CyberCardia Project: Modeling, Verification and Validation of Implantable Cardiac Devices

Md. Ariful Islam*, Hyunkyung Lim‡, Nicola Paoletti‡, Houssam Abbas**, Zhihao Jiang**, Jacek Cyranka†, Rance Cleaveland§, Sicun Gao¶, Edmund Clarke*, Radu Grosu‖, Rahul Mangharam**, Elizabeth Cherry††, Flavio Fenton‡‡, Richard A. Gray[x], James Glimm‡, Shan Lin‡, Qinsi Wang*, and Scott A. Smolka‡

* Carnegie Mellon University
† Rutgers University
‡ Stony Brook University
§ University of Maryland
¶ Massachusetts Institute of Technology
‖ Vienna University of Technology
** University of Pennsylvania
†† Rochester Institute of Technology
‡‡ Georgia Institute of Technology
[x] U.S. Food and Drug Administration

***Abstract*—In this paper, we survey recent progress in *CyberCardia* project, a CPS Frontier project funded by the National Science Foundation. The *CyberCardia* project will lead to significant advances in the state of the art for system verification and cardiac therapies based on the use of formal methods and closed-loop control and verification. The animating vision for the work is to enable the development of a true *in silico* design methodology for medical devices that can be used to speed the development of new devices and to provide greater assurance that their behavior matches designer intentions, and to pass regulatory muster more quickly so that they can be used on patients needing their care.**

The acceleration in medical-device innovation achievable as a result of the *CyberCardia* research will also have long-term and sustained societal benefits, as better diagnostic and therapeutic technologies enter into the practice of medicine more quickly.

***Index Terms*—Cardiac electrophysiology, Implantable cardiac Devices, Formal Methods, Verification and Validation, Closed-loop control.**

I. Introduction

Cyber-physical systems (CPSs) employ a combination of computational and physical components in order to process information about, and influence, the environment in which the systems operate. The history of CPSs may generally be traced back to control systems found in aerospace and automotive domains; in these applications embedded controllers oversee the operation of subsystems, such as flight control or anti-lock breaking. The ongoing durability of Moores law, however, has made it economically feasible to include small, cheap microprocessors in many device classes, from cardiac pacemakers to hair dryers. Indeed, recent estimates suggest that over 98% of new microprocessors are deployed in embedded, non-computer devices.

Medical devices constitute an already hugely important, yet relatively new, class of cyber-physical systems. The worldwide market for medical devices already exceeds $100bn, with the US market being measured at nearly $40bn and robust growth forecast. The industry includes devices ranging from multi-million-dollar imaging and radiation-therapy equipment, to clinical equipment such as infusion pumps, to implanted devices such as pacemakers and defibrillators. Other computer-enabled therapies such as artificial pancreases and seizure-disruption devices are also on the horizon. The beneficial impacts on human health and well-being afforded by the cyber-physical paradigm for medical devices are already being realized, and will continue to grow as new avenues for computer-enabled diagnosis and therapy are pursued.

The *CyberCardia* project involves a cross-disciplinary collaborative research effort devoted to fundamental new approaches for radically accelerating the pace of medical-device innovation, especially in the sphere of cardiac-device design. The goal is a suite of technologies that enable a full in silio design paradigm, in which significant parts of medical-device development may be achieved computationally. The specific areas of research to be pursued include the following; see also Fig. 1.

Approximate Verification. To overcome issues of undecidability of property-checking for models of CPSs, approaches that compute approximate answers to these so-called model-checking questions will be developed. Methods will also be investigated for reasoning about stochastic behavior in CPSs.

Compositional and Quantitative Reasoning. To cope with modeling complexity and device inter-operation issues in CPSs, we will develop mathematically robust approaches to composing models of CPSs, and to using the additional structure in such models to define compositional techniques for reasoning about model behavior. Methods will also be developed for computing quantitative, statistical information about model behavior in the course of undertaking model-checking analyses of such models.

