Theoretical Computer Science 410 (2009) 3149–3165

Contents lists available at ScienceDirect

Theoretical Computer Science

journal homepage: www.elsevier.com/locate/tcs

Modeling and simulation of cardiac tissue using hybrid I/O automata☆

E. Bartocci [a,c,*], F. Corradini [a], M.R. Di Berardini [a], E. Entcheva [b], S.A. Smolka [c], R. Grosu [c]

[a] Department of Mathematics and Computer Science, University of Camerino, Camerino (MC), 62032, Italy

[b] Department of Biomedical Engineering, Stony Brook University, Stony Brook, NY, 11794, USA

[c] Department of Computer Science, Stony Brook University, Stony Brook, NY, 11794, USA

ARTICLE INFO

Keywords:
Computational systems biology
Hybrid automata
Formal analysis
Excitable tissue

ABSTRACT

We propose a new biological framework based on the Lynch et al. theory of Hybrid I/O Automata (HIOAs) for modeling and simulating excitable tissue. Within this framework, we view an excitable tissue as a composition of two main kinds of component: a diffusion medium and a collection of cells, both modeled as an HIOA. This approach yields a notion of decomposition that allows us to describe a tissue as the parallel composition of several interacting tissues, a property that could be exploited to parallelize, and hence improve, the efficiency of the simulation process.

We also demonstrate the feasibility of our HIOA-based framework to capture and mimic different kinds of wave-propagation behavior in 2D isotropic cardiac tissue, including normal wave propagation along the tissue; the creation of spiral waves; the break-up of spiral waves into more complex patterns such as fibrillation; and the recovery of the tissue to the rest via electrical defibrillation.

1. Introduction

Systems biology is a multidisciplinary field whose goal is to provide a systems-level understanding of biological phenomena by uncovering their structure, dynamics and control methods [23]. A main focus of systems biology is to devise mathematical or formal models that capture significant aspects of in vitro or in vivo experimental data, while remaining amenable to both quantitative and qualitative analysis. Currently, the most popular modeling approach is to use complex systems of nonlinear differential equations, describing in great detail the underlying biological phenomena. These models, however, are not particularly suitable for formal analysis, and impose high computational demands on simulation, especially in large-scale two-dimensional (2D) and three-dimensional (3D) networks. Simulation at the organ or even the cell level is thus rendered impractical.

Considering this state of affairs, systems biology could greatly benefit from the development of techniques that, given a system of nonlinear differential equations, (semi-automatically) constructs a more abstract model that preserves the properties of interest. One promising approach is based on the use of Hybrid Automata (HAs) [18,12] as a modeling formalism for complex biological processes. HAs are an extension of finite automata that allows one to associate a continuous behavior with each state. They have been used as mathematical models for a variety of embedded systems, including automated highway systems [9], air traffic management [11] and real-time circuits [1].

☆ This work was supported in part by the Italian FIRB-MIUR LITBIO: *Laboratory for Interdisciplinary Technologies in Bioinformatics*, by UNICAM ASSINT and by NSF Faculty Early Career Award CCR01-33583 and NSF Award CCF05-23863.

* Corresponding author at: Department of Mathematics and Computer Science, University of Camerino, Camerino (MC), 62032, Italy. Tel.: +39 0737 402578.

E-mail addresses: ezio.bartocci@unicam.it (E. Bartocci), flavio.corradini@unicam.it (F. Corradini), mariarita.diberardini@unicam.it (M.R. Di Berardini), emilia.entcheva@sunysb.edu (E. Entcheva), sas@cs.sunysb.edu (S.A. Smolka), grosu@cs.sunysb.edu (R. Grosu).

0304-3975/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.tcs.2009.02.042

More recently, HAs have been used to model the behavior of biological systems [2,3,15,25]. In particular, in [25] we have demonstrated the feasibility of using *cycle linear hybrid automata* (CLHAs) to model the behavior of several representative excitable cells, basing their derivation on the biological interpretation of their single-cell's action potential [17,25]. In contrast, the main focus of this paper is on capturing the behavior of an excitable tissue.

For the problem of *modeling and simulating excitable tissue*, cardiac tissue in particular, one should take into account the behavior of a network of spatially distributed components (cells), each of which has the ability to propagate electrical signals without damping.

In an earlier attempt to model excitable tissue [5], we proposed a model based on *spatial networks of hybrid I/O automata* that extends CLHAs with the concepts of space and synchronization based on shared variables. Within this framework, we considered an excitable tissue as a network of interacting cells disposed according to a 2D spatial lattice, with the electrical behavior of a single cell modeled as a (cycle-linear) hybrid input/output automaton (HIOA). To capture the phenomenon that the strength of communication between automata depends on their relative positions within the lattice, we introduced a new, *weighted parallel composition operator* to specify the influence of one automaton over another. The introduction of this new operator required us to prove again some important properties – for example compositionality – of the classic HIOA theory proposed by Lynch et al. in [12].

In this paper, we propose a different approach (totally compliant with HIOA theory) in which the tissue is modeled as a composition of two main kinds of component (both modeled as an HIOA): a diffusion medium and a collection of cells. By remaining squarely within the HIOA framework, we are able to readily establish compositionality results for excitable tissue. For example, we introduce a notion of decomposition that allows us to describe a tissue as a parallel composition of two (or more) interacting tissues. This interesting property could be exploited to parallelize, and hence improve, the efficiency of the simulation process.

The rest of the paper is organized as follows. Section 2 provides the biological background on excitable cells. Section 3 discusses related work. Section 4 describes the HA model and its extension with I/O variables as advocated in [12]. Section 5 presents our HIOA-based model of excitable tissue and associated compositionality results. Section 6 contains our simulation results. Section 7 offers our concluding remarks and directions for future work.

2. Biological background

An excitable cell has the ability to propagate an electrical signal – known at the cellular level as the *Action Potential* (AP) – to surrounding cells. An AP corresponds to a difference in electrostatic potential between the inside and the 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.

An AP is an externally triggered event: a cell fires an action potential as an all-or-nothing response to a supra-threshold stimulus (i.e. a stimulus that allows the cell to reach the threshold voltage; for more detail see Definition 5.1), and each AP follows the same sequence of phases. 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. It is followed by a "relative refractory period" during which a secondary excitation event is possible if the stimulation strength or duration is raised.

During a sequence of action potentials, two important time periods can be identified: the action potential duration (APD), and the diastolic interval (DI). The first is the period in which the cell is in excited state and the second is the time e between the "end" of the action potential and the next stimulus. The magnitude of the next AP and the APD is proportional to the duration of the last DI.

Examples of excitable cells are neurons, cardiac myocytes and skeletal muscle cells. An impulse over a certain threshold initiates a wave of activity moving across the excitable tissue. As each cell undergoes an excursion from its resting potential, it causes its neighbors to move over the threshold at a rate determined by the diffusion coefficient (a property of the tissue) and the distance from the stimulated 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). Fig. 1 shows the main phases of the AP in a cardiac cell of guinea pig. 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. Due to the universal nature of these AP phases among species and regions, as shown in [25], it is possible to use them as a guide in the construction of HA models.

Excitable-cell networks are important in the normal functioning and in the pathophysiology of many biological processes. In cardiac cells, 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 atria and ventricles and assuring synchronous contractions. Of special interest are cardiac arrhythmias: disruptions of the normal excitation process due

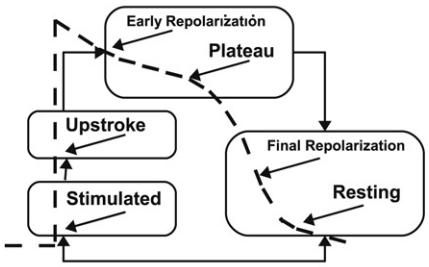

Fig. 1. Main phases of an action potential in a cardiac cell of guinea pig.

to faulty processes at the cellular level, single ion-channel level, or at the level of cell-to-cell communication. The clinical manifestation is a rhythm with altered frequency – tachycardia or bradycardia – or the appearance of multiple frequencies – polymorphic Ventricular Tachycardia (VT) – with subsequent deterioration to a chaotic signal—Ventricular Fibrillation (VF). VF [22] is a typically fatal condition in which there is uncoordinated contraction of the cardiac muscle of the ventricles in the heart. As a result, the heart fails to adequately pump blood, and hypoxia may occur.

3. Related work

Generally, an excitable tissue is modeled in terms of reaction–diffusion systems. Thus, a typical continuous representation would involve partial differential equations (PDEs) for the diffusing species (typically the transmembrane potential), and a system of nonlinear ordinary differential equations describing all other state variables that are normally considered non-diffusing. These may include ion-channel gating variables and ion concentrations. The first mathematical model of ionic processes that underlie cell excitation was empirically developed in 1952 by Hodgkin and Huxley for a squid giant axon [20]. This provided the basis for subsequent models of increasing complexity, using multiple continuous state variables (voltage, ion-channel gates, ion concentrations) to describe APs in different cell types [6,10,13]. Current models of cardiac cells include more than twenty state variables and a large number of fitted parameters. Detailed models of cardiac excitation are perceived as over-determined systems and, as such, make both qualitative – i.e. checking general properties – and quantitative analysis – i.e. by simulation – at the organ or even tissue level impractical.

At the opposite end of the spectrum, completely discrete models based on cellular automata (CAs) have emerged [7, 14]. The first generation of CA models used nearest-neighbor diffusion modeling (Neumann and Moore neighborhoods) and a small number of few discrete states, resulting in unrealistic AP shape and wave propagation. Second-generation CA models [14] focused on correct representation of wavefront curvature effects by employing more complex neighborhood functions, such as Gaussian, circular templates or randomized lattices. Furthermore, the transitions rules for the relaxation states were updated to reflect a higher threshold for excitation and to effectively represent the relative and absolute refractory period. The latest generation is exemplified by Barkley's model [6], in which a standard finite-difference method is used to calculate the diffusive term, but CA-like rules govern the kinetics of the two model variables, with adjustable thresholds.

Recently, modified CA models have been used to study cardiac excitability and for comparison with experimental data [7, 8]. A body of literature provides clear links between the classical continuous PDE representation and the more ad hoc CA-based approach as an alternative description of reaction–diffusion systems. The purely discrete nature of CAs presents some difficulties in capturing subtle non-stepwise features of excitation.

4. Hybrid automata and hybrid input/output automata

We first introduce some basic notions used in [12] as a foundation for the definition of hybrid automata and hybrid I/O automata. In particular, here we report the notions of variables and types for variables, and trajectories. The following mathematical preliminaries are needed.

If f is a function, we denote the domain and the range of f by $dom(f)$ and $range(f)$, respectively. Moreover, if S is a set, we denote with $f\lceil S$ the restriction of f to S, i.e. the function g with domain $dom(f) \cap S$ such that $g(a) = f(a)$ for each $a \in dom(g)$.

We say that two functions f and g are *compatible* if $f\lceil dom(g) = g\lceil dom(f)$. If f and g are compatible functions, we define $f \cup g$ as the unique function h with $dom(h) = dom(f) \cup dom(g)$ satisfying the following condition: for each $a \in dom(h)$, if $a \in dom(f)$ then $h(a) = f(a)$, and if $a \in dom(g)$ then $h(a) = g(a)$.

Finally, if f is a function whose range is a set of functions and S is a set, we write $f \downarrow S$ for the function g with $dom(g) = dom(f)$ such that $g(a) = f(a)\lceil S$ for each $a \in dom(g)$. Also, if f is a function whose range is a set of functions all of which have a particular element d in the domain, we denote with $f \downarrow d$ the function g with $dom(g) = dom(f)$ such that $g(a) = f(a)(d)$.

We fix a time axis T which is the group $(\mathbb{R}, +)$ of the real numbers with addition; $\mathsf{T}^{\geq 0}$ is defined to be the set $\{t \in \mathsf{T} \mid t \geq 0\}$. If $K \subseteq \mathsf{T}$ and $t \in \mathsf{T}$, we define $K + t \triangleq \{t' + t \mid t' \in K\}$. Moreover, for a function f with domain K, we define $f + t$ to be the function with domain $K + t$ and such that $(f + t)(t') = f(t' - t)$, for each $t' \in K + t$.

