Synthesising robust and optimal parameters for cardiac pacemakers using symbolic and evolutionary computation techniques

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Abstract. We consider the problem of automatically finding safe and robust values of timing parameters of cardiac pacemaker models so that a quantitative objective, such as the pacemaker energy consumption or its cardiac output (a heamodynamic indicator of the human heart), is optimised in a finite path. The models are given as parametric networks of timed I/O automata with data, which extend timed I/O automata with priorities, real variables and real-valued functions, and specifications as Counting Metric Temporal Logic (CMTL) formulas. We formulate the parameter synthesis as a bilevel optimisation problem, where the quantitative objective (the outer problem) is optimised in the solution space obtained from optimising an inner problem that yields the maximal robustness for any parameter of the model. We develop an SMT-based method for solving the inner problem through a discrete encoding, and combine it with evolutionary algorithms and simulations to solve the outer optimisation task. We apply our approach to the composition of a (non-linear) multi-component heart model with the parametric dual chamber pacemaker model in order to find the values of multiple timing parameters of the pacemaker for different heart diseases.

1 Introduction

Motivation. The growing demand for wearable health monitoring devices, from fitness apps running on smart watches to implantable devices such as cardiac pacemakers and glucose monitoring, calls for design methodologies that can ensure their safety, effectiveness and energy efficiency. Model-based verification [9,21,32] has proved useful in establishing key correctness properties of cardiac pacemakers [19], but the approach has limitations, in that it is not clear how to redesign the model if it fails to satisfy a given property. Instead, the parameter synthesis problem aims to automatically find optimal values of parameters to guarantee that a given property is satisfied. Similarly to verification, this problem has prohibitive complexity and may suffer from undecidability, typically tackled through discretisation of the parameter space.

In [15], we presented a parameter synthesis method for timed I/O automata (TIOA) that optimises the choice of timing delays for a given objective function to guarantee that a property, expressed in Counting MTL, a generalisation of Metric Temporal Logic, is satisfied. The method is based on exploring finite discrete paths and the corresponding timing constraints. We have applied the techniques to cardiac pacemakers, deriving robust values for safety and energy efficiency, but could only guarantee partial coverage via sampling, as fully exhaustive exploration was not practical.

Contribution. In this paper, we tackle, for the first time, the problem of ensuring effectiveness for pacemakers defined in terms of cardiac output (a heamodynamic indicator of the human heart), as well as safety. To this end, we extend the models and logic of [15] with real-valued data variables, and provide a novel method for synthesising timing delays that are simultaneously safe *and* robust, whilst guaranteeing that a given quantitative objective is optimised. This is formulated as a bi-level optimisation problem, which we solve through a combination of symbolic, SMT-based, analysis of finite paths based on discrete encoding (for the inner problem), with evolutionary computation techniques (for the outer problem). We consider a novel multi-component heart model given as a network of TIOA with data [5] and extend it in order to compute the cardiac output. We apply the developed techniques to the synthesis of multiple pacemaker parameters for different heart conditions, in order to optimise, at the outer level, either energy consumption or cardiac output, on top of the solution space that yields a safe heart rhythm (formulated as a CMTL property) with maximum robustness.

Related work. The undecidability of the parametric reachability problem is proved in [16]. The majority of work for timed systems concerns synthesis from logic formulas, e.g. [8], with the exception of [1,2] who consider a reference valuation. In [7,23], the authors show PSPACE-completeness of the emptiness problem and TCTL, respectively. Robustness under a given timed perturbation is considered in [38] and parameter synthesis for reachability for probabilistic timed automata in [22]. SMT-based verification of timed and hybrid systems has received a lot of attention recently, see e.g. [10]. In [26], the authors present an SMT-based timed system extension to the IC3 algorithm. [25] and [27] respectively develop real-time bounded model checking (BMC) approaches for LTL and CTL. [20] presents an SMT technique to generate inductive invariants for hybrid systems. Sturm et al [37] applies real quantifier elimination tools to synthesise continuous and switched dynamical systems. The dReal solver [18] uses a relaxed notion of satisfiability in order to provide decision procedures for non-linear hybrid systems.

In this paper, we extend the model and logic of [15], and replace the path exploration with a fully symbolic BMC-based algorithm. We adopt the pacemaker model from [21] but consider a different heart model [5], which we enhance with the blood pressure component.

2 Background

2.1 Timed I/O automata with priorities and data

We extend the timed I/O automata model with priorities of [15] with data variables. Let $\mathcal{X}$ be a set of *non-negative* real-valued variables, called *clocks*. Let $\mathcal{D}$ be a set of real-valued variables, called *data*. A variable valuation is a function $\eta = \eta_{|\mathcal{X}} \cup \eta_{|\mathcal{D}}$ where $\eta_{|\mathcal{X}} : \mathcal{X} \to \mathbb{R}_{\geq 0}$ and $\eta_{|\mathcal{D}} : \mathcal{D} \to \mathbb{R}$. We denote the set of variables with $V = \mathcal{X} \cup \mathcal{D}$. Let Γ be a set of real-valued *parameters*. A parameter valuation is a function $\gamma : \Gamma \to \mathbb{R}$ mapping each parameter p to a value in its domain $\mathrm{dom}(p) \subseteq \mathbb{R}$.

Let $\mathcal{Y}$ be a set and $\mathcal{V}(\mathcal{Y})$ denote the set of all valuations over $\mathcal{Y}$. We consider guard constraints of the form $\bigwedge_i v_i \bowtie_i f_i$, where $v_i \in \mathcal{X}$ is a clock, $\bowtie_i \in \{<, \leqslant, >, \geqslant\}$

and $f_i : \mathcal{V}(\mathcal{D}) \times \mathcal{V}(\Gamma) \to \mathbb{R}$ is a real-valued function over data variable and parameter valuations. A variable valuation η and a parameter valuation γ satisfy the above constraint iff $\bigwedge_i \eta(v_i) \bowtie_i f_i(\eta_{|\mathcal{D}}, \gamma)$ holds. We denote with $\mathcal{B}(V)$ the set of guard constraints over V. The reset of a set of variables $V' \subseteq V$ is an arbitrary function $r : V' \times \mathcal{V}(V) \times \mathcal{V}(\Gamma) \to \mathbb{R}$. Given valuations η and γ, η is updated by reset r to the valuation $\eta[r] = \{v \mapsto r(v, \eta, \gamma) \mid v \in V'\} \cup \{v \mapsto \eta(v) \mid v \notin V'\}$ that applies the reset r to the variables in V' and leaves unchanged the others. We denote with $\mathcal{R}$ the set of reset functions. The valuation η after time $\delta \in \mathbb{R}_{\geq 0}$ has elapsed is denoted with $\eta{+}\delta$ and is such that $\eta{+}\delta(v) = \eta(v) + \delta$ if $v \in \mathcal{X}$ and $\eta{+}\delta(v) = \eta(v)$ otherwise. This implies that all clocks proceed at the same speed and data variables are not affected by the passage of time.

Definition 1 (Deterministic Timed I/O Automaton with Priority and Data). *A deterministic timed I/O automaton (TIOA) with priority and data* $\mathcal{A} = (\mathcal{X}, \Gamma, \mathcal{D}, Q, q_0, \Sigma_{\text{in}}, \Sigma_{\text{out}}, \to)$ *consists of:*

- *A finite set of clocks* $\mathcal{X}$*, data variables* $\mathcal{D}$ *and parameters* Γ*.*
- *A finite set of locations* Q*, with the initial location* $q_0 \in Q$*.*
- *A finite set of input actions* Σ_{in} *and a finite set of output actions* Σ_{out}*.*
- *A finite set of edges* $\to \subseteq Q \times (\Sigma_{\text{in}} \cup \Sigma_{\text{out}}) \times \mathbb{N} \times \mathcal{B}(V) \times \mathcal{R} \times Q$*. Each edge* $e = (q, a, pr, g, r, q')$ *is described by a source location* q*, an action* a*, a priority* pr*, a guard* g*, a reset* r *and a target* q'*.*

We require that priorities define a total ordering of the edges out of any location, and that output actions have higher priority than input actions. The TIOAs as defined above are able to synchronise on matching input and output actions, thus forming *networks of communicating automata*. We say that an output edge is *enabled* when the associated guard holds. On the other hand, an input edge is enabled when both its guard holds and it can synchronise with a matching output action fired by another component of the network. A component of a network of TIOAs is enabled if, from its current location, there is at least one outgoing edge enabled. Also, we assume that output edges are *urgent*, meaning that they are taken as soon as they become enabled. As shown in [15], priority and urgency imply that *the TIOA is deterministic*.