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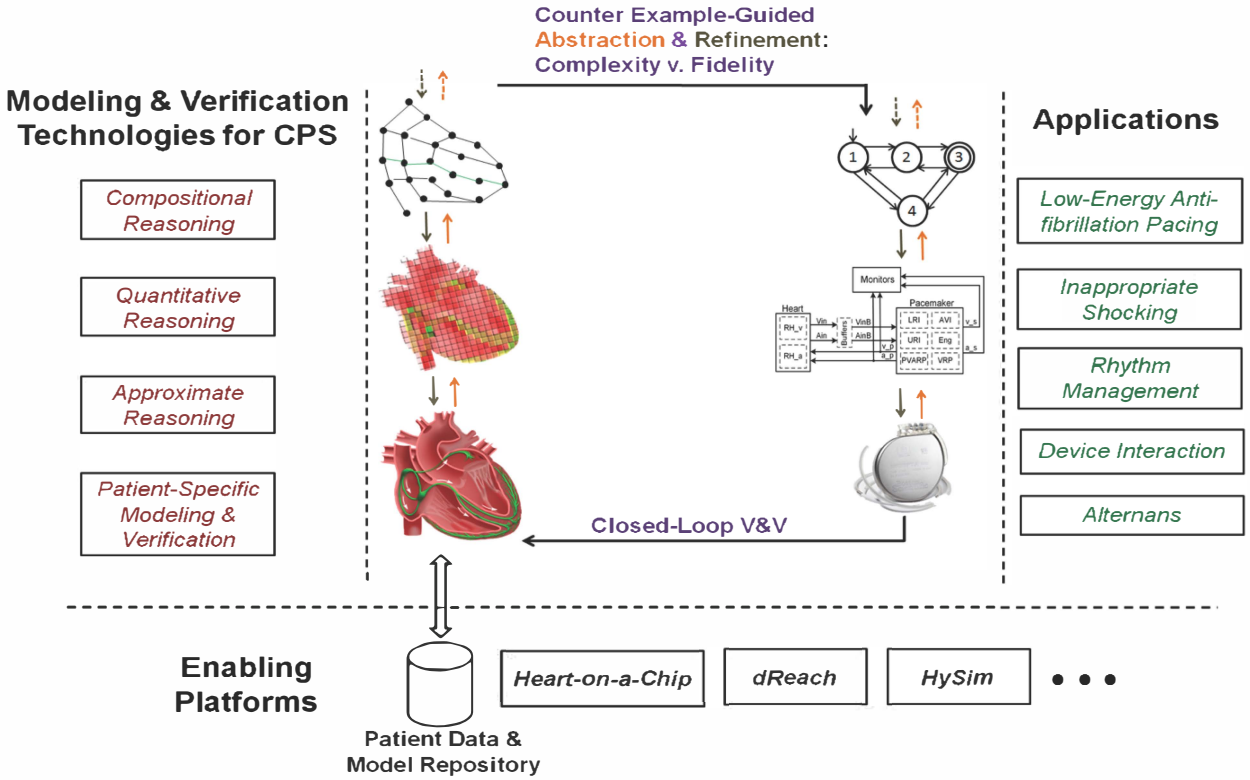

Fig. 1: The CyberCardia framework for closed-loop verification of Medical CPS. The verification technologies we propose to develop are shown on the left, the intended applications on the right, and the supporting computational platforms and repositories along the bottom of the figure

Patient-Specific Modeling. Data from animal experiments, and research into new numerical modeling and simulation techniques, will be undertaken to develop more sophisticated models of the electrophysiology of the heart. These models are intended to provide a basis for a true *in silico* approach to cardiac-device modeling and development, in which impacts of therapeutic approaches can be assessed across a variety of different patient types via simulation.

Closed-loop Control and Verification for Cardiac Therapy. Design methodologies will be developed that use the previously mentioned technologies to support so-called virtual-device development and closed-loop verification. Abstraction-based approaches for modeling complex closed-loop systems, including devices and heart models, will be defined.

Regulatory Concerns. We will conduct research on effective means for analyzing models from the standpoint of the safety and security issues that concern regulatory agencies, and for conveying the results of these analyses in a way that can streamline regulatory approval.

In this paper, we survey current research development under the *CyberCardia* project. Section II highlights our preliminary result on approximate and compositional reasoning for closed-loop verification of cardiac devices. Section III briefly explains a recently developed parsimonious model of cardiac electrophysiology presented in [1]. Section IV presents a bi-domain model for electrocardiac defibrillation. Section V describes an ongoing work on specifying peak detection algorithms for cardiac electrograms in quantitative regular expression. Section VI illustrates a technique for verification of cardiac alternans based on δ-decidability. Section VII offers concluding remarks and a number ongoing research activities under *CyberCardia* project.

