StonyCam: a Formal Framework for Modeling, Analyzing and Regulating Cardiac Myocytes *

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Abstract. This paper presents a formal framework, experimental infrastructure, and computational environment for modeling, analyzing and regulating the behavior of cardiac tissues. Based on the theory of hybrid automata, we aim at providing suitable tools to be used in devising strategies for the pharmacological or other forms of treatment of cardiac electrical disturbances.

1 Introduction

Atrial fibrillation (Afib) is an abnormal rhythm originating in the upper chambers of the heart afflicting 2-3 million Americans and whose incidence rises with increasing age. Due to the "graying" of our population, 12-16 million Americans may be affected by 2050. Not only is its incidence of epidemic proportions, its morbidity is also significant. Among possible sequelae of the disease are thrombi in the fibrillating atria and emboli released to the pulmonic and systemic circulations. Although its importance to public health cannot be questioned, therapies remain problematic. Persistence of the abnormal rhythm results in electrical remodeling of the atria reinforcing its existence. Drugs are frequently ineffective and because of their lack of selectivity can induce arrhythmias themselves. Frequently, electrical cardioversion is tried which is not uniformly successful. Finally, for intractable Afib, the abnormal reentrant pathways are mapped and the tissue is radiofrequency ablated, which may result in a non-functional atrium.

This is a humbling observation from an engineering point of view, highlighting the complexity of the heart and the need for reliable analysis and prediction *in-silico* tools for cardiac behavior. Such tools would be of great use in devising

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rational strategies for pharmacological or other intervention in cardiac electrical disturbances such as Afib. During the last two years, we have worked (see Figure 1) towards a formal framework, experimental infrastructure, and computational environment for modeling, analyzing and controlling the behavior of excitable cells such as cardiac myocytes.

In this paper we provide a brief overview of the results obtained so far and discuss directions for future work. We start in Section 2 by describing how we modeled the behavior of excitable tissue using networks of hybrid automata (HA). With respect to the classical approach which uses systems of non-linear ordinary differential equations HA models, by combining discrete and continuous processes, are able to successfully capture the morphology of the excitation event (action potential) of cardiac cells [22]. In section 3, we show how this approach also enhances the analysis capabilities of this biological phenomena. In particular it renders possible large-scale simulation of cardiac-cell networks and the detection of emergent behavior such as fibrillation [9]. Once such a behavior has been identified, one could use electrical therapy in order to restore normal physiological function. This means that any time a critical behavior is predicted, depending on the type of spatial pattern, the right repair strategy is performed either at low-level, e.g. by introducing an artificial inhibitor or catalyst agent to regulate the ion channels of cell membranes, or at higher-level, e.g. by resetting the behavior of a group of myocytes forcing a global correct behavior. We are investigating solutions from the area of the networks of dynamical elements, where distributed synchronization is obtained by dividing the whole network into groups or regions of fully synchronized elements [18] while elements from different groups are not necessarily synchronized and can be of entirely different dynamics [25]. Section 4 offers our concluding remarks and directions for future work.

2 Modeling Excitable Cells Using Hybrid Automata

An excitable cell has the ability to propagate an electrical signal, known at the cellular level as the *Action Potential* (AP), to neighboring cells. An AP corresponds to a difference in electrostatic potential between the inside and outside of a cell, and is caused by the flow of ions across the cell membrane. The major ion species involved in this process are sodium, potassium and calcium; they flow through multiple voltage-gated ion channels as pore-forming proteins in the cell membrane. Excitation disturbances can occur in the behavior of these ion channels at the cell level, or in the propagation of the electrical waves at the cell-network level.

Generally, an AP is an externally triggered event: a cell fires an action potential as an "all-or-nothing" response to a supra-threshold stimulus, and each AP follows the same sequence of phases and maintains the same magnitude regardless of the applied stimulus. During an AP, generally no re-excitation can occur. The early portion of an AP is known as "absolute refractory period" due to its non-responsiveness to further stimulation. The "relative refractory period" is

Fig. 1. StonyCam Group from left to right: Ezio Bartocci, Flavio Corradini, Emanuela Merelli, Scott Smolka, Oliviero Riganelli, Radu Grosu

the interval immediately following during which an altered secondary excitation event is possible if the stimulation strength or duration is raised. Examples of excitable cells are neurons, cardiac myocytes and skeletal muscle cells.