Definition 2 (Network of TIOAs). *A network of TIOAs with* m *components is a tuple* $\mathcal{N} = (\{\mathcal{A}^1, \ldots, \mathcal{A}^m\}, \mathcal{X}, \Gamma, \mathcal{D}, \Sigma_{\text{in}}, \Sigma_{\text{out}})$ *of TIOAs, where*

- *for* $j = 1, \ldots, m$*,* $\mathcal{A}^j = (\mathcal{X}, \Gamma, \mathcal{D}, Q^j, q_0^j, \Sigma_{\text{in}}, \Sigma_{\text{out}}, \to^j)$ *is a TIOA,*
- $\mathcal{X}, \Gamma, \mathcal{D}, \Sigma_{\text{in}}, \Sigma_{\text{out}}$ *are the common sets of clocks, parameters, data variables, input and output actions, respectively,*

We define the set of network modes by $\boldsymbol{Q} = Q^1 \times \cdots \times Q^m$*, with initial mode* $\boldsymbol{q_0} = (q_0^1, \ldots, q_0^m)$ *and the initial variable valuation* η_0*. A state of the network is a pair* $(\boldsymbol{q}, \eta)$ *where* $q \in \boldsymbol{Q}$ *and* $\eta \in \mathcal{V}(V)$*.*

A *parametric network of TIOAs* is a network where the parameter valuation is unknown, and is denoted by $\mathcal{N}(\cdot)$. $\mathcal{N}(\gamma)$ denotes the network obtained by instantiating valuation γ. We describe the formal semantics of a network of TIOAs in terms of timed paths.

In the following, we use the predicate $\mathsf{enabled}(\mathcal{N}, j, \boldsymbol{q}, \eta, \gamma)$ (see [30] for its formal encoding) to indicate whether the j-th component of network $\mathcal{N}$ is enabled from the network mode $\boldsymbol{q}$ under variable valuation η and parameter valuation γ.

Definition 3 (Path of a TIOA Network). *Let $\mathcal{N}$ be a network of TIOAs and $n \in \mathbb{N}^+$. Let $\rho = (\boldsymbol{q_0}, \eta_0) \xrightarrow{t_0} (\boldsymbol{q_1}, \eta_1) \xrightarrow{t_1} \cdots \xrightarrow{t_{n-2}} (\boldsymbol{q_{n-1}}, \eta_{n-1})$ be a timed sequence of length n where, for $i = 1, \ldots, n-1$, $t_{i-1} \geq 0$, $\boldsymbol{q_i} \in \boldsymbol{Q}$ and η_i is a variable valuation. Then, ρ is the* timed path *of network $\mathcal{N}$ if for any position $i = 0, \ldots, n-2$:*

- *I) there exists at least one component enabled: $\exists j.\ \mathsf{enabled}(\mathcal{N}, j, q_i^j, \eta_i + t_i, \gamma)$; let E_{i,t_i} be the set of such components;*
- *II) each component $j \in E_{i,t_i}$ fires the edge $e_i^j = (q_i^j, a_i^j, pr_i^j, g_i^j, r_i^j, q_{i+1}^j) \in \rightarrow^j$ that is enabled and with maximum priority among the enabled edges;*
- *III) the variable valuation is updated according to the elapsed time and the resets of enabled components[3]: $\eta_{i+1} := \eta_i + t_i[\bigcup_{j \in E_{i,t_i}} r_i^j]$; and*
- *IV) t_i is the least time for which there are enabled components: $\forall t' < t_i.\ E_{i,t'} = \varnothing$.*

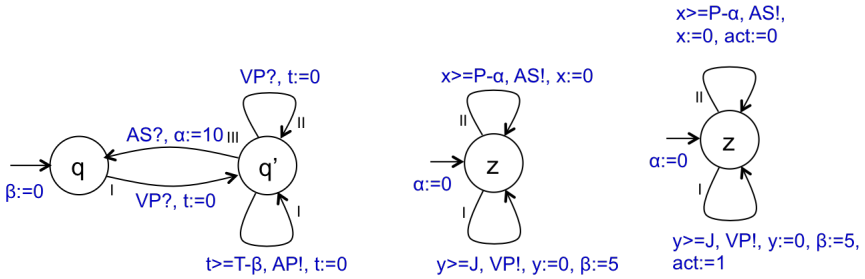
For $k, m \in \mathbb{N}$, $\rho[k] = (\boldsymbol{q_k}, \eta_k)$ is the k-th state of the path, $\rho^{[k,m]}$ is the subpath of length $m - k + 1$ starting at position k, $\rho\langle k \rangle = t_k$ is the k-th delay and $\rho\langle k, m \rangle = \sum_{k'=k}^{m} t_{k'}$ is the total time spent in the subpath $\rho^{[k,m]}$. For $t \in \mathbb{R}_{\geqslant 0}$, we denote with $\rho@t$ the smallest index o such that $\sum_{k=0}^{o} \rho\langle k \rangle > t$. If no such index exists, then $\rho@t = n - 1$. When the network is parametric, i.e. of the form $\mathcal{N}(\cdot)$, the corresponding parametric path is denoted with $\rho(\cdot)$.

In the following, we denote with $\mathit{\Pi}$ the set of finite timed paths. Given $t \in \mathbb{R}^{\geq 0}$, we also define the *path up to time t* as the path ρ with length $|\rho| = \rho@t$, that is, such that: (a) $\rho\langle 0, |\rho| - 1 \rangle \leq t$; and (b) let ρ' be the 1-step extension of ρ, then $\rho'\langle 0, |\rho'| - 1 \rangle > t$. We say that a parametric path $\rho(\cdot)$ is up to time t if, for each $\gamma \in \mathcal{V}(\mathit{\Gamma})$, $\rho(\gamma)$ is up to t.

Example 1. Consider the TIOAs $\mathcal{A}_1$ and $\mathcal{A}_2$ in Fig. 1. The automata $\mathcal{A}_1$ and $\mathcal{A}_2$ form a network. They communicate with each other by means of actions $\{\mathsf{VP}, \mathsf{AP}, \mathsf{AS}\} \in \mathit{\Sigma}_{\text{in}} \cup \mathit{\Sigma}_{\text{out}}$. We distinguish input (marked with ?) and output actions (marked with !). For instance, when automaton $\mathcal{A}_2$ takes a transition and outputs the action VP!, the automaton $\mathcal{A}_1$ synchronises by taking the corresponding transition with the input action VP?. We use Roman numbers to denote priorities, with the lowest number denoting the highest priority. The network $\mathcal{N}$ has three clocks t, x and y, and two variables α, and β. The initial mode of the network is (q, z) and the initial values for the α and β variables are zero. Each edge of the automaton is labelled with an action, a guard over the set of clocks and a reset over the set of clocks and variables. For instance, one of the edges from q' to q' is labelled with the guard $t \geq T - \beta$, action AP and clock reset $t := 0$. The network $\mathcal{N}$ has also three parameters T, P and J.

There are two ways to take an edge. First, when an input action is enabled. Second, when the clock satisfies a given guard. For example, automaton $\mathcal{A}_2$ has two transitions

[3] In order to have consistent resets, we assume that different components cannot update the same variable with different values during the same transition.



(a) $\mathcal{A}_1$ (b) $\mathcal{A}_2$ (c) $\mathcal{A}_2$ with additional variables

Fig. 1: Example network $\mathcal{N}$ with two components, $\mathcal{A}_1$ and $\mathcal{A}_2$.

labelled with the conditions $x \geq P - \alpha$ and $y \geq J$. As soon as the clock y satisfies the guard $y \geq J$, the automaton takes the corresponding transition and outputs the action VP!, resetting to zero the value of the clock y and assigning the value of five to the variable β. When multiple transitions are enabled in a location, then the one with the highest priority will be taken. Consider the finite path below, where transitions are labelled with enabled output actions:

$$\begin{gathered}((q,z),(\alpha=0,\beta=0,t=0,x=0,y=0))\\ \downarrow J,\mathsf{VP}\\ ((q',z),(\alpha=0,\beta=5,t=0,x=J,y=0))\\ \downarrow T{-}5,\mathsf{AP}\\ ((q',z),(\alpha=0,\beta=5,t=0,x=J{+}T{-}5,y=T{-}5))\\ \downarrow P{-}J{-}T{+}5,\mathsf{AS}\\ ((q,z),(\alpha=10,\beta=5,t=P{-}J{-}T{+}5,x=0,y=P{-}J)).\end{gathered}$$

Each element of the tuple represents the state of the network and the values of the variables. The network starts in the initial state (q,z) with the values of the variables $(\alpha=0,\beta=0,t=0,x=0,y=0)$. In the automaton $\mathcal{A}_2$, after J time units have passed, the guard $y \geq J$ becomes true and the corresponding transition is triggered at this point, outputting the action VP and resetting the clock t to 0 and the variable β to 5. The automaton $\mathcal{A}_1$ then synchronises with $\mathcal{A}_2$ via the matching input, VP, which moves the automaton to q'. Then $\mathcal{A}_1$ takes transition labelled with $T-\beta$ and $\mathcal{A}_2$ does no transition. Then the automaton takes the transitions labelled with $P-\alpha$ outputting the action AS and the state of the network becomes (q,z). Note that, in order to take the transition labelled with action VP in $\mathcal{N}$, the parameters P and J have to satisfy the urgency constraint $P-\alpha<J$. Similar relations can be derived for the remaining transitions of the path.

