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Nonlinear Hybrid Automata Model of Excitable Cardiac Tissue (Benchmark Proposal)

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Abstract

Implantable cardiac devices like pacemakers and defibrillators are life-saving medical devices. To verify their functionality, there is a need for heart models that can simulate interesting phenomena and are relatively computationally tractable. In this benchmark we implement a model of the electrical activity in excitable cardiac tissue as a network of nonlinear hybrid automata. The model has previously been shown to simulate fast arrhythmias. The hybrid automata are arranged in a square n-by-n grid and communicate via their voltages. Our Matlab implementation allows the user to specify any size of model n, thus rendering it ideal for benchmarking purposes since we can study tool efficiency as a function of size. We expect the model to be used to analyze parameter ranges and network connectivity that lead to dangerous heart conditions. It can also be connected to device models for device verification.
Category: academic **Difficulty:** high

1 Context and origins

The human heart is a complex system and its scientific study involves multiple aspects: electrical activity is generated and spreads throughout the heart, which determines the mechanical contractions of the myocardium (the heart muscle), which then shapes the blood flow in and out of the heart. The electrical activity itself is determined by mechanical properties of the myocardium and by the complex ionic exchanges between each cell of the heart and its neighboring cells. In this benchmark, we implement a hybrid system model of cardiac tissue that aims to simulate the *generation and spread of electrical activity in the heart*.

Models of the electrical properties of the heart allow us to use simulation and verification for two important applications: first, we can better understand what gives rise to certain dangerous conditions in the heart, such as tachycardia (a class of heart rhythms with dangerously elevated rates). Specifically, what are the parameter ranges, input sequences and cell-to-cell connectivity that increase the likelihood of such conditions arising? This is particularly important given the great variability in physiology between people.

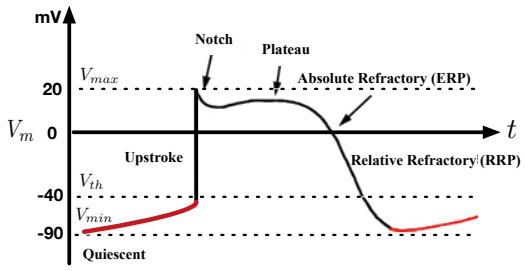


Figure 1: Phases of an action potential (AP). AP figure from [8].

A second use of heart models is in the testing and verification of cardiac medical devices. For example, a model of an Implantable Cardioverter Defibrillator (ICD; an ICD stops fatal tachycardias) may be composed with a model of cardiac electrophysiology, and properties of the ICD may then be tested or even verified in some cases [2].

Relevance. The model of cardiac tissue that we implement in this benchmark is based on *cellular automata (CA)*, which we formalize as nonlinear hybrid automata. Cellular automata have been widely used for modeling biological systems [6]. The model used in this benchmark was described in [9], where the authors demonstrated its ability to simulate meaningful cardiac phenomena such as ectopics (irregular isolated beats) and re-entrant tachycardias (which is a common class of potentially fatal tachycardias). It has also been used to study the measurement process of ICDs. Our implementation of this model follows the description in [9] and modifies it slightly to make the resulting waveform more realistic, as described in the appendix.

Clarity. We provide a Matlab implementation that can be run out of the box. It allows the user to select the size of the model (how many cells), and easily choose values for all the parameters. In particular, the user can model inhomogeneous tissue that is prone to disordered and dangerous rhythms.

Verification advantages. A model instance of size n (with n^2 cells) has $18n^2$ parameters, some of which are time varying. Not all values of these parameters will lead to interesting phenomena like tachycardia. Rechability analysis can be used to study which parameter values lead to phenomena that can be formulated as invariants. Also, recent work [2] shows that this heart model, composed with an ICD model, admits finite bisimulations, which opens the way to the development of model checkers for more complex properties. In the meantime, the high-dimensionality of the model and its complexity (see Section 5) suggest that stochastic falsification will play a prominent role at first.

2 Brief Description

Cardiac cells or *myocytes* are an example of *excitable cells (ECs)*. The defining characteristic of ECs is that if the cross-membrane voltage V_m of its neighbors increases (a process known as *depolarization*), then its own cross-membrane voltage will increase as well. If the voltage reaches a certain threshold V_{th} (which may be cell-specific), then the voltage rises quickly then dies down, in a characteristic shape known as the *action potential (AP)*. See Fig. 1. The AP is usually divided into 7 phases as shown in Fig. 1.