II. Compositional Modeling of Tractable Verification

Techniques, such as model checking and reachability analysis, run into the well known State Explosion Problem when large mechanistic ODE systems, such as the IMW model [2], are used for verification, see Section 3.6 of [3]. Thus, deriving guarantees for an Implantable Cardiac Devices (ICDs) using a detailed cardiac model is a grand challenge. Given a property of interest, the Differential Equation Model (DEM) i) must have the requisite level of detail, and ii) must be amenable to tractable formal verification. We have developed two enabling technologies to facilitate the insightful verification of ICDs using detailed models: i) Abstraction and ii) Compositionality.

Abstraction is the process of reducing the complexity of a model by removing the details that are irrelevant to verifying the desired property. Before elaborating on abstraction, we first describe what constitutes the complexity of a given cardiac

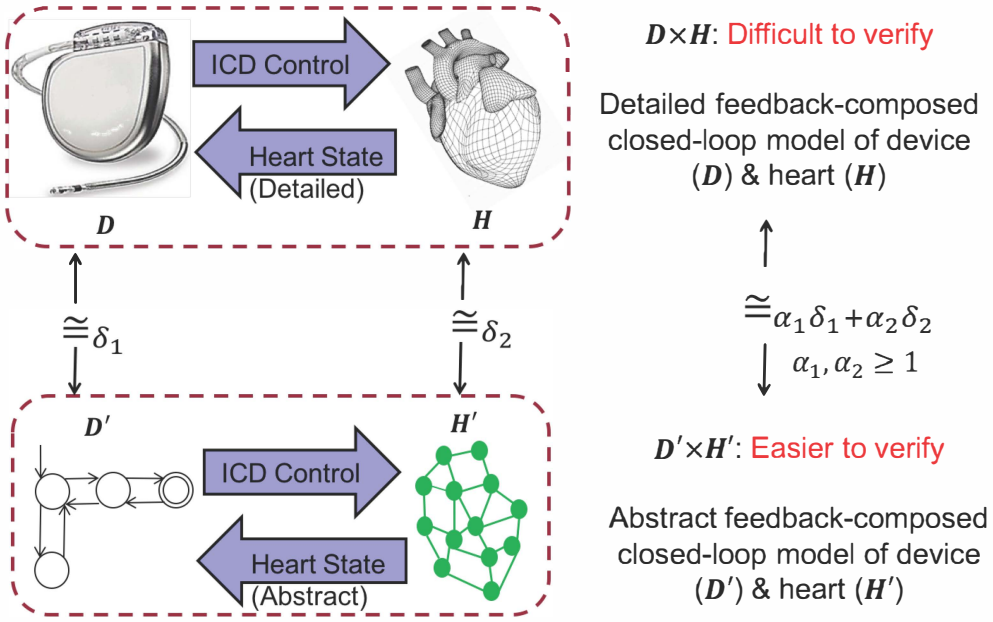

Fig. 2: Approximate and Compositional reasoning for closed-loop verification of ICDs

model. Complexity has two dimensions to it: coverage and depth. Coverage of a cardiac model is a measure of the number of cardiac cells that are used to model the entire cardiac tissue. In other words, coverage is the spatial resolution of the model. In Fig. 1, the most abstract model at the top of the hierarchy of models has only a few representative myocytes, and thus has a low coverage. On the other hand, the intermediate models in the middle have a higher spatial resolution and account for a large number of cardiac cells. A model with higher coverage has relatively more cell-level models and diffusion terms, and thus is more complex as compared to a sparse model with lower coverage. The depth of a cardiac model is the level of detail at which each myocyte is modeled. Detailed models such as the IMW model [2], give an in-depth view of a cardiac cell, which involves various transmembrane ion-transport mechanisms. The model described in Section III on the other hand eliminates all the transmembrane mechanisms and uses abstract variables to sketch a caricature of the APs.

