

A Cycle-Linear Approach to Modeling Action Potentials

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Abstract— We introduce *cycle-linear hybrid automata* (CLHA) and show how they can be used to efficiently model dynamical systems that exhibit nonlinear, pseudo-periodic behavior. CLHA are based on the observation that such systems cycle through a fixed set of operating modes, although the dynamics and duration of each cycle may depend on certain computational aspects of past cycles. CLHA are constructed around these modes such that the per-cycle, per-mode dynamics are given by a time-invariant linear system of equations; the parameters of the system are dependent on a *deformation coefficient* computed at the beginning of each cycle as a function of memory units. Viewed over time, CLHA generate a very intuitive, linear approximation of the entire phase space of the original, nonlinear system. We show how CLHA can be used to efficiently model the action potential of various types of excitable cells and their adaptation to pacing frequency.

I. INTRODUCTION

We present a novel *cycle-linear* approach to modeling dynamical systems that exhibit nonlinear pseudo-periodic behavior. Let S be such a system. The main idea is to model each cycle of S as a hybrid automaton over time-invariant linear equations whose parameters are updated at the beginning of each cycle to reflect S 's nonlinear cycle-dependent dynamics.

The rest of the paper is organized as follows. Section II introduces the biological background of action potential (AP), which serves as a quintessential case study of the cycle-linear approach. Section III gives the formal definition of cycle-linear systems in terms of Hybrid automata [1]. Section IV shows how cycle-linear Hybrid automata can be used to efficiently model the AP and corresponding restitution properties of various types of excitable cells.

II. BACKGROUND

Excitable cells include neurons, cardiac cells and skeletal muscle cells. In cardiac cells for example, on each heart beat, an electrical control signal is generated by the sinoatrial node, the heart's internal pacemaking region. Electrical waves then travel along a prescribed path, exciting cells in the main chambers of the heart (atria and ventricles) and assuring synchronous contractions. At the cellular level, the electrical signal is a change in the potential across the cell membrane which is caused by different ion currents flowing through the cell membrane. This electrical signal for each

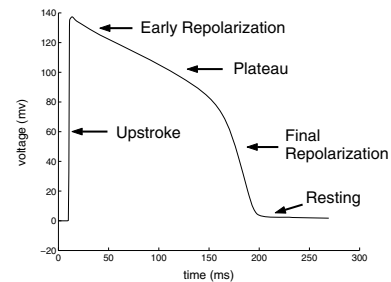


Fig. 1. Relation of HA modes with AP phases

excitation event is known as an *action potential* (AP). The AP of cells from different regions or from different species may vary in shape but when plotted over time they present periodic signals with variable frequency and morphology. In addition, all APs exhibit the following major phases (Fig. 1): *resting*, *upstroke*, *early repolarization*, *plateau* or *later repolarization*, and *final repolarization*.

For non-pacemaking excitable cells, APs are externally triggered events: a cell fires an action potential as an all-or-nothing response to a supra-threshold stimulus current, and each AP follows the same sequence of phases and has more or less the same magnitude regardless of the applied stimulus. After an initial step-like increase in the membrane potential, an AP lasts for a couple of hundred milliseconds in most mammals. During the AP, no re-excitation can occur, which is a safety mechanism to ensure the reliable working of the heart. The early portion of an AP is known as the “absolute refractory period” due to its non-responsiveness to further stimulation. The later portion of an AP is known as the “relative refractory period”, during which an altered secondary excitation event is possible if the stimulation threshold is raised.

When a cardiac cell is subjected to repeated stimuli, two important time periods can be identified: the *action potential duration* (APD), the time the cell is in an excited state, and the *diastolic interval* (DI), the time between the end of the action potential and the next stimulus. Fig. 2 illustrates the two intervals. The function relating APD to DI is called *APD restitution function*. The relationship is nonlinear and captures the phenomenon that a longer recovery time is followed by a longer APD. A physiological explanation of cell's restitution is rooted in the ion channel kinetics as a limiting factor in the cells' frequency response.

III. CYCLE-LINEAR MODEL

The cycle-linear approach can be fruitfully applied to the study of action potentials and their associated restitution properties for the following reasons:

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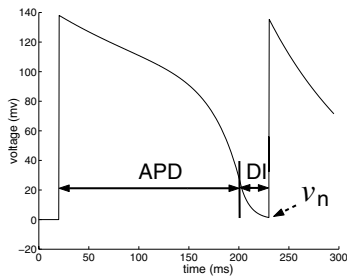


Fig. 2. APD and DI time periods.

- APs in the different cycles share similar morphology, which makes it possible to model them using equations with the same structure.
- According to the restitution property, APD's shape is mainly determined by the length of the previous DI, so that a relatively simple (single-step memory) control can be implemented.