4.1. Variables, types and trajectories

Definition 4.1 (*Variables and Types for Variables*). Assume a universal set of *variables* V. For each $v \in V$, we distinguish a *static type* (*type* for short) that represents the set of values it may take on, and a *dynamic type* that represents the evolutions of v over the time. In more detail, $type(v)$ – the type of v – is a nonempty set of values, and $dtype(v)$ – the dynamic type of v – is a set of functions from left-closed intervals of T to $type(v)$ satisfying the following properties:

- (*Closure under time shift*)
  For each $f \in dtype(v)$ and $t \in \mathsf{T}$, $f + t \in dtype(v)$.
- (*Closure under subinterval*)
  For each $f \in dtype(v)$ and $J \subseteq dom(f)$, $f\lceil J$ is in $dtype(v)$.
- (*Closure under pasting*)
  Let $f_0, f_1, \ldots$ be a sequence of functions in $dtype(v)$ such that, for each index i, if f_i is not the final function of sequence then $dom(f_i)$ is right-closed and $\max(dom(f_i)) = \min(dom(f_{i+1}))$. The function f defined by $f(t) = f_i(t)$, where i is the smallest index such that $t \in dom(f_i)$, is in $dtype(v)$.

Definition 4.2 (*Trajectories*). Let V be a set of *variables*. A *valuation* $\mathbf{v}$ for V is a function that associates to each $v \in V$ a value in $type(v)$. We write $val(V)$ to denote the set of all valuations for V. Let J be an initial segment of $\mathsf{T}^{\geq 0}$ (i.e. a left-closed interval of T with left end-point equal to zero). A *J-trajectory* for V is a function $\tau : J \to val(V)$ such that, for each $v \in V$, $\tau \downarrow v \in dtype(v)$. A trajectory for V is a *J-trajectory*, for any J. In the following we denote with $trajs(V)$ the set of all possible trajectories for V.

If τ is a trajectory then $\tau.ltime$, the *time limit* of τ, is the supremum of $dom(\tau)$. Moreover, we define $\tau.fval$, the *first valuation* of τ, to be $\tau(0)$ and, if τ is closed (that is, its domain is a finite closed interval), we define $\tau.lval$, the *last valuation* of τ, to be $\tau(\tau.ltime)$.

If τ is a trajectory and $t \in \mathsf{T}^{\geq 0}$, we define:

- $\tau \trianglelefteq t \triangleq \tau\lceil[0, t]$;
- $\tau \triangleleft t \triangleq \tau\lceil[0, t)$;
- $\tau \trianglerighteq t \triangleq (\tau\lceil[t, \infty)) - t$.

Finally, the following operations on trajectories are also needed:

Prefix preorder: Let τ and τ' be trajectories for V. We say that τ' is a prefix of τ, written $\tau' \leq \tau$ if τ' can be obtained by restricting τ to a subset of its domain. Formally, $\tau' \leq \tau$ iff $\tau' = \tau\lceil dom(\tau')$.

Concatenation: Let τ and τ' be trajectories for V with τ closed. The concatenation of τ with τ', written $\tau \frown \tau'$, is the union of τ with the trajectory we obtain by shifting the domain of τ' until the start time agrees with the limit time of τ. Formally, $\tau \frown \tau' \triangleq \tau \cup (\tau'\lceil(0, \infty) + \tau.ltime)$.

4.2. Hybrid automata

A hybrid automaton is a state machine whose states are valuations of a set of variables (called *internal variables*). It uses a different set of so-called *external variables* for communication with its environment. It has also a set of internal actions. The state of a hybrid automaton may change either by means of *discrete transitions* (that are atomic and instantaneous) or by *trajectories* that describe the evolution of the state over intervals of time. Discrete transitions are labelled with actions. Trajectories may be described by continuous or discontinuous functions. This is a slight simplification of the definition of hybrid automata given in [12], where we do not distinguish anymore between internal and external actions (but the actions may only be internal). Our aim is that of avoiding unnecessary technicality; indeed, we do not have external actions because automata we use in our framework communicate exclusively via shared variables.

Definition 4.3. A *Hybrid automaton* (HA for short; see [12]) is a tuple $\mathcal{A} = (W, X, Q, \Theta, H, D, \mathcal{T})$, where:

- W is a set of external variables and X is a set of internal variables; we assume that W and X are disjoint from each other and write $V \triangleq W \cup X$.
- $Q \subseteq val(X)$ is a set of *states* and $\Theta \subseteq Q$ is a nonempty set of *initial states*.
- H is a set of internal actions. Actions in H are also called *locally controlled* actions.
- $D \subseteq Q \times H \times Q$ is a set of *discrete transitions*. We use $\mathbf{x} \xrightarrow{a}_{\mathcal{A}} \mathbf{x}'$ as a shorthand for $(\mathbf{x}, a, \mathbf{x}') \in D$. We say that the action a is enabled in $\mathbf{x}$ if there exists an $\mathbf{x}'$ such that $\mathbf{x} \xrightarrow{a}_{\mathcal{A}} \mathbf{x}'$.
- $\mathcal{T}$ is a set of *trajectories* for V such that $\tau(t)\lceil X \in Q$ for every $\tau \in \mathcal{T}$ and $t \in dom(\tau)$. Given a trajectory $\tau \in \mathcal{T}$, we denote $\tau.fval\lceil X$ by $\tau.fstate$ and, if τ is closed, $\tau.lval\lceil X$ by $\tau.lstate$. We require that the set of trajectories $\mathcal{T}$ satisfies the following axioms:

  T1 (*Prefix Closure*)
  For every $\tau \in \mathcal{T}$ and every $\tau' \leq \tau$, $\tau' \in \mathcal{T}$.

  T2 (*Suffix Closure*)
  For every $\tau \in \mathcal{T}$ and every $t \in dom(\tau)$, $\tau \trianglerighteq t \in \mathcal{T}$.

T3 (*Concatenation Closure*)
Let $\tau_0, \tau_1, \tau_2, \ldots$ be a sequence of trajectories in $\mathcal{T}$ such that for each index i, $\tau_i.lstate = \tau_{i+1}.fstate$. Then $\tau_0^\frown \tau_1^\frown \tau_2^\frown \ldots \in \mathcal{T}$.

For our aims it suffices to consider HAs and HIOAs (see Definition 4.4) with real-valued variables (i.e. for each $v \in V$, $type(v) = \mathbb{R}$).

4.3. Hybrid Input/Output Automata

Hybrid Input/Output Automata consist of a refinement of the Hybrid Automata model where, in the description of the automaton external behavior, we distinguish between input and output variables.

Definition 4.4. A *pre-hybrid I/O automaton* (pre-HIOA for short; see [12]) is a tuple $\mathcal{A} = (\mathcal{H}, I, O)$, where:

- $\mathcal{H} = (W, X, Q, \Theta, H, D, \mathcal{T})$ is a hybrid automaton.
- I and O partition W into *input* and *output* variables, respectively.[1] Variables in $Z \triangleq X \cup O$ are called *locally controlled*. Again, we write $V \triangleq W \cup X$.

A *hybrid I/O automaton* (HIOA for short) is a pre-HIOA satisfying the following additional axiom:

E1 *(Input trajectory enabling)*[2]
For every $\mathbf{x} \in Q$ and every $\upsilon \in trajs(I)$, there exists $\tau \in \mathcal{T}$ such that $\tau.fstate = \mathbf{x}$, $\tau \downarrow I \leq \upsilon$ and either
(1) $\tau \downarrow I = \upsilon$, or
(2) τ is closed and some locally controlled action $l \in H$ is enabled in $\tau.lstate$.

Axiom **E1** is a condition for interaction over time intervals. It says that an HIOA can accept any input trajectory (i.e. any trajectory of input variables) υ either by letting time advance for the entire duration of υ or by reacting with a locally controlled action after some part of the input trajectory has occurred. The authors in [12] have shown that axiom **E1** has a main role in proving that an HIOA does not contribute to producing unwanted system behaviors. Indeed, an interesting complication that arises in hybrid settings is the possibility that a state machine could prevent time from passing, for example, by blocking it entirely, or by scheduling infinitely many discrete actions to happen in a finite amount of time—so-called *Zeno behavior*. In order to isolate HIOAs that do not exhibit this kind of behavior, in [12] there has been introduced a notion of *receptiveness*. Informally speaking, an HIOA is receptive if it admits a strategy for resolving non-deterministic choices that never generate infinitely many locally controlled actions in a finite amount of time. An important consequence of this definition is that receptive HIOAs cannot simply stop at some point and refuse to allow time to elapse; they allow time to pass to infinity if the environment does so. Receptiveness is also preserved by composition (under strong compatibility conditions; see Definition 4.5).

Notation: Suppose the time domain T is $\mathbb{R}$; let τ be a trajectory over a set of variables V and $v \in V$. As in [12], we use v as shorthand for the function $\tau \downarrow v : dom(\tau) \to type(v)$ which gives the value of v at all times during the trajectory τ. Similarly, we can view any expression e containing variables from V as a function with domain $dom(\tau)$. These conventions allow us to say that τ satisfies the algebraic equation $v = e$ meaning that $v(t) = e(t)$, for every $t \in dom(\tau)$. Similarly, if for every $t \in dom(\tau)$, $v(t) = v(0) + \int_0^t e(t')\mathrm{d}t'$, we can say that τ satisfies the differential equation $\dot{v} = e$.

Conventions for automata specifications: In what follows, we describe the conventions we use in the specification of an HIOA. Essentially, we inherit the same language used in [21] for the specification of Timed I/O Automata (TIOAs) with some trivial changes due to the fact that TIOAs have only internal variables and, hence, synchronization is only allowed by means of discrete transitions.

An automaton specification consists of four main parts: (1) an *actions signature*, which lists the actions of the automaton together with their parameters types (if any), (2) a *state variables list*, which declares kinds (we distinguish between internal, input and output variables), names and types of the state variables, (3) a collection of *transition definitions* and, finally, (4) a *trajectories definition*.

Static types of variables are always declared explicitly in the state variables list. We write $v : t$ for a variable v of static type t. Moreover, a variable can be initialized to a specific value allowed by its type. If no initial value is given, it is assumed to be arbitrary. The dynamic types of variables are specified implicitly. By default, variables of type $\mathbb{R}$ are assumed to be analog and variables of types other than $\mathbb{R}$ are assumed to be discrete. A variable of type $\mathbb{R}$ is both analog and discrete if its dynamic type consists of piecewise constant functions only. The keyword *discrete* is used to qualify a discrete variable of type $\mathbb{R}$.

Discrete transitions are specified in *precondition–effect* style. The *pre* clause specifies the enabling conditions for an action, while the *effect* clause contains a list of statements that specify the effect of performing that action on the state. All the statements in an effect clause are assumed to be executed sequentially in a single indivisible step.

The trajectories are specified by a combination of algebraic and differential equations and inequalities, and stopping conditions. A given trajectory is legal if it satisfies the predicate in the *stop when* clause, and the equations or inequalities in the *evolve clause*.

[1] In [12], the sets of input and output variables are denoted respectively by U and Y.
[2] This axiom is called **E2** in [12].

A stopping condition is satisfied by a trajectory τ if the only state in which the condition holds is the last one (if such a state there exists) of that trajectory. Hence, time cannot advance beyond the point where the stopping condition is true. Finally, the *evolve* clause specifies the algebraic and differential equations that must be satisfied by all the legal trajectories of the automaton.

4.4. Composition of Hybrid Input/Output Automata

Now, we introduce the parallel composition operator for pre-HIOAs as has been given in [12] in order to describe the behavior of two pre-HIOAs running in parallel.

Definition 4.5. We say that two pre-HIOAs $\mathcal{A}_1$ and $\mathcal{A}_2$ are *compatible* if: (1) $H_1 \cap H_2 = \emptyset$, (2) $X_1 \cap V_2 = X_2 \cap V_1 = \emptyset$ (i.e. if $\mathcal{H}_1$ and $\mathcal{H}_2$ are compatible) and (3) $O_1 \cap O_2 = \emptyset$.[3]

Let $\mathcal{A}_1$ and $\mathcal{A}_2$ be two compatible pre-HIOAs. The parallel composition $\mathcal{A}_1 \| \mathcal{A}_2$ is defined to be the pre-HIOA $\mathcal{A} = (\mathcal{H}, U, Y, I, O)$ where:

- $O = O_1 \cup O_2$
- $I = (I_1 \cup I_2) - O$
- $X = X_1 \cup X_2$ and $W = I \cup O = ((I_1 \cup I_2) - O) \cup O = (I_1 \cup I_2) \cup O = (I_1 \cup O_1) \cup (I_2 \cup O_2) = W_1 \cup W_2$
- $Q = \{\mathbf{x} \in val(X) \mid \mathbf{x}\lceil X_1 \in Q_1 \text{ and } \mathbf{x}\lceil X_2 \in Q_2\}$
- $\Theta = \{\mathbf{x} \in Q \mid \mathbf{x}\lceil X_1 \in \Theta_1 \text{ and } \mathbf{x}\lceil X_2 \in \Theta_2\}$
- $H = H_1 \cup H_2$
- for each $\mathbf{x}, \mathbf{x}' \in Q$ and each $a \in H$, $\mathbf{x} \xrightarrow{a}_{\mathcal{A}} \mathbf{x}'$ iff, for $i = 1, 2$, either (1) $a \in H_i$ and $\mathbf{x}\lceil X_i \xrightarrow{a}_{\mathcal{A}_j} \mathbf{x}'\lceil X_i$ or (2) $a \notin H_i$ and $\mathbf{x}\lceil X_i = \mathbf{x}'\lceil X_i$
- $\mathcal{T} \subseteq trajs(V)$ is given by $\tau \in \mathcal{T}$ iff $\tau \downarrow V_1 \in \mathcal{T}_1$ and $\tau \downarrow V_2 \in \mathcal{T}_2$.