In [4], we employ a hierarchy of Timed automata-based cardiac models which vary in spatial resolution. These models are used to verify timing properties of pacemakers using a CEGAR-based approach. For reducing the detail at the cell level, we have identified a set of approximation techniques that allow one to incrementally remove unobservable variables from the detailed model. The underlying assumption is that the only observable variable for a cardiac cell is its membrane potential. A byproduct of this work is to establish a long-missing formal relation among the existing myocyte models, facilitating the transfer of properties established at one layer of abstraction to the other layers. In [5], [6], we proposed a curve fitting-based technique for identifying two-variable Hodgkin Huxley (HH)-type abstractions for the 13-variable and 10-variable Markovian subsystems corresponding to the sodium and potassium ion channels, used in the IMW[2] model.

Compositionality alleviates the problem of state explosion by enabling us to substitute a detailed cardiac model, which is not amenable to verification, by an abstract model of lower complexity. Compositionality entails reasoning about a complex system in terms of its components, also known as subsystems. The electrophysiological behavior of the heart under the influence of an ICD is modeled using two subsystems: a detailed cardiac model H and a detailed computational model D of the ICD. The composed model, denoted by $(H \times D)$, captures the electrical behaviors of the heart induced by the ICDs control algorithms. The process of abstraction leads to a spectrum of choices for H and D. Consider H' and D' are the abstraction of heart and device model, respectively. Due to the larger state-space of its subsystem, $(H \times D)$ may not be amenable to tractable verification. If the abstract models are approximately equivalent to the detailed models with respect to verifying the property of interest, then establishing the safety of the composed system $(H' \times D')$ amounts to verifying $(H D)$ modulo some bounded error. The notion of equivalence that supports such substitutivity arguments is called bisimilarity, see Definition 4.12 on page 37 of [7].

In [4], we use *Timed Simulation Equivalence* between their detailed and abstract cardiac models for compositional reasoning. The proof of equivalence was derived manually. When applied to cardiac models with real-valued states, inputs, and outputs, bisimilarity is relaxed to account for small errors in the observed outputs of the two models. H is said to be approximately bisimilar to H' with precision , denoted by $H \cong_\delta H'$, if any state-transition performed by H can be matched by a state transition of H' that results in an output

error of at most δ, and vice-versa [8].

Since the cardiac model is composed with the ICD model using feedback, the output error incurred by substituting H by H' or substituting D by D'tends to get amplified. For such feedback-based composed systems, approximate bisimimulation expresses the Input-to-Output Stability (IOS) properties of the subsystems. Compositional reasoning can be performed after establishing approximate bisimulation equivalences between the subsystems. Proving approximate bisimulation between two given dynamical systems involves finding Bisimulation Functions (BFs). BFs are Lyapunov-like contractive functions of a pair of states of the two systems that i) bound the output difference observed for the two states and ii) decay, along all trajectories that are at the two states at any given point in time. Level sets of BFs define forward invariants: two trajectories initialized within the level set remain within the set for all time. We have devised a *Sum-of-Squares* optimization-based automated proof technique [9], [10], [11] for computing BFs that prove IOS-based approximate bisimulation. Compositionality arguments for feedback-based systems $H \times D$ and $H' \times D'$ can be made as follows. Suppose we compute i) a BF S_H between the models H and H' that characterizes IOS between the subsystems and ii) a BF S_D between D and D' that characterizes IOS between the subsystems. The *Small Gain Theorem* [12] provides the Small Gain Condition that must be satisfied by S_H and S_D such that they can be linearly composed to obtain a BF between $H \times D$ and $H' \times D'$, rendering the two composed systems to be approximately bisimilar.

III. Models of the Cardiac Action Potential

Hundreds of *physiological* models of the cardiac action potential have been developed over the past decades and they have been instrumental to furthering our understanding of how specific cellular processes affect a variety of phenomena including electrical wave propagation and arrhythmia as well as the effects of drugs. Existing models are derived almost exclusively from experimental data under a variety of environmental conditions from a variety of species [13]. These models, which are comprised of tens of variables and hundreds of parameters tend to be very complex which make them mathematically unidentifiable and inestimable and are therefore difficult to validate and analyze [14], [2].

