QUANTITATIVE VERIFICATION AND SYNTHESIS FOR DESIGN OPTIMISATION AND PERSONALISATION OF CARDIAC PACEMAKERS

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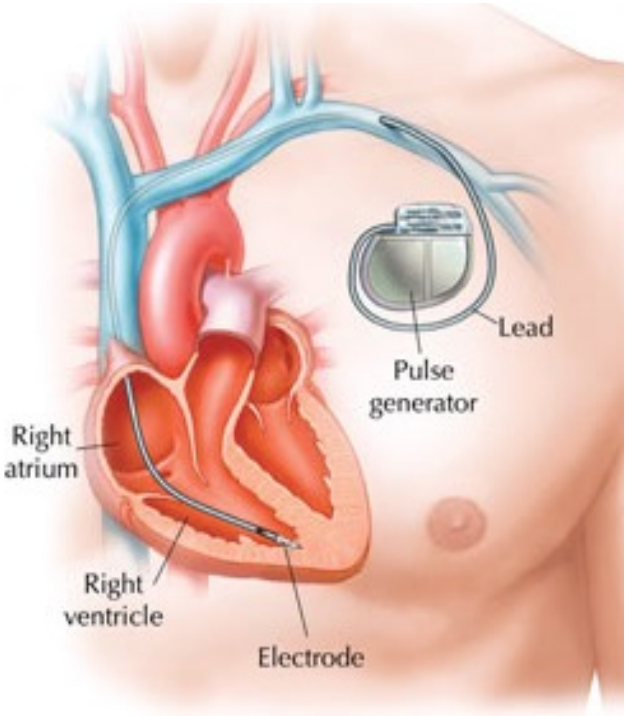
CPS Lunch Talk, TU Wien, 16 Dec 2015

MOTIVATION

- Cardiac pacemakers maintain a "correct" heart rhythm by sensing and stimulating heart beats
- One of the most common surgery procedures
- **Safety-critical**



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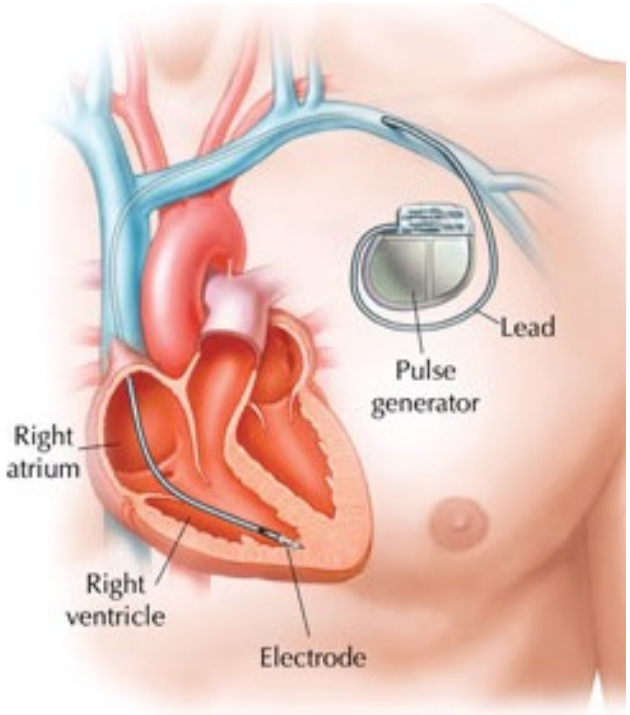
MOTIVATION

- Rigorous design methods for PM safety
  - Failures lead to device recalls, patient death
- Energy efficiency
  - Battery depletion → re-implantation
- Personalised models for personalised treatments



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PLAN OF THE TALK

1. HARDWARE-IN-THE-LOOP ENERGY OPTIMISATION

(Energy efficiency)

2. PARAMETER SYNTHESIS

(Rigorous design)

3. HEART PARAMETERS ESTIMATION FROM ECG DATA

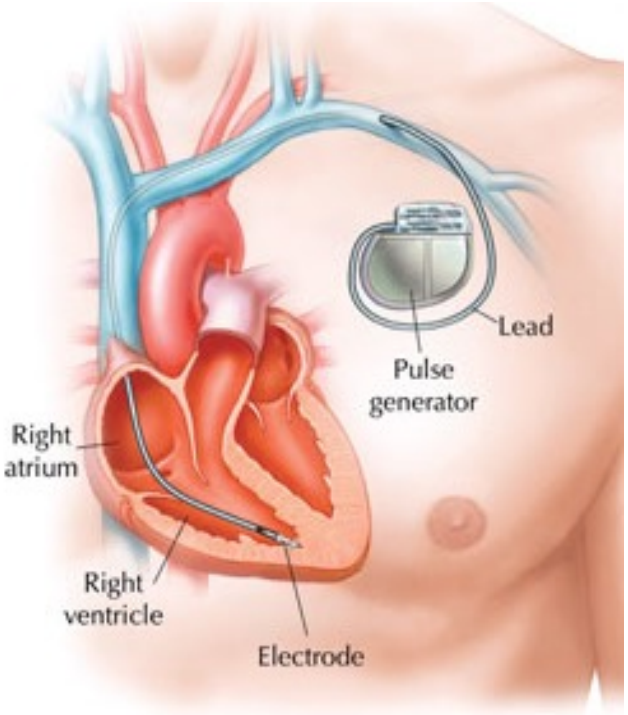
(Personalised models)

1. HARDWARE-IN-THE-LOOP ENERGY OPTIMISATION

C. Barker, M. Kwiatkowska, A. Mereacre, N. Paoletti and A. Patanè.
Hardware-in-the-loop simulation and energy optimization of cardiac pacemakers.
In IEEE Engineering in Medicine and Biology Society, 2015.

HIL ENERGY OPTIMISATION

- Effective energy optimisation needs integrated approaches (HW/SW codesign):
  - **Models are not enough**: need for real-time actual energy consumption data
  - **Hardware is not enough**: need for heart models to reproduce physiological conditions and verify safety



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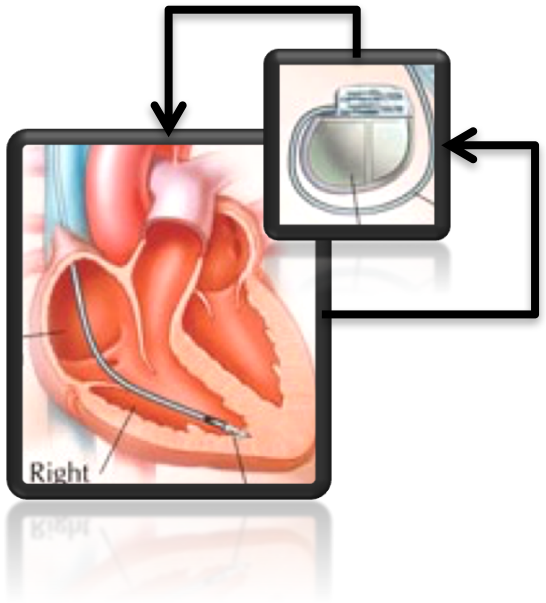
Solution:
HARDWARE-IN-THE-LOOP (HIL) SIMULATION

Execution on hardware



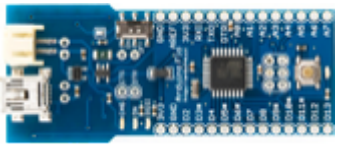
Model simulation

HIL ENERGY OPTIMISATION - FRAMEWORK

POWER MONITOR

Energy measurements

MICROCONTROLLER



Pacemaker Model

New parameters

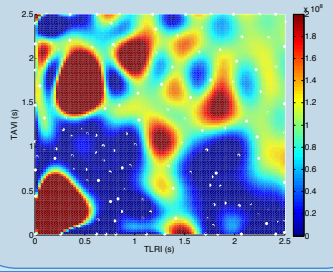
Energy readings

Sensing

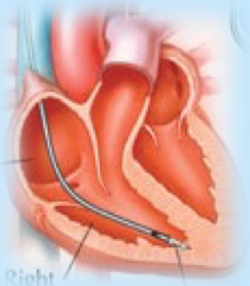
COMPUTER

Optimization Algorithm
(Gaussian Process Optimisation)

