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A Framework for Validation of Implantable Medical Devices

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Designing bug-free medical device software is difficult, especially in complex implantable devices used for rhythm management of the cardiac or the neurological system. There is currently no formal methodology or open experimental platform to validate the correct operation of implantable medical device software. We describe our recent work on heart modeling for the validation and verification of artificial cardiac pacemakers. As we extend this platform to more complex devices such as cardioverter-defibrillators, there are several significant challenges in the modeling of biological systems and their patient-specific response to external stimulus. Our goal over the longer term is to explore the methodologies for experimental evaluation, modeling for validation and verification of implantable devices within the context of the underlying biological system. We present our early and promising results for simplified models and propose steps toward an integrated platform for validation of medical device systems.

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A Framework for Validation of Implantable Medical Devices

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Abstract

Designing bug-free medical device software is difficult, especially in complex implantable devices used for rhythm management of the cardiac or the neurological system. There is currently no formal methodology or open experimental platform to validate the correct operation of implantable medical device software. We describe our recent work on heart modeling for the validation and verification of artificial cardiac pacemakers. As we extend this platform to more complex devices such as cardioverter-defibrillators, there are several significant challenges in the modeling of biological systems and their patient-specific response to external stimulus. Our goal over the longer term is to explore the methodologies for experimental evaluation, modeling for validation and verification of implantable devices within the context of the underlying biological system. We present our early and promising results for simplified models and propose steps toward an integrated platform for validation of medical device systems.

1 Introduction

The use of artificial implantable devices has grown significantly over the recent decades. Rhythm management devices such as pacemakers and cardioverter-defibrillators are currently widely used, while others like neurostimulators are transitioning from clinical trials to mainstream treatment for several neurological disorders such as intractable epilepsy, movement disorders and migraine. Although these devices have demonstrated more than 99% of efficacy for the heart and over 50% for the brain, in the last 20 years failures of medical devices caused more than 30,000 deaths and almost 600,000 injuries [1]. Safety recalls of pacemakers and implantable cardioverter defibrillators due to firmware problems between 1990 and 2000 affected over 200,000 devices, comprising 41% of the devices recalled and are increasing in frequency [2]. There is, therefore, a need for a rigorous approach toward validation and verification of medical devices as is currently done in the automotive and avionics domains.

Medical Device Software and Systems (MDSS) are inherently Cyber-Physical Systems (CPS) where the control and computation within the device is tightly coupled with the sensing and actuation of the biological physical substrate (i.e. the heart and brain). It is therefore essential to model the functioning of the device within the physical environment, where actions performed by the device are determined with the sensed state of the environment. We focus on implantable MDSS that interact only with the human heart and neurological system, since behavior of these systems is a direct result of the underlying electrical activity. The cardiac and the neurological systems' response to a stimulus produced by the device is better understood than other interactions between invasive treatment and a patient. For example, a pharmacological effect of an administered drug is much harder to match to a normal pattern than that of an electrical stimuli produced in the heart by an artificial pacemaker. Currently, the cardiac system is better understood for normal and abnormal conditions within the purview of rhythm management systems.

The modeling of the closed-loop interaction between the cardiac or neurological system and an implantable device is challenging and problematic as the relation between the physical state and the device state is largely nondeterministic, interactive and cannot be fully captured by computation models. The modeling of the physical substrate must therefore be restricted to specific cases and conditions of operation. Thus, the validation and verification observations are only valid for those specific cases.

2 Rhythm Management Devices

The goal of this research is to build a framework that will allow validation and verification of rhythm management devices (RMD), which use different types of therapies to eliminate derangements in the normal heart and neuro signal rhythms. Rhythm management therapies for the heart include demand pacing, cardioversion and defib-

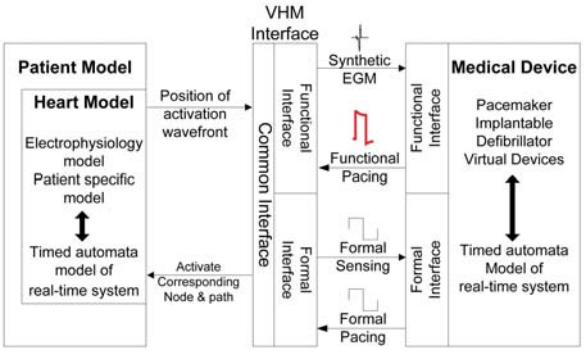


Figure 2. Structure of the VHM platform

rillation, while responsive therapies for the brain are designed to deliver preprogrammed waveforms upon detection of discrete events [3]. We describe below our early efforts to model the heart and basic modes of a pacemaker in a closed-loop platform. Following this, we discuss the challenges and possible approaches to incrementally introduce non-determinism, interactivity and complexity of the physical model.

