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Discrete Semantics for Hybrid Automata

Avoiding Misleading Assumptions in Systems Biology

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Abstract Many natural systems exhibit a hybrid behavior characterized by a set of continuous laws which are switched by discrete events. Such behaviors can be described in a very natural way by a class of automata called hybrid automata. Their evolution are represented by both dynamical systems on dense domains and discrete transitions. Once a real system is modeled in a such framework, one may want to analyze it by applying automatic techniques, such as Model Checking or Abstract Interpretation. Unfortunately, the discrete/continuous evolutions not only provide hybrid automata of great flexibility, but they are also at the root of many undecidability phenomena. This paper addresses issues regarding the decidability of the *reachability* problem for hybrid automata (i.e., "can the system reach a state a from a state b?") by proposing an "inaccurate" semantics. In particular, after observing that dense sets are often abstractions of real world domains, we suggest, especially in the context of biological simulation, to avoid the ability of distinguishing between values whose distance is less than a fixed ϵ. On the ground of the above considerations, we propose a new semantics for first-order formulæ which guarantees the decidability of reachability. We conclude providing a paradigmatic biological example showing that the new semantics mimics the real world behavior better than the precise one.

Keywords Hybrid automata, First-Order Logics, Approximate Semantics, Reachability Problem

1 Introduction

A huge amount of data is available from modern (*wet* and *dry*) technologies employed in studying Biology today. This data is, in general, very heterogeneous and provides "views" at different levels of abstraction, and the ultimate challenge is the attempt to distill from it the *emerging* behavior of a system. Such a behavior can be defined as what is observable only when the entire system and its dynamics are studied as-a-whole. The corresponding field of study is named Systems Biology and is currently enjoying a great success, with contributions given from researchers with very different backgrounds.

In many cases computer scientists have considered mathematical models of biological systems as starting points and rephrased them inside their frameworks in order to exploit automatic analysis tools. We mention here some of such models. In 1969, S.A. Kauffman [1] presented Boolean Networks as a model for genetic regulatory networks. Petri Nets were introduced by C.A. Petri in 1962 [2] as a language to describe discrete distributed systems and are now a classic in modeling biochemical networks and, in general, biological systems (see, e.g., [3,4] where also stochastic and continuous extensions are considered). In this context, [5] establishes a bridge between logical models and Petri net formalism in the study of biological regulatory networks. Process Calculi (see, e.g., [6]) have been devel-

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oped to model networks of communication protocols. In the representation of biological systems processes can be used to model the reactants involved in the system (each molecule is represented by a process). Reactions and, more generally, interactions, are seen as communications between processes. Stochastic Pi-calculus [7] has been successfully used in the modeling of biochemical systems and, in the same spirit, other process algebra have been introduced with the aim of providing languages closer to the requirements of biology (see, e.g., [8] and [9]). A more complete description and classification of the formalisms introduced in Systems Biology can be found in [10], where a distinction between *mathematical* and *computational* models is introduced and investigated.

The above mentioned emerging behavior is clearly touching deep into the intrinsic properties of the systems under study and, hence, the kind of (mathematical) tools employed for their description is a rather delicate point. In this paper we try to give our own contribution to the study of Systems Biology by concentrating on a specific decidability issue arising when tools allowing a mixed form of discrete/continuous description (extremely *natural* for natural phenomena) are used.

The use of such *hybrid* tools is easily justifiable, especially when dealing with biological systems. Continuous approximations simplify the analysis and allow to characterize complex events using—simple, compact, deterministic, and continuous—equations. On the other hand, for example, both artificial digital devices and natural discrete control networks, need to be described by simple—although often large—interaction graphs. Neither one of the methodologies is sufficient and the situation is clear: none is "the winner". Both discrete and continuous approaches have merits, and formal tools allowing to use together the two points of view have a great potential.

Combining discrete and continuous modeling tools and techniques, however, can be done in so many ways that it is easy in principle but can be extremely difficult in practice.

