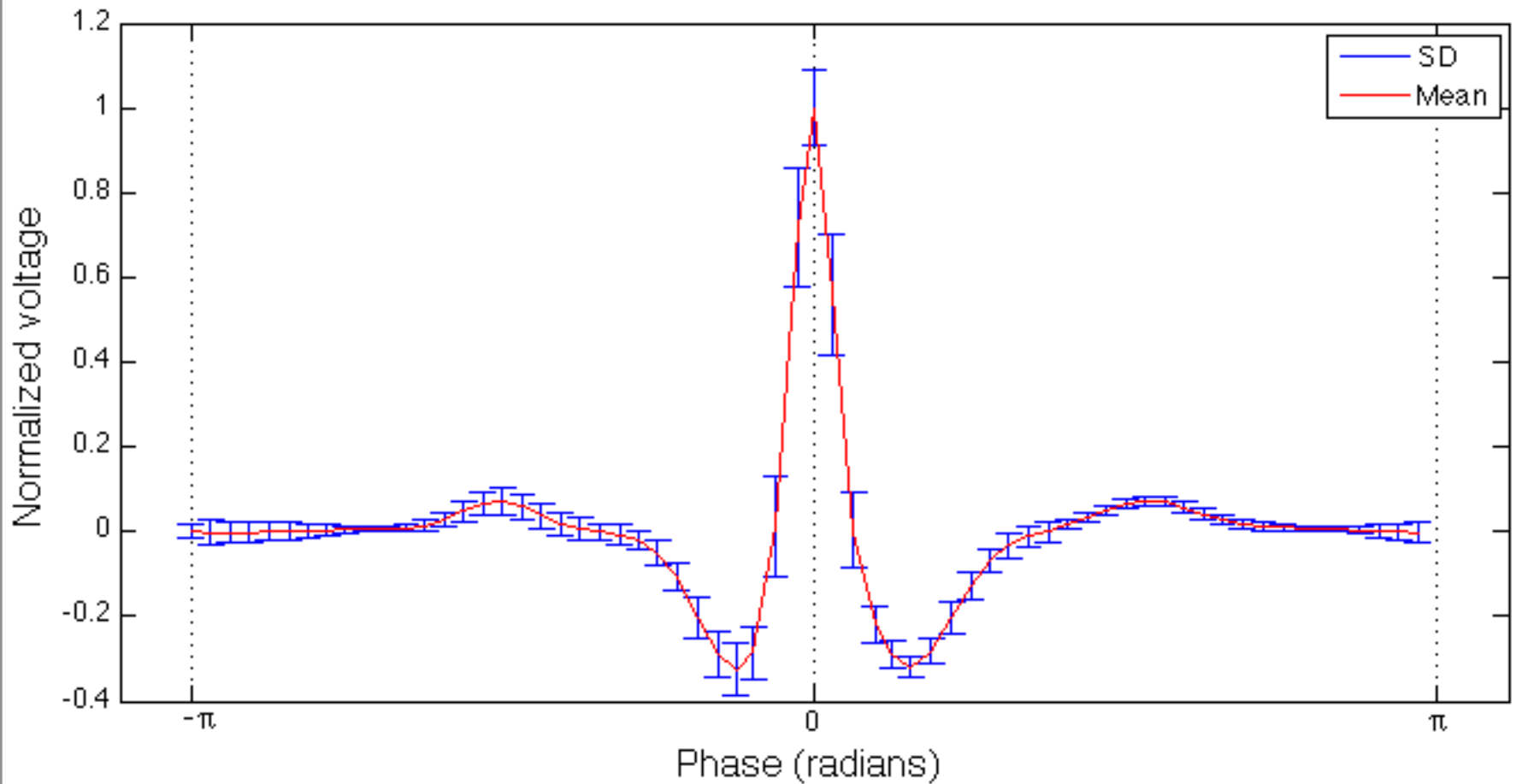
- Produced by the personalised model



Training set ECG

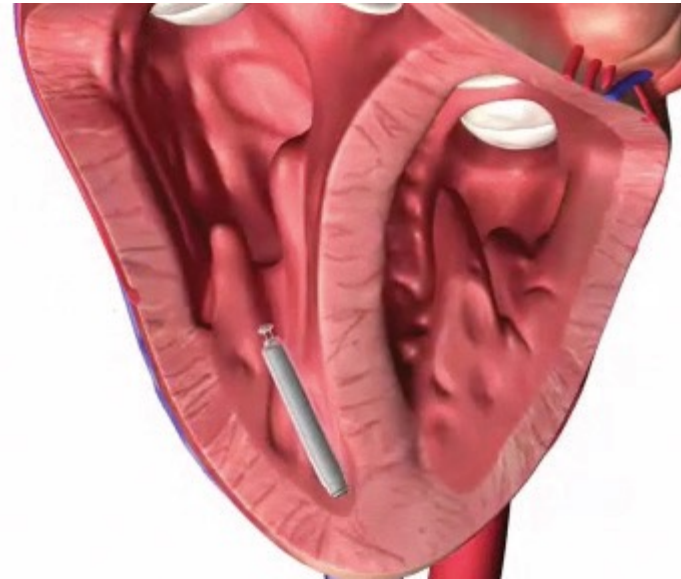


Best synthetic ECG



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

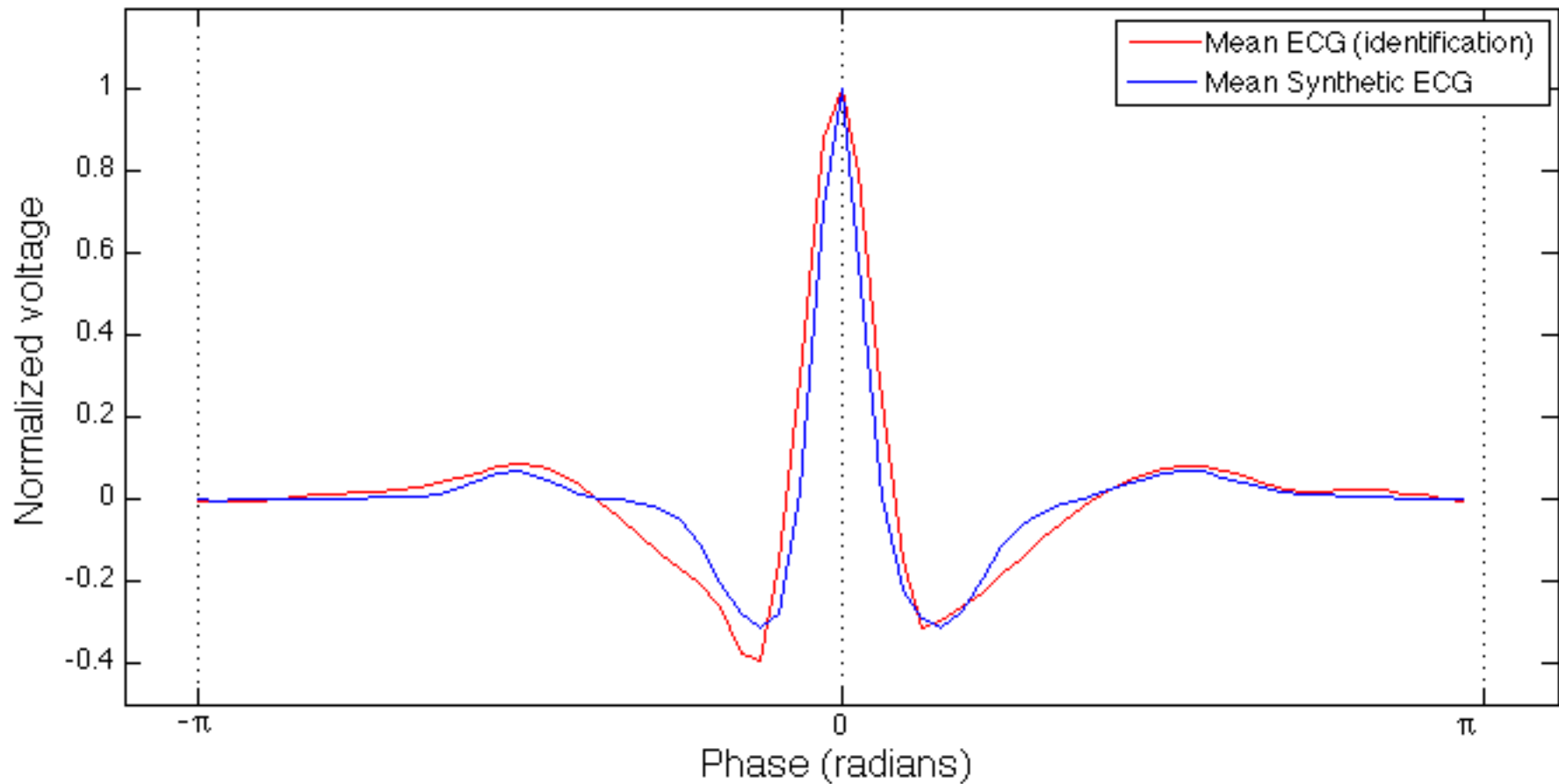