In [12] it has been proven that the parallel composition of two pre-HIOAs is a pre-HIOA (cft. Theorem 6.7). Unfortunately, axiom **E1** is not necessarily preserved by composition. Thus, in order to ensure that the parallel composition of two HIOAs is also an HIOA, the authors in [12] introduced a stronger notion of compatibility, stating that two HIOAs are *strongly compatible* if their parallel composition satisfies axiom **E1**. They also gave some sufficient conditions for this strong compatibility to hold.

4.5. Hiding

In this section we define an hiding operation that allows us to reclassify some output variables of an HIOA—for more details see [12].

Definition 4.6. Let $\mathcal{A}$ be a pre-HIOA and $O \subseteq O_{\mathcal{A}}$. We define $\mathsf{VarHide}(O, \mathcal{A})$ to be the pre-HIOA $\mathcal{B}$ given by:

- $O_{\mathcal{B}} = O_{\mathcal{A}} - O$.
- $I_{\mathcal{B}} = I_{\mathcal{A}}$.
- $\mathcal{H}_{\mathcal{B}} = \mathsf{VarHide}(OY, \mathcal{H}_{\mathcal{A}})$, i.e. the HA that is equal to $\mathcal{H}_{\mathcal{A}}$ except that $W_{\mathcal{B}} = W_{\mathcal{A}} - O$ and $\mathcal{T}_{\mathcal{B}} = \mathcal{T}_{\mathcal{A}} \downarrow (V_{\mathcal{A}} - O)$.

The following lemma – proven in [12], cft. Lemma 6.13 – states that axiom **E1** is preserved by hiding.

Lemma 4.7. *Let $\mathcal{A}$ be a pre-HIOA and $O \subseteq O_{\mathcal{A}}$. If $\mathcal{A}$ satisfies axiom* **E1** *then so do* $\mathsf{VarHide}(O, \mathcal{A})$.

Proposition 4.8. *Let $\mathcal{A}_1 = (\mathcal{H}_1, I_1, O_1)$ and $\mathcal{A}_2 = (\mathcal{H}_2, I_2, O_2)$ be two compatible pre-HIOAs and $O \subseteq O_1 \cup O_2$ such that $O \cap I_1 = O \cap I_2 = \emptyset$. Then:* $\mathsf{VarHide}(O, \mathcal{A}_1 \| \mathcal{A}_2) = \mathsf{VarHide}(O \cap O_1, \mathcal{A}_1) \| \mathsf{VarHide}(O \cap O_2, \mathcal{A}_2)$.

Proof. Let $\mathcal{A} = \mathcal{A}_1 \| \mathcal{A}_2$ and $\mathcal{B} = \mathsf{VarHide}(O, \mathcal{A})$. For $i = 1, 2$, we denote $\mathcal{A}_i' = \mathsf{VarHide}(O \cap O_i, \mathcal{A}_i)$. The components of $\mathcal{A}_i'$ will be denoted by X_i', Q_i', Θ_i', H_i', etc.

By Definition 4.6, for $i = 1, 2$ the automaton A_i' is given by:

- $O_i' = O_i - (O \cap O_i) = O_i - O$. This is because $v \in O_i$ and $v \notin O \cap O_i$ imply $v \notin O$ and, hence, $O_i - (O \cap O_i) = O_i - O$.
- $I_i' = I_i$. Moreover $v \in I_i$ and $O \cap I_i = \emptyset$ imply $v \notin O$ and hence $I_i' = I_i = I_i - O$.
- The HA $\mathcal{H}_i'$ is equal to $\mathcal{H}_i$ except that:
  - (i) $W_i' = I_i' \cup O_i' = (I_i - O) \cup (O_i - O) = (I_i \cup O_i) - O = W_i - O$.
  - (ii) $\mathcal{T}_i' = \mathcal{T}_i \downarrow (V_i - (O \cap O_i))$. Moreover, $V_i = X_i \cup I_i \cup O_i$ with $X_i \cap (O \cap O_i) \subseteq X_i \cap O \subseteq X_i \cap (O_1 \cup O_2) = \emptyset$ ($X_i \cap O_i = \emptyset$ because X_i and O_i are disjoint; if $\{i, j\} \in \{1, 2\}$ then $X_i \cap O_j \subseteq X_i \cap V_j = \emptyset$ due to our compatibility assumption) and $I_i \cap (O \cap O_i) \subseteq I_i \cap O = \emptyset$. Thus $X_i - (O \cap O_i) = X_i$, $I_i - (O \cap O_i) = I_i$ and, similarly, $X_i - O = X_i$ and $I_i - O = I_i$. As a consequence, $V_i - (O \cap O_i) = X_i \cup I_i \cup (O_i - (O \cap O_i)) = X_i \cup I_i \cup (O_i - O) = (X_i \cup I_i \cup O_i) - O = V_i - O$.
    This allows us to conclude that $\tau_i' \in \mathcal{T}_i' \subseteq trajs(V_i - O)$ iff there exists $\tau_i \in \mathcal{T}_i \subseteq trajs(V_i)$ such that $\tau_i' = \tau_i \downarrow (V_i - (O \cap O_i)) = \tau_i \downarrow (V_i - O)$.

By Definitions 4.5 and 4.6 we also have that:

- $O_{\mathcal{B}} = O_{\mathcal{A}} - O = (O_1 \cup O_2) - O = (O_1 - O) \cup (O_2 - O) = O_1' \cup O_2'$.

[3] This is essentially the same condition of compatibility between pre-HIOAs given in [12]. The only changes are related to the fact that in our setting there no external actions and, hence, no input and output actions.

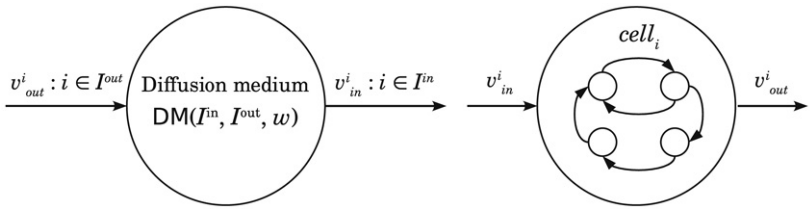

Fig. 2. Main components of a tissue: diffusion medium and cells.

Table 1
Parameter definitions for the NNR model.

$\mathbf{V_R}(\theta)$	$\mathbf{V_T}(\theta)$	$\mathbf{V_O}(\theta)$	$\mathbf{f^0_x}(\theta)$	$\mathbf{f^0_y}(\theta)$	$\mathbf{f^0_z}(\theta)$
$22 + 19.1091\theta$	$39 + 9.7742\theta$	$106.4 - 133.57\theta^2$	$1 + \theta$	$1 + \theta$	$1 + \theta$
$\mathbf{f^3_x}(\theta)$	$\mathbf{f^3_y}(\theta)$	$\mathbf{f^3_z}(\theta)$	$\gamma_{\mathbf{x}}$	$\gamma_{\mathbf{y}}$	$\gamma_{\mathbf{z}}$
1	$1 + 0.5798\theta$	1	0.6609	0.1012	0.0721
$\alpha^0_{\mathbf{x}}$	$\alpha^0_{\mathbf{y}}$	$\alpha^0_{\mathbf{z}}$	$\alpha^1_{\mathbf{x}}$	$\alpha^1_{\mathbf{y}}$	$\alpha^1_{\mathbf{z}}$
−0.0603	−0.0385	−0.0158	−0.0508	−0.0379	−0.0135
$\alpha^2_{\mathbf{x}}$	$\alpha^2_{\mathbf{y}}$	$\alpha^2_{\mathbf{z}}$	$\alpha^3_{\mathbf{x}}$	$\alpha^3_{\mathbf{y}}$	$\alpha^3_{\mathbf{z}}$
0.3999	0.0459	0.0479	−0.0076	0.0266	0.0154

- $I_{\mathcal{B}} = I_{\mathcal{A}} = (I_1 \cup I_2) - (O_1 \cup O_2) = (I_1 \cup I_2) - O_{\mathcal{A}} = (I_1 \cup I_2) - (O \cup (O_{\mathcal{A}} - O))$. Moreover, $O \cap (I_1 \cup I_2) = \emptyset$ implies $I_{\mathcal{B}} = (I_1 \cup I_2) - (O \cup (O_{\mathcal{A}} - O)) = (I_1 \cup I_2) - (O_{\mathcal{A}} - O) = (I'_1 \cup I'_2) - (O'_1 \cup O'_2)$ (see above).
- $W_{\mathcal{B}} = W_{\mathcal{A}} - O = (W_1 \cup W_2) - O = (W_1 - O) \cup (W_2 - O) = W'_1 \cup W'_2$.
- $X_{\mathcal{B}} = X_{\mathcal{A}} = X_1 \cup X_2 = X'_1 \cup X'_2$;
- $Q_{\mathcal{B}} = Q_{\mathcal{A}} = \{\mathbf{x} \in val(X) \mid \mathbf{x}\lceil X_i \in Q_i \text{ for } i = 1, 2\} = \{\mathbf{x} \in val(X') \mid \mathbf{x}\lceil X'_i \in Q'_i \text{ for } i = 1, 2\}$;
- Similarly $\Theta_{\mathcal{B}} = \{\mathbf{x} \in val(X') \mid \mathbf{x}\lceil X'_i \in \Theta'_i \text{ for } i = 1, 2\}$;
- $H_{\mathcal{B}} = H_{\mathcal{A}} = H_1 \cup H_2 = H'_1 \cup H'_2$;
- $\tau' \in \mathcal{T}_{\mathcal{B}} \subseteq trajs(V - O)$ iff there exists $\tau \in \mathcal{T}_{\mathcal{A}}$ such that $\tau' = \tau \downarrow (V - O)$. We have also that $\tau \in \mathcal{T}_{\mathcal{A}} \subseteq trajs(V)$ iff, for $i = 1, 2$, $\tau \downarrow V_i \in \mathcal{T}_i$ iff $(\tau \downarrow V_i) \downarrow (V_i - O) = \tau \downarrow (V_i - O) \in \mathcal{T}_i'$. Thus we can conclude that $\tau' \in \mathcal{T}_{\mathcal{B}}$ iff $\tau' \downarrow (V_i - O) = (\tau \downarrow (V - O)) \downarrow (V_i - O) = \tau \downarrow (V_i - O) \in \mathcal{T}_i'$ for $i = 1, 2$.

Thus, by Definition 4.5, $\mathcal{B} = \mathcal{A}'_1 \parallel \mathcal{A}'_2$. □

5. Modeling cardiac tissue with HIOAs

This section is devoted to introducing the two kinds of system component (see Fig. 2) we use to model a cardiac tissue. Indeed, in our framework a tissue is seen as the parallel composition of a diffusion medium and a collection of cells, both modeled as HIOAs. In the following, we first introduce the automaton modeling a generic cell of the tissue and then the automaton defining a diffusion medium.

5.1. The cells

Below we provide the definition of the automaton cell_i. Such a definition is given in terms of a number of parameters and functions that may vary depending on the specific kind of cardiac cell to be modeled. In more detail, the parameters are $\alpha_x^k, \alpha_y^k, \alpha_z^k$ with $k \in \{0, \ldots, 3\}$, $\gamma_x, \gamma_y, \gamma_z$, *rest* and *delay*, while the functions are V_T, V_O, V_R and f_x^k, f_y^k, f_z^k with $k \in \{0, 3\}$. Except for *rest* and *delay*, these have been obtained by using curve-fitting techniques starting from the ODE-based model (for further details, we refer the reader to [25,17]). As an example, in Table 1 we provide the value of such parameters in the case of cardiac cells of neonatal rats (NNRs).