An alternative, and complementary approach compared to these complex models, is to use *phenomenological* models which are designed to represent specific, often macroscopic phenomena (e.g., rate dependence of action potential (AP) duration) [15], [16], [17]. Phenomenological models are designed to reproduce one (or two) specific phenomena(on) very well, and are: simplistic, computationally efficient, and sometimes amenable to analytical approaches. However, unlike ionic models, phenomenological models do not provide a direct link to physiologically meaningful model parameters derived experimentally. Therefore phenomenological models provide only limited mechanistic insight, and are not amenable for reproducing numerous phenomena, nor can they be easily extended.

Parsimonious Model of Rabbit Action Potential

Recently, we have developed a *hybrid* physiological-phenomenological model which addresses many of the limitations listed above. We call this model a *parsimonious* model of the rabbit action potential. A model is considered parsimonious if it accomplishes a desired level of explanation or prediction with as few parameters as possible. For this model we choose the desired level of prediction to be the reproduction of experiments designed to capture well-known and important action potential phenomena: 1) steady-state sodium current inactivation as determined from voltage clamp experiments; 2) action potential depolarization in single cells; 3) recovery of action potential excitability in single cells; and 4) action potential depolarization dynamics during propagation in the whole heart. All the experimental data used for model calibration were measured from rabbit ventricular myocytes/tissue under nearly identical and physiological conditions.

First, we ensured that the model was identifiable and estimable given the experimental protocols [18]. Next, we calibrated the model to match the experimental data, and ensured that it reproduced the desired phenomena. Finally, we showed that the model could reproduce several important *emergent* phenomena including beat-to-beat cellular alterations and unstable spiral waves. Under some conditions, unstable spiral waves in this model give rise to continuous formation of new spiral waves (i.e., *spiral wave breakup*) which is thought to be the underlying cause of cardiac fibrillation and sudden cardiac death.

Parsimonious Rabbit Action Potential Model Equations

The two most important membrane currents for cardiac excitability are the rapid sodium current (I_{Na}) and the rectifying potassium current (I_K), which are both highly nonlinear functions of transmembrane potential (V_m). I_{Na} is responsible for the rapid all-or-none depolarization of the AP upstroke, and I_K is responsible for maintaining the resting potential near -85 mV.

Modeling I_{Na}:: The equation of I_{Na} current is formalized by Hodgking-Huxely (HH) [19] and modified by Beeler and Reuter [20]:

$$I_{Na} = g_{Na} m^3 h (V_m - E_{Na}) \tag{1}$$

where V_m is the action potential, g_{Na} is the maximal conductance of I_{Na}, m (fast activation), h (fast inactivation) and j (slow inactivation) are gating variables, and E_{Na} is the Narnst equilibrium potential for sodium. The dynamics of the gating variables are of the following form:

$$\dot{y} = \alpha_y(1 - y) - \beta_y y \equiv \frac{y_\infty - y}{\tau_y} \tag{2}$$

where y represents the gating variable, $\alpha_y(V_m)$ and $\beta_y(V_m)$ represent the voltage-dependent on and off rate constant, respectively, $y_\infty(V_m)$ and $\tau_y(V_m)$ are the voltage-dependent