We now formalize cycle-linear model in terms of Hybrid automata. A *hybrid automaton (HA)* is an extended finite automaton where each state has an associated continuous dynamics [2]. An HA therefore consists of: (i) A finite set X of real-valued *variables* x_1, \dots, x_n ; their dotted form $\dot{x}_i \in \dot{X}$ represents first derivatives and their primed form $x'_i \in X'$ represents values at the conclusion of discrete steps. (ii) A finite *control graph* (V, E) , where vertices in V are called *modes* and edges in E are called *switches*. (iii) Vertex-labeling functions *init*, *inv* and *flow* assigned to each mode $v \in V$. Initial condition *init*(v) and invariant *inv*(v) are predicates with free variables from X . Flow *flow*(v) is a predicate with free variables from $X \cup \dot{X}$ representing a set of ordinary differential (in)equations. (iv) An edge-labeling function *jump* assigned to each switch $e \in E$. Jump *jump*(e) is a predicate with free variables from $X \cup X'$ and is usually divided into a *guard* and an *assignment action*. (v) A finite set Σ of *events*, and an edge-labeling function *event* that assigns to each switch an event.

An HA has a natural graphical representation as a state transition diagram, with control modes as the states and control switches as the transitions. Flows and invariants (predicates within curly braces) appear within control modes, while jump conditions (in square brackets) and actions appear near the control switches. Continuous variables are written in lower case (v, v_x , etc); constant parameters in the flows are in upper-case or lower-case Greek (A, B, α_x^0 , etc); constants in invariants and jump conditions (V_T , etc), as well as events (V_S), are in upper case.

A *cycle-linear hybrid automaton (CLHA)* is an HA having the following properties: (i) The control graph is a cycle. (ii) For each execution of the cycle, the flows are defined by linear time-invariant (LTI) systems of ordinary differential equations. (iii) The constants within the flows and jump guards are computed once per cycle.

The CLHA model is illustrated in Fig. 3, where q_0, q_1, \dots, q_n are the control modes; x is a vector of variables; Θ is a vector of *memory units* that record information about

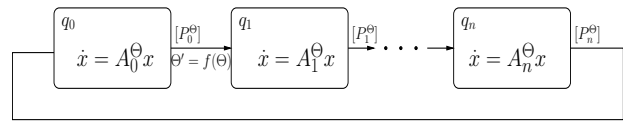


Fig. 3. Cycle-linear model in HA format

previous cycles and can be used to adjust the behavior of the current cycle according to system's memory. $A_0^\Theta, A_1^\Theta, \dots, A_n^\Theta$ are the parameters in the linear equations, for which flow conditions remain constant for each cycle, but are functions of the memory vector Θ ; $P_0^\Theta, P_1^\Theta, \dots, P_n^\Theta$ are the predicates in the jump conditions and are also functions of Θ . $\Theta' = f(\Theta)$ is the jump action which updates the memory units Θ once in each cycle. Thus, from mode q_0 to q_n , the equations in the flow condition remain *linear*, even though the concrete values of matrices $A_0^\Theta, A_1^\Theta, \dots, A_n^\Theta$ vary in different cycles; similarly for the P_i^Θ . As a consequence, the overall behavior of a CLHA is *nonlinear* while being linear in each single cycle.

The model of Fig. 3 should be understood as the *minimal* representation of a cycle-linear model. It can be extended with other switches to describe more complicated system behaviors.

IV. AP DESCRIPTION USING CYCLE-LINEAR MODELS

In this section, we present CLHA for the AP of three different types of excitable cells. The models are of increasing complexity, as is their ability to describe complex biological phenomena. The first CLHA aims to describe AP morphology of an axon as per the classical Hodgkin-Huxley model[3]; the second CLHA captures both the AP morphology and restitution properties of a guinea pig ventricular myocyte according to the dynamic Luo-Rudy model (LRd) [4], [5]; the last model describes neonatal rat ventricular cell behavior, the reference mathematical model is under development in the BME department of Stony Brook University. For the last cell model, a 2-D cell array version was implemented, and spiral wave behavior was successfully simulated.

A. Modeling AP

We first associate a control mode with each major AP phase: *resting and final repolarization (FR)*, *stimulated, upstroke*, and *plateau and early repolarization (ER)*. Initially, the cell is in mode *resting and FR*. When (externally) stimulated with the event V_S , it enters mode *stimulated* and updates its voltage according to the stimulus current. Upon termination of the stimulation, via event \bar{V}_S , with a sub-threshold voltage, the cell returns to *resting* without firing an AP. If the stimulus is supra-threshold, i.e., $v \geq V_T$ holds, the excited cell will generate an AP by progressing to mode *upstroke*. The recovery course of the cell follows transitions to mode *plateau and ER* and then to *resting and FR*. The jump conditions on the control switches monitor the transmembrane potential v , rather than imposing a rigid timing scheme.

