

# Closing the Loop: Validation of Implantable Cardiac Devices With Computational Heart Models

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**Abstract—Objective:** Cardiovascular Implantable Electronic Devices (CIEDs) are used extensively for treating life-threatening conditions such as bradycardia, atrioventricular block and heart failure. The complicated heterogeneous physical dynamics of patients provide distinct challenges to device development and validation. We address this problem by proposing a device testing framework within the in-silico closed-loop context of patient physiology. **Methods:** We develop an automated framework to validate CIEDs in closed-loop with a high-level physiologically based computational heart model. The framework includes test generation, execution and evaluation, which automatically guides an integrated stochastic optimization algorithm for exploration of physiological conditions. **Conclusion:** The results show that using a closed loop device-heart model framework can achieve high system test coverage, while the heart model provides clinically relevant responses. The simulated findings of pacemaker mediated tachycardia risk evaluation agree well with the clinical observations. Furthermore, we illustrate how device programming parameter selection affects the treatment efficacy for specific physiological conditions. **Significance:** This work demonstrates that incorporating model based closed-loop testing of CIEDs into their design provides important indications of safety and efficacy under constrained physiological conditions.

**Index Terms—** Cardiovascular Implantable Electronic Devices (CIEDs), in-silico closed-loop validation, heart modeling, hybrid automaton, pacemaker mediated tachycardia (PMT).

## I. INTRODUCTION

Cardiovascular Implantable Electronic Devices (CIEDs) are used to clinically manage cardiac rhythm problems when drug intervention is not effective. Worldwide, CIEDs use has been extensive [1] and continues to grow, particularly in cardiac resynchronisation therapy for heart failure [2]. Concurrently, there have been significant increases in device recalls, and reported adverse effects, while computer-related recalls have almost doubled [3]. In recent studies, up to 20% of monitored

devices were found to be affected by safety recalls or alerts [4].

These statistics drive interdisciplinary studies of rigorous CIED design testing [5], [6], [7], [8]. Many of these projects are founded on formal methods [9], a sub-discipline in computer science, using models of cardiac electrical activity to analyse system behavior in the design and validation of CIEDs. However, techniques such as model checking are only suitable for the most abstract heart models, and to date cannot be used for models that include the dynamic electrophysiological behaviour associated with cardiac arrhythmic susceptibility [8]. Additionally, the complex programmable features of CIEDs can cause parameter uncertainty in the clinical setting [10], [11], [12]. Model applications could also help clinicians fully understand the effects of device parameters on individual patient heart functions. To this end, testing devices and their parameter settings in closed-loop with a patients physiological context is highly desirable.

In both these CIED problems, the context-awareness of medical cyber physical systems and the apparent lack of suitable patient physiological models [13], [5] is a challenge. Models increasingly play a role in health care. For example, the Virtual Physiological Human project [14] and In Silico Clinical Trials (ISCT) [15], and the United States Food and Drug Administration has recognized that modeling and simulation can support regulatory decision making [16]. But, modeling human physiology is challenging due to its complexity, uncertainty and variability. In particular, there are unique model requirements for medical device validation, such as continuously interacting in closed-loop with CIEDs in real-time.

We have shown that a validated and dynamic heart model based on a hybrid automaton (HA) formalism [17] can interact in closed-loop with a dual chamber (DDD) mode pacemaker [8]. However, to contribute to pre-clinical CIED validation and parameter testing, new objective methods for evaluating both CIED design specifications and undesirable cardiac responses are required. In this work we develop these logic components and combine them into a testing framework that exploits a physiologically based heart model [8]. We show how the framework can be used to assess CIED designs in terms of both design specifications and the risk of device-generated adverse events, by applying it to a DDD pacemaker model. We also illustrate how the CIED parameter space is explored to address parameter uncertainty. This framework can be readily

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extended to validate actual hardware devices, facilitated by emulation techniques [18], [19], [20].

The relationship between model parameters and a target physiological behavior is not straightforward, and an exhaustive exploration of this high dimensional system is infeasible. This is challenging in the closed-loop context, where the heart model behavior is tightly coupled with the device. An automated approach based on stochastic optimization [21] is created to facilitate the parameterisation. For the broadest input spectrum to the CIED, the heart model is parameterised to exhibit key arrhythmias and the simulated risk evaluations agree with clinical observations of pacemaker-mediated tachycardia (PMT). The potential for precision-driven management of cardiac diseases is illustrated by an example of device programming customization for a specific cardiac condition.

## II. METHODS

### A. A closed-loop validation framework

The physiological dynamics of a phenomenological heart model have been validated previously [22], [23], [8]. While it abstracts some details of cardiac electrophysiology, it can exhibit a wide range of useful complex heart rhythms with corresponding cardiac electrophysiological meanings. Therefore, clinical knowledge and observations can be used to derive the parameter ranges of the heart model.

To automatically find a constrained parameter region of interest to test CIEDs, we propose a closed-loop validation framework (Fig. 1). The framework includes test *generation*, *execution* and *evaluation*. The stochastic optimization tool, S-TaLiRo [21], is used to facilitate the parameterisation. It automatically generates new test cases (i.e., new heart model parameters) based on previous evaluation results. The type of evaluation depends on the purpose of testing. In this paper, we show evaluation being used for requirement-based testing of design specifications, risk assessment of device-induced adverse events, and device parameter assessment. For requirement-based testing, the evaluation module incorporates device specifications and coverage calculation, while an adverse event indicator is implemented for risk assessment. The range of parameter constraints may also vary according to the purpose of testing. For requirement-based testing, the broadest input spectrum is used. The parameter constraints can narrow down to some specific regions based on domain knowledge for risk analysis of device-induced adverse events. Fixed heart model parameter settings can be used to explore the effects of device parameter variation. We explore this in a case study.