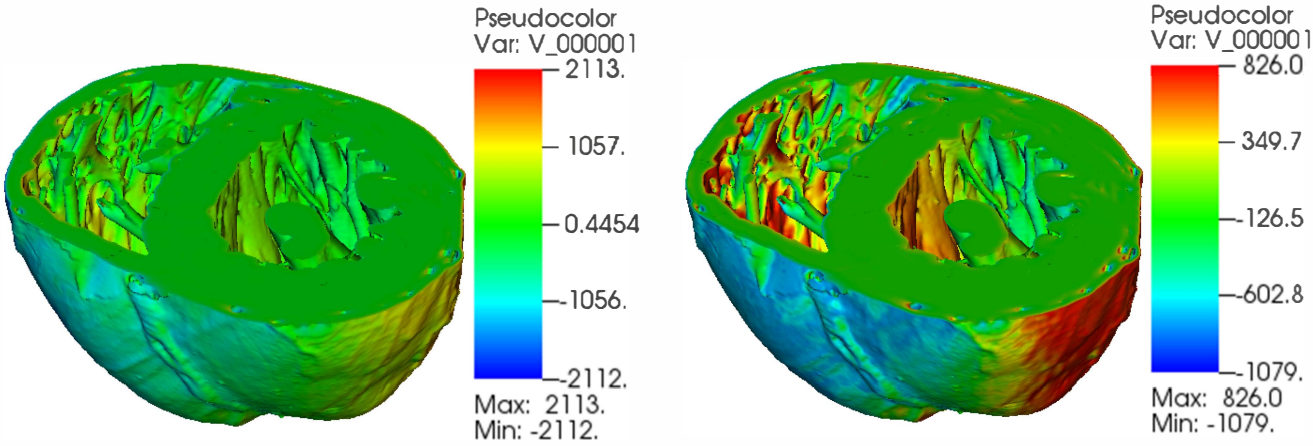

Fig. 3: Transmembrane potential (mV) in a rabbit heart after a strong defibrillation shock (50V/cm) after 1 ms of shock application. Left frame: nonelectroporating cardiac tissue. Right frame: electroporating cardiac tissue. Note the large difference between the two color scales in the left and right frames.

steady state fraction of activation or inactivation and time constant, respectively. The detail of this model can be found in [1].

Modeling I_K: The re-polarization of AP is captured by I_K current, which is described as following equation:

$$I_K = g_K e^{-b(V_m - E_K)}(V_m - E_K) \tag{3}$$

where g_K is the maximum conductance of I_K, b is the parameter controlling AP shape, E_K is the reversal potential for potassium. The nominal parameters values can be found in Table 1 of [21].

IV. Electrocardiac Defibrillation Modeling and Simulations

Fibrillation in the electrocardiac signals as a leading cause of death is commonly treated with a defibrillation electrical shock. We study the mechanism of defibrillation whereby the chaotic signals are disrupted and the signals are reset to normal. The defibrillating electrical shock gives rise to accumulated charges near blood vessels within the heart and also on the surface of the heart. These charges are called virtual electrodes, and are expected to disrupt the turbulent or chaotic electrical signals of the fibrillating state. We are concerned with the interactions among:

- 3D scroll waves and their centers (1D filaments which are driving sources of ventricular fibrillation) as a building block of a fibrillating state [22], [23]
- Charges left at heart tissue surfaces after electrical shock (virtual electrodes) [24], [25], [26]
- Causes for defibrillation failure (post shock reentrant wave fronts in the cardiac interior) [27]
- Influence of LEAP (Low Energy Anti-fibrillation Pacing) [28], [29], [30]

Our goal is a full simulation study of a rabbit heart ventricle, with scroll waves, defibrillating single strong or multiple weak electrical shocks and virtual electrodes associated with blood vessels and the heart surfaces.

We have developed a sharp boundary numerical method to support the defibrillation studies [31]. It solves the bidomain equations, representing the cardiac tissue as composed of intracellular and extracellular tissues, as is needed in defibrillation modeling. The sharp boundaries are defined by the narrow blood vessels and require high resolution to describe their effect. The sharp boundary bidomain model has been applied to defibrillation studies in a slab geometry and some of the features of this code are illustrated in [31]. The larger vessels are well resolved while the smallest blood vessel, with 4 mesh cells in diameter, is marginally resolved.

We will use the two codes in our study: our ElectroCardiac (Stony Brook University) [31] and the well studied Chaste (University of Oxford) [32], [33]. The ElectroCardiac code is based on the finite volume discretization of the bidomain equation, using sharp boundary method. The Chaste (Cancer, Heart and Soft Tissue Environment) is an open source software based on the finite element method and used for the Oxford tetrahedral rabbit heart mesh. We have improved the membrane current model in the Chaste code to include the experimentally observed electroporation currents during strong defibrillating shocks [34], [35], [36]. Fig. 3 shows the influence of the electroporation, representing the saturation of the shock-induced transmembrane voltage, needed for a strong shock defibrillation. The defibrillation electrical shock creates the virtual electrodes in realistic rabbit heart geometry. The transmembrane potential with the electroporation model is relatively constant in time during the period of shock application, as illustrated by the similarity of Fig. 3 right (1 ms) and Fig. 4 (2 ms).