2.2 Counting MTL

We work with the *Counting Metric Temporal Logic* (CMTL), which is an extension of MTL with the counting operator (#) [34,15], now interpreted over TIOAs with data.

Let $\mathcal{E}(V)$ be the set of constraints $\bigwedge_i c_i \bowtie_i g_i$ over variables in $V = \mathcal{X} \cup \mathcal{D}$, where $c_i \in \mathbb{R}, \bowtie_i \in \{<, \leq, =, \geq, >\}$ and $g_i : \mathcal{V}(V) \to \mathbb{R}$ is a real-valued function over V. To this end, we replace CMTL atomic propositions by predicates from $\mathcal{E}(V)$. For instance, given two variables $x, y \in V$, a constraint from $\mathcal{E}(V)$ is $x = 1 \wedge y \geq 10$. The syntax of CMTL is defined by

$$\varphi ::= e \mid \sum_{j \in J} c_j \#_{\ell_j}^{u_j} e_j \bowtie b \mid \varphi \wedge \varphi \mid \neg\varphi \mid \varphi \, \mathcal{U}^{[\ell,u]} \varphi,$$

where J is a finite set of indices, $\bowtie \in \{>, \geqslant, <, \leqslant\}$, $b \in \mathbb{Z}$, $c_j \in \mathbb{Z}$, $\ell \in \mathbb{R}_{\geqslant 0}$, $\ell_j \in \mathbb{R}_{\geqslant 0}$, $u \in \mathbb{R}_{\geqslant 0} \cup \{\infty\}$, $u_j \in \mathbb{R}_{\geqslant 0} \cup \{\infty\}$ are time points such that $\ell \leqslant u$ and $\ell_j \leqslant u_j$, and $e, e_j \in \mathcal{E}(V)$ for all $j \in J$. The counting term $\#_{\ell_j}^{u_j} e_j$ counts how many times, in the interval of time $[\ell_j, u_j]$, e_j holds true. Such terms can be combined to form a so-called basic counting formula $\sum_{j \in J} c_j \#_{\ell_j}^{u_j} e_j \bowtie b$, i.e. a linear constraint (with integer coefficients) over counting terms. The semantics of CMTL is defined over timed paths as follows.

Definition 4. *Let $\rho = (\boldsymbol{q_0}, \eta_0) \xrightarrow{t_0} (\boldsymbol{q_1}, \eta_1) \xrightarrow{t_1} \cdots \xrightarrow{t_{n-1}} (\boldsymbol{q_n}, \eta_n)$ be the finite timed path of the network $\mathcal{N}(\gamma)$ of TIOAs with parameter valuation γ and $i \in \mathbb{N}$ be an index. We say that $\mathcal{N}$* satisfies *φ at i, denoted $(\rho, i) \models^{\mathcal{N}} \varphi$, iff*

$$\begin{aligned}
&(\rho,i) \models^{\mathcal{N}} e && \text{iff } \eta_i \models e \\
&(\rho,i) \models^{\mathcal{N}} \sum_{j \in J} c_j \#_{\ell_j}^{u_j} e_j \bowtie b && \text{iff } \left(\sum_{j \in J} c_j \sum_{k=\rho^{[i,|\rho|]}@\ell_j}^{\rho^{[i,|\rho|]}@u_j - 1} \mathbf{1}\left(\eta_k \models e_j\right) \right) \bowtie b \\
&(\rho,i) \models^{\mathcal{N}} \varphi_1 \wedge \varphi_2 && \text{iff } (\rho,i) \models^{\mathcal{N}} \varphi_1 \wedge (\rho,i) \models^{\mathcal{N}} \varphi_2 \\
&(\rho,i) \models^{\mathcal{N}} \neg\varphi_1 && \text{iff } (\rho,i) \not\models^{\mathcal{N}} \varphi_1 \\
&(\rho,i) \models^{\mathcal{N}} \varphi_1 \, \mathcal{U}^{[\ell,u]} \varphi_2 && \text{iff } \exists i'.\ i \leqslant i' \text{ s.t. } \sum_{k=i}^{i'} \rho\langle k \rangle \in [\ell,u] \wedge (\rho,i') \models^{\mathcal{N}} \varphi_2 \wedge \\
& && \quad \forall i''.\ i \leqslant i'' < i' \wedge (\rho,i'') \models^{\mathcal{N}} \varphi_1,
\end{aligned}$$

where φ_1, φ_2 are CMTL formulas, $i', i'' \in \mathbb{N}$, $e \in \mathcal{E}(V)$, $\ell_j \in \mathbb{R}_{\geqslant 0}$ and $\mathbf{1}\left(\eta_k \models e_j\right)$ is the characteristic function that returns 1 if $\eta_k \models e_j$ and 0 otherwise.

We define $\Diamond^{[\ell,u]}\varphi := \mathbf{true}\, \mathcal{U}^{[\ell,u]}\varphi$ and $\Box^{[\ell,u]}\varphi := \neg\Diamond^{[\ell,u]}\neg\varphi$. Details on the decidability and complexity of the logic can be found in [33,34].

Example 2. Let $\mathcal{A}_2$ from Fig. 1c be the modified version of the TIOAs $\mathcal{A}_2$ from Fig. 1, where we add a new variable act. The variable act identifies the presence of the action VP or AS through expression $act = 1$ or $act = 0$, respectively. We also modify automaton $\mathcal{A}_1$ by adding the update $act := 2$ to the edge labelled with the action AP!. We set the initial valuation to $act := -1$. We consider the following CMTL formula which states that, starting from any time in the interval $[0, 100]$, the number of performed VP actions in the interval of time $[0, 7]$ has to be no lower than 1 and at most 4:

$$\Box^{[0,100]} \left(\#_0^7(act = 1) \geq 1 \wedge \#_0^7(act = 1) \leq 4 \right) \tag{1}$$

3 Robust Optimal Synthesis Problem

We introduce a parameter synthesis problem for networks of TIOAs that asks for the parameter valuation that, first, maximises parameter robustness and, second, minimises some cost function, e.g. energy consumption. This problem is motivated by the fact that, in the design of medical devices, safety is of paramount importance and it is desirable to maintain patient's physiological properties in a robust way w.r.t. perturbations of parameter values. We express such properties in CMTL, which we use to formulate the requirement of a safe heart rhythm (see Sect. 4). We also assume a cost function $f : \Pi \to \mathbb{R}$ that maps timed paths to reals.

Thus, we aim at finding a valuation γ with maximum *robustness radius*, i.e. a quantity $\epsilon \in \mathbb{R}^+$ such that a CMTL formula ϕ is guaranteed to hold for any perturbation of γ bounded by ϵ. Then, we synthesise parameters that yield the minimum cost on top of the solution space with maximum ϵ. This problem can be effectively formulated as a *bi-level optimisation* problem (see e.g. [12]), where robustness maximisation and cost optimisation represent the so-called *inner and outer problems*, respectively.

Let $\epsilon \in \mathbb{R}^+$ and $\gamma \in \mathcal{V}(\Gamma)$. The ϵ-bounded perturbations of γ are denoted by the set $B_\epsilon(\gamma) = \{\gamma' \mid \forall p \in \Gamma.\ |\gamma'(p) - \gamma(p)| \leq \epsilon\}$. Given property ϕ and path $\rho(\cdot)$ of network $\mathcal{N}(\cdot)$, we say that a parameter valuation γ is *ϵ-robust* w.r.t. ϕ if it holds that $\forall \gamma' \in B_\epsilon(\gamma).\ \rho(\gamma') \models^{\mathcal{N}(\gamma')} \phi$. Note that, for arbitrary ϵ, there can exist perturbed valuations outside the domain of parameters, i.e. $B_\epsilon(\gamma) \not\subseteq \mathcal{V}(\Gamma)$. In the following, we only admit the case when $B_\epsilon(\gamma) \subseteq \mathcal{V}(\Gamma)$.