Online Energy model



Heart Model

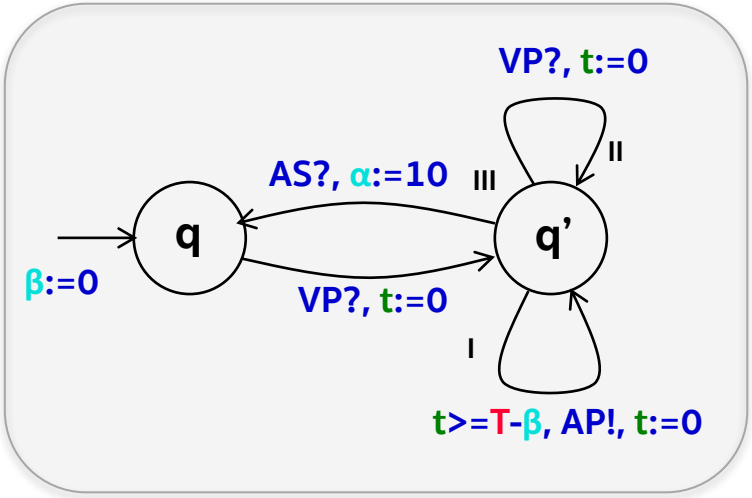


Pacing

MODELLING FORMALISM

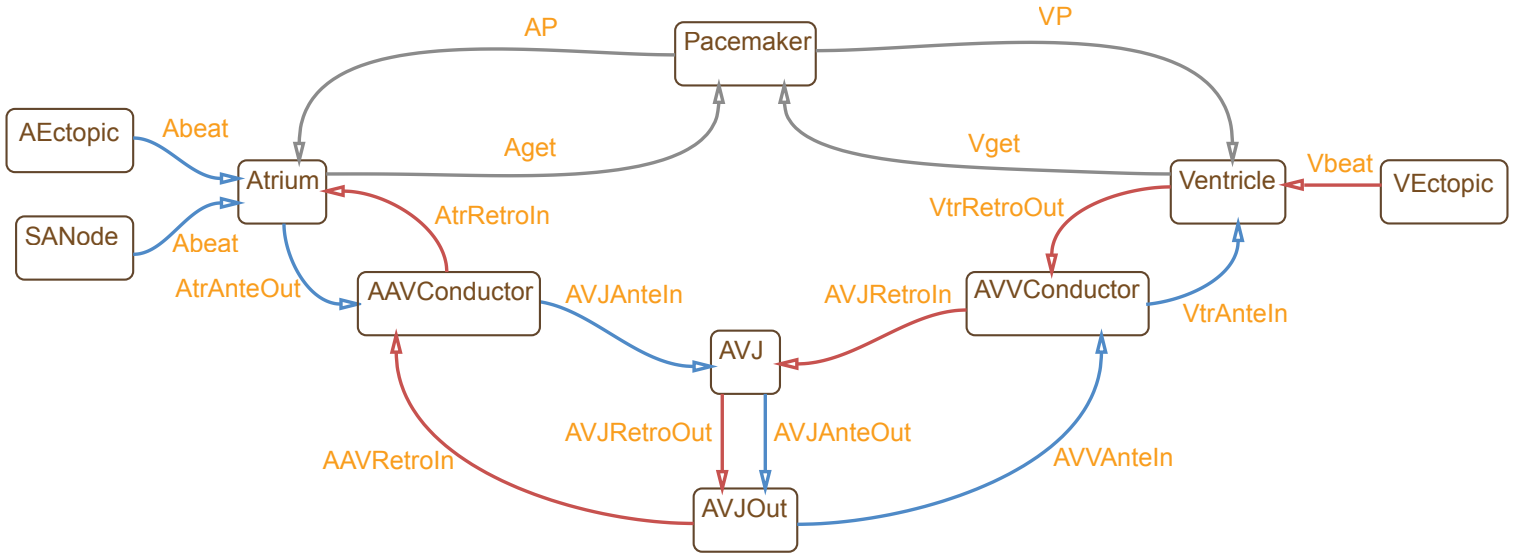
TIMED I/O AUTOMATA WITH PRIORITY AND DATA **(TIOA)**

- A subset of Stateflow modelling language
- Real-valued **variables** (**clocks** and **data**) + **parameters**
- **Guards** and **resets** may depend (non-linearly) on variables and parameters
- **Priorities** define a total ordering of the edges out of each location
- No continuous flows
- Extends [EMSOFT14] with data and non-linear guards and resets



M. Diciolla et al. *Synthesising Optimal Timing Delays for Timed I/O Automata*. EMSOFT'14

HEART AND PACEMAKER NETWORK



HEART

- Based on [Lian2010]
- Antegrade and retrograde conduction paths
- 9 conduction nodes
- Ectopic and fusion beats
- Cardiac Output estimation
- Personalization from ECG

PACEMAKER

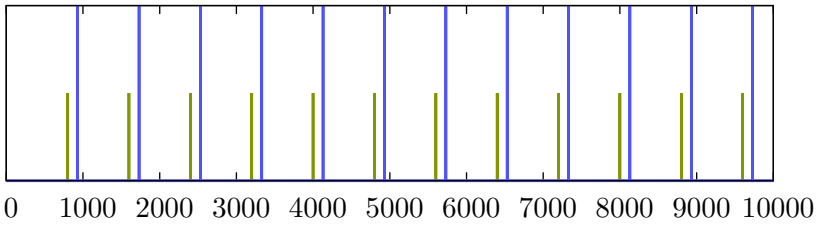
- Based on [TACAS12] and Boston Scientific specification
- Dual chamber (pace and sense both chambers)

Lian et al., Open Pacing Electrophysiol Ther J, 3:4, 2010.

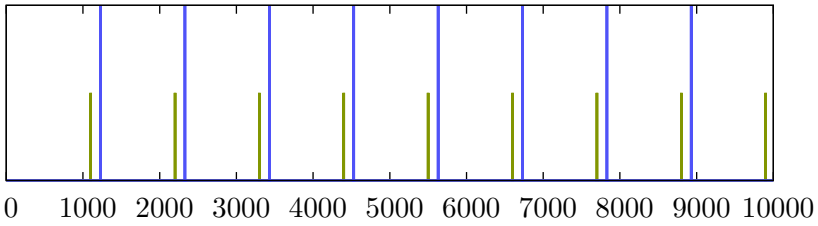
Jiang et al., TACAS 2012, LNCS 7214

HEART MODEL - SIMULATION

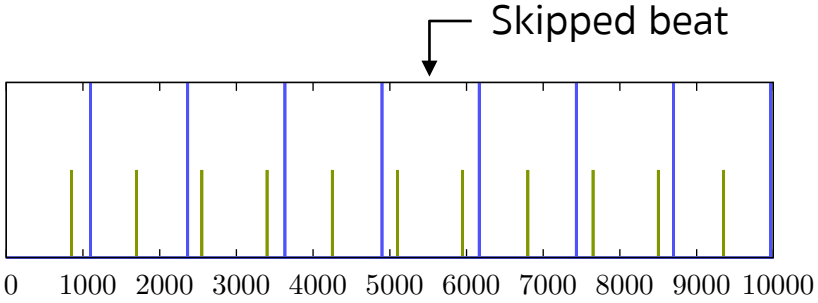
Atria beat Ventricles beat



Normal heart rhythm
(default parameters)



Bradycardia
(SA_d += 100 ms)



Wenckebach AV Block
(AV_Vt += 20 mV)

OPTIMISATION ALGORITHM

OPTIMIZATION PROBLEM

Arguments: pacemaker parameters
Objective function: energy consumption of the device

→ REQUIRES A BLACK-BOX METHOD!