V. Regular Expressions for Irregular Rhythm

Medical devices seamlessly blend signal processing (SP) algorithms with decision algorithms such that the performance

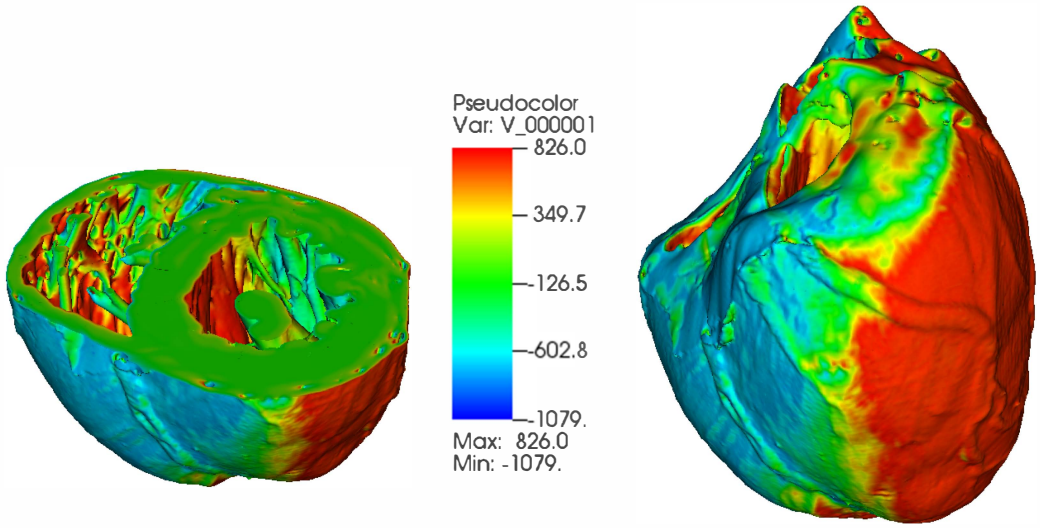

Fig. 4: Transmembrane potential (mV) in a rabbit heart after the defibrillation shock (50V/cm) is applied for 2 ms (electroporating cardiac tissue

and correctness of the latter critically depends on that of the former. As such, analyzing a device's decision making in isolation of SP offers at best an incomplete picture of the device's overall behavior. For example, an Implantable Cardioverter Defibrillator (ICD) will first perform Peak Detection (PD) on its input signal, also known as an electrogram. The output of PD is a timed boolean signal where a 1 indicates a peak, i.e., a local maximum or minimum, which is used by the downstream discriminators to differentiate between fatal and non-fatal rhythms.

The detected electrogram peaks indicate when a heartbeat occurs, and the accuracy of PD directly affects the correctness of the discriminators' decisions. Over-sensing (too many false peaks detected) and under-sensing (too many true peaks missed) can be responsible for as much as 10% of an ICD's erroneous decisions [37], as they lead to inaccuracies in estimating the heart rate.

Motivated by the desire to verify ICD algorithms for cardiac arrhythmia discrimination, we seek a unified formalism for expressing and analysing the SP and discrimination tasks commonly found in ICD algorithms. We focuses on peak detection because of the important role it plays in arrhythmia discrimination, and because PD is a fundamental SP primitive in its own right.

The signals we analyze (electrograms) have time-varying frequency content, thereby motivating us to consider the PD problem in the wavelet domain [38]. We are therefore working on general, wavelet-based characterizations of peaks in time-series data (i.e., signals), with and without a blanking period : a period of time, typically defined by a cardiologist, during which at most one peak can occur.

An implementation of our wavelet-based characterizations of peaks would require one to store different values of the input (wavelet-domain) signal, and to perform complex numerical operations on the signal. It is therefore unlikely that these peak characterizations can be expressed succinctly (if at all) in temporal logic (TL) [39], despite the increasingly sophisticated variety of TLs that have appeared in the literature. This is the case even if we use a quantitative semantics [40].

We are therefore working on proposing the use of Quantitative Regular Expressions (QREs) to describe wavelet-based peak detection. QREs are a formal language based on classical regular expressions for specifying complex numerical queries on data streams [41]. QREs' ability to interleave user-defined computation at any nesting level of the underlying regular expression, and the fact that their design is parameterized by the domain of their input data (time, frequency or other domains), gives them significant expressive power. We will show that our wavelet-based peak detection algorithms are easily expressed in QREs. We will also formalize a commercial peak detector as a QRE. This will allow us to readily study the accuracy and sensitivity of the resulting algorithms on real patient electrograms.