### B. Execution Module

The closed-loop system of the heart model and the device is the execution module. Once a parameter set has been specified, the heart model is autonomous with its own automaticity [23] driving the rhythm that the device interacts with.

1) *The HA-based heart model*: The heart model [8] is a virtual cardiac conduction network which simulates the dynamics of electrical pulse generation and propagation in the heart. As shown in Fig. 2, the network is comprised of nodes, regional tissue clusters, providing electrical activation response along

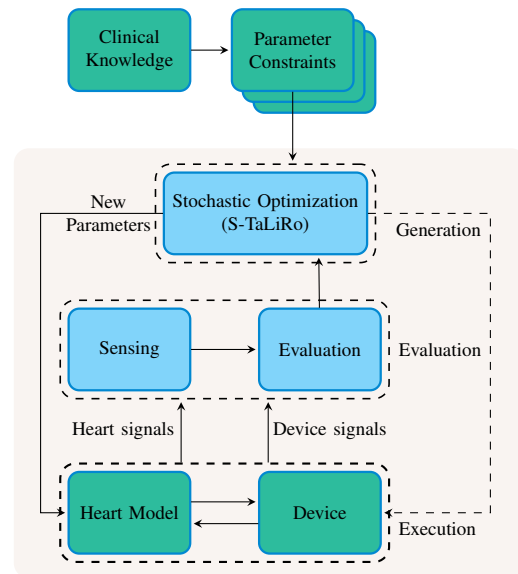


Fig. 1: The closed-loop device validation framework. The input to the framework is clinical knowledge that is used to set constraints on the heart model parameters.

the cardiac conduction system (CCS) and the myocardium. The regional cellular electrophysiology model types, including cardiomyocyte models [22] and various pacemaker cell models [23], together with the conduction path model [8] are all formalized using HA.

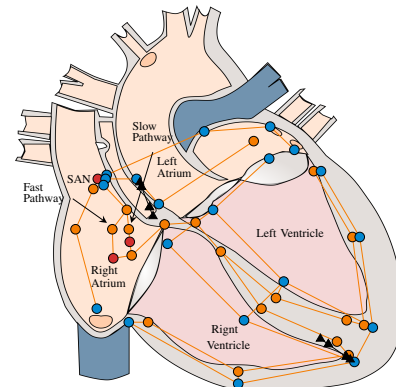


Fig. 2: A cardiac conduction network. The circles represent clusters of tissue, which generate or/and respond to electrical excitation. The triangles indicate the locations of implanted device leads.

The heart model [8] can capture non-linear physiological dynamics, such as action potential duration (APD) restitution, conduction velocity (CV) restitution, and overdrive suppression. Additionally, the automaticity and rate variability are integrated so that the hierarchy ensures the sinoatrial node (SAN) starts a heartbeat under normal physiological conditions, while subsidiary pacemaker cells contribute to initiating activation under pathological circumstances.

When the heart model receives the pacing stimuli from the device, it provides physiologically relevant responses, i.e., the model takes device output as its input and changes its states

according to the underlying physiological dynamics. With the heart model, we can validate the device under prescribed arrhythmias by imposing constraints on the parameters. For experiments, we vary the heart model parameters based on their physiological roles in heart rhythm formation (see Supplemental Material). At discrete points in the heart model (device leads: Fig. 2), atrial electrograms, Aegm, and ventricular electrograms, Vegm, are generated [24] for interaction with the device.

2) *The device*: In this study, the device is a dual chamber (DDD) mode pacemaker model [25]. A timing diagram is shown in Fig. 3, which depicts a finite synthetic signal trace between the heart and the pacemaker.

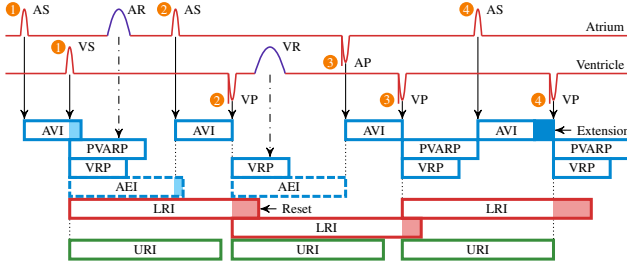


Fig. 3: Timing diagram reproduced from [26]. The timing parameter definitions appear in the main text.

The pacemaker can sense the electrical excitation from the dual chambers (right atrium, AS; ventricle, VS). The lower rate interval (LRI) defines the longest interval between a ventricular pacing pulse (VP) and previous paced or sensed ventricular events (VP or VS), while the maximum pacing rate is limited by the upper rate interval (URI). The refractory periods are used to block noise and unexpected signals. The Post-Ventricular Atrial Refractory period (PVARP) is a timer following ventricular events (VS or VP). If the atrial activity occurs during the PVARP, the signal (marked as AR) is filtered and does not affect the pacing schedule. This timing constraint is designed to prevent oversensing the ventricular pacing stimulus and its afterpotential, far-field ventricular electrogram (EGM), and retrograde P wave on the atrial channel. Similarly, the Ventricular Refractory Period (VRP), applied on the ventricular channel, is designed to avoid sensing the pacing stimulus and its afterpotential (marked as VR).