Gaussian Process Optimization

- Approximate optimization method
- Builds online a **statistical model** of the response function from available samples using **Gaussian Process regression**
- Uses the model for finding new parameters to sample
- Trade-off between improving objective function (**exploitation**) and reducing variance (**exploration**)

Advantage: returns not just (sub-)**optimal parameters**, but also a **predictive model**

RESULTS

Pacemaker parameters:

- TLRI : (affects the) time the PM waits before pacing atrium
- TAVI : conduction time from atrium to ventricle (affects the pacing of ventricle)

- Total electrical current during 1 min HIL simulation
- 150 samples
- Penalty (10^5 A) to parameters yielding unsafe heart rates

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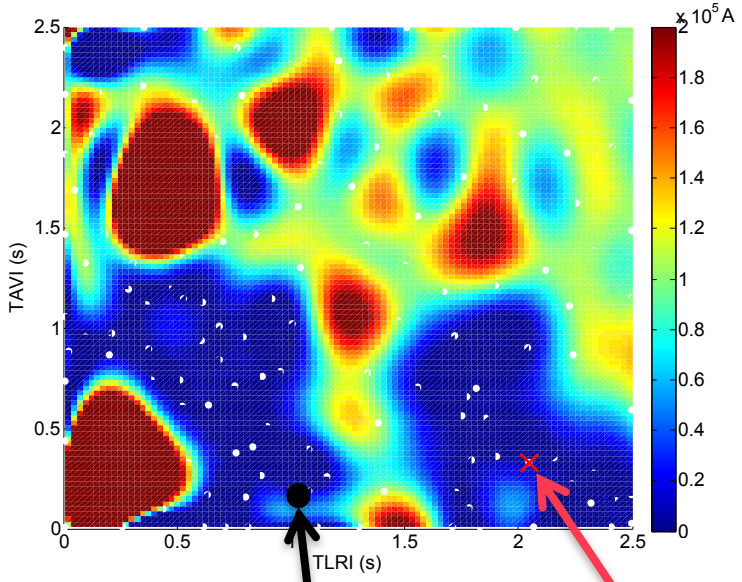
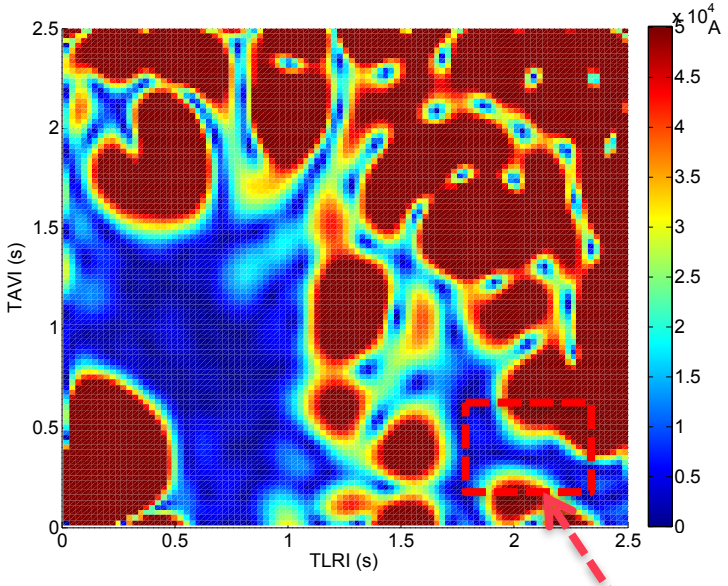
AV block: conduction defect in the AV node

Mean



Standard deviation



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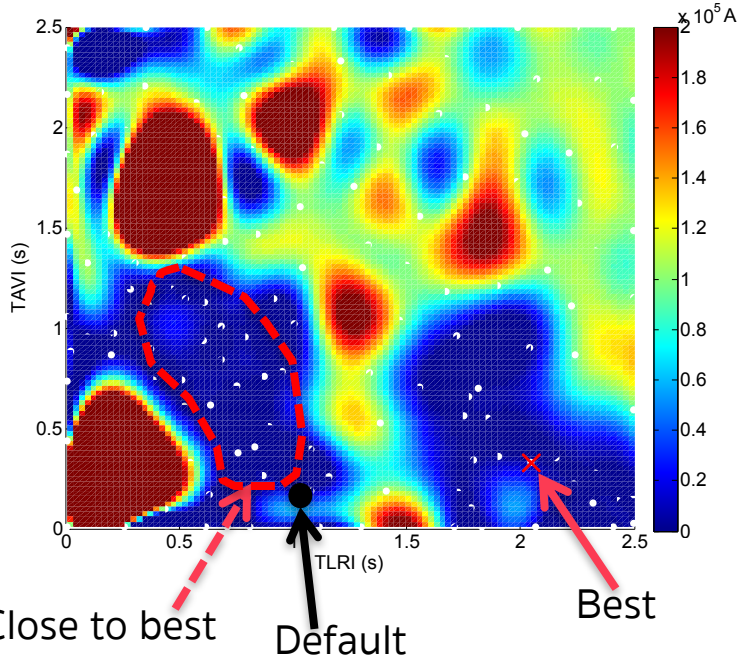

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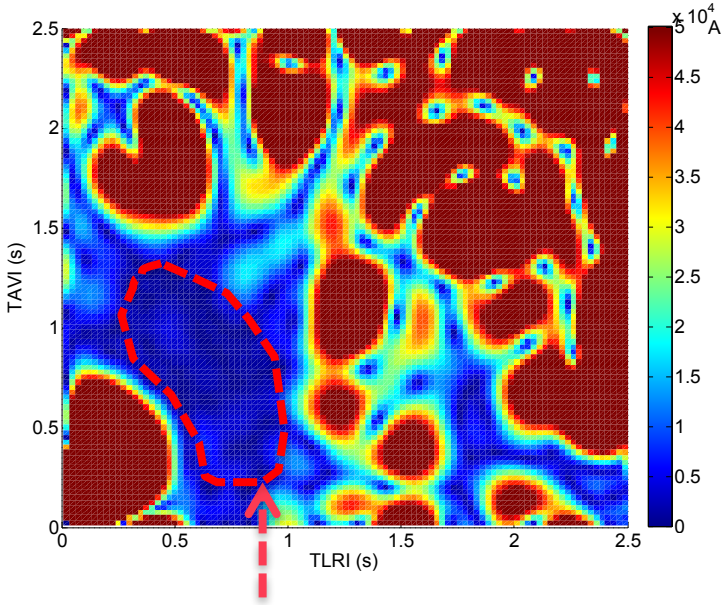


DRAWBACKS AND LIMITATIONS

PROBLEM:

High penalty for unsafe parameters introduces “artificially” high variance, affecting search and optimisation results.

SOLUTION:

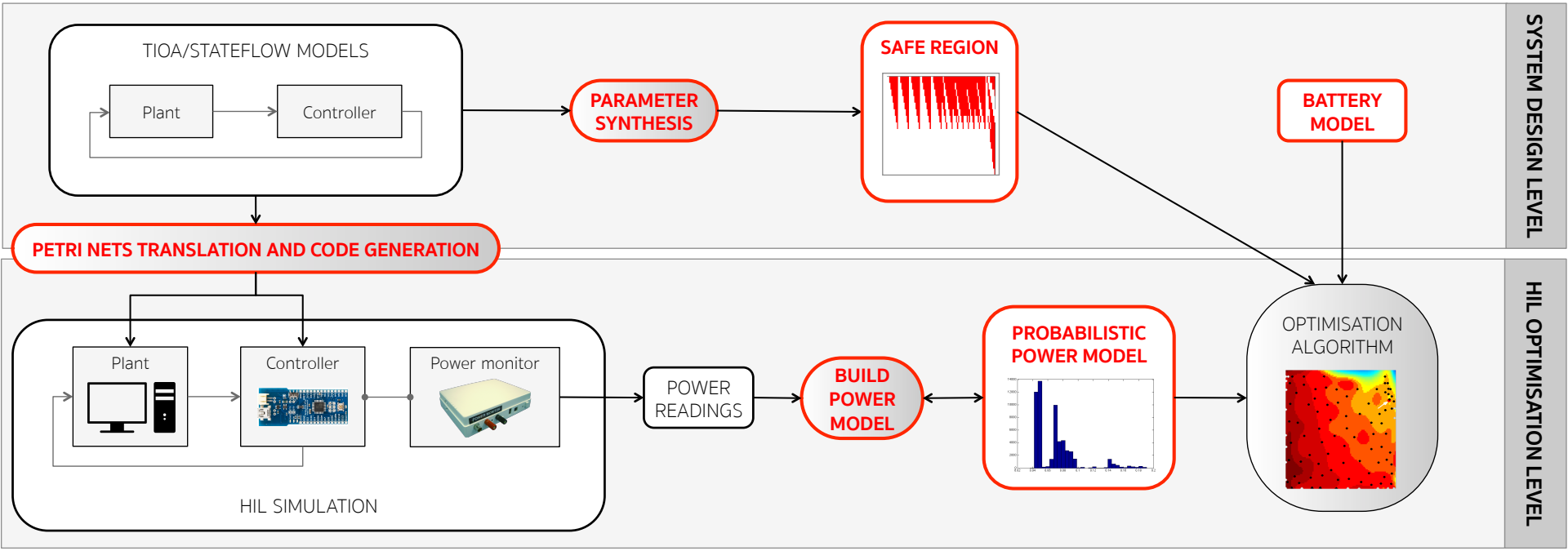
Synthesise unsafe parameters a-priori and exclude them from the search

PROBLEM:

HIL simulation (as it is) cannot be used for maximization of battery lifetime, because it requires simulating until the battery is depleted (time consuming!).