Hybrid automata (see, e.g., [11,12]) were proposed to model hybrid systems and, due to their flexible dynamics, have obtained a growing consensus in the scientific community. Automatic deduction of properties for such systems, however, often forces us to deal with *undecidability* phenomena. Since the first half of the 20-th century, there exist decision problems (i.e., problems having a yes/no answer) which cannot be tackled algorithmically. In particular, it has been proved that algorithms which provides the correct answer for any instance of such problems cannot exist. Such problems are said be *undecidable* as opposed to *decidable* problems for which there exists a decision algorithm. For example, in the context of hybrid automata, one may inquire which questions are decidable, i.e., what we can hope to deduce automatically about hybrid automata. Unfortunately, expressiveness and the assumption of a dense and infinite state space bring along difficulties and limitations. Many undecidability and heavy-complexity results have been proved for general hybrid automata exploiting density of state space [13]. If the possible discrete/continuous configurations of hybrid automata are restricted *by definition*, as in the family of *o-minimal* systems [14], one could hope to maintain a level of faithfulness of the representation that surpasses by far either that of finite automata or a that of a solvable (numerically or analytically) system of differential equations. Following the above considerations, many decidable classes of hybrid automata, characterized by a specific set of restrictions, have been proposed (see, e.g., [12,14,15]). Nevertheless, most of them have high computational complexity and are not suitable for applications.

Our aim here is to tackle the undecidability/complexity problem of hybrid automata from a different perspective. Starting from practical considerations on the application of hybrid automata to biological systems, we propose different semantics allowing us simplifications in the study of the hybrid automata. In accordance with J.T. Schwartz's observations [16], we think that classical models have a "*pernicious influence*" on the investigation of Nature, as they are too abstract and their infinite precision introduces regrettable complexity which has no correspondence with the phenomenon to be modeled. For such reasons, we consider the possibility of distilling conditions ensuring a more realistic semantics for our models.

Biological systems have been the inspiration for the above mentioned semantics. This must be intended in the sense that Nature provides scenarios in which, often, either a complete understanding of the underlying physical mechanisms is lacking (and must be approximated), or some form of noise must be taken into account. Boolean regulatory networks, signaling pathways, biochemical networks in general, can therefore be modeled by hybrid automata (see [17,9]), in which the continuous component is basically approximating a dynamics which is either not fully understood or too costly to simulate. Moreover, another usual measure taken to better approximate natural behaviors, consists in introducing—either on top of a discrete events network description or on a hybrid system—some stochastic ingredients. We, therefore, do not consider a chance that one of the most popular simulation

algorithms on the market starts with an observation very similar to our starting point. As observed by Gillespie in [18], "it is physically meaningless to talk about the number of molecules whose centers lie inside ..." a sphere "... in the required limit of vanishingly small δt ...". We will ultimately formalize the intuition that (natural) noise does not allow the (un-natural) undecidability results obtained, for example, by an infinite partitioning of a continuous bounded portion of the states space.

As already done in [19], we want to address undecidability results in hybrid automata by imposing bounded guards and a sort of "quantic value". However, our proposal diverges from such work because we consider continuous both time and space domains, while the previously mentioned paper discretizes both of them. Our work differs also from regularization method introduced in [20]: the latter is a technique to deduce models which guarantee a minimal time distance $\epsilon > 0$ between discrete events as opposed the former which is a method working on the original models and admitting continuous time events. In some sense, our work is more similar to the idea expressed in [21–23]. In particular, these papers suggest an approximate (bi)simulation relation which ensure to group all the continuous evolutions of an hybrid automaton whose reciprocal distances are upper bounded. Nevertheless, our method seems to be more general as it does not distinguish between continuous and discrete evolutions and it is based on a new semantics framework which in theory can be applied to any class of hybrid automata. As far as other works concerning biological inspired hybrid models, we mention here [24] where the interplay between continuous, discrete and stochastic aspects in molecular processes is analyzed.

As a "significant" biological example we consider the Delta-Notch signaling mechanisms. Such mechanism is at the basis of cell differentiation in many biological systems (e.g., emergence of ciliated cells in *Xenopus* embryonic skin [25], sensory cell differentiation in the zebrafish ear [26], and neurogenesis in *Drosophila* [27,28]). It relays on the concentrations of two proteins, Delta and Notch, inside neighboring cells. In particular, Notch production is triggered by high Delta levels in neighboring cells, while Delta production is triggered by low Notch concentrations in the same cell. High Delta concentration leads to differentiated cells. If we consider a system involving two cells starting with the same values of Delta and Notch, the classical models (both continuous and hybrid) exhibit a Zeno behavior which never reaches one of the two possible stable states, i.e., a state in which one of the two cells is differentiated and the other is not. However, this is a mathematical artifact which never occurs in Nature where after a finite amount of time an equilibrium is always obtained. Using our approach with hybrid automata and ϵ-semantics, the Zeno behavior disappears and, coherently with what one can observe in Nature, each evolution eventually reaches an equilibrium.