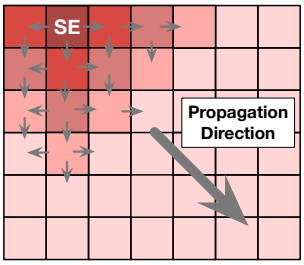


Figure 2: Cardiac tissue is modeled as a 2D grid of cells. *SE* is a self-exciting cell. After SE depolarizes, the neighboring cells depolarize as well. The delay in propagation is determined by the velocity of depolarization, how long the cell remains depolarized, the resistance to current flow between cells, and the current state of the neighboring cell. The chain reaction of depolarization causes an aggregate wave of AP propagation.

The triggering of an AP in a given cell contributes electric charge to its neighboring cells. If a neighbor's voltage in turn exceeds its own V_{th}, an AP is triggered in the neighbor, and so on across the myocardium. See Fig. 2. It is by this mechanism that electrical signals propagate through the myocardium as a moving wavefront. Note that in a *self-exciting* cell, this AP repeats itself periodically without external input from neighbors.

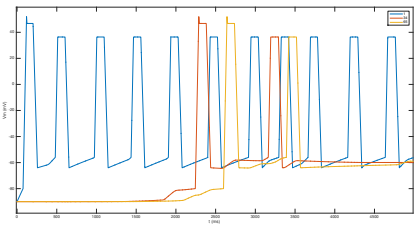
Each cell is modeled as a 7-mode nonlinear hybrid automaton with 2 continuous state variables and 18 parameters (some of which change on mode switches). The modes of the automaton map directly onto the phases of the AP. Automata are connected to each other through their voltages: specifically, voltage from a cell's neighbors affects the derivative of that cell's voltage. Details of the model are presented in the appendix.

3 Key Observations

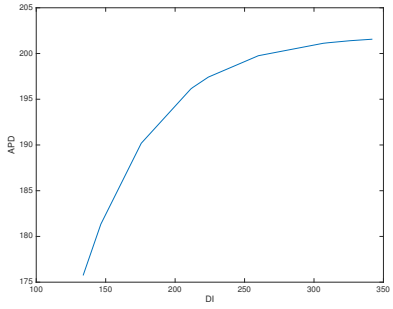
We start by showing a few outputs of simulating the model. Fig. 3a shows 3 APs from 3 non-contiguous cells in a 10-by-10 grid: a self-exciting cell (at position (1,1)) and two excitable cells from the middle of the grid, at positions (4,4) and (5,7). As can be seen the AP travels from the self-exciting cell (which is the first to depolarize) to its neighbors.

The restitution curve is an important feature of cardiac tissue, and is responsible for the non-linearity of this model. Broadly speaking, it gives the duration of the next AP, known as action potential duration (APD), as a function of the Diastolic Interval DI_{n-1} which lasts from the end of the previous AP and the current upstroke. We measured the successive (DI, APD) pairs for cell (1,1) and plotted the resulting curve. Fig. 3b shows that the simulated curve matches the shape of the experimentally obtained curves in vivo. Finally in Fig. 4 we show the progression of the electrical wave in an inhomogeneous tissue (i.e., whose resistance changes spatially) from three self-exciting cells in the lower left corner.

The first key observation is that the large number of parameters in this model ($18n^2$ for an n-by-n grid) makes it very challenging to select values that lead to desired phenomena. E.g., simply sustaining a propagating wavefront is not trivial: if we choose upstroke slopes too large, then the AP durations decrease progressively which can compromise propagation. If the upstroke velocities are too small on the other hand, cell voltages may never exceed the



(a) Three APs in a 10-by-10 grid showing propagation.



(b) The DI vs APD curve for a self-exciting cell in a 4-by-4 instantiation.

Figure 3: Sample outputs from model

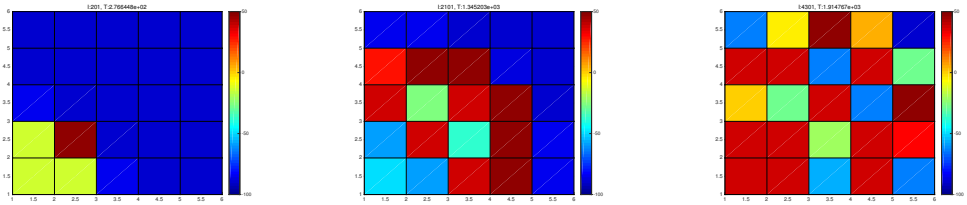


Figure 4: Three time snapshots of tissue, showing a depolarization wave propagating, left to right. Warmer colors indicate a more recent upstroke. Because the tissue is inhomogeneous, propagation does not proceed uniformly across the tissue, whence the observed eventual fractionation (last panel on the right).

depolarization threshold a second time and the tissue is electrically dead. This highlights the need for parameter synthesis in this model and others like it [4]. We also emphasize that obtaining desired phenomena is also a matter of neighborhood structure, and depend on the restitution curve.