The atrioventricular interval (AVI) ensures the device synchronizes the ventricular pacing to the atrial activity, triggered by atrial sensed (AS) or paced events (AP). When the AVI expires and the intrinsic ventricular activation (VS) is absent, the device will deliver a pacing pulse (e.g., VP ②,③ in Fig. 3). If the scheduled VP violates the URI constraints, the device will postpone the pacing until the URI expires, like VP ④ in Fig. 3. The atrial escape period (AEI) is the difference between the LRI and AVI (i.e.,  $AEI=LRI-AVI$ ), which is used to schedule atrial pacing (e.g., AP ③ in Fig. 3). We use the timing requirements derived in [25] and extend some of the requirements to describe specific scenarios (for a full description of the timing requirements, see the Supplementary Material).

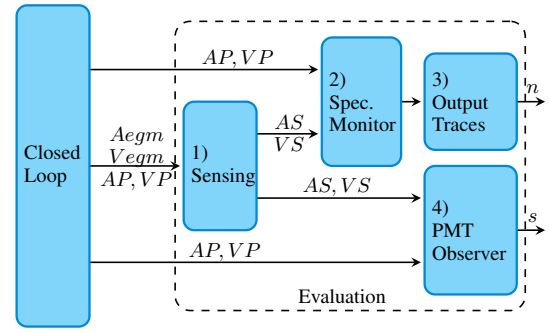


Fig. 4: The composition of the evaluation module.

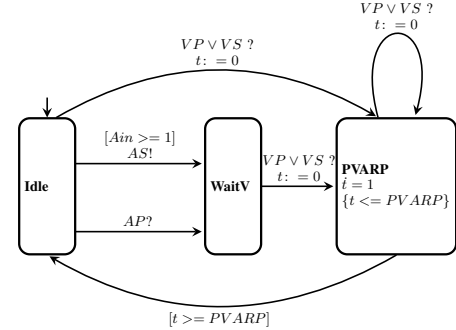


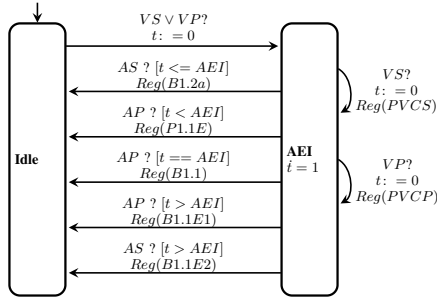
Fig. 5: A timed automaton to describe AS generation that is constrained by the PVARP. Inputs:  $A_{in}$ , AP, VP, VS; Output: AS. The VP/VS starts or resets the PVARP timer, but only  $A_{in}$  that occurs beyond the PVARP generates AS.

### C. Evaluation Module

The *Evaluation* module takes inputs from the closed-loop system, i.e., EGM signals  $A_{egm}$ ,  $V_{egm}$  and pacing artifacts AP, VP, and generates the testing evaluation results. The signals from the closed-loop system first go to a sensing block, which generates events AS/VS for the following evaluation process, as shown in Fig. 4. The evaluation incorporates specification monitors and output traces registration, as well as an extra PMT observer. The sensing block and specification monitors implement the timing requirements of the pacemaker model [25]. While examples of the implementation are shown in the following sections, the full models and explanations can be found in the Supplemental Material.

1) *Sensed events generation*: The inputs to the sensing block, discrete signals  $A_{in}$ ,  $V_{in}$  are generated if the amplitude of the continuous signals  $A_{egm}$ ,  $V_{egm}$  exceeds a threshold voltage. We use a timed automaton (TA) [27] model to describe the AS generation logic, shown in Fig. 5.

The total atrial refractory period in dual-chamber modes is initiated by an atrial event AS/AP followed by the PVARP [28]. The TA in Fig.5 stays in *Idle* until one of three scenarios are encountered. (1) When ventricular events VP/VS happen, the TA transitions to the location *PVARP* and the clock  $t$  is reset to 0. (2) When a sensed intrinsic atrial excitation signal exceeds the threshold, i.e.,  $A_{in} \geq 1$ , the transition from *Idle* to *WaitV* takes place and event AS is emitted, denoted as AS!. (3) When an atrial pacing event AP is received AP?, the TA also goes to *WaitV*. The transition from *WaitV* to



**Fig. 6:** A timed automaton for monitoring the AP delivery, constrained by the AEI=LRI-AVI. Inputs: AS, AP, VP, VS; Output: Reg(), which stores the requirements that have been executed.

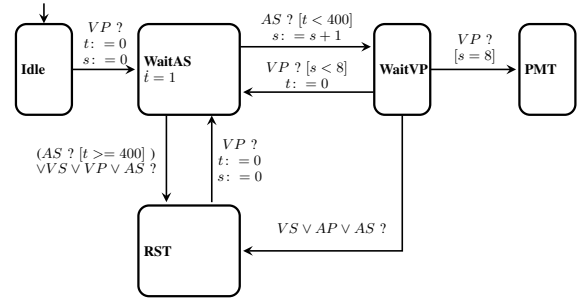
PVARP is triggered by ventricular events VP/VS, while the clock is initialized to 0. The TA stays in the location PVARP as long as the invariant  $t \leq PVARP$  is true. During the location PVARP, the atrial events are ignored while the ventricular events can reset the clock. Atrial activation beyond the PVARP will be detected as the TA will have transitioned back to Idle.

2) *The specification monitors:* The specification monitors continuously oversee the closed-loop system and determine whether the system behaviors meet the requirements. The specific requirements are mapped to the transitions of a TA. Fig.6 shows an example of a TA for monitoring AP delivery. The ID of the specification (e.g., B1.2a) that has been tested during the execution is recorded by a registration function Reg(). The requirement ID is registered with the symbol E when a certain specification is not satisfied during testing, e.g., P1.1E denotes that the requirement P1.1 fails during testing.