Parameters *rest* and *delay* are constant values that represent, respectively, the transmenbrane potential in the resting phase and the upper time bound to the duration of the cell stimulation.

Definition 5.1. We define the i-th cell of a cardiac tissue to be the pre-HIOA cell_i we describe in Figs. 3–5.

The list of state variables of the automaton cell_i is given in Fig. 3 where, as usual, we use $\mathbb{R}^{>0}$ to denote the set of positive real numbers and $\mathbb{R}^{\geq 0}$ to denote the set $\mathbb{R}^{>0} \cup \{0\}$. The input variable v^i_{in} represents an external stimulus due to the cells that surrounds the i-th one. Symmetrically, the output variable v^i_{out} keeps the voltage of the i-th cell, a value that is propagated to all its neighbors through the diffusion medium (as we will see in the next section). The variable θ_i is a

Actions Signature

Internal: $resting_i, stimulated_i, end\_stimulus_i,$
$plateau_i, upstroke_i$

State Variables

Input: $v^i_{in} : \mathbb{R}$

Output: $v^i_{out} : \mathbb{R} := rp$

Internal: $voltage^i : \mathbb{R} := rp,$
$v^i_x, v^i_y, v^i_z : \mathbb{R}^{\geq 0} := 0,$
$clock^i : \mathbb{R}^{\geq 0},$
$s^i_x, s^i_y, s^i_z : discrete\ \mathbb{R} := 0,$
$\beta^i_x : discrete\ \mathbb{R} := \alpha^0_x,$
$\beta^i_y : discrete\ \mathbb{R} := \alpha^0_y,$
$\beta^i_z : discrete\ \mathbb{R} := \alpha^0_z,$
$\theta^i : discrete\ \mathbb{R}^{>0},$
$mode^i : \{0, 1, 2, 3\} := 0,$

Fig. 3. The cell_i Hybrid I/O Automaton—actions and state variables.

normalized approximation of the diastolic interval, that is the time elapsed between the end of an AP and the occurrence of a subsequent stimulus. This is used to calculate the duration of the next AP, a duration that is proportional to the diastolic interval. The internal variable $mode^i$ indicates the phase in which the cell is involved. Initially (i.e. in the resting phase), the value of $mode^i$ is zero; then it is set to 1, 2 and 3 when the cell moves, respectively, to the stimulated, upstroke and plateau phase.

The internal variable $voltage^i$ represents the voltage of the i-th cell. As stated by Eq. (4) in Fig. 5, we obtain its value from those of variables v^i_x, v^i_y and v^i_z. In order to properly define the evolution over the time of the last three variables, we use other variables – namely, β^i_x, β^i_y, β^i_z, s^i_x, s^i_y and s^i_z; see Equations (1)–(3) in Fig. 5 – that take on values that are specific to each cell phase. In particular, variables s^i_x, s^i_y and s^i_z specify whether external stimuli can contribute to the value of $voltage^i$ or not. If such variables are set to zero no further stimulation is possible.

We define Θ_i to be the set of valuations in $val(X_i)$ that associate to each internal variable its initial value (as specified in Fig. 3). Finally, a given $\mathbf{x} \in val(X_i)$ belongs to set of states Q_i if either $\mathbf{x} \in \Theta_i$ or the values that $\mathbf{x}$ associates to variables in $\tilde{X}_i \triangleq \{mode^i, clock^i, \theta^i, \beta^i_x, \beta^i_y, \beta^i_z, s^i_x, s^i_y, s^i_z\} \subseteq X_i$ are compatible with the execution of some discrete transition, i.e. the values associated with such variables in $\mathbf{x}$ can be obtained as the result of the execution of a certain the list of statements we use in the specification of the automaton cell_i discrete transitions.

Fig. 4 defines the set of discrete transitions that a cell can perform. The discrete transition labelled with $stimulated_i$ models the reaction of the cell to an external stimulus $v^i_{in} \neq 0$ and it results in a changing of the cell from its resting phase to the stimulated one. A stimulated cell can either perform the action $upstroke_i$, moving to the upstroke mode, or the action $end\_stimulus_i$, coming back to its resting phase (this kind of transition corresponds to the so-called *failed initiations* of the AP. The first transition is possible only if the applied stimulus is sufficiently strong to allow the cell to reach the threshold voltage (this happens when $voltage^i \geq V_T(\theta_i)$) before the termination of the stimulus. Otherwise, that is if after *delay* time units $voltage^i < V_T(\theta_i)$, the cell can only perform the action $end\_stimulus_i$ and come back to the resting without firing an AP. Notice that negative values of the variable v^i_{in} can stimulate the cell "negatively", meaning that, in all probability, such a stimulus will give rise to a failed initiation of the AP in the cell.

The current duration of the stimulus is determined by means of the internal variable $clock^i$ that is set to zero when the cell moves to the stimulated mode and has rate 1. It behaves as a clock variable in the sense of timed automata theory.

Once in the upstroke mode, the cell enters its "absolute refractory period" and, as a consequence, s^i_x, s^i_y and s^i_z are set to zero to avoid any further stimulation. A cell remains in its upstroke mode until it reaches an overshoot voltage. Indeed when $voltage^i \geq V_O(\theta_i)$) it starts the repolarization phase by performing a $plateau_i$ action. Finally, when $voltage^i \leq V_R(\theta_i)$, the recovery course of the cell follows the transitions to resting mode with an action $resting_i$.

Finally, Fig. 5 describes the set of trajectories of the automaton. Each legal trajectory must satisfy both the differential and algebraic equations (Equations (1)–(6)) and the stopping condition $\mathsf{p}_{stm} \vee \mathsf{p}_{end\_stm} \vee \mathsf{p}_{ups} \vee \mathsf{p}_{plt} \vee \mathsf{p}_{rst}$, where we use p_{stm}, p_{end_stm}, p_{ups}, p_{plt} and p_{rst} as shorthands for the enabling conditions of the automaton cell_i discrete transitions, i.e. respectively:

- $mode^i = 0 \wedge v^i_{in} \neq 0$,

Transitions

$stimulated_i$

Pre: $(mode^i = 0) \wedge (v_{in}^i \neq 0)$

Effect:

$mode^i := 1;\ clock^i := 0;\ \theta^i := voltage^i / V_R(\theta^i);$

$\beta_x^i := \alpha_x^1;\ \beta_y^i := \alpha_y^1;\ \beta_z^i := \alpha_z^1;$

$s_x^i := \gamma_x v_{in}^i;\ s_y^i := \gamma_y v_{in}^i;\ s_z^i := \gamma_z v_{in}^i$

$end\_stimulus_i$

Pre: $(mode^i = 1) \wedge (clock^i = delay) \wedge (voltage^i < V_T(\theta^i))$

Effect:

$mode^i := 0;\ s_x^i := 0;\ s_y^i := 0;\ s_z^i := 0;$

$\beta_x^i := \alpha_x^0 f_x^0(\theta^i);\ \beta_y^i := \alpha_y^0 f_y^0(\theta^i);\ \beta_z^i := \alpha_z^0 f_z^0(\theta^i)$

$upstroke_i$

Pre: $(mode^i = 1) \wedge (voltage^i \geq V_T(\theta^i))$

Effect:

$mode^i := 2;\ s_x^i := 0;\ s_y^i := 0;\ s_z^i := 0;$

$\beta_x^i := \alpha_x^2;\ \beta_y^i := \alpha_y^2;\ \beta_z^i := \alpha_z^2$

$plateau_i$

Pre: $(mode^i = 2) \wedge (voltage^i \geq V_O(\theta^i))$

Effect:

$mode^i := 3;\ s_x^i := 0;\ s_y^i := 0;\ s_z^i := 0;$

$\beta_x^i := \alpha_x^3 f_x^3(\theta^i);\ \beta_y^i := \alpha_y^3 f_y^3(\theta^i);\ \beta_z^i := \alpha_z^3 f_z^3(\theta^i)$

$resting_i$

Pre: $(mode^i = 3) \wedge (voltage^i \leq V_R(\theta^i))$

Effect:

$mode^i := 0;\ s_x^i := 0;\ s_y^i := 0;\ s_z^i := 0;$

$\beta_x^i := \alpha_x^0 f_x^0(\theta^i);\ \beta_y^i := \alpha_y^0 f_y^0(\theta^i);\ \beta_z^i := \alpha_z^0 f_z^0(\theta^i)$

Fig. 4. The cell_i Hybrid I/O Automaton—discrete transitions.

Trajectories

stop when: $\mathsf{p}_{stm} \vee \mathsf{p}_{end\_stm} \vee \mathsf{p}_{ups} \vee \mathsf{p}_{plt} \vee \mathsf{p}_{rst}$

evolve:

$$\dot{v}_x^i = \beta_x^i v_x^i + s_x^i \quad (1)$$

$$\dot{v}_y^i = \beta_y^i v_y^i + s_y^i \quad (2)$$

$$\dot{v}_z^i = \beta_z^i v_z^i + s_z^i \quad (3)$$

$$\dot{voltage}^i = v_x^i - v_y^i + v_z^i + rest \quad (4)$$

$$\dot{clock}^i = 1 \quad (5)$$

$$v_{out}^i = voltage^i \quad (6)$$

Fig. 5. The cell_i Hybrid I/O Automaton—trajectories.

- $mode^i = 1 \wedge clock^i = delay \wedge voltage^i < V_T(\theta^i)$,
- $mode^i = 1 \wedge voltage^i \geq V_T(\theta^i)$,
- $mode^i = 2 \wedge voltage^i \geq V_O(\theta^i)$, and
- $mode^i = 3 \wedge voltage^i \leq V_R(\theta^i)$.

Since, as soon as the stopping condition becomes true, time cannot further advance we have that enabled transitions cannot be arbitrarily ignored.

Notation: if $I \subseteq \mathbb{N}$ is a finite nonempty set of indexes, we write $\|_{i\in I}$ cell_i to denote the pre-HIOA we obtain by composing all cells whose indexes belong to I. Moreover, we often denote the components of cell_i by X_i, Q_i, Θ_i, E_i, etc.

Proposition 5.2. *Let $I \subseteq \mathbb{N}$ be a finite set of indexes and $i, k \in I$. Then:*

(1) *if $i \neq k$ then* cell_i *and* cell_k *are compatible;*
(2) $\{\mathsf{cell}_i \mid i \in I\}$ *is a finite set of pairwise compatible pre-HIOAs.*

Proof. Item 2 comes directly from Item 1. Item 1 trivially follows since, if $i \neq k$, then the sets of actions and the sets of variables of cell_i and cell_k are mutually disjoint. □

The theorem below provides us with a sufficient condition for strong compatibility between a collection of HIOAs. This result will be useful to prove that the parallel composition of a set of cells is an HIOA.

Theorem 5.3. *Let $\{\mathcal{A}_i \mid i \in I\}$ be a set of pairwise compatible HIOAs such that $I_i \cap O_k = \emptyset$ for each $i, k \in I$. Then all HIOAs in $\{\mathcal{A}_i \mid i \in I\}$ are pairwise strongly compatible and $\|_{i\in I}\ \mathcal{A}_i$ is an HIOA.*

Proof. This is a trivial extension (that can be proved by means of inductive reasonings) of a result given in [12] (cft. Theorem 6.18) stating that if $\mathcal{A}_1$ and $\mathcal{A}_2$ are two compatible HIOAs such that $I_1 \cap O_2 = \emptyset$ then $\mathcal{A}_1$ and $\mathcal{A}_2$ are strongly compatible and, hence, $\mathcal{A}_1 \| \mathcal{A}_2$ is an HIOA. □

The next proposition shows two main results. First we prove that each cell is an HIOA (this we do by proving that each automaton cell_i preserves axiom **E1**). Then we prove that also the parallel composition of a set of cells is also an HIOA.