Another observation is that in this model the transitions of the various automata can be extremely close in time, since cells that are electrically near will naturally synchronize with each other. This can create numerical issues for ODE solvers. E.g. with Matlab's ode45 (which implements Runge-Kutta (4,5) method), in mostly homogeneous tissue, a few mode switches were either doubly detected leading to fake transitions, or incorrectly reported as being duplicate and thus transitions were missed. We have written code to detect some of these cases, but we feel that such an issue is best dealt with by the solvers themselves, e.g. by the usage of verified integrators. Mode switches are also very frequent as cells go through their APs and this slows down simulation. E.g., on a 2.2 GHz, 16 GB Intel Core i7, simulating 6 seconds of a 6-by-6 grid took an average 872secs, and an 8-by-8 grid took 2252secs.

4 Sample properties

One important example of how the model can be used is to study the effect of the restitution curve's slope on the development of alternans. **Electrical alternans** is a condition in which the APD oscillates beat-to-beat between long and short. I.e., if APD_n is the APD of the n^{th} beat, then $APD_n > APD_{n-1}$ and $APD_{n+1} < APD_n$. The occurrence of alternans is related to

the shape of the restitution curve. Thus we may use the model to explore the effects of different shapes on the emergence of alternans in the model. **Ventricular fibrillation** is a potentially fatal condition in which the electrical activity of the heart is very disorganized. Because of the disorganized activity, the heart muscle does not contract in a unified, coordinated fashion. Rather, different parts of the muscle will contract at different times, resulting in poor blood flow to the body. If fibrillation persists, it is fatal. A rough indicator of fibrillation is a large temporal variance in the average upstroke rate between heart regions. Again we may analyze what leads to such variance.

5 Outlook

The current model can be extended in several directions. Expanding the neighborhood of cell-to-cell interaction via a weighting function [7] is a possible direction. We may also use more realistic single cell models, although this has to be carefully weighted against the resulting complexity.

The model we presented is a (network of) nonlinear hybrid automata. Current tools can perform some degree of reachability on HA, but the properties of interest are not restricted to invariants. On the practical/computational side, an n-by-n grid has 7^{n^2} modes with and $2n^2$ continuous state variables. Because of the theoretical and scalability issues, we expect test-based falsification tools like S-Taliro [3] and Breach [5] to play an important role in testing these systems. Such tools only need to simulate the model. Associated convergence results for hybrid systems [1] provide probabilistic guarantees about the tool's performance.

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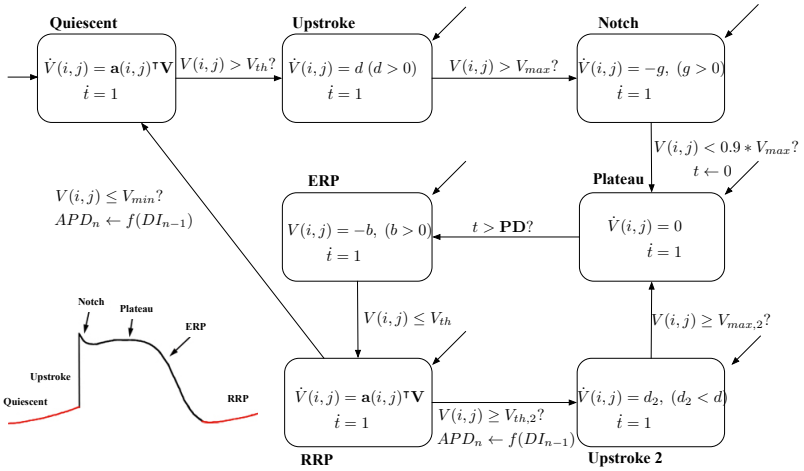

Figure 5: Hybrid model of one hybrid cellular automaton. AP figure from [8]. $V_{th,2} > V_{th}$, $V_{max,2} < V_{max}$. DI_n is the Diastolic Interval of n^{th} beat, and f is the restitution function which determines the APD for the subsequent cycle based on the DI of the current cycle.

A Appendix: Model description

Note: values for all thresholds and parameters are available in the accompanying code, see method generate_params of class MyocyteVisibleEP.

See Fig. 1. Initially, the cell is in a *quiescent*, polarized state where the membrane potential is at a *resting potential*. The typical resting potential is about $V_m = -90mV$. The complex interactions within a neighborhood of the cell allow the possibility that a net influx of current can occur within the cell causing V_m to rise. If V_m rises above a threshold value V_{th}, an AP is triggered. $V_{th} = -40mV$ in a typical cardiac myocyte. The cell enters a *depolarization* phase where the cell's voltage V_m rapidly increases. V_m increases until a maximum potential V_{max} is reached (nominally around $56mV$), at which point the cell begins an *initial repolarization* phase. This phase can be represented as a 'notch' in the signal. Due to the ion-channel interactions at the cellular level, cardiac myocytes demonstrate an extended, slower repolarization phase called a *plateau* phase. Afterwards, a phase of rapid repolarization occurs. The repolarization phase can be further divided into an *absolute refractory* phase, where the cell is unreactive to external stimuli, and a *relative refractory* phase, where external stimuli can cause an additional AP of lesser magnitude. Finally the cell returns to its initial fully repolarized state.