SOLUTION:

Estimate through HIL simulation (probabilistic) power consumption models that map controller actions to power required with HIL simulation. Use the consumption model + battery model in the optimisation algorithm.



B. Barbot, M. Kwiatkowska, A. Mereacre and N. Paoletti.
Building Power Consumption Models from Executable Timed I/O Automata Specifications.
Submitted to HSCC 2016

2. PARAMETER SYNTHESIS

M. Kwiatkowska, A. Mereacre, N. Paoletti and Andrea Patanè.
Synthesising robust and optimal parameters for cardiac pacemakers using symbolic and evolutionary computation techniques. In HSB 2015.

PARAMETER SYNTHESIS

- **AIM:** Find better pacemaker parameters, automatically **(synthesis)**

- Better means
  1. Safe and robust
  2. Able to optimise additional cost functions (e.g. clinical indicators or power consumption)

Priority between objectives is well-captured by bilevel optimisation problems

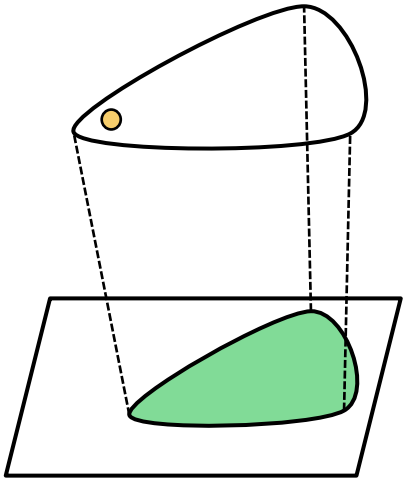
SYNTHESIS AS BILEVEL OPTIMISATION

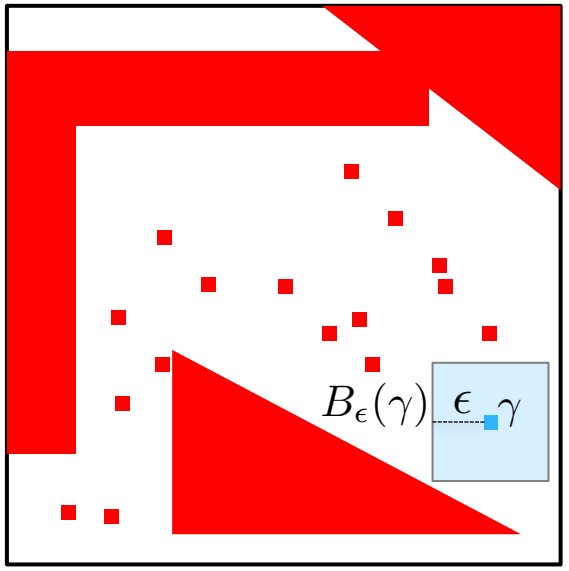
ROBUST OPTIMAL SYNTHESIS PROBLEM

1. Find parameter valuations γ with maximum robustness radius ϵ, i.e. such that the specification holds for any ϵ-bounded perturbation of γ, called $B_\epsilon(\gamma)$
2. Minimize cost function on the solution space that gives maximum robustness

Outer problem
(minimize cost)

Inner problem
(maximize robustness)

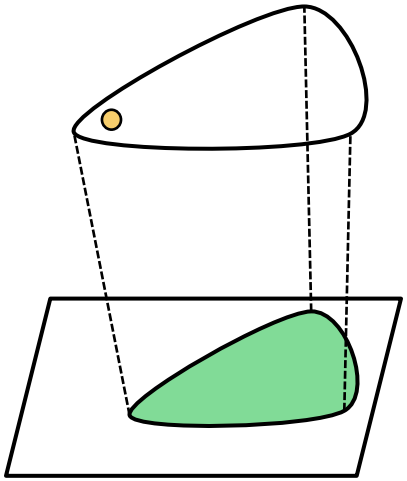




METHOD OVERVIEW

Outer problem
(minimize cost)

Inner problem
(maximize robustness)



Evolutionary strategies

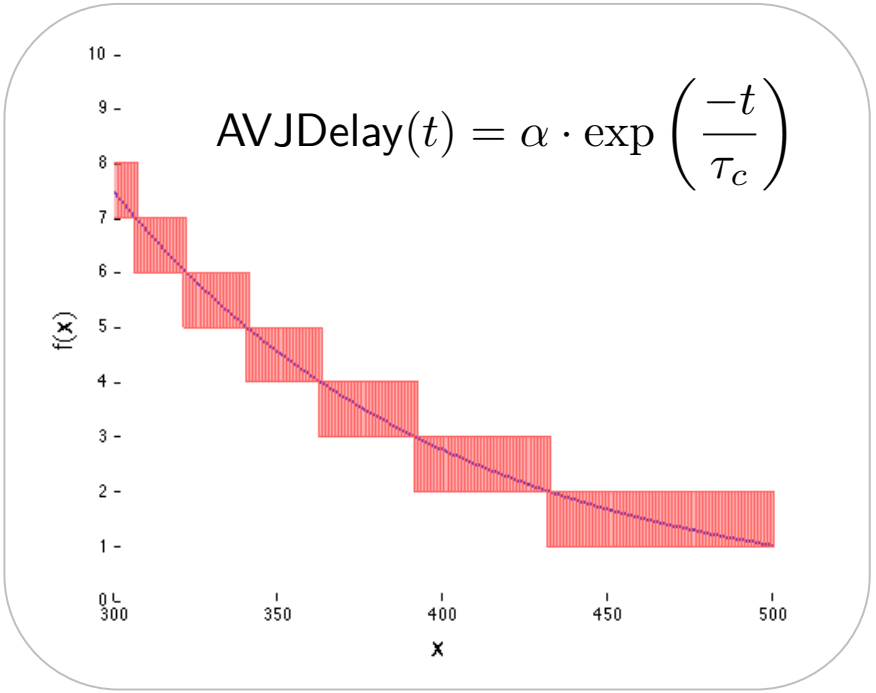
SMT-based algorithm

(Safety properties are specified using **CMTL** = MTL + counting operator)

SMT ENCODING

- Encoding of TIOA model and synthesis problem as a **Satisfiability Modulo Theories problem** - **discrete encoding** (SMT UF_BV)
- How to deal with real-valued and non-linear functions? **Interval-based abstraction**

  - Introduce **non-deterministic (ND) variables** in TIOA, that can be reset non-deterministically to multiple possible values
  - Pre-compute safe bounds for the functions $[f(x)^{\perp}, f(x)^{\top}]$
  - Replace deterministic resets $y = f(x)$ with ND ones $y \in [f(x)^{\perp}, f(x)^{\top}]$



INNER PROBLEM ALGORITHM

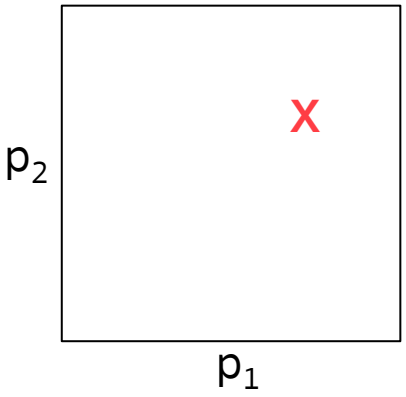
- Extends **Bounded Model Checking** for finding counter-example (CE) parameters
- **Enumeration of CEs at the full path length is infeasible**

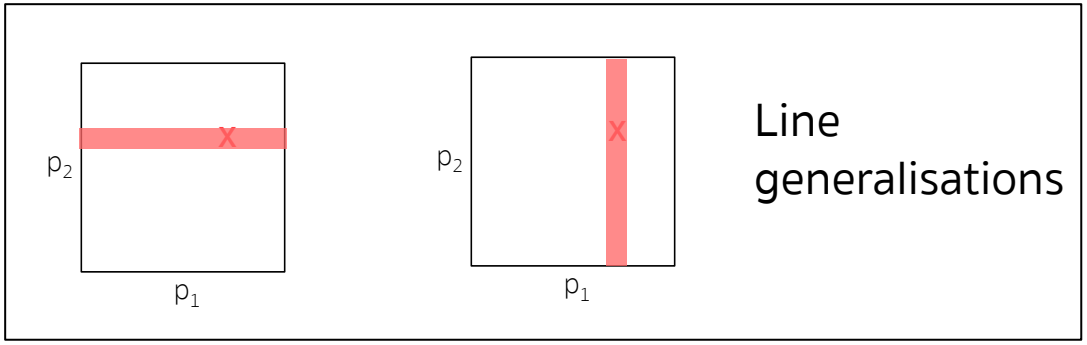
Approach:

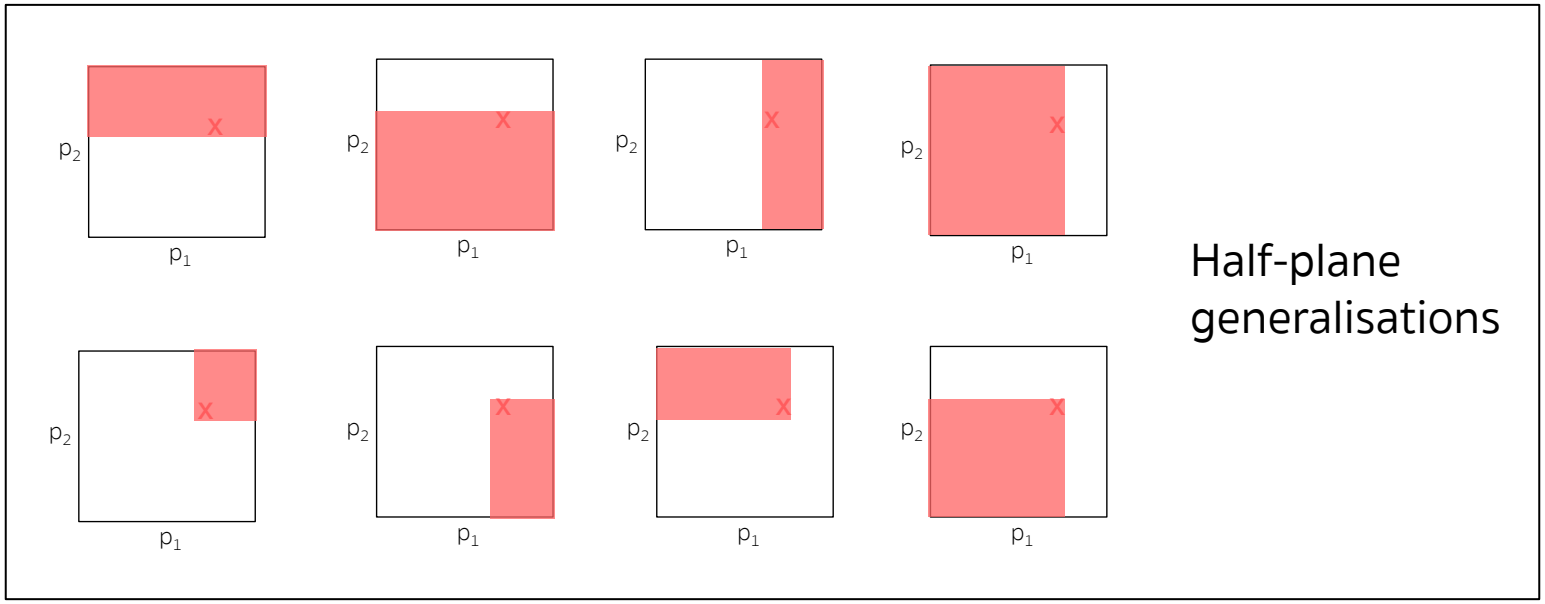
- **Incremental solving**: CEs are computed step-wise for increasing path lengths
- **CE generalization**: found a CE, try to derive a larger unsafe region containing it
- **Search space restriction**: need not to explore the whole parameter space, but only the current largest region without CEs
- **Separate solver** (SMT_QBVF) is used to compute the current max robust radius and parameter