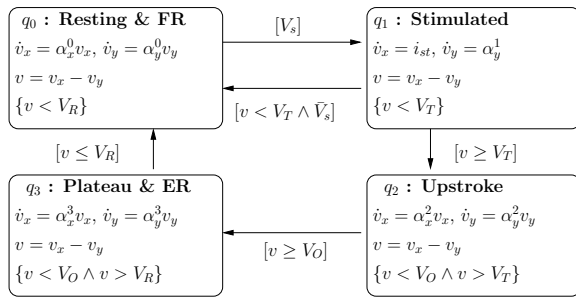


Fig. 4. Cycle-linear model for Hodgkin-Huxley model.

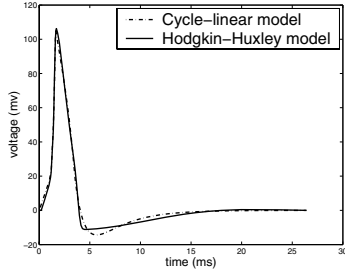


Fig. 5. Comparison of single AP morphology

The transition relation of a CLHA model also reflects the refractory period of excitable cells. Only during mode *resting and FR*, the cell can respond to external stimuli, thus this period is defined as *relative refractory period*. In the modes before, the cell will not be responsive, thus it is within *absolute refractory period*.

Within each mode, we use abstracted systems of linear equations to describe the dynamics of the transmembrane voltage. CLHA models of this nature are attractive because they offer rich descriptive power, while still remaining amenable to formal analysis. CLHA models can be obtained from more detailed systems of nonlinear differential equations by standard methods for linearization and order reduction. We used curve-fitting techniques to match the behavior of the corresponding models and optimize the model parameters. Due to the space limitation, their values are omitted here.

The CLHA for the Hodgkin-Huxley model of an axon is shown in Fig. 4 and a comparison of the AP morphology is given in Fig. 5

B. Modeling AP Restitution

Classic models of AP restitution are highly nonlinear models, making them difficult to analyze. Such models can be simplified via piecewise linearization, i.e. by introducing linear or affine-linear differential equations for different portions of the cycle. Linearization can be done around equilibrium points of the full nonlinear systems using series expansion or by geometric approximations (e.g. simplex techniques) over the whole state space. In both cases, usually a relatively large number of pieces or modes are needed for faithful representation of the dynamics of the original

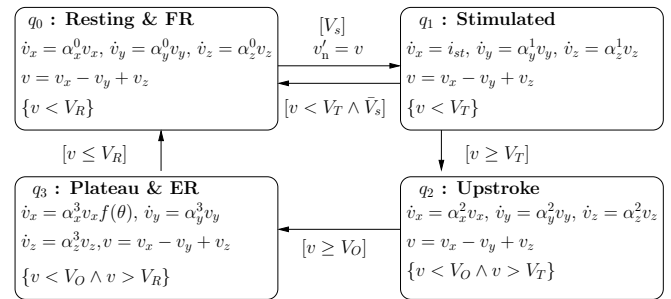


Fig. 6. The cycle-linear model for both AP and restitution

system. Alternatively, expert knowledge about the different phases in the behavior of the biological system can be used in order to define the separation of modes for linearization purposes. The switch between modes can be accomplished by voltage-dependent step functions (Heaviside functions). Within a mode, slowly changing variables can be substituted by constants. Such piecewise linear models result in more efficient formulations with less modes. Previously formulated models of this kind have had two deficiencies: they are either not precise enough (fail to match AP morphology) or remain highly nonlinear thus not suitable for formal analysis.

In this section, we show how adaptation to pacing frequency (i.e. APD restitution) can be modeled within the CLHA framework. The CLHA model of Section IV-A has no memory. It therefore produces exactly the same AP every cycle. To introduce adaptability to pacing frequency into the model we define a memory unit, v_n , that remembers the current voltage every time a new stimulus arrives. The value of v_n will control the AP morphology of the current cycle, thus making the APD adaptive to the previous DI. The definition of v_n is also illustrated in Fig. 2. As v_n remains constant for the current AP cycle, the model is still cycle-linear.

Let $\theta = v_n/V_R$ be a deformation coefficient, where the value of v_n is the one in the current mode and V_R serves as a threshold between cell's absolute refractory period and relative refractory period. Only when the cell is in resting mode where the membrane potential v is such that $v \leq V_R$, can the value of v_n be reset. Thus we have $0 < \theta \leq 1$. We incorporate function $f(\theta) = 1 + 13\sqrt[6]{\theta}$ (our choice of a 6th root function is inspired by the fact that the APD is not proportional to DI but a convex function of it) into mode *Plateau and ER*, which determines the length of the APD. The resulting CLHA appears in Fig. 6 and the comparison of the restitution curve with that of the LRd model is given in Fig. 7.