The starting location of the AP delivery TA is Idle. A ventricular event VS/VP causes a transition to AEI and starts the timer. During AEI, if a ventricular event VS/VP takes place before an atrial event AS/AP, the TA outputs PVCS (premature ventricular complex induced by intrinsic ventricular events) or PVCP (premature ventricular complex induced by pacing artifacts).

A requirement can be covered and either satisfied or violated. For example, consider requirement B1.2a: when AS occurs within AEI, AP should not be applied in the atrium before AS. If AS occurs at  $t \leq AEI$ , the requirement is both covered and satisfied (Fig. 3 AS ②). This requirement also stipulates that AP should not be applied before AS. If AP occurs at  $t < AEI$ , requirement P1.1 is not satisfied and this is registered as covered but violated. If AP occurs at  $t = AEI$ , requirement B1.1 (if AS does not occur within AEI an AP should occur at  $t = AEI$ ) is tested and satisfied (Fig. 3 AP ③). Finally, if AP or AS occurs at  $t > AEI$ , requirement B1.1 is covered but violated. Any atrial event AS/AP moves the TA back to the Idle state, waiting for ventricular events to start the next cycle.

3) *The output trace registration:* The output traces block takes the outputs from the specification monitors to calculate the coverage of the requirements that have been tested. In addition, it records the requirement output traces, and calculates



**Fig. 7:** A timed automaton monitoring the PMT. Inputs: AS, AP, VS, VP; Output: s.

the size of the traces set (see Supplemental Material).

4) *The PMT observer:* PMT is a typical complication induced when a device keeps pacing the ventricles at the predefined maximum rate. This reflects complicated interactions between the device and a patient's heart, and it has been observed clinically since the early days of DDD pacing [29], [30]. Most modern CIEDs are equipped with algorithms for prevention, detection, and termination of PMT [28]. We want to assess if the pacemaker model introduces the PMT phenomenon under a variety of heart conditions. We use a standard PMT definition [31] of a ninth ventricular pace following eight consecutive ventricle to atria retrograde (VA) signals that meet all of the following conditions:

- They start with a ventricular paced event (VP).
- They end with an atrial sensed event (AS).
- Their duration is less than 400 ms.

The PMT observer is also modeled with a TA (Fig. 7), in which the variable  $s$  records the number of consecutive VP-AS sequences as defined above. Other events interrupting the train reset  $s$  to 0. When  $s$  reaches 8, a PMT is recorded.

#### D. Generation Module

A simulated annealing algorithm from S-TaLiRo [21] is used to find the optimal parameter sets in our experiments. The search space is the parameters of the heart model. The evaluation results provide the objective functions to S-TaLiRo. In our case studies, the optimization objectives are the number of output traces,  $n$ , and the PMT indicator,  $s$ , for requirement coverage guided testing and PMT risk evaluation. For a given parameter set, the closed-loop system simulates 30 seconds of cardiac activity. During this, the *Evaluation* module monitors the closed-loop system and passes objective function values to S-TaLiRo as soon as the simulation terminates. The *Generation* module uses the optimizer to determine new parameters for the next run. The algorithm guides the parameter selections to an approximate global optimum. The convergence of the algorithm is discussed in [32], which is beyond the scope of this paper.

#### E. Case studies

Using clinical observations, physician perspectives and cardiac activation data (Fig. 1) [28], [33], [34], six constrained

regions for the HA heart model parameter space were specified (Fig. 8). Five key observations were encoded into each region: intrinsic sino-atrial (SA) rate, the possibility of atrial premature complexes (APC), the possibility of additional delay through the atrio-ventricular node (AV delay), the possibility of premature ventricular complexes (PVC) and the possibility of retrograde ventricle to atria (VA) conduction (Table I) (for the comprehensive parameter description see Supplementary Material).

For case studies 1 and 2, the DDD pacemaker programmable timing parameters were fixed at standard values (ms):  $LRI=1000$ ,  $AVI=170$ ,  $URI=500$ ,  $PVARP=250$  and  $VRP=230$ . The heart model parameters were varied to test requirements coverage and PMT risk. In contrast, case study 3 fixed the heart model parameters while some of the DDD pacemaker parameters were varied.

1) *Requirement based testing*: The broadest parameter regions, HA1 and HA2, were used for this testing. The new heart parameter sets from the *Generation* module were found by optimization using the number of output traces  $n$  from the *Evaluation* module (Fig. 4).

2) *Device induced PMT risk evaluation*: All HA1-HA6 scenarios were used for this case study. For each scenario, the S-TaLiRo in the *Generation* module was run up to four times to generate 12,000 test cases. The *Evaluation* module PMT flag  $s$  was input to the *Generation* module and perturbed the heart parameters toward regions where device interaction was likely to cause PMT.

3) *Device programming customization*: One heart parameter set that caused PMT was fixed (see Supplemental Material) and the DDD pacemaker parameter AVI was varied between [150,180] ms and PVAP was varied between [250,500] ms with step sizes of 5 ms. For each parameter setting the average atrial rate (sensed and paced) and the maximum paced atrial rate were recorded over 30 seconds of cardiac simulation to assess parameter combinations likely to cause PMT.

### III. RESULTS

#### A. Requirement based testing

With the broad HA1 and HA2 parameter bounds, all the DDD mode pacemaker timing requirements (see Supplementary Material) were tested (100% coverage).

#### B. Device induced PMT risk evaluation over constrained physiological settings

All six constrained HA heart model parameter regions were explored to assess the risk of PMT under those conditions. Table I summarizes the likelihood of the DDD mode settings causing PMT for each parameter constraint set.