The paper is organized as follows: after giving some basic definitions in Sections 2 and 3, we present our proposal in Sections 4, we motivate the use of a limited but decidable class of hybrid automata to model any kind of hybrid systems in Section 5, and we illustrate it on the Delta-Notch biological example in Section 6. Finally, we comment on our work by comparing it with some further results from the literature, in Section 7.

This is an extended version of [29].

2 Logics and Theories

In this section, we review the notion of first-order theory. For a more detailed treatment of these notions, the reader may refer, for example, to [30,31].

A *first-order language* $\mathcal{L}$ is a tuple $\langle Var, Const, Funct, Rel, \mathrm{Ar}\rangle$, where *Var* is a set of variables, *Const* is a set of constant values, *Funct* is a set of functional operators, *Rel* is a set of relational symbols, and the "arity" function $\mathrm{Ar} : Funct \cup Rel \to (\mathbb{N} \setminus \{0\})$ associates to each element of *Funct* and *Rel* the number of arguments it takes.

A *term* of $\mathcal{L}$ can be defined as:

$$term ::= X \mid c \mid \mathbf{f}(term_1, \ldots, term_{\mathrm{Ar}(\mathbf{f})})$$

where X is a variable in *Var*, c is a constant in *Const*, and $\mathbf{f}$ is a function in *Funct*.

An *atomic formula* φ_a of $\mathcal{L}$ has the form $\top$ or $\bot$ (*true* and *false*, respectively) or $\mathbf{R}(term_1, \ldots, term_{\mathrm{Ar}(\mathbf{R})})$, where $\mathbf{R}$ is a relational operator in *Rel* and $term_i$ is a term of $\mathcal{L}$ for all $i \in [1, \mathrm{Ar}(\mathbf{R})]$. Moreover, a *formula* φ of $\mathcal{L}$ is defined as follows:

$$\varphi ::= \varphi_a \mid \varphi_1 \vee \varphi_2 \mid \neg\varphi_1 \mid \forall X\, \varphi_1$$

where φ_a is an atomic formula of $\mathcal{L}$, X is a variable in *Var*, and φ_i is a formula of $\mathcal{L}$ for all $i \in \{1, 2\}$. We define $\varphi_1 \wedge \varphi_2$ as a short hand for $\neg(\neg\varphi_1 \vee \neg\varphi_2)$, $\varphi_1 \rightarrowtriangle \varphi_2$ as a short hand for $(\neg\varphi_1) \vee \varphi_2$, and $\exists X\, \varphi_1$ as a short hand for $\neg\forall X\, \neg\varphi_1$. The two symbols $\exists$ and $\forall$ are called *quantifiers*.

An occurrence of a variable $X \in Var$ is *bound* or *quantified* in a formula φ, if it occurs in a φ's sub-formula of the kind either $\forall X\, \bar{\varphi}$ or $\exists X\, \bar{\varphi}$. An occurrence of a variable is *free* if it is not bound. Modulo renaming we can safely assume that the variables which occur bound in a formula do not occur free, and vice-versa. A *sentence*

is a formula such that all the variable occurrences are bound. The set of free variables occurring in the first-order formula φ is denoted by $Free(\varphi)$. We will use the notation $\varphi[X_1, \ldots, X_m]$ ($\varphi[X]$, where $X = (X_1, \ldots, X_m)$) to stress the fact that $Free(\varphi)$ includes the set of variables $\{X_1, \ldots, X_m\}$ (the set of components of the vector X, respectively).

A *model* or *semantics* of a language $\mathcal{L}$ is a tuple $\langle M, \texttt{Const}, \texttt{Funct}, \texttt{Rel}\rangle$, where:

- M is a nonempty set called *support*;
- $\texttt{Const} : Const \to C \subseteq M$ is an interpretation for (the elements of) *Const*;
- $\texttt{Funct} : Funct \to \bigcup_{k=1}^{\infty}\left(\prod_{i=1}^{k} M \to M\right)$, with $\texttt{Funct}(\mathbf{f}) : \prod_{i=1}^{\mathrm{Ar}(\mathbf{f})} M \to M$, is an interpretation for (the elements of) *Funct*;
- $\texttt{Rel} : Rel \to \bigcup_{k=1}^{\infty}\left(\prod_{i=1}^{k} M \to \{\top, \bot\}\right)$, with $\texttt{Rel}(\mathbf{R}) : \prod_{i=1}^{\mathrm{Ar}(\mathbf{R})} M \to \{\top, \bot\}$, is an interpretation for (the elements of) *Rel*.