Problem 1 (Robust Optimal Synthesis).
Let $\mathcal{N}(\cdot)$ be a parametric network of TIOAs, $t \in \mathbb{R}^{\geq 0}$, $k \in \mathbb{N}^+$, ϕ be a CMTL property and f be a cost function. Let $\rho(\cdot)$ be the parametric path of $\mathcal{N}(\cdot)$ of length k and $\rho'(\cdot)$ be the parametric path up to time t. The *robust optimal synthesis problem* is finding a parameter valuation γ that solves the following bi-level optimisation problem:

$$\min_{\gamma_o \in \mathcal{V}(\Gamma)} f(\rho'(\gamma_o)) \quad \text{subject to } \gamma_o \in \arg\max_{\gamma_i \in \mathcal{V}(\Gamma)} \epsilon$$
$$\text{subject to } B_\epsilon(\gamma_i) \subseteq \mathcal{V}(\Gamma) \text{ and } \forall \gamma' \in B_\epsilon(\gamma_i).\ \rho(\gamma') \models^{\mathcal{N}(\gamma')} \phi.$$

Note that in the above problem the path lengths for the inner and outer problem are arbitrary and in general not interrelated. In practice, as explained in Sect. 5.3, f is evaluated through simulation and thus we can support longer lengths for ρ'.

Running example. We formulate an instance of Problem 1 by taking the CMTL property in Example 2 and the modified network defined therein. In the inner problem, we take the parametric path ρ of length $k = 15$. In the outer problem, we consider the path ρ' up to time $t = 100$ and aim to minimise the number of AS actions performed along ρ', leading to the objective $f(\rho') = \#_0^{100}\,(act = 0)$.

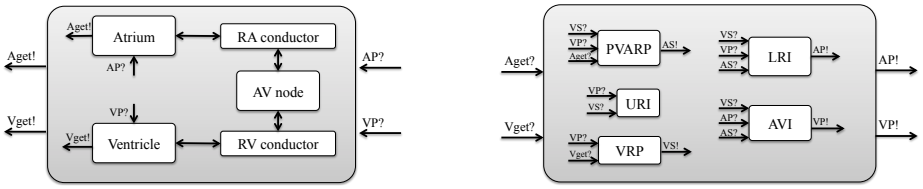
4 Heart and Pacemaker Models

In this section we describe the heart and the pacemaker models, and provide the properties and functions for the synthesis problem. The pacemaker has the role of maintaining

the synchronisation between the atrium and the ventricle. In particular, we consider a basic DDD pacemaker specification [36], that is, pacing and sensing both the atrium and the ventricle, and provide a TIOA network adapted from [21].

The heart model is used to reproduce the propagation of the cardiac action potential, and is a TIOA translation of the model by Lian et al [31] (see [5] for details). In [5], the authors provide a probabilistic model where parameters are drawn from probability distributions derived from patients data. Here, parameters are set to a given fixed value, thus resulting in a fully deterministic model. The composed heart-pacemaker model consists of 11 TIOA components, with 11 clock variables, 7 data variables and 18 action labels.

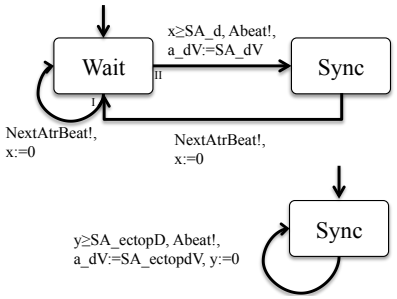
Heart model. The high-level structure of the model is depicted in Fig. 2a. It comprises five main conduction nodes and two main conduction paths: from the atrium to the ventricle (*antegrade* conduction) or vice-versa (*retrograde*). The *Atrium* component is responsible for modelling the sinoatrial (SA) node, i.e. the natural pacemaker of the heart. This has a predefined firing rate, given by parameter $\mathrm{SA\_d}$. It can also produce ectopic beats with rate $\mathrm{SA\_ectopD}$. In Fig. 3 we depict the sub-network that models the atrium. In Fig. 3a, we illustrate the automata for the SA node and the ectopic beat generator, respectively. When their clocks (x and y) satisfy the corresponding guards, the output action Abeat is produced, which indicates the generation of an atrial impulse. a_dV is a variable storing the action potential in the atrium, which might vary depending on whether the beat is regular or ectopic. The TIOA in Fig. 3b models the current state of the atrium. In the *Refractory* mode the atrium component starts a timer, modelled by clock z. After the atrial refractory period has elapsed ($z \geq$ Atr_refrD), the atrium changes its mode to *Excitable*. In this mode, it can receive three types of actions: an SA node signal, Abeat; a pacing signal from the pacemaker, AP; or a retrograde signal from the ventricle, AtrRetroReached. Finally, the atrium generates the output action Aget to notify the pacemaker of the atrial impulse, and returns to the *Refractory* mode. The $aPeriod$ variable is used to store the duration of the last atrial cycle.



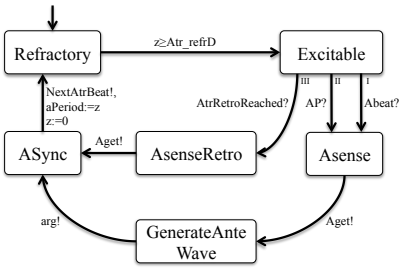
(a) Heart model (b) Pacemaker model

Fig. 2: Heart and pacemaker models.

The *Ventricle* component is similar to the *Atrium* component, i.e., it has an intrinsic beat generator and an ectopic beat generator. In addition, it has a variable $vPeriod$ to store the ventricular period. The *RA conductor* and *RV conductor* are used to model the propagation delay of the action potential from the atrium to the ventricle and back (antegrade or retrograde conduction).



(a) SA node (top) and ectopic beat generation (bottom) components



(b) Atrium state component

Fig. 3: The *Atrium* component.

The *AV node* component is responsible for delaying the entrance of the action potential from the atrium into the ventricle. The AV conduction delay (AVD) is given by an exponential function $\text{AVD} := \text{AVD}_{\min} + \alpha \exp(\frac{-T_{\text{rec}}}{\tau_c})$, where T_{rec} is the AV recovery time, $\text{AVD}_{\min}$ is the shortest AVD when $T_{\text{rec}} \to \infty$, α is the longest extension of AVD when $T_{\text{rec}} = 0$ and τ_c is the conduction time constant. More details of the AV node constants and parameters are provided in [5]. We remark that some guards of the heart model components contain non-linear functions.

Pacemaker model. We briefly describe the components of the basic DDD pacemaker model shown in Fig. 2b (see [9] for details): *AVI* maintains the synchronisation between the atrium and the ventricle, *LRI* sets a lower bound for the heart rate, *URI* sets an upper bound for the heart rate, *PVARP* detects intrinsic atrial events, and *VRP* detects intrinsic ventricle events. The pacemaker communicates with the heart model by means of four actions: AP (atrial pace), VP (ventricle pace), Aget (atrial sense) and Vget (ventricle sense). Every component has associated a timing parameter, which we discuss in Sect. 6. By changing these parameters one can control, for instance, the pacing rate in the atrium or ventricle, or the signal propagation delay from the atrium to the ventricle.

Cardiac output. Cardiac output (CO, $\text{cm}^3 \cdot \text{s}^{-1}$) is an important heamodynamic indicator that describes the volume of blood pumped by a ventricle over time and is used in clinical practice to monitor patients with heart conditions.

We compute CO following the modified Windkessel method in [17] for modelling the cardiovascular system, where the aortic flow is modelled as a square wave, which is more realistic than the standard Windkessel model (see e.g. [3]) where it is approximated as a series of impulses.

The ventricular period alternates in two parts: the systole (T_S) and the diastole (T_D). During systole the ventricles first contract and

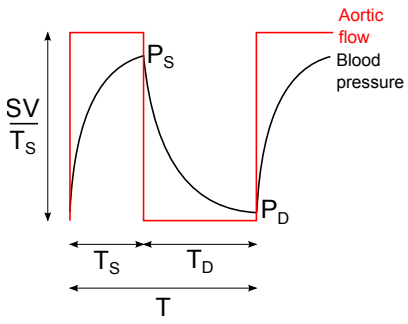


Fig. 4: Blood pressure (black) computed considering a square wave aortic flow (red).

reach a maximum pressure giving rise to a heart beat. Then, they drive the blood flow to the pulmonary and aortic valves. During diastole, ventricular pressure drops to its minimum and blood starts flowing from the atria to the ventricles until it is ejected in the next systole. Therefore, each wave in the the aortic flow signal has amplitude $\frac{SV}{T_S}$ and period T_S (see Fig. 4), where SV (cm^3) is the stroke volume, i.e. the difference between the volume at diastole and that at systole.