Retrograde ventricle to atria (VA) conduction was essential for PMT [28], as was atrioventricular (AV) dissociation [34]. In this case study, PMT did not occur for the HA6 constraints where there was no retrograde VA conduction. While retrograde VA conduction was present in HA5, without PVC or APC, AV dissociation did not occur and PMT was impossible. The constraint space and simulations showed that PMT was the combined consequence of retrograde VA conduction and

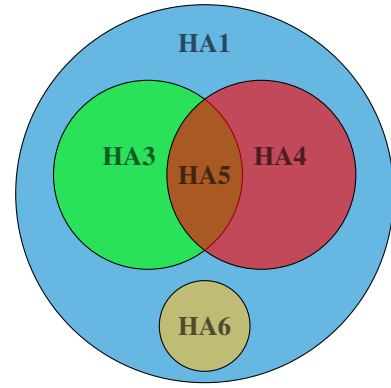


Fig. 8: The relationship of the parameter constraints. HA2 is the union of HA3 and HA4.

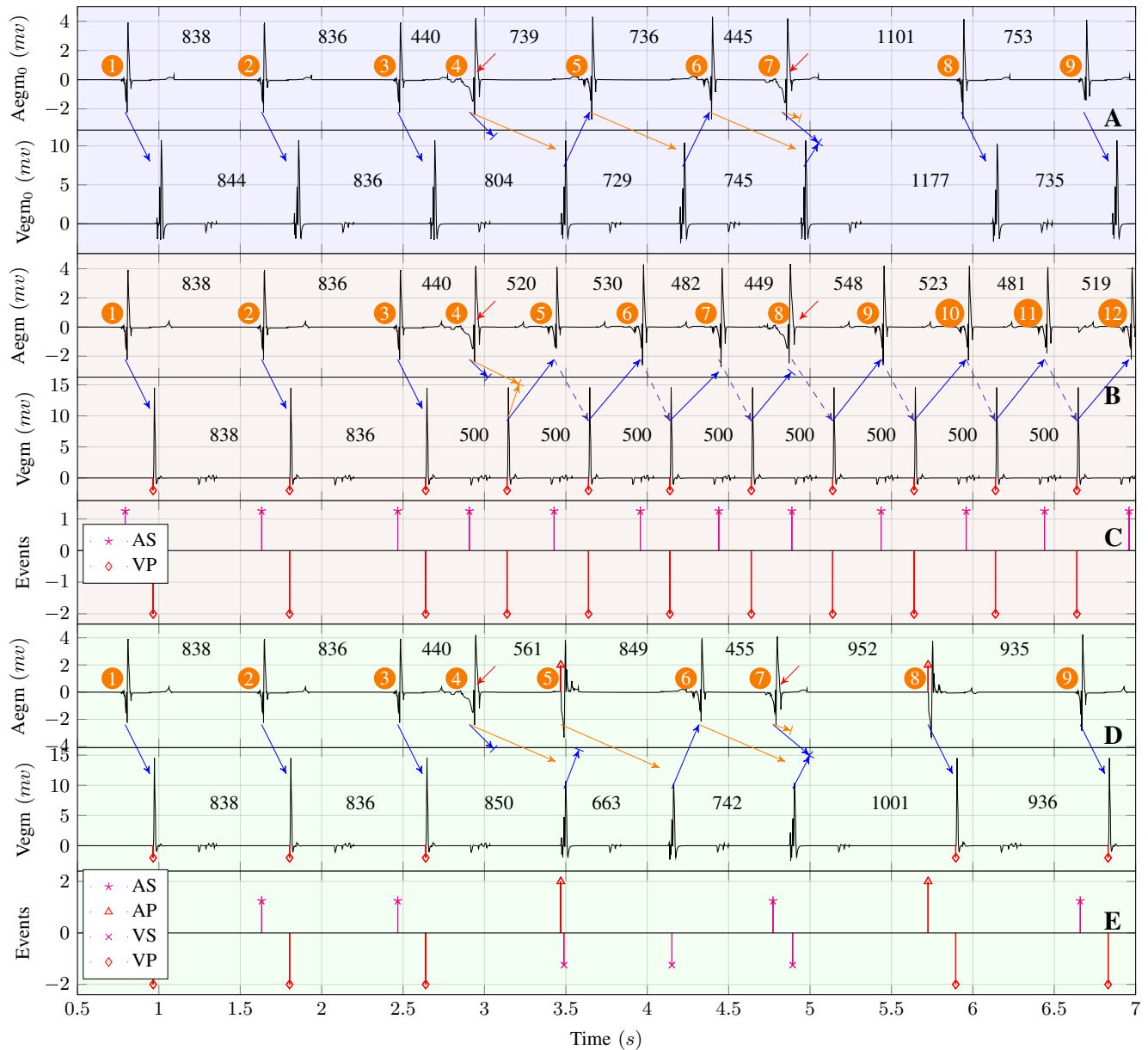
AV asynchrony, which follows the clinical understanding [28], [34]. The implication is that PVC are more likely to facilitate PMT than APC alone given the higher incidence for HA4 settings compared to HA3. This also agrees with clinical observations [33], [34]. For the HA2 constraints, both PVC and APC may be present. The incidence of PMT with the HA4 constraints was slightly higher than HA2 as the presence of APC in HA2 removes some search resources from the PVC zone, while APC was less likely to incur PMT. When higher heart rates occurred (HA1), the incidence of PMT increases as the high-frequency atrial excitation introduced more AV dissociation.