COUNTER-EXAMPLE GENERALIZATION

Based on asserting CE (X) + Safety (contradiction) and generating **UNSAT core**

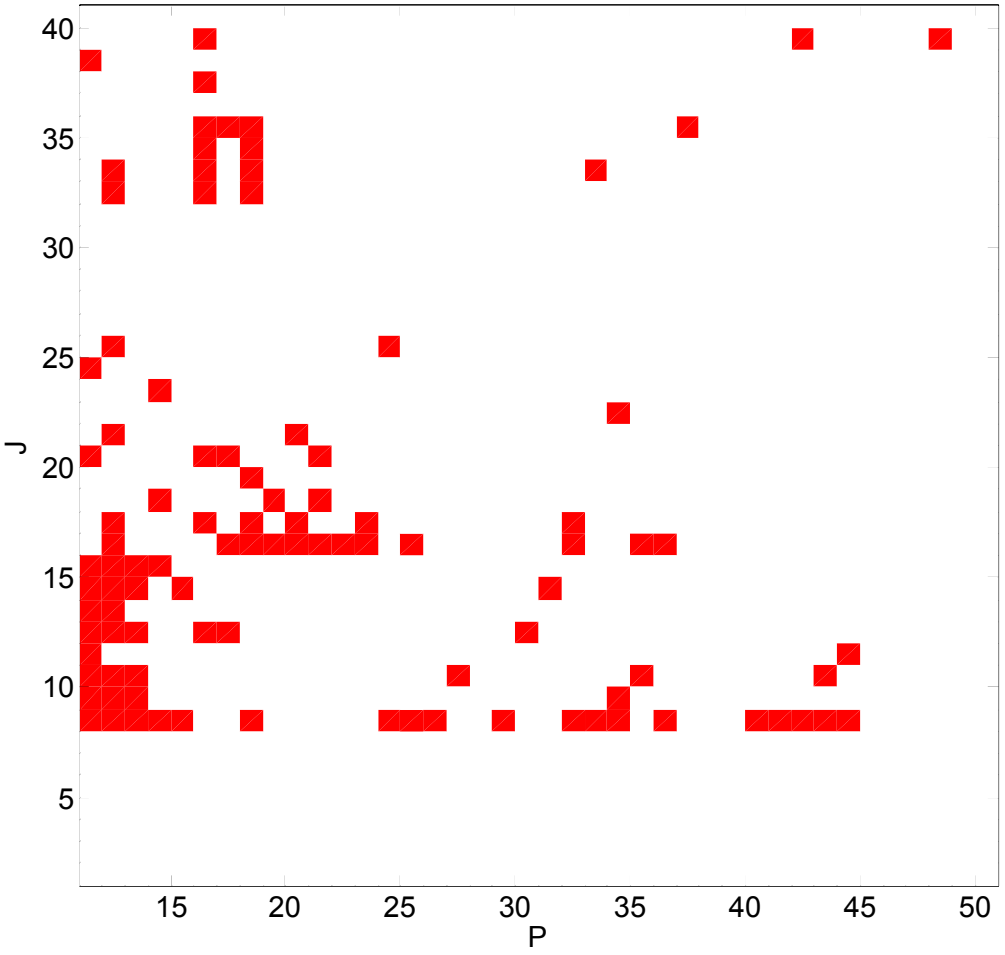






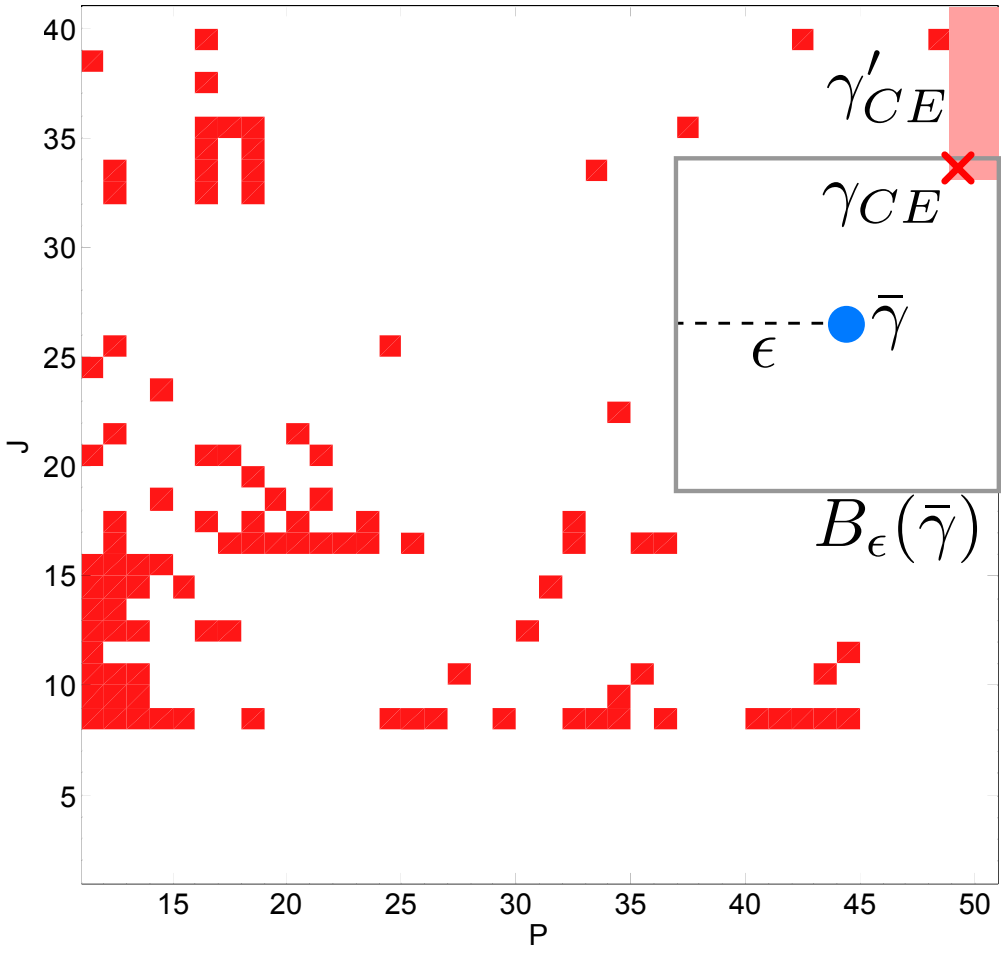
EXAMPLE

Unsafe region at step *k=1*



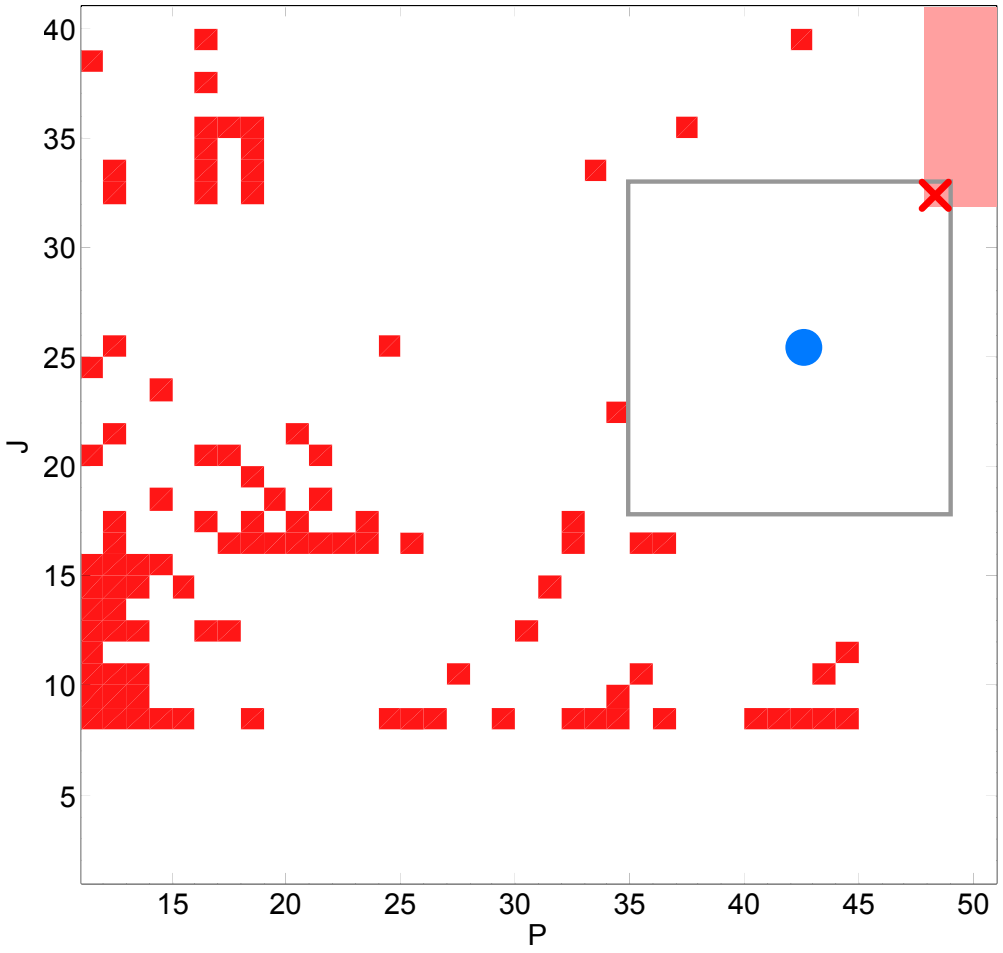
EXAMPLE

Restrict the search to current max robust region and generalize



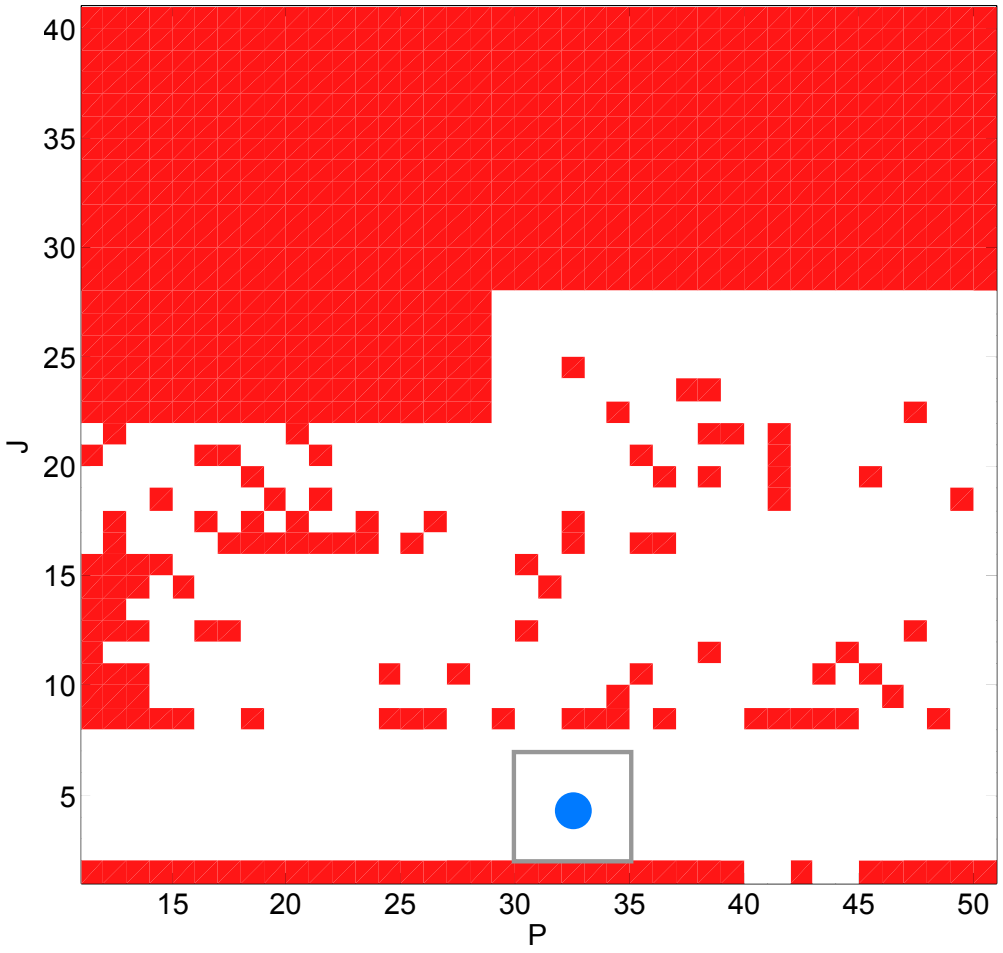
EXAMPLE

Update max robust region



EXAMPLE

Final step



APPROXIMATE SOLUTION WITH EVOLUTIONARY STRATEGIES

- ES are a class of **black-box stochastic optimisation methods** that **mimic Darwinian evolution**
- Work on a **population** (set of candidate solutions) which, at each **generation** (iteration of the algorithm), is subject to a number of **natural operators** (random recombination)
- Only a subset of the best solutions are kept for the next generation

HOW TO COMPARE SOLUTIONS OF A BI-LEVEL OPTIMISATION PROBLEM?