Let $\mathcal{M}$ be a model of $\mathcal{L}$ with support M, $\varphi[X_1, \ldots, X_i, \ldots, X_m]$ be a formula of $\mathcal{L}$, and $p \in M$. The expression obtained by syntactically replacing X_i by p is denoted by $\varphi[X_1, \ldots, X_{i-1}, p, X_{i+1}, \ldots, X_n]$ and, strictly speaking, is to be intended as obtained after adding a new constant c_p to the language. With a slight abuse of notation we will use formulæ to also denote such expressions.

The semantics of $\mathcal{L}$-formulæ with respect to a model $\mathcal{M}$ is defined in the standard way (see [30,31]). In particular, we say that a formula $\varphi_a[p_1, \ldots, p_m]$, where φ_a is atomic, holds in $\mathcal{M}$ if applying the interpretations of the constant, functional, and relational operators we obtain the truth value $\top$. The formula $\varphi_1[p_1, \ldots, p_m] \vee \varphi_2[p_1, \ldots, p_m]$ holds in $\mathcal{M}$ if either the first or the second disjunct holds in $\mathcal{M}$. The formula $\neg\varphi_1[p_1, \ldots, p_m]$ holds in $\mathcal{M}$ if $\varphi_1[p_1, \ldots, p_m]$ does not. The formula $\forall X\, \varphi_1[X, p_1, \ldots, p_m]$ holds in $\mathcal{M}$ if for each $p \in M$ the formula $\varphi_1[p, p_1, \ldots, p_m]$ holds. We say that a formula $\varphi[X_1, \ldots, X_m]$ in $\mathcal{L}$ is *satisfiable* in $\mathcal{M}$ if there exist m values in M, $p_1, \ldots, p_m$, such that $\varphi[p_1, \ldots, p_m]$ holds in $\mathcal{M}$. Moreover, we say that $\varphi[X_1, \ldots, X_m]$ is *valid* if $\varphi[p_1, \ldots, p_m]$ holds in $\mathcal{M}$ for all $p_1, \ldots, p_m \in M$. When the model $\mathcal{M}$ is clear from the context we will simply say that a formula holds (is satisfiable or is valid, respectively).

When we speak of models over M, where M is a nonempty set, we are referring to those models whose support is M. Moreover, when $\texttt{Const} : Const \to C$ is clear from the context, we use $\langle M, C, \texttt{Funct}, \texttt{Rel}\rangle$ to mean $\langle M, \texttt{Const}, \texttt{Funct}, \texttt{Rel}\rangle$.

Given a set Γ of sentences and a sentence φ, we say that φ is a *logical consequence* of Γ (denoted by $\Gamma \models \varphi$) if for each model $\mathcal{M}$ it holds that if each formula of Γ is valid in $\mathcal{M}$ ($\mathcal{M} \models \Gamma$), then φ is valid in $\mathcal{M}$. As a consequence of completeness of first-order logic, we may equivalently say that φ is provable from Γ (see [30,31]). A *theory* $\mathcal{T}$ is a set of sentences such that if $\mathcal{T} \models \varphi$, then $\varphi \in \mathcal{T}$. Given a language $\mathcal{L}$ and a model $\mathcal{M}$ the *complete theory* $\mathcal{T}(\mathcal{M})$ of $\mathcal{M}$, is the set of all the sentences of $\mathcal{L}$ which are valid in $\mathcal{M}$. Given a model $\langle M, C, \texttt{Funct}, \texttt{Rel}\rangle$, we also indicate its complete theory by either $\langle M, C, \texttt{Funct}, \texttt{Rel}\rangle$ or $\langle M, C, f_0, \ldots, f_n, r_0, \ldots r_m\rangle$, where $\texttt{Funct} = \{f_0, \ldots, f_n\}$ and $\texttt{Rel} = \{r_0, \ldots, r_m\}$. If there exists an algorithm for deciding whether a sentence φ belongs to $\mathcal{T}$ or not, we say that $\mathcal{T}$ is *decidable*. By analogy, we say that $\mathcal{M}$ is decidable, if $\mathcal{T}(\mathcal{M})$ is decidable. It is easy to see that given a model $\mathcal{M}$, its complete theory $\mathcal{T}(\mathcal{M})$ is decidable if and only if both the satisfiability and the validity of formulæ in $\mathcal{M}$ are decidable.