2.1 Case Study: Pacemaker Validation and Verification

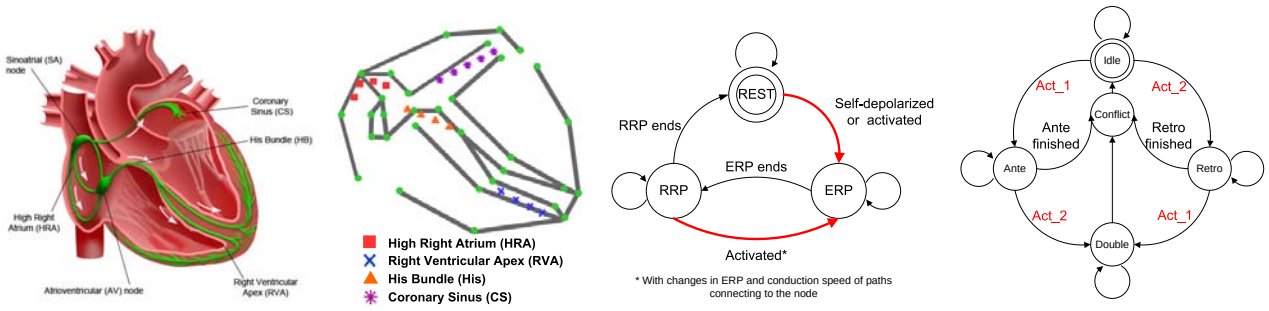
In [4, 5] we have presented early efforts toward the development of a real-time Virtual Heart Model (VHM) to evaluate the electrophysiological operation of the functioning (i.e. during normal sinus rhythm) and malfunctioning (i.e. during arrhythmia) heart. A Real-Time (RT) view of the heart naturally mimics the electrophysiological (EP) view of the heart in terms of intrinsic and artificial synchronization and re-synchronization. The design the VHM, shown in Fig. 1 and Fig. 2, exposes functional and formal interfaces derived from the common kernel, which can be utilized for validation and verification of implantable cardiac devices.

The kernel models the cardiac action potential which is a principal phenomena of the heart's conduction system. This allows us to model the heart as a network of nodes, which are abstractions of localized electrically active tissue. Conduction between nodes is modeled by paths with know propagation and timing behavior. The functional model emulates the behavior of the heart and enables validation through simulation and black-box testing of the implantable devices. The kernel was designed using the timed-automata approach as the timing of the heart's electrical system is fundamental to the cardiac function [6].

To model the heart we considered the electrical signals that pass through the heart, stimulating all triggered heart cells. The behavior of the tissue is described using the total refractory period, which can be defined as the amount of time it takes for an excited cell to be ready for a second stimulus once it returns to its resting state. The period can be divided into two time periods, the effective refractory period (ERP) and relative refractory period (RRP). The cell cannot be activated by an electrical stimulus in the ERP, which acts as a blocking interval. In the RRP, the cell can be activated again, but this causes changes in the action potential morphology.