Following [17], the maximum arterial pressure at systole P_S (mmHg) is computed as $P_S = P_D \cdot \exp\left(\frac{-T_S}{R \cdot C}\right) + R \cdot \frac{\text{SV}}{T_S}\left(1 - \exp\left(\frac{-T_S}{R \cdot C}\right)\right)$, where R ($\text{mmHg}\cdot\text{s}\cdot\text{cm}^{-3}$) and C ($\text{cm}^3\cdot\text{mmHg}^{-1}$) are the aortic resistance and compliance parameters, respectively. The first term of the equation describes the decay of the diastolic pressure at the previous cycle with rate $\frac{1}{R \cdot C}$ during T_S, while the second term accounts for the pressure given by the aortic flow. The equation for the minimum pressure at diastole, P_D (mmHg), is $P_D = P_S \cdot \exp\left(\frac{-T_D}{R \cdot C}\right)$, which describes the decay of the pressure at systole during T_D. Finally, $CO = C \cdot (P_S - P_D)/T$ depends on the difference between P_S and P_D over the heart period $T = T_S + T_D$.

At each ventricular event (actions Vget or VP), we compute the CO of the previous cycle, assuming $T_S = 0.25 \cdot T$ and $T_D = 0.75 \cdot T$, where T is the time elapsed from the previous ventricular event. We consider the parameters of a healthy patient, namely, $C = 1.3$, $R = 0.9$ and $\text{SV} = 90$ [24]. The initial diastolic pressure is set to 80.

Properties. We consider two variants of the robust optimal synthesis problems (Probl. 1) where, in the outer problem, we minimise the energy consumption of the pacemaker or optimise the cardiac output, respectively. In the first variant, we take a simplified model assuming that only atrial and ventricular pacing contribute to energy consumption, with weights 2 and 3 respectively. Thus, the cost function is given by $f(\rho') = 2 \cdot \#_0^{60000}(act = AP) + 3 \cdot \#_0^{60000}(act = VP)$, where act is a variable storing the last performed action, and $AP, VP \in \mathbb{R}$ identify an AP or a VP action, respectively. By abuse of notation, the operator $\#$ denotes a function of ρ', i.e., it counts how often an expression from $\mathcal{E}(V)$ holds true in the path ρ'. In the second variant, we seek to find parameters that make the computed cardiac output as close as possible to a given reference value $\overline{CO}$ (set to 80 $\text{cm}^3\cdot\text{s}^{-1}$). Let $Vbeat(\rho')$ be the set of states along path ρ' where a ventricular beat happens. Then, $f(\rho') = \left(\sum_{(\boldsymbol{q},\eta)\in Vbeat(\rho')} |\eta(CO) - \overline{CO}|\right) / \left(|Vbeat(\rho')|\right)$ is the cost function, i.e. the mean difference between the valuations of CO in $Vbeat(\rho')$ and the reference $\overline{CO}$.

For both variants, in the inner problem we find parameters that guarantee a safe heart rhythm with maximum robustness. We express this requirement by imposing that the ventricular period (the time distance between two consecutive ventricular beats) is always within the interval $[500, 1000]$ ms, i.e. between 60 and 120 BPM. The corresponding CMTL property is $\phi = \Box^{[0,T]}(vPeriod \in [500, 1000])$, where the time bound $T = \rho\langle 0, |\rho| - 1\rangle$ is chosen to cover the whole length of path ρ.

5 Parameter Synthesis Algorithms

We now present methods to solve the bi-level optimisation problem introduced in Sect. 3. For space reasons, we restrict ourselves to *safety properties*, i.e. formulas of the

form $\Box^{[\ell,u]}\phi$, where ϕ is a CMTL formula without temporal operators. In [30], we also provide algorithms for the reachability fragment. First, we describe the algorithm for the inner problem, namely maximising the robustness radius w.r.t. a given safety property. Second, we devise a method for optimising the outer objective by exploiting the solution of the inner problem. Both methods are based on encoding the TIOA model and the synthesis problem as a Satisfiability Modulo Theories (SMT) problem, which we describe below and, in more detail, in [30]. In our implementation, we use the Z3 theorem prover [13].

5.1 SMT encoding

We now introduce the notion of TIOAs extended with *non-deterministic variables*, which are necessary to provide a sound encoding of the problem. Intuitively, such variables can be updated in a non-deterministic way to a number of possible values.

Let $\bar{V}$ be the set of non-deterministic variables; let $\bar{v} \in \bar{V}$ and η and γ be valuations of variables and parameters, respectively. Then, the reset r of $\bar{v}$ induces a set of admissible values $r(\bar{v}, \eta, \gamma)$ and a set of admissible updated valuations $\eta[r] = \{\eta' \mid \eta'(\bar{v}) \in r(\bar{v}, \eta, \gamma)$ and $\eta'(v') = \eta(v')$ for $v' \neq \bar{v}\}$. This implies that a network $\mathcal{N}$ of thus extended TIOAs can have multiple admissible paths. We denote with $\Pi(\mathcal{N})$ the set of such paths. Clearly, fixing a valuation for the non-deterministic variables at each state of the path induces a deterministic path according to Def. 3. We provide a discrete encoding of the problem in the theory of bit-vectors (SMT $\mathrm{UF\_BV}$). Clocks, parameters and variables are expressed as bit-vectors and therefore have finite domains. Non-deterministic variables are used to provide an interval-based abstraction for non-integer values and non-linear functions as follows. Consider a generic update $y := f(x)$ with $f : \mathbb{D} \to \mathbb{R}$, where $y \in V$ and $\mathbb{D}$ is the discrete and finite domain of f. For each $x \in \mathbb{D}$, we pre-compute the discrete bounds of f on x, $[f(x)^{\perp}, f(x)^{\top}]$ as

$$f(x)^{\perp} \leq \left\lfloor \min_{x' \in [x, x+1)} f(x') \right\rfloor \text{ and } f(x)^{\top} \geq \left\lceil \max_{x' \in [x, x+1)} f(x') \right\rceil$$

Then, we encode the update $y := f(x)$ as $y' \in [f(x)^{\perp}, f(x)^{\top}]$ using a non-deterministic variable $y' \in \bar{V}$. In this way, we provide a *conservative over-approximation* of the original system, since the above interval-based abstraction induces additional behaviours but preserves the original ones. As discussed later, this potentially leads to spurious counter-examples, i.e. valuations that violate the given property in the abstracted system but not in the original one. In this work, we did not implement a refinement step for excluding spurious counter-examples [11], but we experimentally evaluated their number (see Sect. 6). In general, the quality of the abstraction is affected by the dynamics of the functions involved, e.g. the presence of large variations in small intervals.

Through this discrete SMT encoding, the verification problem for TIOAs with data and CMTL formulas is NEXPTIME [28].

5.2 The inner problem

The main algorithm for solving the inner problem is given in Alg. 1, which extends the SMT-based method for *bounded model checking (BMC)* [4] in order to synthesise

the space of parameters that yields maximum robustness. Given a safety property φ, the algorithm returns the maximum robustness radius ϵ, a parameter valuation $\bar{\gamma}$ that is ϵ-robust w.r.t. φ, and an *under-approximation* Unsafe of the true unsafe parameter valuations. We encode an SMT problem where the Unsafe region is built by searching for counter-examples (CEs) to safety, which amounts to finding valuations s.t. $\neg\varphi$ holds at some point in the path, up to a fixed length n. Enumerating all possible counter-examples up to n, especially when n is large, is clearly infeasible. Here, we implement several solutions to overcome this problem.

First, we exploit *incremental solving*, so that CEs are computed step-wise, for increasing path lengths, exploiting the fact that SMT solvers can use the clauses learned in the previous steps to improve the solution time of the current step. Second, we include an algorithm for *counter-example generalization* (procedure GeneralizeCE, Alg. 2), that, given a CE, attempts to derive an unsafe region that contains the CE. Third, we *restrict the search space for counter-examples* to the extent necessary to prove the actual maximum robustness radius ϵ, thus avoiding the computation of irrelevant CEs.

Counter-example generation. In Alg. 1, we first initialize ϵ, Unsafe and $\bar{\gamma}$ (lines 2-4). The $Init$ predicate (line 5) is used to constrain the initial automata locations and variable valuation. Command Assert adds in the SMT solver a formula that must hold true. At a generic step k of the path, we first assert the safety property up to the current total time $\rho\langle 0, k\rangle$ if this is lower than the time bound u (line 7). In this case, the assertion is named with a literal p_k, meaning that the satisfaction value of $\square^{[\ell,\min(u,\rho\langle 0,k\rangle)]}\phi$ is the same as p_k. During the counter-example generation cycle (lines 8-17), MaxRadius procedure is called to update the maximum ϵ and ϵ-robust valuation $\bar{\gamma}$ according to the current Unsafe region. This information is used to temporarily restrict the search space for CEs to the region $B_\epsilon(\bar{\gamma})$ (line 11). Solve $\neg p_k$ checks if the negated safety is satisfied under the current assertions. If so, the solver returns a model, in our case a counter-example γ_{CE}, which we generalize to γ'_{CE} by calling GeneralizeCE. γ'_{CE} is then excluded from the search space (line 15) and added to Unsafe (line 16). The Pop command removes from the solver all the constraints asserted after the last Push (in this case, only $B_\epsilon(\bar{\gamma})$). If instead no CEs can be found in $B_\epsilon(\bar{\gamma})$, we can conclude that, up to step k, ϵ is the actual max radius and $\bar{\gamma}$ is ϵ-robust. Thus, we can exit the CE generation loop, assert the transition constraints (line 21) and increase the step to $k+1$. When $\epsilon < 1$, the algorithm terminates since it implies that no robust parameters exist (lines 18-19). In the algorithm, T indicates the transition predicate between states of the path, i.e. $T(s, s') = \exists t.\ s \xrightarrow{t} s'$. We remark that, by bounding and discretising the parameter space, we can ensure that the cycle at lines 8-17 always terminates. Note that the bound n on the path length is given in input to the algorithm. Other stopping criteria could be considered based on, for instance, the size of Unsafe or the worst-case time bound.