Parameter Ranges	SA Rate(bpm)	APC	AV delay	PVC	VA conduction	PMT
HA1	30-150	Yes	Yes	Yes	Yes	45.77%
HA2	30-74	Yes	Yes	Yes	Yes	27.76%
HA3	30-74	Yes	Yes	No	Yes	6.69%
HA4	30-74	No	Yes	Yes	Yes	30.6%
HA5	30-74	No	Yes	No	Yes	0%
HA6	30-74	Yes	Yes	Yes	No	0%

TABLE I: The six constraint regions of the HA heart model and calculated frequency of PMT occurrence. “Yes” indicates the constraints cover the condition, but whether the condition presents depends on the specific parameters selected by the *Generation* module. For an APC or PVC ectopic, “No” means the entrance path to the subsidiary pacemaker cell is intact and under normal sinus rhythm the pacemaker is suppressed. However, it can initiate a beat if the external stimulation rate is lower than the intrinsic rate.

#### C. Device programming customization for specific physiological conditions

Modern cardiac devices are equipped with algorithms for prevention, detection, and termination of endless loop tachycardia (ELT) [33], mostly focusing on PVARP extension [28]. However, if retrograde P waves fall within the extended PVARP, the subsequent atrial stimulus may occur during the absolute atrial myocardial refractory period generated by the preceding retrograde atrial depolarization [33], [35], [36]. Such pacing stimuli cannot be captured by the atrial myocardium but are followed by ventricular pacing. This is another form of



**Fig. 9:** A simulated cardiac episode demonstrating how the device programming affects occurrence of PMT. The orange and blue arrows show the conduction via the slow and fast pathway (see Fig. 2), respectively. The red arrows indicate where an APC happens. A. Heart activity without device intervention. B. Heart activity and the onset of PMT with device pacing (PVARP=250ms). C. Events in B sensed by device. D. Heart activity and interaction with device at long PVARP (340ms). E. Events in D sensed by device.

PMT, repetitive nonreentrant VA synchrony (RNRVAS) [36]. Hence, the programming of PVARP 50-75 ms beyond the duration of the retrograde VA conduction can reduce the ELT in general [33], but may promote RNRVAS.

With the HA heart model [8], we investigated the impact of the device programming on specific heart conditions. Here, we chose one of the heart model parameter settings which led to ELT during the experiment of PMT risk evaluation. The heart had a duration of retrograde VA conduction varying from 289 ms to 321 ms. The variation was influenced by the frequency

of the activation because of the conduction velocity (CV) restitution [8]. Fig. 9 illustrates how the device programming affects the onset of PMT.

The original heart presented a normal sinus rhythm with slightly lengthened AV delay in the first three beats (Fig. 9A). An APC took place at ④, with the propagation blocked on the fast pathway but successfully reaching the ventricles via the slow pathway. Meanwhile, the activation conducted retrogradely back to the atria through the fast pathway. After that, the activation propagates to the ventricles via the slow

pathway again and an atrioventricular nodal reentry tachycardia (AVNRT) formed. At ⑦, another APC was issued. This activation was blocked on the slow pathway and collided with the retrograde pulse on the fast pathway. The endless loop excitation ceased and was followed by two sinus beats ⑧ and ⑨.

The heart model was then connected to the DDD pacemaker model (Fig. 2 shows the lead locations) with PVARP=250 ms. As shown in Fig. 9B, the device delivered three VPs due to long AVI at the first three beats. When the APC took place at ④, the propagation was blocked on the fast pathway. The conduction on the slow pathway met the retrograde paced ventricular activation. When the retrograde pulse reached the atrioventricular junction (AVJ), the fast pathway had recovered which enabled the excitation to propagate to the atria. The activation was beyond the PVARP and sensed by the device. After that, the device kept pacing the ventricles to track the preceding retrograde P wave and the PMT was formed. The APC at ⑧ collided with the retrograde P wave. However, it did not break the device induced virtual reentry circuit.

We prolonged the programmable PVARP to 340 ms. As shown Fig. 9D, the APC at ④ fell into the PVARP, and the device delivered an AP at ⑤. The activation caused by the pacing pulse collided with the retrograde P wave on the fast pathway caused by the preceding APC, while the activation reached the ventricles via the slow pathway. Another APC at ⑦ broke the loop, and the subsequent activation resumed the AV synchrony.

The example shows that the extended PVARP filters the APC and avoids PMT for the specific cardiac condition, while the subsequent atrial stimulus is captured. Additionally, since another measure to prevent both ELT and RNRVAS is to shorten AVI [34], [36], we validate the closed-loop system with AVI from 150 to 180 ms. Shortening AVI did not avoid the formation of PMT for the specific parameterised cardiac conditions.

The parameter safe zone was found by iteratively exploring the combinations of AVI and PVARP. When  $150 \leq AVI \leq 180$  and  $330 \leq PVARP \leq 500$ , the device did not introduce PMT for the specific heart condition. Fig. 10 shows that the average atrial rate decreases with the increased PVARP because no PMT takes place with the PVARP >330 ms.

#### IV. DISCUSSION

We have presented a new framework for rigorously testing CIEDs. It has been illustrated using a DDD pacemaker model. The framework can be used to explore both the model and device constrained parameter space to determine if the device timing requirements are covered, assess the risks of undesirable device-heart interactions and understand the effects of device parameter settings.