Proposition 5.4. *Let $I \subseteq \mathbb{N}$ be a finite set of indexes and $i \in I$. Then:*

(1) cell_i *is an HIOA;*
(2) $\|_{i\in I}$ cell_i *in an HIOA.*

Proof. (1) Let $\mathbf{x} \in Q_i$, $\upsilon \in \mathit{trajs}(I_i)$ and let us choose a trajectory $\tau \in \mathit{trajs}(V_i)$ that satisfies Equations (1)–(6) and such that $\tau.\mathit{fstate} = \mathbf{x}$, $\tau \downarrow I_i = \upsilon$. We can distinguish two possible cases: either $\tau \in \mathcal{T}_i$ or $\tau \notin \mathcal{T}_i$. If $\tau \in \mathcal{T}_i$ then, since $\tau \downarrow I_i = \upsilon$, axiom **E1** is trivially true. Assume $\tau \notin \mathcal{T}_i$ and, hence, by Definition 5.1, that τ violates the stopping condition. Hence, there are one or more states (that are not the last one) where such a condition holds. Let us consider the first of them, i.e. let t_0 be the first $t \in \mathit{dom}(\tau)$ such that $t_0 < \tau.\mathit{ltime}$ and $\tau(t_0) \in Q_i$ satisfies the stopping condition. Let, moreover, τ' be the prefix of τ defined as $\tau' = \tau\lceil[0, t_0]$.
Such a trajectory satisfies both Equations (1)-(6) – simply because they were satisfied by τ and $\tau' \leq \tau$ – and the stopping condition, i.e. $\tau' \in \mathcal{T}_i$. Moreover, $\tau'.\mathit{fstate} = \tau.\mathit{fstate} = \mathbf{x}$ and $\tau' \downarrow I_i \leq \tau \downarrow I_i = \upsilon$. Finally, τ' is closed and, since the stopping condition holds, there is some locally controlled action $l_i \in H_i$ enabled in $\tau'.\mathit{lstate}$. Also, in this case, we can conclude that the axiom **E1** is satisfied.
(2) The statement follows by Theorem 5.3 since $\{\mathsf{cell}_i \mid i \in I\}$ is a set of pairwise compatible HIOAs (see Proposition 5.2-(2) and Item (1)) such that $I_i \cap O_k = \{v^i_{in}\} \cap \{v^k_{out}\} = \emptyset$ for each $i, k \in I$. □

5.2. The diffusion medium

As we have already discussed, an AP propagates as a wave along an excitable tissue. Indeed, when a cell fires an AP, this may cause a similar AP in all the cells that surround it. The way in which an AP propagates corresponds to a parabolic PDE (a Laplace operator) which depends on the distance between the involved cells and the associated diffusion coefficients. In order to approximate this operator, we introduce a special kind of component, the so-called *diffusion medium*, that has the responsibility to propagate electrical signals due to supra-threshold voltages along the tissue.

A diffusion medium is described by the HIOA $\mathsf{DM}(I^{in}, I^{out}, w)$ defined below. This uses $\{v^i_{out} \mid i \in I^{out}\}$ as set of input variables, and $\{v^i_{in} \mid i \in I^{in}\}$ as set of output variables; I^{in} and I^{out} are two sets of indexes that represent, respectively, the cells of which the tissue is made of and the cells we need to manage stimuli propagation between neighboring cells. In more detail, $\mathsf{DM}(I^{in}, I^{out}, w)$ uses the voltages of the cells whose indexes are in I^{out} to ascertain the stimulus for each cell whose index belongs to I^{in}. As we will see in Section 5.3, in a stand-alone tissue (i.e. a tissue that has not been decomposed into two or more interaction tissues), the sets I^{in} and I^{out} coincide; but, due to the decomposition operation, we also allow I^{in} to be a proper subset of I^{out}.

The third parameter we use in the definition of a diffusion medium, i.e. w, is a *distance-based weight function* as defined below.

Actions Signature

State Variables

Input: for each $i \in I^{out}$, $v^i_{out} : \mathbb{R}$

Output: for each $i \in I^{in}$, $v^i_{in} : \mathbb{R}$

Internal:

Transitions

Trajectories

stop when:

evolve:

$$\text{for each } i \in I^{in}, \quad v^i_{in} = \sum_{k \in I^{out}} w(i,k) \cdot (v^k_{out} - v^i_{out}) \qquad (7)$$

Fig. 6. The $\mathsf{DM}(I^{in}, I^{out}, w)$ Hybrid I/O Automaton.

Definition 5.5 (*Distance and Distance-Based Weight Function*). Let $I \subseteq \mathbb{N}$ be a finite set of cell indexes and let $\mathbf{p} = \{p_i \mid i \in I\}$ be a set of positions where each p_i is of the form $\langle s_i, \phi_i \rangle$ and represents the position (in a polar coordinate system) of the i-th cell.[4] For each $i, k \in I$, the *distance* between the corresponding cells is then given by

$$\mathsf{d}(i,k) = \sqrt{(s_i \cos\phi_i - s_k \cos\phi_k)^2 + (s_i \sin\phi_i - s_k \sin\phi_k)^2}.$$

We say that a function $w : I \times I \to \mathbb{R}^{\geq 0}$ is a *distance-based weight function* (a weight function, for short) if it satisfies the following properties:

(1) for each $i \in I$, $w(i,i) = 0$;
(2) for each $i, k \in I$, $w(i,k) = w(k,i)$;
(3) $0 \leq \mathsf{d}(i,k) < \mathsf{d}(i',k) \leq d$ implies $w(i,k) > w(i',k)$.

Intuitively, weight functions allow us to take distances between cells into account when modeling AP propagation. An AP fired by a cell of index k is propagated to all its neighboring (i.e. all cells whose indexes are in $neig(k) \triangleq \{i \in I \mid w(i,k) \neq 0\} = \{i \in I \mid 0 < \mathsf{d}(i,k) \leq d\}$). The propagation of such an AP results in an external stimulus that, for each $i \in neig(k)$, also depends on the weight $w(i,k)$—see Equation (7) in Fig. 6. This, together with property (3), means that the way in which an AP propagates along a tissue is inversely related to distance between the cells involved. Moreover, the behavior of all cells whose indexes are not in $neig(k)$ is not affected by an AP and hence by electrical stimuli coming from k. This is because such cells are not near enough to the cell k. In Section 5.3, it becomes more clear how the weight functions we use in the definition of a tissue actually depend on distances (see Definition 5.10). Here, we simply describe the main features than any reasonable weight function based on distance must have. This will allow us to choose the right weight function depending on the specific tissue we are modeling.

In the following, if $I' \subseteq I$, we denote with $w\lceil I' \times I'$ the restriction of w to I' (i.e. for each $I' \subseteq I$, we define $w\lceil I' \times I' : I' \times I' \to \mathbb{R}^{\geq 0}$ such that $(w\lceil I' \times I')(i,k) = w(i,k)$ for each $i, k \in I'$).

Now, we are ready to define the HIOA $\mathsf{DM}(I^{in}, I^{out}, w)$.

Definition 5.6 (*Diffusion Medium*). Let $I^{in}, I^{out} \subseteq \mathbb{N}$ with $I^{in} \subseteq I^{out}$ and let $w : I^{out} \times I^{out} \to \mathbb{R}^{\geq 0}$ be a distance-based weight function such that, for each $k \in I^{out}$, there exists an $i \in I^{in}$ with $w(i,k) \neq 0$. The *diffusion medium* $\mathsf{DM}(I^{in}, I^{out}, w)$ is the HIOA described in Fig. 6.

It is easy to show that $\mathsf{DM}(I^{in}, I^{out}, w)$ satisfies axiom **E1**. This is because, according to Equation (7) in Fig. 6, a diffusion medium can always accept any input trajectory be letting time advance for its entire duration.

In the previous definition, I^{out} represents the set of the cells that are near enough to the ones in I^{in} (this is because we require that, for each $k \in I^{out}$, there exists one $i \in I^{in}$ with $w(i,k) \neq 0$). Moreover, each output variable v^i_{in} (that the diffusion medium shares with the automaton cell_i) represents the stimulus that is propagated to the i-th cell of the tissue. Each of v^i_{in} varies over the time according to Equation (7). This states that, when calculating the value of v^i_{in}, we consider differences in electrostatic potential between the inside (i.e. v^i_{out}) and the outside (i.e. v^k_{out}, for each $k \in I^{out}$) of the i-th cell; moreover, we associate to each of these differences a weight given by $w(i,k)$. Notice that only cells whose index belong to $neig(i)$ can contribute to the value of v^i_{in}, and each of them contributes in a different way depending on the value of $w(i,k)$.

Proposition 5.7. *Two diffusion media* $\mathsf{DM}(I^{in}_1, I^{out}_1, w_1)$ *and* $\mathsf{DM}(I^{in}_2, I^{out}_2, w_2)$ *are compatible iff* $I^{in}_1 \cap I^{in}_2 = \emptyset$.

[4] We use this set of polar coordinates to represent the location of each cell in a 2D space. We recall that cells may be located in a 2D space according to different lattices; for instance, we may have a square or a triangular space lattice, as we have introduced in [5].

Proof. By Definition 5.6, two diffusion media are compatible iff their sets of output variables are disjoint. This is simply because each diffusion medium has no internal actions (i.e. $H = \emptyset$) and no internal variables (i.e. $X = \emptyset$). Moreover, since $O_1 = \{v_i^{in} \mid i \in I_1^{in}\}$ and $O_2 = \{v_i^{in} \mid i \in I_2^{in}\}$, $O_1 \cap O_2 = \emptyset$ iff $I_1^{in} \cap I_2^{in} = \emptyset$. □

The next proposition states that we can always compose two compatible diffusion media $\mathsf{DM}(I_1^{in}, I_1^{out}, w_1)$ and $\mathsf{DM}(I_2^{in}, I_2^{out}, w_2)$ and obtain an *equivalent* diffusion medium $\mathsf{DM}(I_1^{in} \cup I_2^{in}, I_1^{out} \cup I_2^{out}, w)$ provided that we properly choose the weight function w.

Proposition 5.8. *Let* $\mathsf{DM}_1 = \mathsf{DM}(I_1^{in}, I_1^{out}, w_1)$ *and* $\mathsf{DM}_2 = \mathsf{DM}(I_2^{in}, I_2^{out}, w_2)$ *be two compatible diffusion media,* $I^{in} = I_1^{in} \cup I_2^{in}$, $I^{out} = I_1^{out} \cup I_2^{out}$, *and* $w : I^{out} \times I^{out} \to \mathbb{R}^{\geq 0}$ *a distance-based weight such that:*

(1) $w_1 = w\lceil I_1^{out} \times I_1^{out}$ *and* $w_2 = w\lceil I_2^{out} \times I_2^{out}$;
(2) *for each* $i \in I^{in}$ *and* $k \in I^{out}$ *such that either* (1) $i \in I_1^{in}$ *and* $k \in I_2^{out} - I_1^{out}$ *or* (2) $i \in I_2^{in}$ *and* $k \in I_1^{out} - I_2^{out}$, $w(i, k) = 0$.

Then: $\mathsf{DM}(I^{in}, I^{out}, w) = \mathsf{DM}_1 \parallel \mathsf{DM}_2$.

Proof. First we prove that for each $k \in I^{out}$ there exists an $i \in I^{in}$ such that $w(i, k) \neq 0$ (as required by Definition 5.6). Assume $k \in I^{out}$ and, hence, $k \in I_1^{out}$ or $k \in I_2^{out}$. Let us only consider the former case (the latter one can be proven similarly). If $k \in I_1^{out}$ then, by Definition 5.6, there is an $i \in I_1^{in} \subseteq I^{in}$ such that $w_1(i, k) \neq 0$. Finally, $i, k \in I_1^{out}$ implies $w(i, k) = w_1(i, k) \neq 0$, and we are done.