The hybrid automata (HA) model we propose in this benchmark is based off the CA model described in [9]. The excitable heart tissue is composed of individual cells arranged in a 2D grid of $N \times N$. Cells interact with each other via a four-neighborhood structure. Each cell is modeled as a nonlinear hybrid automaton. The continuous state of cell (i, j) is $[V_m(i, j), t_{ij}]$, where $V_m(i, j)$ is the cross-membrane voltage and t_{ij} is a local timer. The cell automaton has 7 modes, which model the 7 phases of an AP. See Fig. 5. They are *Quiescent, Upstroke, Notch, Plateau, absolute refractory period (ERP),relative refractory period (RRP),* and *Secondary upstroke.* We now describe the dynamics in all modes.

Quiescent Initially a cell is in the quiescent mode. Typically, $V_m(0) = V_{min} = -90mV$ in this mode. The $(i,j)^{th}$ cell's voltage at time t in this phase depends on that of its 4 neighbors and its own as follows [9]

$$\begin{aligned} \dot{V_m}(i,j,t) &= V_{intr} + \frac{[V(i-1,j,t) + V(i+1,j,t) - 2V_m(i,j,t)]}{R_h(i,j)} \\ &\quad + \frac{[V_m(i,j-1,t) + V_m(i,j+1,t) - 2V_m(i,j,t)]}{R_v(i,j)} \\ &= V_{intr} + a(i,j)^\top \mathbf{V}(t),\ a(i,j) \in \Re^{N^2} \end{aligned} \tag{1}$$

where R_h, R_v are resistance constants that can vary across the myocardium. In Quiescent mode, $V_{intr} = 0$ for most ECs whereas $V_{intr} > 0$ for a self-exciting cell. $\mathbf{V} = (V(1,1), \ldots, V(N,N)) \in \Re^{N^2}$ contains all voltages in the grid.

Upstroke - Depolarization In Upstroke, the voltage increases exponentially according to $\dot{V}(i,j) = d > 0$.

Notch - Initial Repolarization. Upon reaching V_{max}, the voltage decreases slightly per $\dot{V}(i,j) = -g < 0$.

Plateau. While the cell is in the plateau mode, V_m remains constant for a given duration PD (Plateau Duration). Biologically, the delayed reaction time of slower Ca^{++} ion channels is the cause for the plateau. In a more realistic AP, the plateau is not exactly constant but decreases slightly.

ERP - Absolute Refractory Period. Next, the cell begins a secondary repolarization phase which can additionally be divided into two phases, the first of which is ERP. During this mode, the cell is resilient to external stimuli which is reflected in update equations for the state.

From Upstroke to the end of ERP, the cell can not be excited by its neighbors. This is reflected in the dynamics, which depend solely on the intrinsic voltage of the cell.

RRP - Relative Refractory Period After ERP, the cell enters the last phase of repolarization, the RRP mode. During this period, the cell is susceptible to current flows from neighboring cells. In this mode, the dynamics follow Eq. 1. If the voltage increases above a threshold $V_{th,2} > V_{th}$ due to the interactions with its neighbors, the cell can enter a secondary depolarization mode, Secondary upstroke. If this occurs, the cell depolarizes to a voltage $V_max' < V_max$ albeit with a smaller slope. If on the other hand, the voltage goes back to the quiescent level, the cell enters Quiescent.

Action Potential Duration Restitution Curve The time interval between the time of transition to the Upstroke mode to the point where the cell achieves 90% of repolarization, t_{APD90} is considered the APD. The interval from the t_{APD90} to the upstroke of the next AP is called the diastolic interval (DI). If ADP_n and DI_n are the APD and DI of the n^{th} beat respectively, they have been experimentally observed to be related via a non-linear function: $APD_n = f(DI_{n-1})$. Function f is called the restitution curve. Numerous hypotheses and studies exist about how to measure the restitution curve and its implications for arrhythmogenesis. It is also observed that multiple restitution curves might exist. We implement a restitution curve from the literature whose parameters can be found in the accompanying code.

Assumptions and Simplifications Within a mode for a single cell, we limit the cell to linear dynamics. This affects the shape of the action potentials, although not in a manner that precludes the simulation of interesting phenomena. See Section 3 for sample APs. Furthermore, we limit the interaction between cells to the 4-neighborhood of the individual cell. This is a simplification of the interaction between cells, which occurs up to a certain radius.