##### A. Related work

For CIED verification and validation, abstract heart models [37], [6], [7] have been proposed. The extended TA based model developed by Jiang et al. [37] abstracts away the electrical activation, retaining only timing properties, making

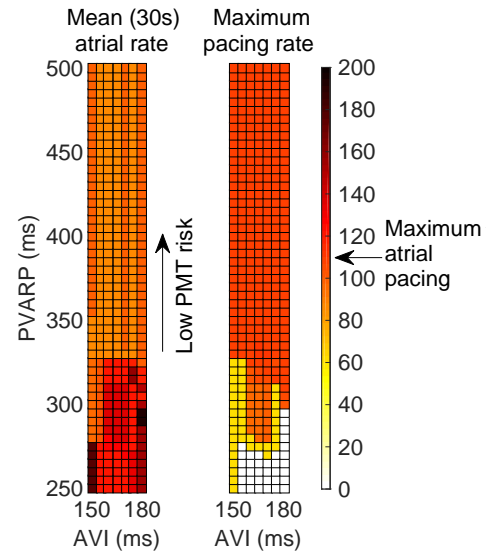


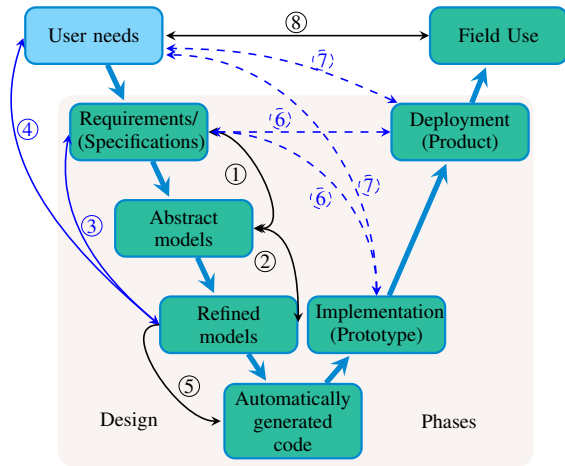
Fig. 10: The mean atrial response rate over 30 seconds of simulated response to device pacing at the indicated maximum pacing rate. The device parameter space is shown.

it feasible for formal verification. HA [17] heart models [6] have previously been developed for approximate quantitative verification of CIEDs [38] and further simplified models [39] have recently been used [7]. These models were developed explicitly for formal verification, which limits the non-linear dynamics of the models. To capture essential but complex physiological dynamics that affect device operations, new HA-based heart models have been developed [22], [8], which can efficiently capture the non-linear dynamics of the cardiac electrophysiology while maintaining potential amenability to formal analysis.

Model-based development [40], [41], [42] improves the confidence of design by advocating the use of models at different levels of abstraction throughout the development phases, (Fig. 11), which is a promising design paradigm for safety-critical systems like CIEDs. Ideally, end-to-end modeling, automatic verification, and code-generation can guarantee the correctness of design.

Usually, rigorous techniques such as model checking can be applied to the abstract models (Fig.11 ①). For example, an analysis tool UPPAAL [43] has been used to verify an infusion pump [44] and an implantable pacemaker [45]. The amenability of formal analysis relies on the restricted formalism of the model, which may be confined to the abstraction level with limitations on expressiveness. In [45], TA [27] is used and the heart model is a non-deterministic random event generator, which is devoid of physiological context. In addition, only a subset of the specifications can be formally expressed [13].

To capture more complex behaviors, high-fidelity models are needed. This raises another challenge, i.e., the establishment of the correctness of automated model translation (Fig.11 ②) and code generation (Fig.11 ⑤). For example, Jiang et al. developed the UPP2SF compiler to automatically convert the verified UPPAAL models to simulation models [46]. Afterward, they used Simulink code generation for code synthesis



**Fig. 11:** Development cycle of model-based design (V-model). The cycled numbers indicate various verification and validation activities. ① Verifying that the abstract models fulfill (a subset of) system requirements using formal analysis, such as model checking. ② Establishing a relationship between the abstract and high-fidelity models. ③ Verifying that the refined models fulfill the system requirements by simulation. ④ Validating that the refined models meet specific user needs by closed-loop simulation with plant models. ⑤ Automatic code generation. ⑥ Verifying that the prototype and end product fulfill the system requirements by testing. ⑦ Validating that the product meets specific user needs by closed-loop testing with plant models. ⑧ Validating that the prototype and end product meet user needs by field testing. While the blue solid annotations denote the case studies in this work, the dashed ones are the activities supported by the framework but not included.

and to test the final implementation [25]. In order to preserve the semantics of UPPAAL [43], additional logic operations were added to control the execution of the simulation model, which made the design more complicated.

High-fidelity models often contain complex physical processes, referred to as cyber-physical systems (CPS), which combine non-linear continuous physical dynamics with discrete controllers, i.e., hybrid systems. Researchers in [47], [48] tried to resolve the scalability issues of hybrid system verification. Due to the well-known undecidability of HA verification [47], simulation and statistical model checking [49], [7] are usually utilized (Fig.11 ③).

For instance, S-TaLiRo [21] provides a comprehensive tool chain to automate CPS verification and validation (Fig.11 ①,②,③,⑥), including falsification, parameter mining, coverage-guided testing, conformance testing and runtime verification. The toolbox is designed to search for counterexamples for Metric Temporal Logic (MTL) [50] properties for non-linear hybrid systems. It aims to falsify a given property of interest through global minimization of the robustness metric [51]. As the essence of the tool chain is optimization guided testing rather than exhaustive formal analysis, it can be applied to any non-linear real-time CPS. A more general review on modeling CPS and verification and validation techniques can

be found in [52], while a series of formal techniques for cardiac devices are given in [53].