Despite differences in AP duration, morphology and underlying ion currents, the following major AP phases can be identified across different species of excitable cells: *resting*, *rapid upstroke*, *early repolarization phase*, *plateau and late repolarization*, and *final repolarization* (identical to the resting phase due to the cyclic nature of an AP). The resting state features a constant transmembrane potential (difference between the inside and outside potential of the cell) that is about -80 mV for most species of cardiac cells; i.e. the membrane is polarized at rest. During the AP upstroke, the transmembrane potential rapidly changes, from negative to positive; i.e. the membrane depolarizes. This is followed by an early repolarization phase. A slower, plateau phase is present in most mammalian action potentials, during which calcium influx facilitates muscle contraction. After this phase, a faster final repolarization brings the potential back to the resting state.

The classical mathematical model [4, 14, 11] of excitable cell involve complex systems of nonlinear differential equations. Such models not only impair formal analysis but also impose high computational demands on simulations, especially in large-scale 2D and 3D cell networks. To address this state of affairs, we have developed *Cycle-Linear Hybrid Automata* (CLHA) models (see Figure 2). The CLHA formalism was designed to be both abstract enough to admit formal analy-

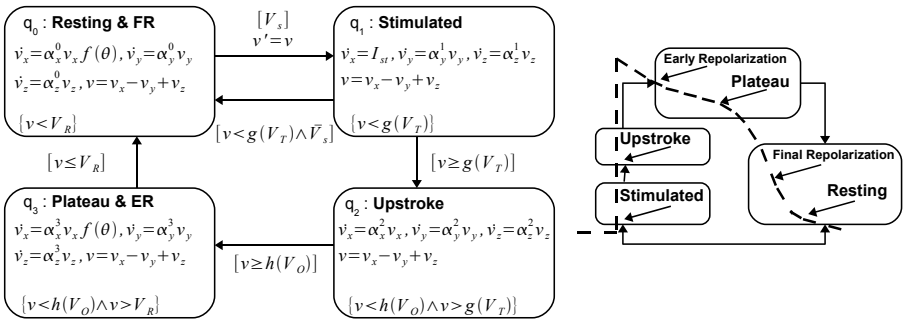

Fig. 2. CLHA and the corresponding Action Potential

sis and efficient simulation and expressive enough to capture the AP morphology and restitution properties exhibited by classical non linear excitable-cell models. The basic idea behind the CLHA model is the observation that, during an AP, an excitable cell cycles through four basic modes of operations - resting, stimulated, upstroke, early repolarization, plateau final repolarization - and the dynamics of each mode is essentially linear and time-invariant. To capture possible non linear, frequency-dependent properties such as restitution, the CLHA model is equipped with one-cycle memory of the cells voltage and per-mode parameters of the current cycle's linear time invariant system of differential equations are updated according to this voltage. Consequently, the models behavior is linear in any one cycle but appropriately non linear overall. For more details on CLHA, we refer the reader to [22]. A CLHA approximates AP and other bio-electrical properties of several representative excitable-cell types, with reasonable accuracy [21, 22, 10]. This derivation was first performed manually [21, 22]. In [10], we showed that it is possible to automatically learn a much simpler cycle-linear hybrid automaton for cardiac myocytes, which describes their action potential up to a specified error margin. Moreover, as we have shown in [2, 3], one can use a variant of this model [21, 20, 23, 24, 22] to efficiently (up to an order of magnitude faster) and accurately simulate the behavior of myocyte networks, and, in particular, induce spirals and fibrillation. The term *Cycle-Linear* is used to highlight the cyclic structure of CLHA, and the fact that while in each cycle they exhibit linear dynamics, the coefficients of the corresponding linear equations and mode-transition guards may vary in interesting ways from cycle to cycle. These CLHA models were found to capture essential cell features, are amenable to formal analysis, and exhibit, respect to the classical models, a nearly ten-fold speedup in a simulation of 400x400 cell network.