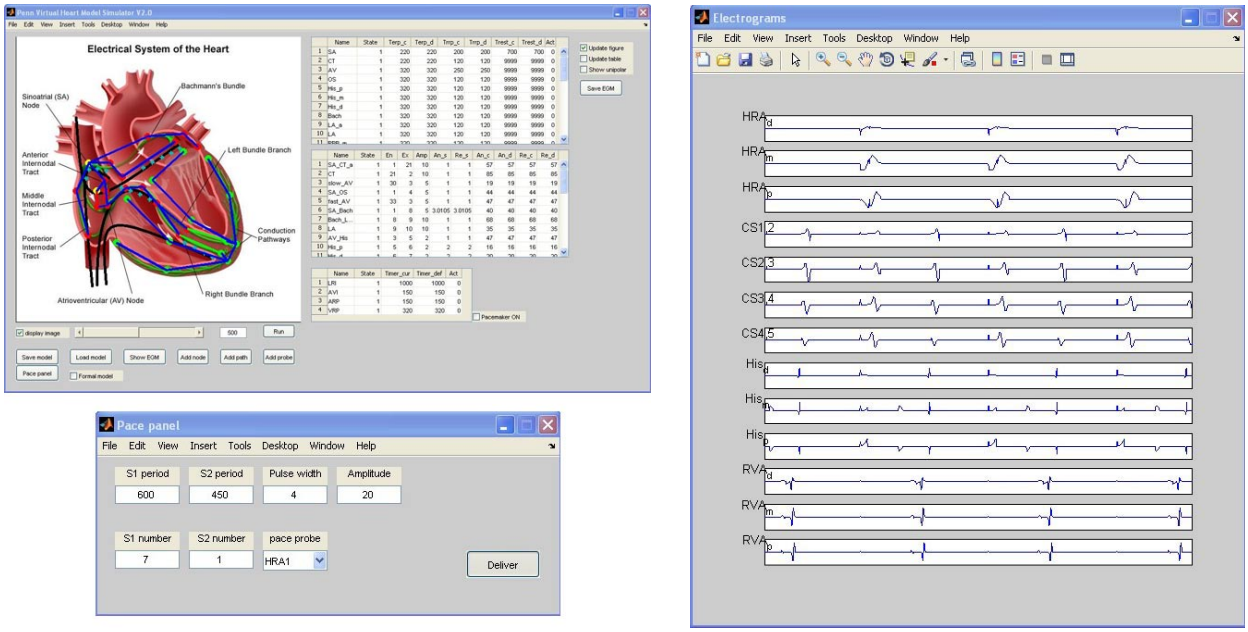
A simplified state transitions of the node and path automatas are shown in Fig. 1(c) and Fig. 1(d)). In the node automata, the refractoriness is modeled with *ERP*, *RRP* and *Rest* states, where state durations are determined by appropriate timers (T_{erp}, T_{rrp}, and T_{rest}). The refractory parameters are tuned relative to the true refractory periods measured in clinical EP studies [7], thus enabling an extraction of clinically-relevant results. In the path automata, the conduction properties are modeled using the following states: 1) no conduction state (*Idle*); 2) antegrade or forward conduction state (*Ante*); 3) retrograde or backward conduction state (*Retro*); 4) both directions conduction state (*Double*); and 5) conflict state (*Conflict*). In addition, the conduction delays are modeled by the timers T_{ante} and T_{retro}.

Fig. 3(a) shows the simulation GUI we developed in Matlab which allows users to view electrograms and deliver programmed pacing in real-time. Fig. 3(b) shows the electrograms measured from the probes placed in the model. In our previous work [4], we presented a methodology to extract timing properties of the heart, in order to construct the timed-automata model which corresponds to specific heart conditions. The electrogram signals have been validated to be clinically-relevant by an electrophysiologist for a spe-



(a) (b) (c) (d)

Figure 1. (a) The basic physiology and electrical conduction system of the heart; (b) Corresponding setup of nodes (dots), paths (lines) and probes (shapes) in our heart model; (c)Node automata. (d)Path automata



(a) Simulation environment along with the Pace panel

(b) Synthetic electrogram

Figure 3. Graphical user interace

cific set of common arrhythmias.

2.2 Complex Rhythm Management Devices

Following the simpler VHM, we now move our focus to more complex RMD which include implantable cardioverter-defibrillators (ICD) and neurostimulators. Modeling an ICD is the next step in understanding implantable medical devices and how they interact with the heart. An ICD is used for patients at risk of developing ventricular tachycardia, a dangerous arrhythmia, and ventricular fibrillation, a life-threatening arrhythmia. To treat these problems, the ICD must be able to diagnose these arrhythmias and deliver a high-voltage shock to the heart. Arrhythmia detection utilizes more complicated algorithms than simple threshold detection used in a pacemaker. This makes modeling of the ICD a more difficult task, but also increases the need of a VHM for device certification before its use on a real patient.

In order to accommodate closed-loop implementations of the heart model with an ICD, we must consider the mechanical interactions between the heart and the device. The high voltages and mechanical fixation mechanism used by the ICD can injure the muscle tissue of the heart. The heart model must be able to interpret this tissue damage and alter its timing parameters accordingly. In order to extract the affected timing parameters, the mechanical injury must be mapped to the tissue, down to the cellular and molecular level. Problems arise due to the complexity of this injury issue. Saxonhouse et al. [8] have investigated injury due to fixation of the lead into the heart muscle, but few have been able to quantify this injury or conclude a cause-and-effect relationship between the ICD shocks and progressive muscle injury. The challenge is to incorporate these injury-timing parameters into our VHM while maintaining the complexity of the original model.