For medical devices, clinical trial is an essential validation process (Fig.11 ⑧). However, this is expensive and imposes potential risks to patients. It is desirable to validate devices on virtual trial populations before their clinical use (Fig.11 ④,⑦). Clinical trials cannot be replaced, but pre-clinical validation can improve the confidence in the functional safety and efficacy of the device.

In this paper, we showed device validation using a simulated physiological environment, including requirement-based testing (Fig.11 ③,⑥) and we analyzed the device operations under specific heart conditions (Fig.11 ④,⑦). We used a pacemaker model as the basis for our case studies. Our framework can be readily extended to validate physical devices (Fig.11 ⑥,⑦) facilitated by emulation techniques [18], [19].

## B. The Requirements of Physiological Models in Device Validation

The requirements of the physiological model used for device validation depend on the application. For instance, for the physiological models used in clinical trials, like the ISCT models [15], the accuracy to which the individualized models can predict the physical reality is a crucial aspect. As the application presented in this paper is mainly in the design stage and for clinical programming assistance, the requirements of the model are different.

1) *Requirement Based Testing*: For the requirement based testing during the design stage, the model should be generic enough to exhibit the physiological conditions of a large population of patients. Ideally, the model should cover all possible physiological inputs to the device. Another demand is the simplicity, ease of use and potential real-time simulation. This requires a phenomenological model to encapsulate most of the mesoscopic consequences of channel physiology.

2) *Device Validation with Constrained Physiological Conditions*: The complexity of device functionality has been growing rapidly [10], which may account for the reported adverse incidents, such as the problems observed in [11], [12]. Apart from the basic operation modes classified using NBG Code [54], a large number of algorithms and specific features have been developed by manufacturers [28]. These advanced algorithms are designed to handle certain complex cardiac conditions and improve treatment quality.

The HA heart model enables device designers to validate specific functions under the intended spectrum of inputs. We can evaluate the PMT risk with the clinically identified physiological factors, such as APC, PVC, and the presence of VA retrograde conduction. Furthermore, the flexibility and compositional nature of HA make heart model refinements readily achievable, enabling device validation under more complicated clinical settings.

Ideally, the synthetic cohort of patients follows the same distributions of real heart conditions and the statistical simulation results predict the clinical performance. In the PMT case study, we can capture the main physiological factors as reported in [55]. The simulated statistical results provide relative risk



assessment. For example, the simulation results show that PMT occurrence probability is 30.6% with a PVC and 6.69% with an APC. This conforms to the clinical observation that PVCs are the most frequent cause of PMT other than an APC.

PMT is a well-studied phenomenon when a DDD mode pacing protocol is applied. We use it to show how the closed-loop framework validates the device efficacy in a simulated environment. The proposed framework can also be applied to validate any new pacing algorithm and more complicated scenarios before potential clinical incidents occur. Similarly, the physiological parameter constraints are derived based on domain knowledge and a library of heart models is created. The framework automatically guides the parameterization around the physiological zone of interest to check if the new algorithm can handle the conditions properly. In addition, the approach can be applied to validate different versions of a device design and analyze different parameter settings.

3) *Device Programming Customization*: Cardiac devices have general programming recommendations for a class of heart conditions. However, device programming options sometimes contradict each other. For example, PVARP extension can reduce ELT, but possibly promote RNRVAS [33], [36] or even introduce atrial fibrillation [36]. On the other hand, the programmable features are manufacturer-specific and can cause confusion in the clinical setting [10].

A virtual heart model customized to patient-specific features would enable validation of programmable settings, providing useful insights into the safety and efficacy of a device. We have demonstrated how a safe parameter zone can be found for a specific heart condition. The framework can also be used to hold the heart parameters fixed and dynamically test the CIED parameter space. In case study 3 we enumerated the parameter space to ascertain the PMT risk domain in terms of the AVI and PVARP settings. However, selective sampling of this relationship guided by the optimization algorithm is also an option (Fig. 1).

### C. Extensions

The physiological model provides realistic responses within a constrained space. In this paper, we varied 19 parameters of the heart model to achieve multiple cardiac conditions. However, there is scope for larger parameter spaces. For instance, if we want to validate biventricular devices, the parameters affecting the right or left bundle branch would need to be included. For larger parameter spaces automatic search techniques become increasingly important. Here, our PMT sequence observer facilitated the exploration of physiological heart conditions promoting PMT in closed loop with the pacing device.

The personalization of our heart model is beyond the scope of this study. However, the testing framework supports extensions to the heart model [8]. It can capture a number of physiological features, such as action potential heterogeneity, rate-dependent action potential duration (APD) restitution and CV restitution under physiological and pathological conditions [23], [8]. We have shown how to parameterize the dynamics at the cellular level [8]. At the organ level, the challenge is

to quantify how well the model behavior captures specific physiological dynamics to guide the parameter selection.

The Simulated Annealing (SA) algorithm implemented in the S-TaLiRo [21] is used to achieve stochastic optimization, but other optimization methods and machine learning techniques, could be incorporated into future work. Although S-TaLiRo [21] is a tool built on the Matlab<sup>®</sup> platform, the framework is not limited to simulated devices and can be extended to perform physical device testing.

## V. CONCLUSION

We have demonstrated the in-silico validation of a DDD mode pacemaker with a virtual physiological heart model in the closed-loop. Optimization techniques can be employed to accomplish the automatic model parameterization in the closed-loop context. The environment model provides realistic physiological responses, which drive the device to operate in the intended input spectrum, ideal for design testing. The PMT risk evaluation findings agree with the clinical observations. Furthermore, the case study of device customization suggests that a physiological model could be useful in clinical settings.

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