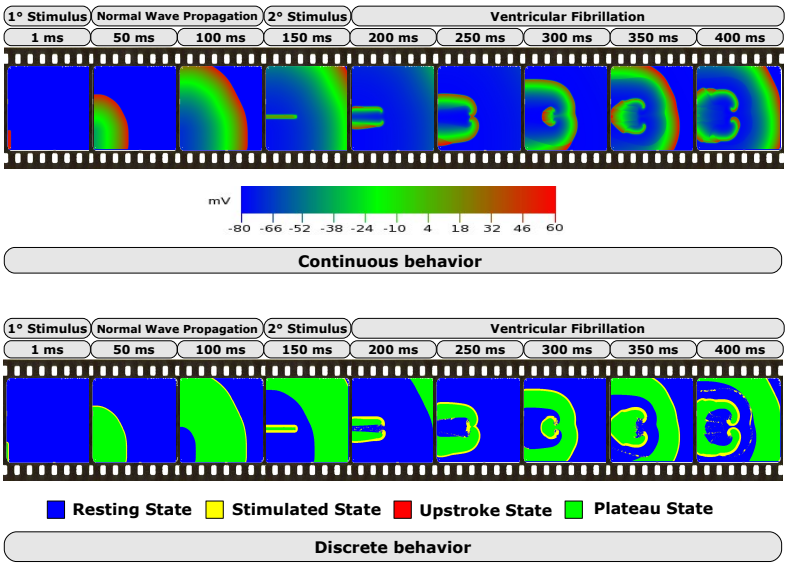

Fig. 3. Simulation of continuous and discrete behavior of CLHA network.

3 Simulation and Analysis of Networks of Cardiac Myocytes

3.1 Simulation

In order to simulate the emergent behavior of cardiac tissue, we have developed CellExcite [3], a CLHA-based simulation environment for excitable-cell networks. CellExcite allows the user to sketch a tissue of excitable cells, plan the stimuli to be applied during simulation, and customize the arrangement of cells by selecting the appropriate lattice. Figure 3 presents our simulation results for a 400×400 CLHA network. The network was stimulated twice during simulation, at different regions. The results we obtain demonstrate the feasibility of using CLHA networks to capture and mimic different spatiotemporal behavior of wave propagation in 2D isotropic cardiac tissue, including normal wave propagation (1-150 ms); the creation of spirals, a precursor to fibrillation (200-250 ms); and the break-up of such spirals into more complex spatiotemporal patterns, signaling the transition to ventricular fibrillation (250-400 ms).

As can be clearly seen in Figure 3, a particular form of discrete abstraction, in which the action potential value of each CLHA in the network is *discretely abstracted* to its corresponding mode, faithfully preserves the network's waveform and other spatial characteristics. Hence, for the purpose of learning and detecting spirals within CLHA networks, we can exploit discrete mode-abstraction to dramatically reduce the system state space.

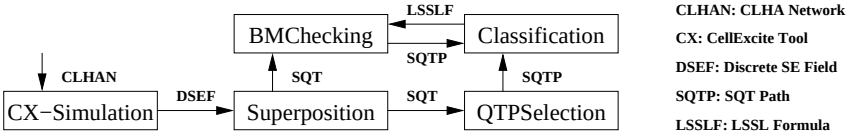

Fig. 4. Overview of our method for learning and detecting the onset of spiral waves.

3.2 Detecting Emergent Behavior

One of the most important and intriguing questions in systems biology is how to formally specify *emergent behavior in biological tissue*, and how to efficiently predict and detect its onset. A prominent example of such behavior is electrical *spiral waves* in spatial networks of cardiac myocytes (heart cells). Spiral waves of this kind are a precursor to a variety of cardiac disturbances, including *atrial fibrillation*, an abnormal rhythm originating in the upper chambers of the heart. Moreover, the likelihood of developing atrial fibrillation increases with age.

In [9], we addressed this question by proposing a simple and efficient method for learning and automatically detecting the onset of spiral waves in cardiac tissue (see Figure 4). Underlying our method is a *linear spatial-superposition logic* (LSSL), which we have developed for specifying properties of spatial networks. LSSL is discussed in greater detail below. Our method also builds upon hybrid-automata, image-processing, machine-learning and model-checking techniques to first learn an LSSL formula (LSSLF) that characterizes such spirals. The resulting LSSLF is then automatically checked against a *quadtree* representation [17] of the scalar electric (SE) field, produced by simulating a hybrid automata network modeling the myocytes, at each discrete time step. The quadtree representation is obtained via hybrid abstraction [19] and hierarchical superposition of the elementary units within the field.

A key observation concerning our simulations (see Figure 3) is that a particular form of hybrid abstraction, in which the action potential value of each CLHA in the network is *discretely abstracted* to its corresponding mode, faithfully preserves a spiral's topological characteristic; i.e. its shape. Hence, for the purpose of learning and detecting the onset of spirals within CLHA networks, we can exploit hybrid abstraction to dramatically reduce the system state space. A similar hybrid abstraction is possible for voltage recordings in live cell networks, but this is outside the scope of this paper.