Feasible over infeasible approach: $\gamma_1 \preceq \gamma_2$ if

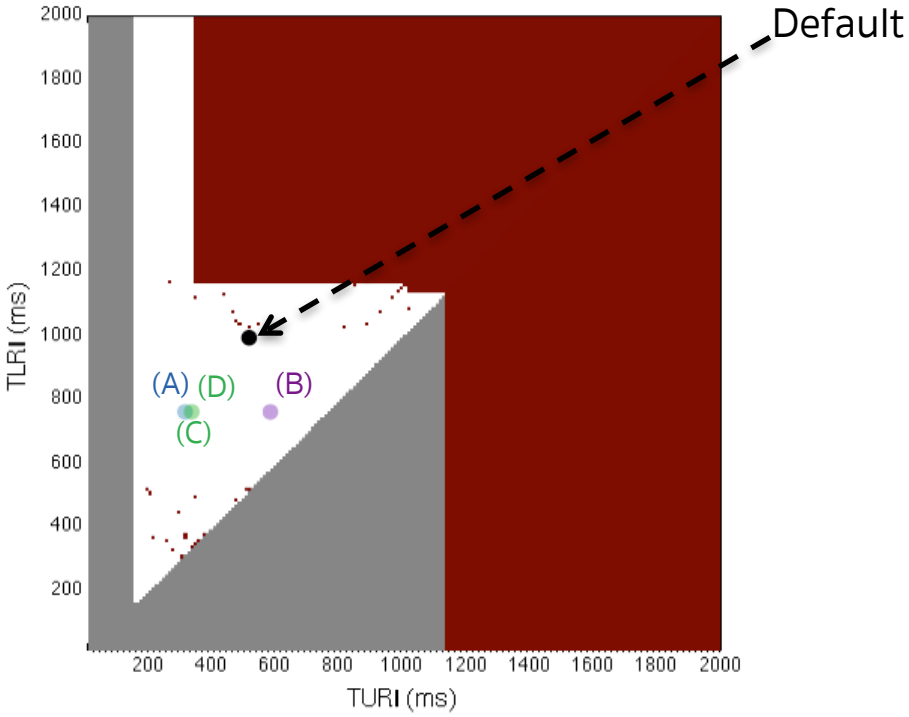
1. γ_1 is a solution of the inner problem, and γ_2 is not
2. γ_1 and γ_2 are solutions of the inner problem, and γ_1 has lower objective function

ROBUST OPTIMAL SYNTHESIS FOR PACEMAKER

Pacemaker parameters:

- `TLRI`: (affects the) time the PM waits before pacing atrium
- `TURI`: time the PM waits before pacing ventricle after atrial event

Bradycardia: slow heart rate



INNER PROBLEM

- Path length: 20
- Runtime: 7354 s

OUTER PROBLEM: ENERGY

	Method	Obj value	Runtime (s)
A)	Exact	158	2369
B)	ES	158 (-0%)	1101 (-54%)

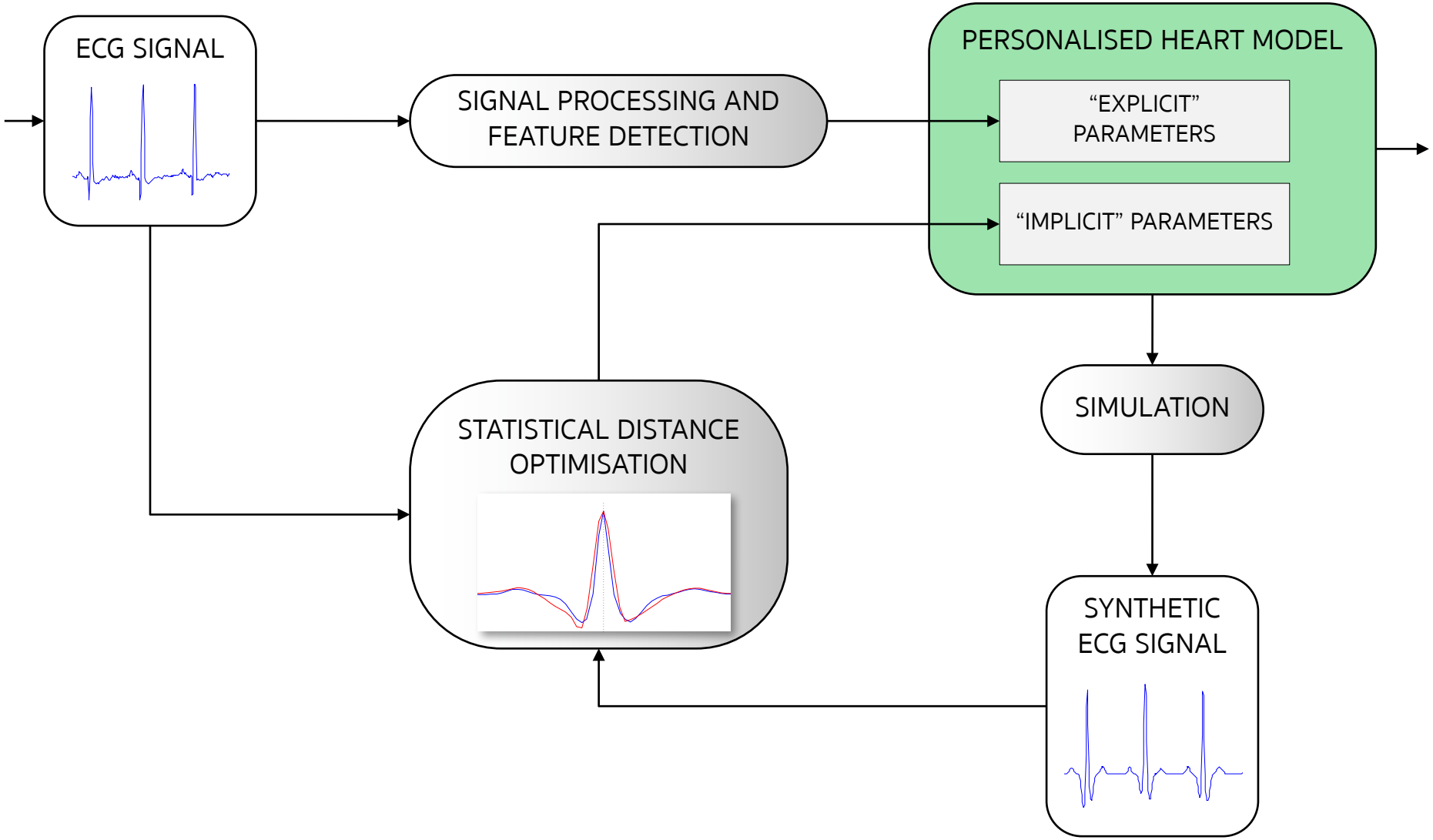
OUTER PROBLEM: CARDIAC OUTPUT

	Method	Obj value	Runtime (s)
C)	Exact	9.14	1547
D)	ES	9.14 (-0%)	118 (-92%)

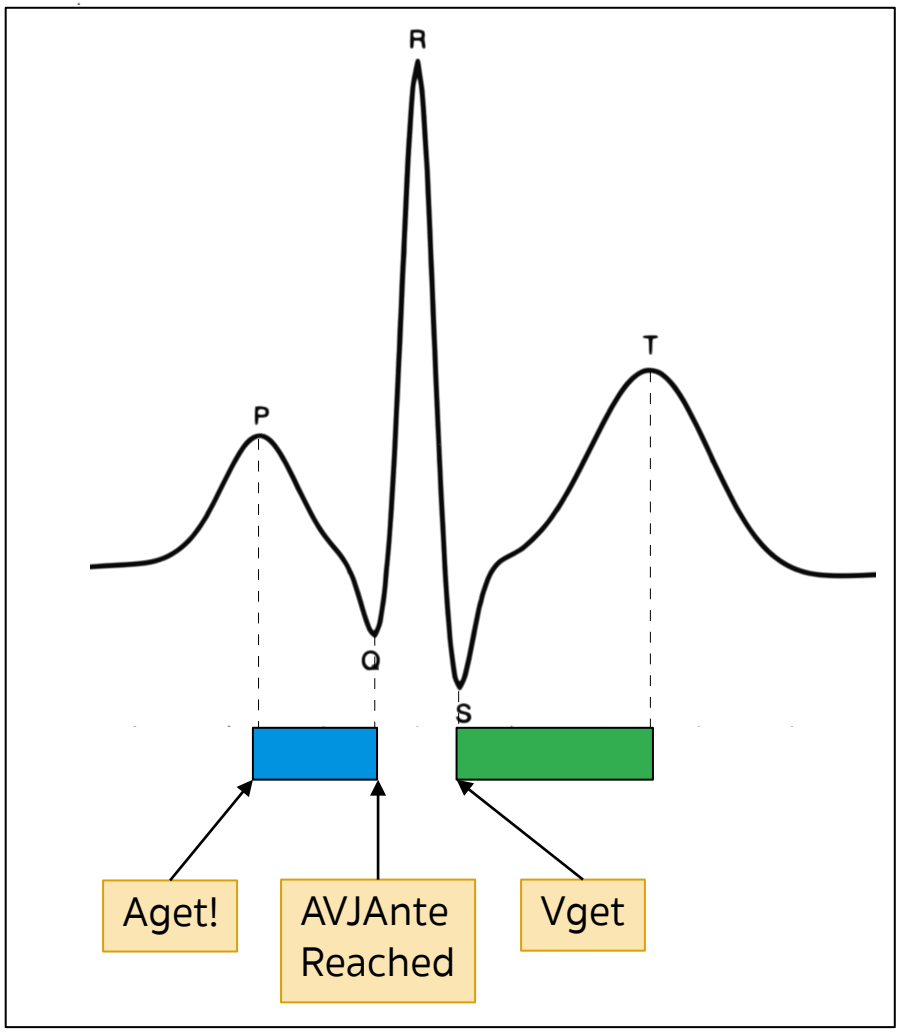
3. HEART PARAMETERS ESTIMATION FROM ECG DATA