Spurious counter-examples. Due to the abstraction induced by the non-deterministic variables, a CE γ_{CE} can be spurious, i.e. it does not violate the property in the original system. Let $\boldsymbol{\eta} = \bar{\eta}_1, \ldots, \bar{\eta}_k$ be a sequence of valuations over $\bar{V}$, $\gamma \in \mathcal{V}(\Gamma)$, and $\rho(\gamma, \boldsymbol{\eta})$ be the path of $\mathcal{N}(\gamma)$ where the non-deterministic variables at i-th state are set to $\bar{\eta}_i$. Let $\boldsymbol{\eta}^*$ be the sequence of valuations describing the evolution of the original system. For a safety property φ, any CE γ_{CE} generated by Alg. 1 is such that $\exists \boldsymbol{\eta}.\ \rho(\gamma_{CE}, \boldsymbol{\eta}) \in \Pi(\mathcal{N}(\gamma_{CE})) \wedge \rho(\gamma_{CE}, \boldsymbol{\eta}) \not\models^{\mathcal{N}(\gamma_{CE})} \varphi$, i.e. γ_{CE} violates φ for some valuations $\boldsymbol{\eta}$ of $\bar{V}$.

The first term of the conjunction expresses that $\boldsymbol{\eta}$ is admissible, that is, $\rho(\gamma_{CE}, \boldsymbol{\eta})$ is a path of $\mathcal{N}(\gamma_{CE})$. Then, γ_{CE} is spurious if $\rho(\gamma_{CE}, \boldsymbol{\eta}^*) \models^{\mathcal{N}(\gamma_{CE})} \varphi$.

Counter-example generalisation. The GeneralizeCE procedure is executed on top of the solver used in Alg. 1 and exploits the ability of SMT solvers to generate unsatisfiable cores, i.e., when a formula is unsatisfiable under the current assertions, produce a subset of its clauses whose conjunction is still unsatisfiable. Given a CE γ_{CE}, the idea is to derive a larger unsafe region γ'_{CE} that contains γ_{CE}. This is achieved by asserting the safety property (line 3) and the valuation γ_{CE} (line 4). In particular, we associate each assertion $p = \gamma_{CE}(p)$ for $p \in \Gamma$ (used to assert γ_{CE}) with a literal g_p. If formula $\bigwedge_{p\in\Gamma} g_p$ (line 5) is unsatisfiable, the solver returns an unsat core, i.e. a set $\mathsf{UnsatCore} \subseteq \{g_p \mid p \in \Gamma\}$. If UnsatCore is a strict subset of the g_p literals, we say that the generalization is successful since we obtain a larger region: $\gamma'_{CE} = \{\gamma \mid \gamma(p) = \gamma_{CE}(p) \text{ if } g_p \in \mathsf{UnsatCore}\}$. Otherwise, $\gamma'_{CE} = \gamma_{CE}$. As an example, let $\gamma_{CE} = (p_1 = 3 \wedge p_2 = 5)$, and let g_{p_1} and g_{p_2} be the corresponding literals. If $\mathsf{UnsatCore} = \{g_{p_2}\}$, then the generalization $\gamma'_{CE} = (p_2 = 5)$ strictly contains γ_{CE}. Importantly, $\bigwedge_{p\in\Gamma} g_p$ being unsatisfiable means that γ_{CE} violates safety for any valuation of the non-deterministic variables and, therefore, it is a CE also for the original system, i.e., it holds that

$$\forall \boldsymbol{\eta}.\ \rho(\gamma_{CE}, \boldsymbol{\eta}) \in \Pi(\mathcal{N}(\gamma_{CE})) \implies \rho(\gamma_{CE}, \boldsymbol{\eta}) \not\models^{\mathcal{N}(\gamma_{CE})} \varphi. \tag{2}$$

This applies also to its generalization γ'_{CE}. In the implementation, we use a more advanced algorithm that can rule out even larger unsafe regions, which is reported in [30].

Maximum robustness radius. Procedure MaxRadius (Alg. 3) takes the current Unsafe region and the previous maximum radius ϵ, and returns the updated maximum ϵ together with an ϵ-robust valuation $\bar{\gamma}$, such that $B_\epsilon(\bar{\gamma}) \wedge \mathsf{Unsafe}$ is unsatisfiable. To this aim, we just need to find a valuation $\bar{\gamma}$ such that

$$B_\epsilon(\bar{\gamma}) \subseteq \mathcal{V}(\Gamma) \wedge \forall \gamma' \in B_\epsilon(\bar{\gamma}).\neg(\gamma' \wedge \mathsf{Unsafe}). \tag{3}$$

Procedure FindRobustParam (not shown) performs this check and returns such $\bar{\gamma}$ if any exists. In this case, we increment ϵ and repeat the procedure as long as an ϵ-robust valuation is found. Otherwise, we decrement it and repeat the procedure until Eq. 3 is met. In our implementation, ϵ is discretized too. We remark that this procedure uses a separate SMT solver (SMT QBVF) so it can be efficiently parallelized. Since we consider parameters with bounded domains, $B_\epsilon(\bar{\gamma}) \subseteq \mathcal{V}(\Gamma)$ in Eq. 3 implies that ϵ is bounded too, and thus, that the algorithm terminates.

Spurious robust valuations. Since we do not exhaustively search for CEs, Unsafe is an under-approximation of the true unsafe set. For the same reason, there could be[4] *spurious ϵ-robust valuations* γ s.t. they meet Eq. 3, but CEs exist in $B_\epsilon(\gamma)$. This happens when Alg. 1 terminates without inspecting region $B_\epsilon(\gamma)$. The following proposition characterises when a valuation is in the solution space of the inner problem.

Proposition 1 (Inner problem solution). *Let $\gamma \in \mathcal{V}(\Gamma)$,* Unsafe *and ϵ be as returned by Alg. 1. Then, γ is a solution of the inner problem in Probl. 1 iff it holds that:*

[4] Not to be confused with the spurious counter-examples discussed before.

i) γ *is* ϵ*-robust w.r.t.* Unsafe*, i.e. it satisfies Eq. 3; and*
ii) no counter-examples can be found in $B_\epsilon(\gamma)$*.*

Note that ii) can be decided with one iteration of the CE generation loop in Alg. 1 within region $B_\epsilon(\gamma)$. Nevertheless, the algorithm guarantees that the returned ϵ is the maximum robust radius and that $\bar{\gamma}$ is a solution of the inner problem. Indeed, $\bar{\gamma}$ is computed by Alg. 3 and therefore meets Eq. 3. Further, no CEs exist in $B_\epsilon(\bar{\gamma})$ ($\bar{\gamma}$ is not spurious), otherwise the incremental synthesis algorithm could not exit the loop at lines 8-17 and would proceed by updating ϵ and $\bar{\gamma}$.