The state space of a 400×400 CLHA network is still prohibitively large even after applying the above-described hybrid abstraction: it contains $4^{160,000}$ states, as each CLHA has four modes! To combat this state explosion, we use a spatial abstraction inspired by [12]: we regard the state of each automaton as a probability distribution and define the *superposition* of a set of states as the probability that an arbitrary state in this set has a particular mode. By successively applying superposition to the network, we obtain a tree structure, the root of which is the state-superposition of the entire CLHA network, and the leaves of which are the states of the individual CLHA. The particular superposition tree structure we employ, quadtrees, is inspired by image-processing techniques [17]. We shall refer to quadtrees obtained in this manner as *superposition-quadtrees* (SQT).

Our LSSL is an appropriate logic for reasoning about *paths* in superposition-quadtrees, and the spatial properties of a CLHA network in which we are interested, including spirals, can be cast in LSSL. For example, we have observed that the presence of a spiral can be formulated in LSSL as follows: Given an SQT, is there a path from its root leading to the core of a spiral? Based on this observation, we build a machine-learning classifier, the training-set records for which correspond to the probability distributions of the nodes along such paths. Each node distribution corresponds to an attribute of a training-set record, with the number of attributes bounded by the depth of the SQT. An additional attribute is used to classify the record as either spiral or non-spiral. For spiral-free SQTs, we simply record the path of maximum distribution.

For training purposes, we use the CellExcite simulator [2, 3] to generate, upon successive time steps, snapshots of a 400×400 CLHA networks and their hybrid abstraction; see Figures 4,3. Training data for the classifier is then generated by converting the hybrid-abstracted snapshots into SQTs and selecting paths leading to the core of a spiral (if present). The resulting table is input to the decision-tree algorithm of the Weka machine-learning tool suite [8], which produces a classifier in the form of a predicate over the node-distribution attributes.

The syntax of LSSL is similar to that of linear temporal logic, with LSSL's Next operator corresponding to *concretization* (anti-superposition). Moreover, a (finite) sequence of LSSL Next operators corresponds to a path through an SQT. The classifier produced by Weka can therefore be regarded as an LSSL formula. The meaning of such a path is that of a magnifying glass, which starting from the root, produces an increasingly detailed but more focused view of the image. This effect is analogous to *concept hierarchy* in data mining [13] and arguably similar to the way the brain organizes knowledge: a human can recognize a word or a picture without having to look at all of the characters in the word or all of the details in the picture, respectively.

We are now in a position to view spiral detection as a bounded-model-checking problem [5]: Given the SQT Q generated from the discrete scalar electric field of a CLHA network and an LSSL formula φ learned through classification, is there a finite path $\pi \in Q$ satisfying the LSSL formula φ, i.e. $\pi \models \varphi$? We use this observation to check in real time, i.e. at each discrete simulation time step, whether or not a spiral has been created. More precisely, the LSSL formula we use states that no spiral is present, and we thus obtain as a counterexample one or all the paths leading to the core of a spiral. In the latter case, we can identify the number of spirals in the scalar field and their actual position.

4 Conclusion

The StonyCam collaboration has been a highly fruitful one to date, resulting in the development of HA-based models of complex networks of excitable cells, the CellExcite simulator for such networks, and techniques for learning and detecting emergent behavior (spirals) in cardiac tissue. Much work remains to

be done, especially in the engineering of distributed coordination and control algorithms for myocyte networks.

In other ongoing and future work, analyzing large-scale networks of cardiac myocytes requires a flexible and powerful simulation environment. Along these lines, we are investigating the use of multiagent systems (MAS) and graphical processing units (GPU). MASs would offer us increased flexibility while GPUs would offer us increased computational power. A MAS is an autonomous software entity able to perceive and react to the changes of the surrounding environment. A MAS consists of a collection of interactive agents and a set of coordination rules. It constitutes a suitable benchmark for simulating the actions and interactions of autonomous real entities in a network to assess their effects on the system as a whole. This programming paradigm allows to easily add new entities and to modify the behavior of existing ones even in a zooming-in and zooming-out approach [6]. Following [7, 1], we would like to investigate a distributed coordination model based on simulation-time model checking for the online prediction of critical behaviors in cardiac tissue.

Regarding GPUs, they implement a number of graphical primitive operations in a very efficient manner. The use of graphics hardware has recently shown promising results in massive simulations of complex behavioral models [15] and in general-purpose stream computations [16]. We would like to explore their computational power as well in our simulation environment for cardiac tissue.

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