In the following, we denote the components of the automata DM_1, DM_2 and $\mathsf{DM}(I^{in}, I^{out}, w)$ by $\mathcal{H}_1, I_1, O_1$, etc., $\mathcal{H}_2, I_2, O_2$, etc. and $\mathcal{H}, I, O$, etc., respectively. By Definitions 4.5 and 5.6 we have:

- $O = \{v_{in}^i \mid i \in I^{in}\} = \{v_{in}^i \mid i \in I_1^{in}\} \cup \{v_{in}^i \mid i \in I_2^{in}\} = O_1 \cup O_2$
- $I = \{v_{out}^i \mid i \in I^{out}\} = (\{v_{out}^i \mid i \in I_1^{out}\} \cup \{v_{out}^i \mid i \in I_2^{out}\}) - O = (I_1 \cup I_2) - O$
- $X = X_1 \cup X_2 = \emptyset$
- $H = H_1 \cup H_2 = \emptyset$
- $\mathcal{D} = \emptyset = \{\mathbf{x} \in val(X) \mid \mathbf{x}\lceil X_1 \in \mathcal{D}_1$ and $\mathbf{x}\lceil X_2 \in \mathcal{D}_2\}$ (this is because both sets $\mathcal{D}_1$ and $\mathcal{D}_2$ are empty)
- A trajectory $\tau \in \mathcal{T}$ iff, for each $i \in I^{in}$, τ satisfies the equation

$$v_{in}^i = \sum_{k \in I^{out}} w(i, k) \cdot (v_{out}^k - v_{out}^i).$$

Since $i \in I_1^{in}$ and $k \in I^{out} - I_1^{out} = I_2^{out} - I_1^{out}$ implies $w(i, k) = 0$ and $w\lceil I_1^{out} \times I_1^{out} = w_1$,

$$\sum_{k \in I^{out}} w(i, k) \cdot (v_{out}^k - v_{out}^i) = \sum_{k \in I_1^{out}} w_1(i, k) \cdot (v_{out}^k - v_{out}^i)$$

for each $i \in I_1^{in}$. Similarly we can prove that, if $i \in I_2^{in}$, then

$$\sum_{k \in I^{out}} w(i, k) \cdot (v_{out}^k - v_{out}^i) = \sum_{k \in I_2^{out}} w_2(i, k) \cdot (v_{out}^k - v_{out}^i).$$

We can conclude that $\tau \in \mathcal{T}$ iff, for each $i \in I_1^{in}$, it satisfies the equation

$$v_{in}^i = \sum_{k \in I_1^{out}} w(i, k) \cdot (v_{out}^k - v_{out}^i)$$

and, for each $i \in I_2^{in}$, it satisfies the equation

$$v_{in}^i = \sum_{k \in I_2^{out}} w(i, k) \cdot (v_{out}^k - v_{out}^i).$$

That is, $\tau \in \mathcal{T}$ iff $\tau \downarrow V_1 \in \mathcal{T}_1$ and $\tau \downarrow V_2 \in \mathcal{T}_2$. □

The next proposition shows how a diffusion medium can be equivalently given as the parallel composition of two diffusion media. The intuition behind this result is that we can always partition the set I^{in} (the output) into two (nonempty) disjoint subsets I_1^{in} and I_2^{in}, and associate each of them to different diffusion medium. The set I^{out} (the input) is instead partitioned into two, not necessarily disjoint, subsets I_1^{out} and I_2^{out}. In more detail, we have that the set I_1^{out} (and symmetrically for I_2^{out}) contains all indexes of all the cells that are near enough to those in I_1^{in}. It may happen that a given index k may belong to both I_1^{out} and I_2^{out}. In such a case we allow the variable v_{out}^k to be an input variable for both the diffusion media (see Fig. 7).

Proposition 5.9. *Let* $\mathsf{DM}(I^{in}, I^{out}, w)$ *be a diffusion medium,* $I_1^{in} \subset I^{in}$, *with* $I_1^{in} \neq \emptyset$, *and* $I_2^{in} = I^{in} - I_1^{in}$. *Let, moreover:*

- $I_1^{out} = I_1^{in} \cup \{k \in I^{out} \mid \exists i \in I_1^{in} : w(i, k) \neq 0\} \subseteq I^{out}$,

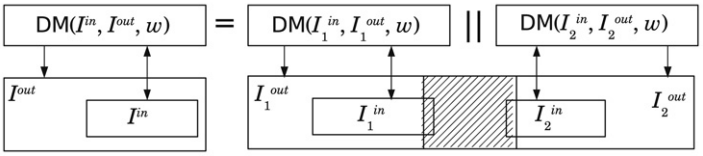

Fig. 7. Decomposition of a diffusion medium.

- $I_2^{out} = I_2^{in} \cup \{k \in I^{out} \mid \exists i \in I_2^{in} : w(i,k) \neq 0\} \subseteq I^{out}$,
- $w_1 = w\lceil I_1^{out} \times I_1^{out}$ *and* $w_2 = w\lceil I_2^{out} \times I_2^{out}$.

Then $\mathsf{DM}(I^{in}, I^{out}, w) = \mathsf{DM}(I_1^{in}, I_1^{out}, w_1) \parallel \mathsf{DM}(I_2^{in}, I_2^{out}, w_2)$.

Proof. We want to prove this proposition directly by Proposition 5.8. To this aim we have to show that $\mathsf{DM}(I_1^{in}, I_1^{out}, w_1)$ and $\mathsf{DM}(I_2^{in}, I_2^{out}, w_2)$ are two compatible diffusion media, that $I^{in} = I_1^{in} \cup I_2^{in}$ and $I^{out} = I_1^{out} \cup I_2^{out}$ and, finally, that the function w satisfies conditions (1) and (2) given in Proposition 5.8.

$I_2^{in} = I^{in} - I_1^{in}$ implies both $I_1^{in} \cap I_2^{in} = \emptyset$ (this and Proposition 5.7 imply that the two diffusion media $\mathsf{DM}(I_1^{in}, I_1^{out}, w_1)$ and $\mathsf{DM}(I_2^{in}, I_2^{out}, w_2)$ are compatible) and $I^{in} = I_1^{in} \cup I_2^{in}$.

Now we prove that $I^{out} = I_1^{out} \cup I_2^{out}$. The implication "$\supseteq$" is trivial since both I_1^{out} and I_2^{out} are subsets of I^{out}. To prove the reverse implication we observe that, if $k \in I^{out}$, then, by Definition 5.6, there exists an $i \in I^{in}$ such that $w(i,k) \neq 0$. If $i \in I_1^{in}$ then $k \in I_1^{out}$; otherwise, i.e. if $i \in I_2^{in}$, $k \in I_2^{out}$. In both cases we are done.

Condition (1) in Proposition 5.8 is satisfied by hypothesis. Finally, by definition of I_1^{out}, if $k \in I_2^{out} - I_1^{out}$ then $w(i,k) = 0$ for each $i \in I_1^{in}$. So, $i \in I_1^{in}$ and $k \in I_2^{out} - I_1^{out}$ or (similarly) $i \in I_2^{in}$ and $k \in I_1^{out} - I_2^{out}$ imply $w(i,k) = 0$ (i.e. also condition (2) in Proposition 5.8 holds). □

5.3. The tissue

We conclude our model of a cardiac tissue by describing how a tissue can be obtained by composing a given number of cells and a diffusion medium.

Definition 5.10. Let:

- $I^{in}, I^{out} \subseteq \mathbb{N}$ be two nonempty sets of indexes with $I^{in} \subseteq I^{out}$;
- $\mathbf{p} = \{p_i \mid i \in I^{out}\}$ be a set of positions in a polar coordinate system;
- $d \in \mathbb{N}$ that represents the maximum distance between interacting cells, i.e. two cells can influence each other by means of electrical stimuli iff their distance is less than or equal to d. Given such a d, we define the distance-based weight function $w_d : I^{out} \times I^{out} \to \mathbb{R}^{\geq 0}$ as follows[5]:

$$w_d(i,k) = \begin{cases} \frac{D}{d^2} \exp\left(d - \frac{\mathsf{d}(i,k)^2}{d}\right) & \text{if } 0 < \mathsf{d}(i,k) \leq d \\ 0 & \text{otherwise.} \end{cases}$$

We assume that for each $k \in I^{out}$ there exists at least an $i \in I^{in}$ with $0 < \mathsf{d}(i,k) \leq d$ and, hence, an $i \in I^{in}$ such that $w_d(i,k) \neq 0$.

We define the *tissue* $T(I^{in}, I^{out}, \mathbf{p}, d)$ to be the automaton we obtain by first composing the set of cells whose indexes are in I^{in} and the diffusion medium $\mathsf{DM}(I^{in}, I^{out}, w_d)$, and then hiding all output variables in $O^{in} = \{v_{in}^i \mid i \in I^{in}\}$ to the external environment, i.e.

$$T(I^{in}, I^{out}, \mathbf{p}, d) \triangleq \mathsf{VarHide}\big(O^{in}, (\|_{i \in I^{in}} \mathsf{cell}_i) \parallel \mathsf{DM}(I^{in}, I^{out}, w_d)\big).$$

We say that two tissues $T(I_1^{in}, I_1^{out}, \mathbf{p}_1, d)$ and $T(I_1^{in}, I_2^{out}, \mathbf{p}_2, d)$ are *compatible* if the following conditions hold:

- $I_1^{in} \cap I_2^{in} = \emptyset$;
- for each i, k such that either (1) $i \in I_1^{in}$ and $k \in I_2^{out} - I_1^{out}$ or (2) $i \in I_2^{in}$ and $k \in I_1^{out} - I_2^{out}$, $\mathsf{d}(i,k) > d$.

Remark 5.11. Let I^{in}, I^{out}, $\mathbf{p}$ and d be as in Definition 5.10. Then, by Definition 4.5, the components of $\mathcal{A} = (\|_{i \in I^{in}} \mathsf{cell}_i) \parallel \mathsf{DM}(I^{in}, I^{out}, w_d)$ are obtained as follows, where we denote the components of each cell_i, of $\mathsf{DM}(I^{in}, I^{out}, w_d)$ and $\mathcal{A}$, by X_i, Q_i, Θ_i, H_i, etc., X_d, Q_d, Θ_d, H_d, etc. and X, Q, Θ, H, etc., respectively.

- $O = (\cup_{i \in I^{in}} O_i) \cup O_d = \{v_{out}^i \mid i \in I^{in}\} \cup \{v_{in}^i \mid i \in I^{in}\} = \{v_{in}^i, v_{out}^i \mid i \in I^{in}\}$;

[5] The Gaussian function we use for the weights is the solution of the parabolic PDE.

- $I = ((\cup_{i\in I^{in}} I_i) \cup I_d) - O = (\{v^i_{in} \mid i \in I^{in}\} \cup \{v^i_{out} \mid i \in I^{out}\}) - O = \{v^i_{out} \mid i \in I^{out} - I^{in}\}$;
- $H = \cup_{i\in I^{in}} H_i$, where each H_i is the set of internal actions of the automaton cell_i, i.e. $H_i = \{resting_i, stimulated_i, end\_stimulus_i, upstroke_i, plateau_i\}$;
- $\mathbf{x} \in Q$ iff $\mathbf{x}\lceil X_i \in Q_i$, for each $i \in I^{in}$, and $\mathbf{x}\lceil X_d \in Q_d$;
- a given $l_i \in H_i$ is enabled in $\mathbf{x} \in Q$ iff it is enabled in $\mathbf{x}\lceil X_i \in Q_i$;
- $\tau \in \mathcal{T}$ iff, for each $i \in I^{in}$, $\tau_i = \tau \downarrow V_i \in \mathcal{T}_i$, and $\tau_d = \tau \downarrow V_d \in \mathcal{T}_d$.

In Definition 5.10 we have hidden all variables that we need to manage the propagation of stimuli along the tissue (i.e. all variables in $O^{in} = \{v^i_{in} \mid i \in I^{in}\}$) to its external environment. This allows us to render visible only the output of the cells, i.e. only the variables v^i_{out}.

Proposition 5.12. *Any tissue $T = T(I^{in}, I^{out}, \mathbf{p}, d)$ is an HIOA.*

Proof. By Lemma 4.7, to prove our statement it will suffice to show that the pre-HIOA $\mathcal{A} = (\|_{i\in I^{in}} \mathsf{cell}_i) \parallel \mathsf{DM}(I^{in}, I^{out}, w_d)$ preserves axiom **E1**. This we do following the same lines in the proof of Proposition 5.4-(1).

Below we denote the components of each cell_i, of $\mathsf{DM}(I^{in}, I^{out}, w_d)$ and $\mathcal{A}$ by X_i, Q_i, Θ_i, H_i, etc., X_d, Q_d, Θ_d, H_d, etc. and X, Q, Θ, H, etc., respectively.

Let $\mathbf{x} \in Q$ and $\upsilon \in traj(U)$ and let us choose a $\tau \in trajs(V)$ such that: (1) $\tau.fstate = \mathbf{x}$ and $\tau \downarrow I = \upsilon$; (2) $\tau_d = \tau \downarrow V_d \in \mathcal{T}_d$; and (3) for each $i \in I^{in}$, $\tau_i = \tau \downarrow V_i$ satisfies Equations (1)–(6) in Fig. 5. Notice that, for each $i \in I^{in}$, $V_i \cap I = \emptyset$ and hence such a condition cannot affect the given input trajectory υ.

If $\tau \in \mathcal{T}$ then, as in the proof of Proposition 5.4-(1), we are easily done. Assume $\tau \notin \mathcal{T}$. In this case $\tau_d \in \mathcal{T}_d$ and $\tau \notin \mathcal{T}$ imply (see Remark 5.11) that $\tau_i \notin \mathcal{T}_i$ for some $i \in I^{in}$. This, together with (3), implies that if $\tau \notin \mathcal{T}$ then there exists one or more $i \in I^{in}$ such that τ_i violates the cell_i stopping condition. Let us denote $J = \{i \in I^{in} \mid \tau_i$ violates the cell_i stopping condition$\}$ and, for each $i \in J$, let t^i_0 be the first $t \in dom(\tau_i) = dom(\tau)$ such that $t^i_0 < \tau_i.ltime$ and $\tau_i(t^i_0)$ satisfies the stopping condition. Let, moreover, t_0 be the minimum of such t^i_0.