B. Barbot, M. Kwiatkowska, A. Mereacre and N. Paoletti.
Estimation and Verification of Hybrid Heart Models for Personalised Medical and Wearable Devices. In CMSB 2015

METHOD OVERVIEW



ECG FEATURES AND EXPLICIT PARAMETERS



Heart network actions

Explicit parameters:

Atrium-AV node conduction time

Ventricle refractory period

SYNTHETIC ECG

- Probabilistic heart model (extracted ECG features induce discrete prob. distributions)
- **Synthetic ECG** generated from simulation trace (sum of Gaussian curves)

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

Center of the Gaussian
(ECG wave location)

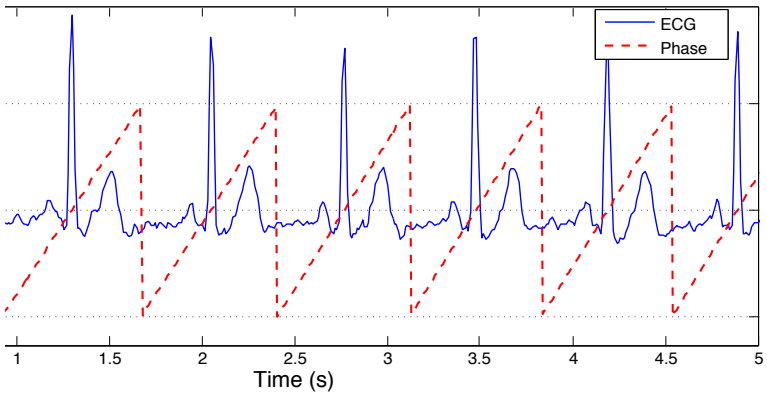
Height
(ECG wave amplitude)

Standard deviation
(width of ECG wave)

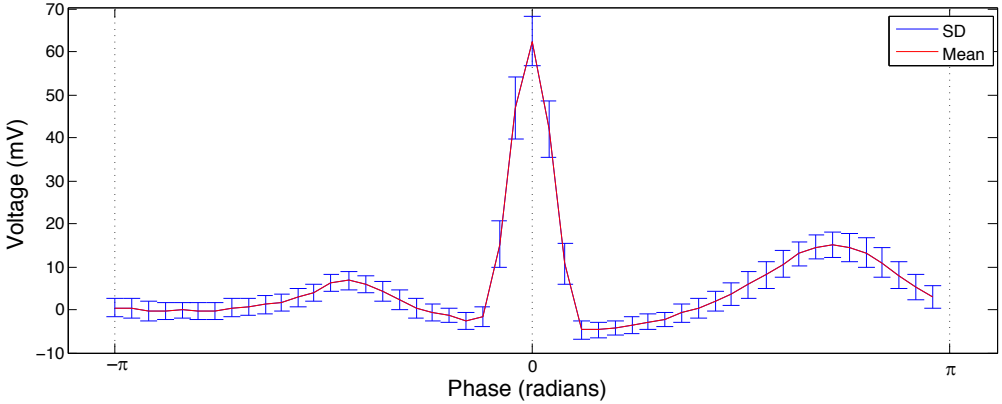
McSharry et al. IEEE Transactions on Biomedical Engineering 50(3), 289–294 (2003)

STATISTICAL ECG WAVEFORM

Linear phase assignment for deriving statistical descriptors of ECG, **independent from the heart rate**



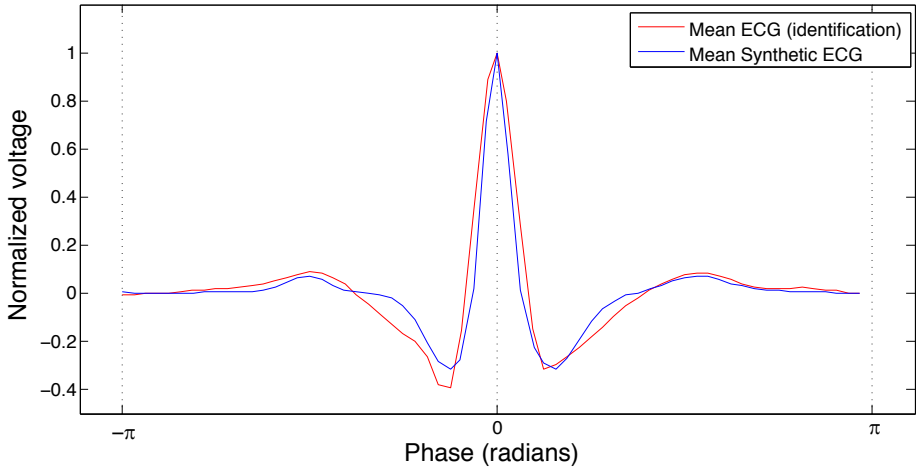
Phase assignment (R peaks map to 0/2π)

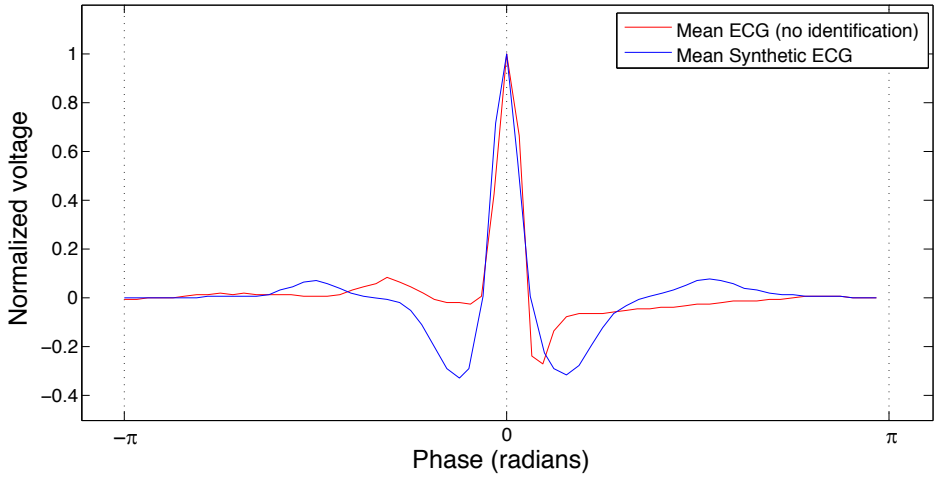


Statistical waveform (the fingerprint)

Sameni et al. IEEE Transactions on Biomedical Engineering 54(12), 2172–2185 (2007)

ECG WAVEFORMS STATISTICAL DISTANCE





A biometrics tool as well!

Signals from same patient (different recordings)

Distance: 0.42

Signals from different patients

Distance: 0.78

Summary

1. HARDWARE-IN-THE-LOOP ENERGY OPTIMISATION

- Supports cardiac pacemakers and more general embedded devices
- Energy-efficient parameters + Predictive energy consumption model

2. PARAMETER SYNTHESIS

- Supports TIOA models and CMTL properties
- Problem as bilevel optimization: max robustness + min cost
- Combination of SMT solving and evolutionary strategies

3. HEART PARAMETERS ESTIMATION FROM ECG DATA

- Based on generation of model-based synthetic ECGs
- Applications to verification/synthesis of personalised treatments and biometrics

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Projects

ERC VERIWARE
ERC VERIPACE

www.veriware.org/pacemaker.php