Neurosimulators are used for management of nervous system disorders, mostly for recording and localizing neural signals along with closed-loop control of specific networks to treat (or prevent) specific disease states [3]. The idea of closed-loop control first appeared in [9]. The authors in [3] propose a fine-grained feedback control laws, where states are translated into control actions, which automatically desynchronize or hypersynchronize, at will, the model of neural synchronization.

3 Integrated Validation and Verification

According to the Food and Drug Administration (FDA) Quality System Requirements, the validation is defined as '*confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled*'. Also FDA defines verification as *confirmation by examination and provision of objective evidence that specified requirements have been fulfilled*.

Validation of the VHM is done by comparing the behavior of the VHM to the common arrhythmias seen in real patients as a result of failure of impulse generation and/or propagation. While the clinical relevance of the model electrogram outputs have been validated by an electrophysiolo-

gist, there is no practical means to formally prove any of the heart properties. Since we have validated the VHM on several cases of normal and abnormal heart rhythms, we are able to use it in a closed-loop operation for validation and verification of specific cases and conditions of implantable medical devices' operation.

Validation of the implantable devices is usually done using exhaustive testing. In [4] we have shown its use in a case of pacemaker design validation/verification. By connecting the VHM to a pacemaker model, we were able to pace and synchronize the heart during the onset of irregular heart rhythms. The existence of the functional interface enables an emulation of the heart behavior and the use of simulation with black-box testing for devices validation.

An important class of implantable cardiac devices includes devices designed with the event-triggered architecture. We propose an approach that can be used for their verification in a closed-loop, in cases when only interaction between a patient and the device includes event triggering. In this case, a procedure is proposed that can be used to derive a formal description of the VHM as a composition of synchronous components, from which a UPPAAL model [10] of the system is extracted. Also, after the patient model is translated into UPPAAL model, the composition of these models can be used for the formal system verification.

To describe the technique we consider a closed-loop system where a pacemaker is used to control the heart rhythm. Verification of the artificial pacemakers can be significantly simplified since pacemakers are implemented in the event driven manner. Since the VHM was designed in Simulink using timed-automatas, we propose a simple technique that can be used to extract formal description of the model. Here we would like to emphasize that we only consider a translation of the blocks used to model the VHM and not to design general case translation procedure from Simulink to UPPAAL. The VHM design exposes two interfaces, formal and functional, which allows separation of the timed-automata sub-components that can be used for to extract the formal description of the VHM with the respect to closed-loop interaction with a pacemaker. Composition of this description with the pacemaker model enables a translation of the VHM and pacemaker models into UPPAAL, therefore allowing a closed-loop system verification using UPPAAL built-in verification procedures.

4 Research Challenges and Outlook

The primary challenge in verification of closed-loop systems with implantable medical devices is due to the fact that *more complex devices*, such as ICDs and neurostimulators, do not use threshold-based and event-driven reactions to the sensed-state of the physical environment. ICDs use a specialized algorithms to detect arrhythmias using previous electrogram recordings. This is the case even for more complex pacemaker model, which utilizes rate-adaptive pacing [7]. Unlike the approach employed in cardiac devices, neurosimulators use a control design where stimulation value is determined on the fly, at every discrete time instant, based on the evolving state variables estimated from sensed Electroencephalography (EEG) during an epileptiform event [3].

For these cases, the basic formal interface, as one currently used in VHM, is not sufficient for formal verification, since there will exist a significant discrepancy between the formal interface and the functional interface. Thus, we consider a translation of the VHM to Linear Hybrid Systems (LHS) in order to use a *symbolic analysis framework* proposed in [11].

Currently we are in the process of evolving the VHM in order to include patient-specific morphological description of muscle tissue. Therefore, the updated VHM has to incorporate an *increased level of non-determinism* to try to cover all possible changes in timing parameters due to mechanical injuries of the muscle tissue. In addition, we plan to further investigate this integrated approach to functional and formal modeling with the incremental introduction of more non-determinism and complexity in the patient and device models.

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