Fig. 8 illustrates the impact of v_n on the shape of the AP morphology. Recall that the value of v_n , and hence deformation coefficient θ , is updated at the beginning of each new AP cycle on the switch from mode q_0 to q_1 . Compare this relatively simple control strategy with what would be required with the finite-element method. In this case, to achieve AP adaptability, a dense enough grid has to

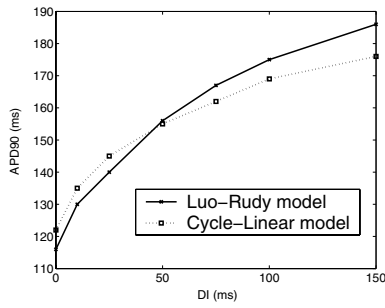


Fig. 7. Comparison of restitution curve with Luo-Rudy model

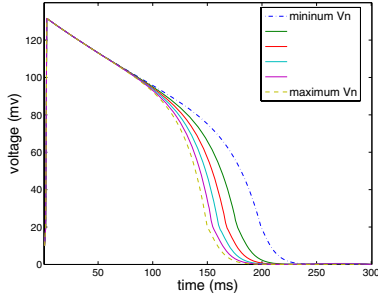


Fig. 8. AP morphology dependence on v_n

be placed on the state space so that system traces at different regions are covered.

C. Further Extensions and Spatial Simulations

Further developments of an excitable cell model can include adaptive threshold for stimulation alongside a realistic AP morphology and APD restitution. These extensions are implemented in the cycle-linear model for the neonatal rat (NNR), where $g(\theta) = 1 + 2\theta$ and thresholds V_T^θ and V_O^θ are functions of the deformation coefficient θ . The resulting CLHA is shown in Fig. 9. Note that by making the parameters of the automaton dependent on the deformation coefficient θ , we are able to cover the phase space of the nonlinear system in a very simple and generic way as an HA with only four modes. Compare this with the huge (and barely readable) “automaton” that is obtained, for example, by a finite element method, when each element (simplex) is associated with a set of linear functions in each mode.

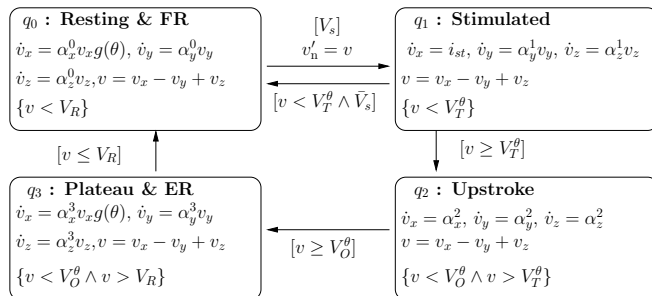


Fig. 9. Cycle-linear model for neonatal rat

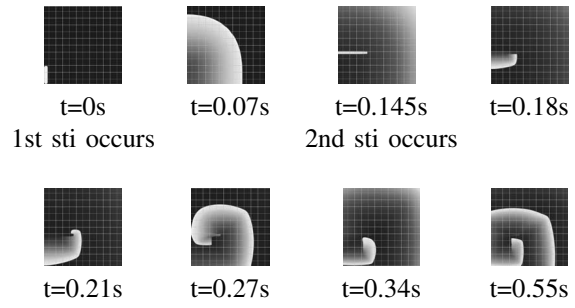


Fig. 10. Spatial simulation of excitation propagation in cycle-linear model.

The CLHA model can be applied to a network of cells. To implement that, we need a diffusion model describing the interaction of a cell with its neighbors. Here, we use a classical diffusion model based on the Laplacian. When a crossfield stimulation is applied, both the original model and its CLHA rendition reproduce the induction of a spiral wave (Fig. 10). Spiral waves are common phenomena in reaction-diffusion systems, including cardiac tissue.

V. CONCLUSIONS AND FUTURE WORK

A cycle-linear model of a dynamical system enjoys both the computational efficiency of a linear model and the descriptive power of a nonlinear model. Moreover, a cycle-linear model is much more amenable to formal analysis (e.g. stability analysis) than its nonlinear counterpart. We illustrated the cycle-linear approach by modeling the behavior of excitable cells. In doing so, we succeed in capturing the action-potential morphology and its adaptation to pacing frequency. The method is, however, generally applicable to systems where some level of periodicity plus adaptation is observed.

Future work includes applying formal analysis to our cycle-linear models of excitable cells in order to study their fundamental properties, including stability, observability and safety (absence of arrhythmia). We also plan to investigate techniques for further improving the efficiency of our approach. For example, in some modes of a cycle-linear model, it is possible to analytically solve the mode’s linear differential equations, thereby eliminating the integration steps that would otherwise be required.

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