Then, for each $i \in J$ we have that $\tau_i\lceil[0, t^i_0] \in \mathcal{T}_i$ and, by the prefix closure property, $\tau'_i = \tau_i\lceil[0, t_0] \leq \tau_i\lceil[0, t^i_0] \in \mathcal{T}_i$. Moreover, for each $i \in J$ with $t^i_0 = t_0$, there is some locally controlled action $l_i \in H_i \subseteq H$ that is enabled in $\tau'_i.lstate$. Finally, again by the prefix closure property, $\tau'_i = \tau_i\lceil[0, t_0] \leq \tau_i \in \mathcal{T}_i$, for each $i \in I^{in} - J$ and $\tau'_d = \tau_d\lceil[0, t_0] \leq \tau_d \in \mathcal{T}_d$.

Exactly as in the proof of Proposition 5.4-(1), we can conclude that $\tau' = \tau\lceil[0, t_0] \in \mathcal{T}$ such that $\tau'.fstate = \tau.fstate = \mathbf{x}$, $\tau' \downarrow \leq \tau \downarrow = \upsilon$; moreover, τ' is closed and some locally controlled action $l_i \in H$ is enabled in $\tau'.lstate$ (this is because l_i is enabled in $\tau'_i.lstate = (\tau'.lstate)\lceil X_i$). Hence, axiom **E1** is satisfied. □

Now we start proving some interesting properties of a tissue. Namely, our first result is that the parallel composition of two compatible tissues is also a tissue.

Proposition 5.13. *Let $T_1 = T(I^{in}_1, I^{out}_1, \mathbf{p}_1, d)$ and $T_2 = T(I^{in}_2, I^{out}_2, \mathbf{p}_2, d)$ be two compatible tissues. Let, moreover, $I^{in} = I^{in}_1 \cup I^{in}_2$, $I^{out} = I^{out}_1 \cup I^{out}_2$, and $\mathbf{p} = \mathbf{p}_1 \cup \mathbf{p}_2$. Then: $T = T(I^{in}, I^{out}, \mathbf{p}, d) = T_1 \parallel T_2$.*

Proof. In the remainder of this proof we use the following notations:

- $C_1 = \|_{i\in I^{in}_1} \mathsf{cell}_i$, $C_2 = \|_{i\in I^{in}_2} \mathsf{cell}_i$ and $C = \|_{i\in I^{in}} \mathsf{cell}_i$;
- $O^{in}_1 = \{v^i_{in} \mid i \in I^{in}_1\}$, $O^{in}_2 = \{v^i_{in} \mid i \in I^{in}_2\}$ and $O^{in} = \{v^i_{in} \mid i \in I^{in}\}$;
- $w_1 = w_d\lceil I^{out}_1 \times I^{out}_1$ and $w_2 = w_d\lceil I^{out}_2 \times I^{out}_2$;
- $\mathsf{DM}_1 = \mathsf{DM}(I^{in}_1, I^{out}_1, w_1)$, $\mathsf{DM}_2 = \mathsf{DM}(I^{in}_2, I^{out}_2, w_2)$ and, finally, $\mathsf{DM} = \mathsf{DM}(I^{in}, I^{out}, w_d)$.

Then, by Definition 5.10, we have that $T_1 = \mathsf{VarHide}\big(O^{in}_1, C_1 \parallel \mathsf{DM}_1\big)$, $T_2 = \mathsf{VarHide}\big(O^{in}_2, C_2 \parallel \mathsf{DM}_2\big)$ and $T = \mathsf{VarHide}\big(O^{in}, C \parallel \mathsf{DM}\big)$.

We first prove that $C \parallel \mathsf{DM} = (C_1 \parallel \mathsf{DM}_1) \parallel (C_2 \parallel \mathsf{DM}_2)$. Since composition is both associative and commutative, we have that $(C_1 \parallel \mathsf{DM}_1) \parallel (C_2 \parallel \mathsf{DM}_2) = (C_1 \parallel C_2) \parallel (\mathsf{DM}_1 \parallel \mathsf{DM}_2) = C \parallel (\mathsf{DM}_1 \parallel \mathsf{DM}_2)$. Now we prove that $\mathsf{DM} = \mathsf{DM}_1 \parallel \mathsf{DM}_2$. This comes directly from Proposition 5.8 because sure $w_1 = w_d\lceil I^{out}_1 \times I^{out}_1$ and $w_2 = w_d\lceil I^{out}_2 \times I^{out}_2$; moreover, for each i, k such that either (1) $i \in I^{in}_1$ and $k \in I^{out}_2 - I^{out}_1$ or (2) $i \in I^{in}_2$ and $k \in I^{out}_1 - I^{out}_2$, $\mathrm{d}(i, k) > d$ and, hence, $w_d(i, k) = 0$.

Now, for $i = 1, 2$, $O^{in} \cap I_i = O^{in} \cap \{v^i_{out} \mid i \in I^{out}_i - I^{in}_i\} = \emptyset$ and $O^{in} \cap O_i = O^{in} \cap \{v^i_{out}, v^i_{in} \mid i \in I^{in}_i\} = O^{in}_i$ (here I_i and O_i are the sets of input and output variables of the automaton $C_i \parallel \mathsf{DM}_i$; see Remark 5.11). Thus by Proposition 4.8 we have that

$$\begin{aligned} T_1 \parallel T_2 &= \mathsf{VarHide}\big(O^{in}_1, C_1 \parallel \mathsf{DM}_1\big) \parallel \mathsf{VarHide}\big(O^{in}_2, C_2 \parallel \mathsf{DM}_2\big) \\ &= \mathsf{VarHide}(O^{in}, (C_1 \parallel \mathsf{DM}_1) \parallel (C_2 \parallel \mathsf{DM}_2)) = \mathsf{VarHide}((O^{in}, C \parallel \mathsf{DM}) = T. \quad \square \end{aligned}$$

The next proposition shows the main result of this section. It proves how a tissue can be decomposed into two compatible tissues. As we will see in Section 6, this result will permit us to significantly improve the speedup of the simulation process. Our process of decomposition of a tissue is described in Fig. 8. It illustrates a possible decomposition of a tissue made of eight cells into two tissues, each of which is made of four cells. The diffusion medium DM_1 shares its input variables with the cells of indexes in $I^{out} = \{1, 2, 3, 4, 5, 6\}$. Each such variable is represented by an arrow exiting from a cell and entering into the

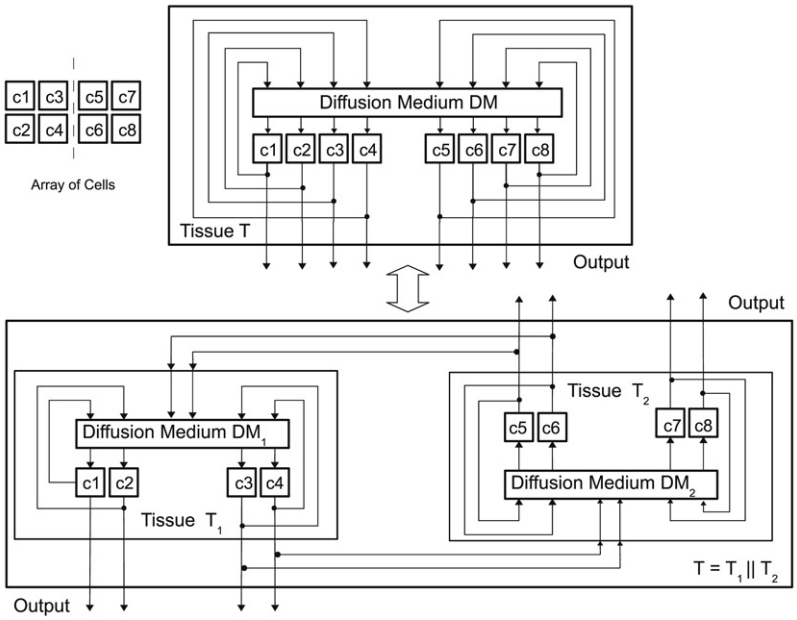

Fig. 8. Decomposition of tissue.

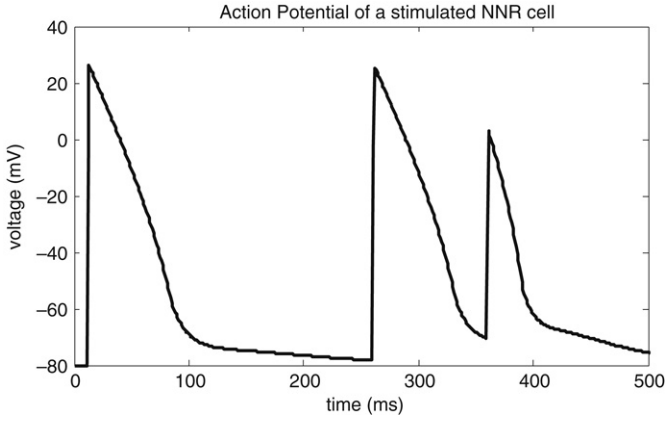

Fig. 9. Action Potential (AP) of a neonatal rat cell.

diffusion medium. It also shares its output variables with the cells whose indexes are in $I^{in} = \{1, 2, 3, 4\}$ that represents the cells of which the tissue T_1 is made of. We represent such variables with an arrow exiting from the diffusion medium and entering into a cell. Notice that all of them are internal to the tissue T_1. Indeed the external behavior of this tissue is given in terms of variables in $\{v^i_{out} \mid i \in I^{in}\}$.

Proposition 5.14. *Let $T = T(I^{in}, I^{out}, \mathbf{p}, d)$ be a tissue, and I^{in}_1 and I^{in}_2 be two nonempty sets that partition I^{in} into two disjoint subsets. Let, moreover:*

- $I^{out}_1 = I^{in}_1 \cup \{k \in I^{out} \mid \exists i \in I^{in}_1 : 0 < d(i, k) \leq d\}$,
- $I^{out}_2 = I^{in}_2 \cup \{k \in I^{out} \mid \exists i \in I^{in}_2 : 0 < d(i, k) \leq d\}$,
- $\mathbf{p}_1 = \{p_i \mid i \in I^{out}_1\}$ *and* $\mathbf{p}_2 = \{p_i \mid i \in I^{out}_2\}$,
- $T_1 = T(I^{in}_1, I^{out}_1, \mathbf{p}_1, d)$ *and* $T_2 = T(I^{in}_2, I^{out}_2, \mathbf{p}_2, d)$.

Then: $T = T_1 \parallel T_2$.

Proof. We prove this proposition by Proposition 5.13. To this aim, we have to show that the tissues T_1 and T_2 are compatible, that $I^{in} = I^{in}_1 \cup I^{in}_2$ (this is trivially true by hypothesis), that $I^{out} = I^{out}_1 \cup I^{out}_2$ and, finally, that $\mathbf{p} = \mathbf{p}_1 \cup \mathbf{p}_2$.

We first prove that $I^{out} = I^{out}_1 \cup I^{out}_2$ (and hence that $\mathbf{p} = \mathbf{p}_1 \cup \mathbf{p}_2$). The implication "$\supseteq$" is trivial since both I^{out}_1 and I^{out}_2 are subsets of I^{out}. On the other hand, if $k \in I^{out}$ then, by Definition 5.10, there exists at least an $i \in I^{in}$ such that $0 < \mathrm{d}(i, k) \leq d$. If $i \in I^{in}_1$ then $k \in I^{out}_1$; otherwise, i.e. if $i \in I^{in}_2$, $k \in I^{out}_2$. In both cases we are done.