Algorithm 1: Incremental Synthesis

Require: Parametric network $\mathcal{N}(\cdot)$, CMTL property $\square^{[\ell,u]}\phi$, path length $n \in \mathbb{N}^+$
Ensure: Maximum robust radius ϵ, ϵ-robust valuation $\bar{\gamma}$ and Unsafe region
1: **function** IncrementalSynth($\mathcal{N}(\cdot), \phi, n$)
2: $\epsilon := 1$
3: Unsafe $:= \bot$
4: $\bar{\gamma} := \bot$
5: Assert $Init(\rho[0])$
6: **for** $k = 0, \ldots, n-1$ **do**
7: Assert $p_k : \square^{[\ell, \min(u, \rho\langle 0,k\rangle)]}\phi$
8: **repeat** ▷ CE generation cycle
9: $(\epsilon, \bar{\gamma}) :=$ MaxRadius(Unsafe, ϵ)
10: Push
11: Assert $B_\epsilon(\bar{\gamma})$
12: $(SAT, \gamma_{CE}) :=$ Solve $\neg p_k$
13: Pop
14: $\gamma'_{CE} :=$ GeneralizeCE(γ_{CE})
15: Assert $\neg\gamma'_{CE}$
16: Unsafe $:=$ Unsafe $\vee\ \gamma'_{CE}$
17: **until** SAT
18: **if** $\epsilon < 1$ **then**
19: **return** $(0, \bot, \top)$
20: **if** $k < n-1$ **then**
21: Assert $T(\rho[k], \rho[k+1])$
22: **return** $(\epsilon, \bar{\gamma}$, Unsafe)

Algorithm 2: CE generalization

Require: Counter-example γ_{CE}
Ensure: Generalization γ'_{CE} s.t. $\gamma_{CE} \implies \gamma'_{CE}$
1: **function** GeneralizeCE(γ_{CE})
2: Push
3: Assert p_k
4: **for all** $p \in \Gamma$ **do** Assert $g_p : p = \gamma_{CE}(p)$
5: $(SAT, \gamma) :=$ Solve $\bigwedge_{p\in\Gamma} g_p$
6: **if** SAT **then** $\gamma'_{CE} := \gamma_{CE}$
7: **else** $\gamma'_{CE} := \bigwedge_{p.g_p \in \text{UnsatCore}} p = \gamma_{CE}(p)$
8: Pop
9: **return** γ'_{CE}

Algorithm 3: Computation of maximum robust radius

Require: Unsafe region, starting radius ϵ
Ensure: Maximum robust radius ϵ and valuation $\bar{\gamma}$ that is ϵ-robust
1: **function** MaxRadius(Unsafe, ϵ)
2: $\bar{\gamma} :=$ FindRobustParam(Unsafe, ϵ, $\bot$)
3: **if** $\bar{\gamma} = \bot$ **then** $inc := -1$
4: **else** $inc := 1$
5: **repeat**
6: $\epsilon := \epsilon + inc$
7: $\bar{\gamma} :=$ FindRobustParam(Unsafe, ϵ)
8: **until** $(inc < 0 \iff \bar{\gamma} = \bot) \wedge \epsilon > 0$
9: **if** $inc > 0$ **then** $\epsilon := \epsilon - inc$
10: **return** $(\epsilon, \bar{\gamma})$

The incremental synthesis algorithm for reachability formulas (explained in [30]) follows the same structure as Algorithm 1 and proceeds by finding CEs to reachability, i.e. valuations such that the property never holds.

Running example. To simplify the presentation, we fix $T = 10$ and consider only parameters $J \in [1, 41]$ and $P \in [11, 51]$. Fig. 5 shows the incremental synthesis algorithm run on our example. The counter-example $J = 33$ and $P = 49$ indicated in plot (b) clearly violates the property (Eq. 1), since it gives the following path:

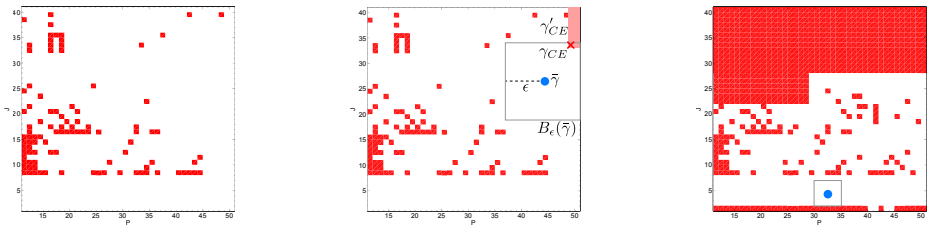
$$((q,z),(\alpha=0,\beta=0,t=0,x=0,y=0,act=-1)) \xrightarrow{33} ((q',z),(\alpha=0,\beta=5,t=0,x=33,y=0,act=1))\ldots$$

where, starting from position 0, no VP action is fired in the time interval $[0, 7]$. At the final step, we obtain $\epsilon = 2$ and $\bar{\gamma} = \{J \mapsto 4, P \mapsto 32\}$. Such parameters lead to the

following path which can be shown to meet our CMTL property:

$$((q,z),(0,0,0,0,0,-1)) \xrightarrow{4} ((q',z),(0,5,0,4,0,1)) \xrightarrow{4} ((q',z),(0,5,0,8,0,1)) \xrightarrow{4}$$
$$((q',z),(0,5,0,12,0,1)) \xrightarrow{4} ((q',z),(0,5,0,16,0,1)) \xrightarrow{4} ((q',z),(0,5,0,20,0,1)) \xrightarrow{4}$$
$$((q',z),(0,5,0,24,0,1)) \xrightarrow{4} ((q',z),(0,5,0,28,0,1)) \xrightarrow{4} ((q',z),(0,5,0,32,0,1)) \xrightarrow{0}$$
$$((q,z),(10,5,0,0,0,0)) \xrightarrow{4} ((q',z),(10,5,0,4,0,1)) \xrightarrow{4} ((q',z),(10,5,0,8,0,1)) \xrightarrow{4}$$
$$((q',z),(10,5,0,12,0,1)) \xrightarrow{4} ((q',z),(10,5,0,16,0,1)) \xrightarrow{4} ((q',z),(10,5,0,20,0,1))$$

In the above, variable names are omitted and their ordering is as in the previous path. The validity of Eq. 1 can be shown for every valuation in $B_\epsilon(\bar{\gamma})$ in a similar way.



(a) (b) (c)

Fig. 5: Counter-examples generation cycle for the running example. Plot (a) shows the Unsafe region (red points) during step $k = 1$. Procedure MaxRadius computes the maximum ϵ (here, 8) and the ϵ-robust valuation $\bar{\gamma}$ ($J = 25, P = 43$, blue dot in plot b). The search for further CEs is restricted to $B_\epsilon(\bar{\gamma})$ (grey-bordered). Then, a CE γ_{CE} is found ($J = 33, P = 49$, red cross). The GeneralizeCE procedure manages to find the larger unsafe region $\gamma'_{CE} = J \geq 33 \wedge P \geq 49$ (light red). Plot (c) shows the results at the final step ($k = 15$) with $\epsilon = 2$ and $\bar{\gamma} = \{J \mapsto 4, P \mapsto 32\}$.

5.3 The outer problem

We present two methods for solving the outer problem. The former is based on the enumeration of ϵ-robust valuations, thus providing an exact solution to the outer problem, but is infeasible with high-dimensional parameter spaces. Note that enumeration is possible because we discretise the parameter space. The latter method provides an approximate solution by exploiting evolutionary strategies (ES). In both methods, the outer objective is evaluated through simulation. Importantly, simulation can cover path lengths that are prohibitive for BMC, which allows us to consider objective functions over large time bounds.

Exact solution. The method consists of the following three steps:

1. Enumerate all valuations that meet Eq. 3. Let Γ' be the set of such valuations.
2. Simulate all $\gamma \in \Gamma'$ and compute the outer objective $f(\gamma)$.
3. Following the ordering by the cost function $f(\gamma)$, return the first valuation that meets condition ii) of Prop. 1.

Optimisation with Evolutionary Strategies. ES are a class of stochastic optimisation methods which mimic the principles of Darwinian evolution in order to optimise a given objective. They work on a set of candidate solutions, the *population*, which at each iteration of the algorithm (*generation*) is subjected to various *natural operators*, until a pre-defined termination criterion is satisfied (e.g. max number of generations).

We implement a *non-isotropic self-adaptive* $(\mu/\rho + \lambda)$-ES, i.e. μ parents are used to generate λ offspring candidates through a ρ-parents recombination, and only the μ best solutions of the combined parents together with the offspring set are used in the next generation. In particular, we consider a 2-*parents dominant recombination*, which randomly takes two candidates from the parents set and generates a child by a parameter-wise random selection of the two parents' valuations. Since we deal with discrete parameters, we use the mutation operator in [35], which extends the principle of *maximum entropy* used in real ES problems to the integer case. We also include a *self-adaptation* mechanism [6] that changes the parameters of the mutation operator at each iteration.

In order to determine the best valuations at each generation, we define an order $\preceq$ that takes into account the outer objective and, following the *feasible-over-infeasible* principle [14], *penalizes valuations outside the solution space of the inner problem*. Let γ_i and γ_j be two valuations, $f(\gamma_i)$ and $f(\gamma_j)$ be their objective function values. Then, $\gamma_i \preceq \gamma_j$ if either:

1. γ_i meets condition i) of Prop. 1, and γ_j does not; or
2. γ_i meets i) and ii), and γ_j meets only i); or
3. both γ_i and γ_j meet i) and ii), and $f(\gamma_i) \leq f(\gamma_j)$

We say that a solution is feasible for the outer problem if it solves the inner problem as per Prop. 1. Note that, if the population at a generic iteration i, $\mathcal{P}^i$, contains feasible solutions, then, for any $j > i$, $\mathcal{P}^j$ will contain feasible solutions too. Indeed, by the order defined, if $\mathcal{P}^i$ has at least one feasible point, then the best solution in $\mathcal{P}^i$ is also feasible. Since, for any k, the best solutions of $\mathcal{P}^k$ are kept in $\mathcal{P}^{k+1}$, we conclude that, for $j > i$, $\mathcal{P}^j$ will contain feasible solutions too. For the full ES algorithm, see [30].