ECG-based authentication

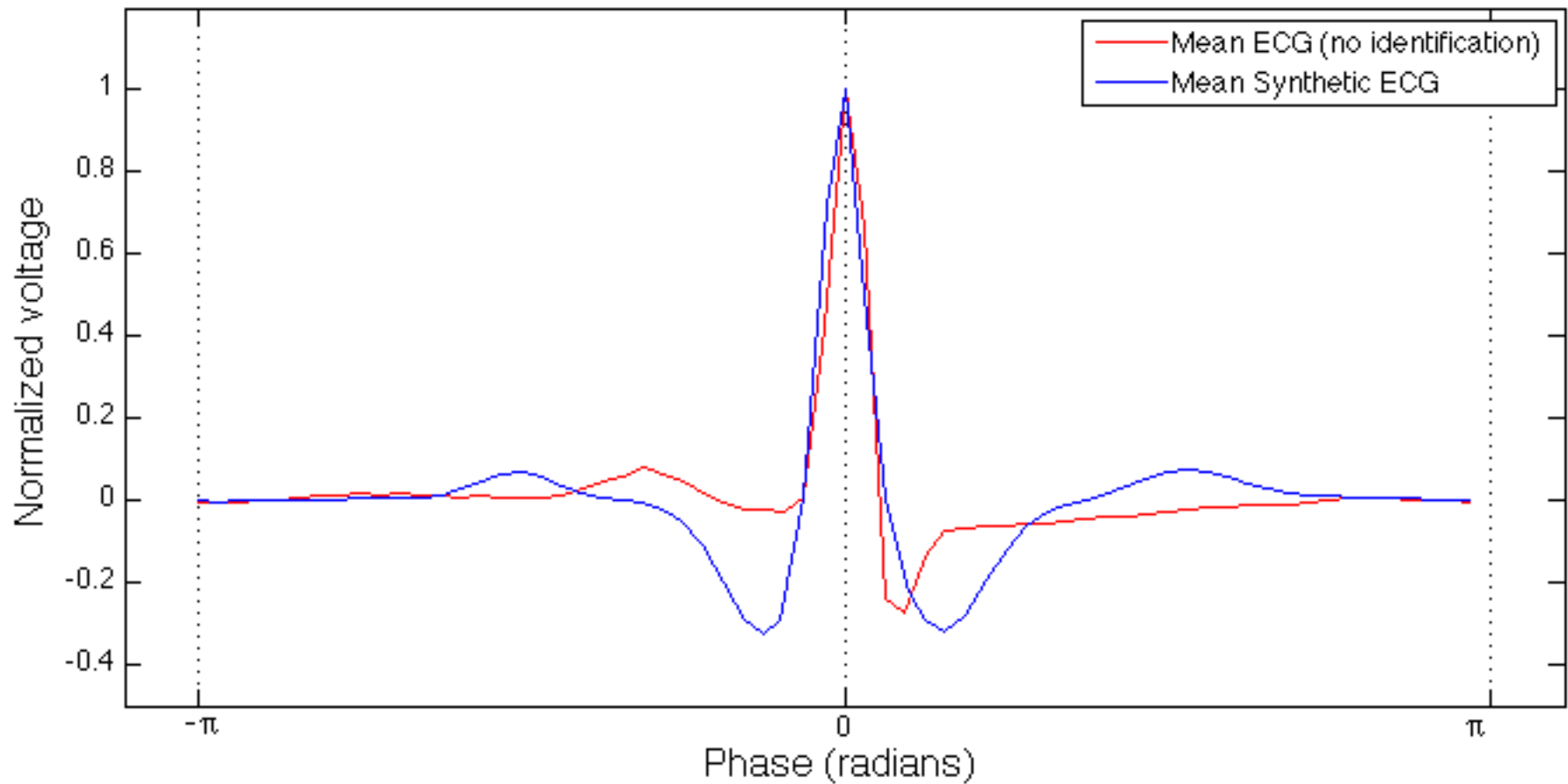
- Growing interest in biometrics based on ECG
 - good level of accuracy
 - can be continuously monitored
 - difficult to falsify
 - unlike fingerprints
 - typically used in conjunction with other methods
- Enrolment
 - capture and processing of ECG
 - generation of the **biometric template**
- Authentication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



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