As ongoing work, we have used QREs to capture a number of ICD discriminators. This makes us highly confident that QREs will serve as the unifying formalism we seek for expressing and analyzing the SP and discrimination tasks found in ICD algorithms.

In summary, our main contribution will be the following:

- We will present general wavelet-based characterization of peaks along with two PD algorithms based on this characterization.
- We will show that our wavelet-based PD algorithms, and a commercial PD algorithm from Medtronic Inc. found in defibrillators currently on the market,, are easily expressible in Quantitative Regular Expressions (QREs).
- Finally, we study the accuracy and sensitivity of the resulting QRE-based PD algorithms on real patient data and show that the wavelet-based algorithm peakWPM outperforms the other two PD algorithms, yielding results

that are on par with those provided by a cardiologist.

VI. Formal Verification of Cardiac Alternans using δ-Decidability

An important component of cardiac electrodynamic modeling is the ability to understand and predict qualitative changes that take place in the dynamics as model parameters are varied [42], [43], [44]. One well-known change involves a transition to *alternans*: a phenomenon characterized by a period-doubling bifurcation where, while cells are paced at a constant period, their response has different dynamics between even and odd beats, with one long action potential following a short one [45]. Alternans are known to destabilize waves [46] and initiate re-entrant waves and represent an important physiological indicator of an impending life-threatening arrhythmia such as ventricular fibrillation [47], [48].

About 100 mathematical models [49] have been developed to recreate and study, to varying degrees of complexity, the electrical dynamics of a cardiac cell (i.e., cardiomyocyte). A particularly appealing one in terms of its mathematical tractability is the model of Mitchell and Schaeffer [50], which represents the cellular electrodynamics using only two state variables: a voltage variable v that describes the transmembrane potential, and a gating variable h that describes the internal ionic state of the cell.

In [51], we present a bifurcation analysis of electrical alternans in the two-current Mitchell-Schaeffer (MS) cardiac-cell model[1] using the theory of δ-decidability over the reals [52]. The bifurcation analysis we perform determines, for each parameter τ of the MS model, the *bifurcation point* in the range of τ such that a small perturbation to this value results in a transition from alternans to non-alternans behavior. To the best of our knowledge, our analysis represents the first formal verification of non-trivial dynamics in a realistic cardiac-cell model.

Our approach to this problem rests on encoding alternans-like behavior in the MS model as an 10-mode, multinomial hybrid automaton (HA). For each MS model parameter, we then apply a sophisticated, guided-search-based reachability analysis to this HA to estimate ranges for both alternans and non-alternans behavior. The bifurcation point separates these two ranges, but with an uncertainty region due to the underlying δ-decision procedure. This uncertainty region, however, can be reduced by decreasing δ at the expense of increasing the model exploration time. Experimental results are provided that highlight the effectiveness of this method.

VII. Conclusion

In this paper, we present a brief summary of current research progress in the *CyberCardia* project. The goal of the project is to develop the state of the art techniques for system verification and cardiac therapies based on the use of formal methods and closed-loop control and verification. We envision the development of a true *in silico* design methodology for medical devices that can be used to speed the development of new devices and to provide greater assurance that their behavior matches designer intentions, and to pass regulatory muster more quickly so that they can be used on patients needing their care. The fundamental research directions we are pursuing to achieve our goal and vision are: 1) accurate modeling of patient's heart and device, 2) specifying safety property for appropriate therapy in formal language and 3) Closed-loop verification and validation of devices using compositional, quantitative and approximate reasoning. In this paper, we summarize the preliminary research in 1) approximate and compositional reasoning for closed-loop verification of cardiac devices, 2) a parsimonious model of cardiac electrophysiology, 3) bidomain model of cardiac defibrillation, 4) formal specification language to express peak detection algorithms of cardiac devices, and 5) formal verification of cardiac alternans. As per ongoing research activities, we are continually working on the development of personalize patient heart model, model-based clinical trial, devising an algorithm to discriminate fatal and non-fatal arrhythmia to administer appropriate therapy and reachability-based safety verification of the device and heart model.

[1] A third current I_s, which is not intrinsic to the MS model, is used to stimulate the cell to produce an action potential.

Acknowledgments

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