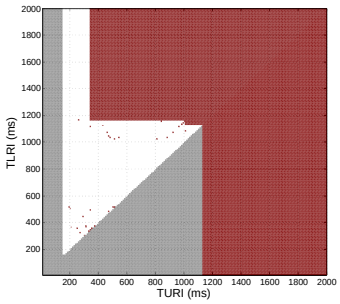
Running example. We obtain the exact solution $J = 4, P = 48$, which gives an outer objective of 2 (the number of AS actions fired within time 100). Due to the size of the problem, this required enumerating and simulating only 133 valuations at step 1 of the exact method. For the same reason, the ES algorithm is also able to achieve the optimal solution, being in this case $J = 4, P = 45$. In particular, this was obtained at the *first* iteration of the algorithm, run with $\lambda = 100$, $\mu = 50$ and $\rho = 2$.

6 Results

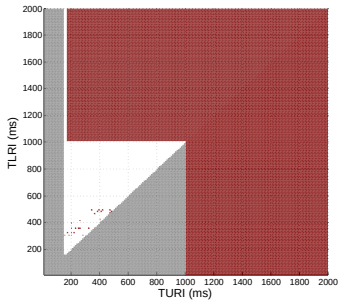
We apply our method to synthesise pacemaker parameters that ensure a safe heart rhythm and optimise either energy consumption or cardiac output (see Sect. 4 for the formulation of the problem and properties). In [30], we provide a more detailed experimental evaluation of our methods, with different numbers of parameters and path lengths. Here we consider two parameters that are critical for the correct functioning of the pacemaker device. The first parameter, TLRI, regulates the frequency of atrial

impulses: $\mathrm{TLRI} - \mathrm{TAVI}$ is the amount of time that the pacemaker waits before delivering an atrial pace when no atrial or ventricular events are detected, where TAVI is the pacemaker atrioventricular delay (default value: 150 ms). The second parameter, TURI, sets an upper bound on the heart rate. In particular, it is the amount of time that the pacemaker waits before pacing the ventricle, after an atrial stimulus has occurred and TAVI elapsed. We set the domain of both parameters to $[10, 2000]$ ms, and add constraints to exclude from the search pacemaker parameters that are not physiologically meaningful: we require $\mathrm{TLRI} \geq \mathrm{TURI}$, $\mathrm{TLRI} > \mathrm{TAVI}$ and $\mathrm{TURI} \geq \mathrm{TAVI}$. Note that the approach can be applied also to other pacemaker parameters: TAVI, TVRP (ventricular refractory period), TPVARP (post-ventricular atrial refractory period) and TPVABP (post-ventricular atrial blanking period).

Fig. 6 summarizes the synthesis results obtained with the following heart conditions: *bradycardia*, i.e. slow heart rate, reproduced through an increased SA node firing rate ($\mathrm{SA\_d} = 1500$ ms, i.e. 40 BPM), and the *AV conduction defect* obtained by increasing the AV delay ($\mathrm{AVD}_{\min} = 150$ ms, default: 50 ms). In the experiments we consider a path length of 20 for solving the inner problem and solve the outer problem with both exact and ES methods.



(a) Bradycardia. Inner problem solution time: 7354 s, $\epsilon = 250$ ms.



(b) AV defect. Inner problem solution time: 6601 s, $\epsilon = 240$ ms.

Outer objective:	Energy				Cardiac Output			
Condition:	Bradycardia		AV defect		Bradycardia		AV defect	
Method:	Exact	ES	Exact	ES	Exact	ES	Exact	ES
Best:	770,300	770,640	750,480	750,320	770,320	770,320	750,630	750,350
Cost:	158	158	400	400	9.14	9.14	9.37	9.37
Runtime:	2369	1101	913	1268	1547	118	848	111

Fig. 6: Unsafe regions (red areas and dots) returned by Alg. 1 in the two experiments. Grey areas indicate pacemaker parameters that are not physiologically relevant and thus are excluded from the search space. The table shows the results of the outer optimisation for the energy and cardiac output objectives (see Sect. 4), comparing the exact and the ES-based methods. The best solutions are in the format $\mathrm{TLRI}, \mathrm{TURI}$. Runtimes are in seconds. ES parameters are $\lambda = 100$, $\mu = 50$, $\rho = 2$ and 50 generations.

The two experiments return similar robustness radii: $\epsilon = 240$ for bradycardia and $\epsilon = 250$ for AV defect. In the bradycardia case, we obtain $\mathrm{TLRI} = 770$ ms, i.e. a

pacing rate in the atrium of 77.92 BPM, for all objectives and solution methods for the outer problem. In the AV defect case, the synthesis experiments yield a similar TLRI value (750 ms, i.e. 80 BPM) and optimal cardiac output. However, the energy consumption of the pacemaker is much higher since, with this heart condition, impulses from the atrium are not correctly propagated, and thus a higher number of paces is required in the ventricle. We remark that, with our method, we are able to find the parameters that guarantee a safe heart rhythm despite large perturbations. For instance, the exact solution γ_o to the AV defect and energy experiment is $\mathrm{TLRI} = 750$ ms and $\mathrm{TURI} = 480$ ms, which implies that safety holds for all the parameters in $B_\epsilon(\gamma_o)$, i.e., with $\epsilon = 250$, for all $\mathrm{TLRI} \in [500, 1000]$ ms and $\mathrm{TURI} \in [230, 730]$ ms. For all our results, we observe that the nominal parameter values ($\mathrm{TLRI} = 1000$ ms and $\mathrm{TURI} = 500$ ms [36]) are included in $B_\epsilon(\gamma_o)$, meaning that the default pacemaker settings are safe but have a smaller tolerance.

Notably, the evolutionary approach is able to yield the same optimal objective value as the exact method. This is due to the fact that, with two parameters, the solution space of the inner problem (which corresponds to the domain of the outer problem) is quite small. Indeed, we obtain only 107 ϵ-robust valuations for bradycardia, and 52 for the AV defect. With the ES algorithm, we also achieve better performance in most cases, and the runtime improvement becomes even more marked with higher-dimensional parameter spaces, as reported in [30]. The only exception is the runtime obtained for the energy objective in the AV defect experiment, where the exact method performs slightly better than ES, which is explained by the small number of feasible points in the outer problem.

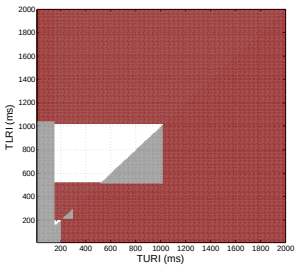


Fig. 7: Full Unsafe region for bradycardia (see Fig. 6 a).

In Fig. 7, we illustrate the full synthesis region for the bradycardia experiment, obtained without restricting the search space for CEs (lines 9-13 of Alg. 1). By comparing with the region in Fig. 6a, we observe that the algorithm explores considerably fewer CEs, thus improving the runtime. We also report that the abstraction of real-valued and non-linear variables is adequate, in the sense that only a few CEs are *potentially* spurious, i.e. such that Eq. 2 does not hold. These constitute only 0.31% of the parameter space and are given by the set

$$\{\gamma \in \mathcal{V}(\Gamma) \mid (\gamma(\mathrm{TLRI}) = 510 \wedge \gamma(\mathrm{TURI}) \in [150, 510]) \vee (\gamma(\mathrm{TLRI}) = 1020 \wedge \gamma(\mathrm{TURI}) \in [150, 1010])\}$$

With our approach, we can also synthesise parameters that are safe for a range of possible heart conditions, thus taking into account uncertainty in the heart dynamics [30].

7 Conclusion and Future Work

We have studied the problem of robust optimal parameter synthesis for networks of TIOAs with priorities and data and proposed a solution based on SMT solving and evolutionary strategies. We have applied the method to synthesise pacemaker parameters

that are both safe and robust, while optimising energy consumption or cardiac output. As the main property specification language, we have considered the safety and reachability fragments of CMTL, which are sufficient to express relevant properties for cardiac pacemakers.

As future work we plan to apply the approach to additional safety properties, validate synthesis results with cardiologists and include advanced pacemaker features like rate-modulation [29], hysteresis and a battery model for optimising the expected lifetime of the device.

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