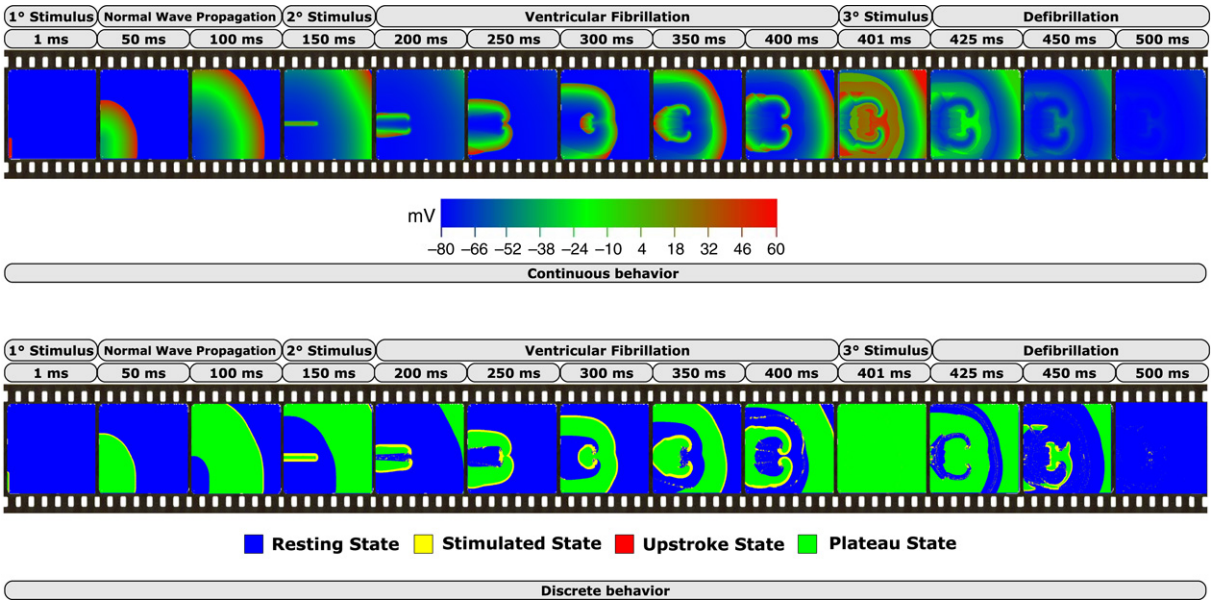

Fig. 10. Snapshots during simulation of cardiac tissue stimulation using Hybrid I/O Automata.

It remains to prove that the tissues T_1 and T_2 are compatible. By hypothesis, $I_1^{in} \cap I_2^{in} = \emptyset$. Moreover, if $i \in I_1^{in}$ and $k \in I_2^{out} - I_1^{out}$ then (by definition of I_1^{out}) either $\mathrm{d}(i,k) = 0$ or $\mathrm{d}(i,k) > d$. The former case is not possible since, if $\mathrm{d}(i,k) = 0$, then $k = i \in I_1^{in} \subseteq I_1^{out}$. As a consequence, we have that if $i \in I_1^{in}$ and $k \in I_2^{out} - I_1^{out}$ then $\mathrm{d}(i,k) > d$. Similarly, we can prove that $i \in I_2^{in}$ and $k \in I_1^{out} - I_2^{out}$ imply $\mathrm{d}(i,k) > d$. Finally, by Definition 5.10, T_1 and T_2 are compatible. □

In other ongoing work, we are investigating the use of abstraction techniques that allow us to the learn and predict spatiotemporal properties in networks of excitable cells. Specifically, in [16], we show that, in a network of excitable cells represented using CLHAs, it is possible to predict the onset of spiral waves by examining the discrete structure given by the distribution of CLHA modes.

6. Simulation of a tissue

In this subsection, we instantiate the cardiac-tissue model of Definition 5.10 to the neonatal rat (NNR) AP. Fig. 9 shows the AP waveform for a single NNR cell. All parameters used are reported in Table 1 and are taken from [25].

Fig. 10 shows the simulation results for a cardiac tissue of 400 × 400 NNR cells, stimulated three times during the simulation in different regions. The results of this simulation demonstrate the feasibility of HIOAs to capture and mimic different spatiotemporal behavior of wave propagation in 2D isotropic cardiac tissue, including: normal wave propagation along the tissue (1–150 ms); the onset of spirals (200–250 ms); the break-up of spirals into more complex spatiotemporal patterns, indicating the transition to fibrillation (250–400 ms); and the recovery of the tissue to the rest with the elimination of all waves through electrical defibrillation (400–500 ms).

Proposition 5.14 allows us to decompose a tissue into several interacting sub-tissues whose *parallel composition is guaranteed to have the same behavior as the original tissue*. This property can be used to parallelize the simulation of a tissue by using multi-core processors with shared memory. As the Fig. 8 shows, we can split the tissue in two parts (or more) and assign the computation of each part to a different core. We implemented a simulator, based on time-step integration, using C++ and the OpenMP library [24] in order to distribute the computation on different cores. To test such a simulator we have used a Mac Book (MB) equipped with an Intel Dual-Core Duo *2,2* GHz and 2 Gbytes of RAM, and a Mac Pro (MP) equipped with a 2 × 3 GHz Dual-core Intel Xeon 5100 and *5* Gbytes of RAM. Table 2 shows the results of the obtained speedup comparing the computational time of a single core with the performance of multiple cores, in an experiment of 1 s of wave propagation and a time step of 0.005 ms.

7. Conclusions

In this paper, we have presented a new HIOA-based modeling framework for capturing the spatiotemporal behavior of electrical waves in a 2D excitable tissue. This framework extends cellular-automata-based approaches by employing HIOAs (instead of finite automata) to capture single-cell behavior and by factoring out the diffusion-based communication into another HIOA. These extensions allow a better approximation, for a large variety of excitable tissues, of the nonlinear single-cell reaction and of the possibly non-isotropic Laplacian diffusion, while still being amenable to formal analysis.

Table 2
Speedup of 1 s simulation with a time step of 0.005 ms.

Tissue size	1-core MB (min)	2-core MB (min)	Speedup	1-core MP (min)	4-core MP (min)	Speedup
100 × 100	41,7	23.6	1.76×	28.3	11.3	2.50×
200 × 200	176.7	96.7	1.82×	136.7	50	2.73×
300 × 300	403.3	224	1.80×	310	113.6	2.73×
400 × 400	730	425	1.71×	561.7	213.3	2.63×

A primary benefit of using the HIOA formalism is compositionality. In particular, our decomposition result (Proposition 5.14) allows one to hierarchically decompose a tissue composed of excitable-cell automata and the diffusion-medium automaton into sub-tissues. This result was exploited to considerably enhance the performance of simulation via parallelization. Compositionality is also exploited in ongoing work to devise efficient algorithms for proving spatiotemporal properties of excitable tissue (see [16] for a discussion of various spatial logics).

HIOA models of single cells are also amenable to formal analysis. Symbolic reachability analysis is a well-established technique in the model checking of linear hybrid systems and are now supported by several tools such as d/dt [4] and HyTech [19]. We are interested in extending these techniques from linear to cycle-linear hybrid automata (CLHAs) so that they can be applied to excitable-cell phenomena. Recent progress in this direction, for the symbolic analysis of the bifurcation and period-doubling properties of the neuron action potential, is reported in [26].

Acknowledgements

The authors would like to thank the anonymous reviewers for their constructive contributions. The authors also acknowledge Prof. Erez Zadok and Sean Callanan who provided the Mac Pro multicore machine necessary to test the distributed version of our simulator.

References

[1] R. Alur, R. Grosu, Y. Hur, V. Kumar, I. Lee, Modular specifications of hybrid systems in CHARON, in: Hybrid Systems: Computation and Control, Third International Workshop, in: Lect. Notes Comp. Sci., vol. 1790, 2001, pp. 6–19.
[2] K. Amonlirdviman, R. Ghosh, J.D. Axelrod, C.J. Tomlin, A hybrid systems approach to modelling and analyzing planar cell polarity, in: Proceedings of the International Conference on Systems Biology, 2002.
[3] M. Antoniotti, B. Mishra, C. Piazza, A. Policriti, M. Simeoni, Modeling cellular behavior with hybrid automata: Bisimulation and collapsing, in: Computational Methods in Systems Biology, First International Workshop, in: Lect. Notes Comp. Sci., vol. 2602, 2003, pp. 57–74.
[4] E. Asarin, T. Dang, O. Maler, The d/dt tool for verification of hybrid systems, in: Proc. of the 14th International Conference, Computer Aided Verification, 2002, pp. 365–370.
[5] E. Bartocci, F. Corradini, M.R. Di Berardini, E. Entcheva, R. Grosu, S.A. Smolka, Spatial networks of hybrid I/O automata for modeling excitable tissue, in: The Proceedings of 1st Workshop from Biology to Concurrency and Back, 2007, pp. 86–102.
[6] D. Barkley, M. Knees, L.S. Tuckerman, Spiral-wave dynamics in a simple-model of excitable media — the transition from simple to compound rotation, Phys. Rev. A 42 (4) (1990) 2489–2492.
[7] G. Bub, L. Glass, N.G. Publicover, A. Shrier, Bursting calcium rotors in cultured cardiac myocyte monolayers, Proc. Natl. Acad. Sci. USA 95 (17) (1998) 10283–10287.
[8] G. Bub, A. Shrier, Propagation through heterogeneous substrates in simple excitable media models, Chaos 12 (3) (2002) 747–753.
[9] A. Deshpande, D. Godbole, A. Gollu, P. Varaiya, Design and evaluation of tools for automated highway systems, in: Hybrid Systems III: Verification and Control, in: Lect. Notes Comp. Sci., vol. 1066, 1996, pp. 138–148.
[10] D. Di Francesco, D. Noble, A model of cardiac electrical activity incorporating ionic pumps and concentration changes, Philos. Trans. R Soc. Lond. B Biol. Sci. 307 (1985) 353–398.
[11] C. Lividas, J. Lygeros, N.A. Lynch, High-level modeling and analysis of TCAS, in: Proc. of the IEEE Real-Time Systems Symposium, 1999, pp. 115–125.
[12] N.A. Lynch, R. Segala, F.W. Vaandrager, Hybrid I/O automata, Inform. Comput. 38 (1) (2003) 105–107.
[13] C.H. Luo, Y. Rudy, A dynamic model of the cardiac ventricular action potential. I. Simulations of ionic currents and concentration changes, Circ. Res. 74 (6) (1994) 1071–1096.
[14] M. Gerhardt, H. Schuster, J.J. Tyson, A cellular automation model of excitable media including curvature and dispersion, Science 247 (4950) (1990) 1563–1566.
[15] R. Ghosh, A. Tiwari, C. Tomlin, Automated symbolic reachability analysis; with application to delta-notch signaling automata, in: Hybrid Systems: Computation and Control, 6th International Workshop, in: Lect. Notes Comp. Sci., vol. 2623, 2003, pp. 233–248.
[16] R. Grosu, E. Bartocci, F. Corradini, E. Entcheva, S.A. Smolka, A. Wasilewska, Learning and detecting emergent behavior in networks of cardiac myocytes, in: Proc. of 11th International Conference on Hybrid Systems: Computation and Control, in: Lect. Notes Comp. Sci., vol. 4981, 2008, pp. 229–243.
[17] R. Grosu, S. Mitra, P. Ye, E. Entcheva, I.V. Ramakrishnan, S.A. Smolka, Learning cycle-linear hybrid automata for excitable cells, in: Proc. of the 10th International Conference of Hybrid Systems: Computation and Control, in: Lect. Notes Comp. Sci., vol. 4416, 2007, pp. 245–258.
[18] T.A. Henzinger, The theory of Hybrid Automata, in: Proc. of the 11th IEEE Symposium on Logic in Computer Science, 1996, pp. 278–293.
[19] T.A. Henzinger, P. Ho, H. Whong-Toi, HYTECH: A model checker for hybrid systems, in: Proc. of the 9th International Conference, Computer Aided Verification, 1997, pp. 460–463.
[20] A.L. Hodgkin, A.F. Huxley, A quantitative description of membrane currents and its application to conduction and excitation in nerve, J. Physiol. 117 (1952) 500–544.
[21] D.K. Kaynar, N.A. Lynch, R. Segala, F.W. Vaandrager, The theory of timed I/O automata, in: Synthesis Lecture on Computer Science, Morgan & Claypool Publishers, 2006.
[22] A. Karma, New paradigm for drug therapies of cardiac fibrillation, Proc. Natl. Acad. Sci. USA 97 (11) (2000) 5687–5689.
[23] H. Kitano, Computational systems biology, Nature 420 (2002) 206–210.
[24] The OpenMP Architecture Revew Board. OpenMP 3.0 API Specifications, May 2008.
[25] P. Ye, E. Entcheva, S.A. Smolka, R. Grosu, Efficient modeling of excitable cells using cycle-linear hybrid automata, IET Syst. Biol. 2 (1) (2008) 24–32.
[26] P. Ye, R. Grosu, S.A. Smolka, Symbolic analysis of the neuron action potential, in: The Proc. of 2nd IEEE International Conference on Bioinformatics and Biomedical Engineering, ICBBE2008, IEEE, 2008.