Example 1 The theory $\langle \mathbb{R}, 0, 1, +, *, <\rangle$ is the first-order theory of polynomials over the reals and it is also known as Tarski theory [32]. Such theory is decidable and many algorithms have been proposed to decide whether a formula belongs to it or not [33–37].

Notice that any theory defines both syntax and semantics of the corresponding language. For such a reason, from time to time, we refer to a theory $\mathcal{T}$ meaning the language associate to $\mathcal{T}$.

In the rest of this paper we will only refer to theories of the form $\mathcal{T}(\mathcal{M})$ for some model $\mathcal{M}$.

3 Hybrid Automata

We introduce some notations and conventions. Capital letters X, X', X_m, and $X_m{}'$, where $m \in \mathbb{N}$, denote variables ranging over $\mathbb{R}$. Analogously, Z denotes the vector of variables $\langle X_1, \ldots, X_d\rangle$ and Z' denotes the vector $\langle X_1{}', \ldots, X_d{}'\rangle$. The temporal variables T, T', $T_0, \ldots$, T_n model time and range over $\mathbb{R}_{\geq 0}$. We use the small letters p, q, r, s, $\ldots$ to denote d-dimensional vectors of real numbers.

We are now ready to define hybrid automata. For each node of a graph we have an invariant condition and a dynamic law. The dynamic law may depend on the initial conditions, i.e., on the values of the continuous variables at the beginning of the evolution in the state. Jumps from one discrete state to another are regulated by activation and reset conditions.

Definition 1 (Hybrid Automata - Syntax) A *hybrid automaton* $H = (Z, Z', \mathcal{V}, \mathcal{E}, Inv, \mathcal{F}, Act, Res)$ of dimension $d(H)$ consists of the following components:

1. $Z = \langle X_1, \ldots, X_{d(H)}\rangle$ and $Z' = \langle X_1{}', \ldots, X_{d(H)}{}'\rangle$ are two vectors of variables ranging over the reals $\mathbb{R}$;

2. $\langle \mathcal{V}, \mathcal{E} \rangle$ is a graph. Each element of $\mathcal{V}$ will be dubbed *location* or *mode*.
3. Each vertex $v \in \mathcal{V}$ is labeled by the formula $Inv(v)\,[Z]$;
4. $\mathcal{F}$ is a function assigning to each vertex $v \in \mathcal{V}$ a continuous vector field over $\mathbb{R}^{d(H)}$; we will use $f_v : \mathbb{R}^{d(H)} \times \mathbb{R}_{\geq 0} \longrightarrow \mathbb{R}^{d(H)}$ to indicate the solution of the vector field $\mathcal{F}(v)$ and $Dyn(v)[Z, Z', T]$ to identify the corresponding formula, i.e., $Dyn(v)[Z, Z', T] \stackrel{\text{def}}{=} Z' = f_v(Z, T)$;
5. Each edge $e \in \mathcal{E}$ is labeled by the two formulæ $Act(e)[Z]$ and $Res(e)[Z, Z']$.

If $Dyn(v)$, $Inv(v)$, $Act(e)$, and $Res(e)$ are formulæ belonging to the same logic theory $\mathcal{T}$ (e.g., the first-order theory of polynomials $\langle \mathbb{R}, 0, 1, +, *, < \rangle$ [32]), then we say equivalently that the hybrid automaton is *definable in* $\mathcal{T}$ or that it is a $\mathcal{T}$ *hybrid automaton*.

We present hybrid automaton semantics as transition systems: given an initial state, we can deduce the evolution of a hybrid automaton by iteratively applying of the transition relation which is associated to the automaton itself. Since hybrid automata have a double nature, the transition systems defining their semantics contains two different transition relations: the *continuous reachability transition relation* and the *discrete reachability transition relation*.

Definition 2 (Hybrid Automata - Semantics) A *state* ℓ of H is a pair $\langle v, r \rangle$, where $v \in \mathcal{V}$ is a location and $r = \langle r_1, \ldots, r_{d(H)} \rangle \in \mathbb{R}^{d(H)}$ is an assignment of values for the variables of Z. A state $\langle v, r \rangle$ is said to be *admissible* if $Inv(v)\,[r]$ is true.

The *continuous reachability transition relation* $\xrightarrow{t}_C$ between admissible states, with $t \geq 0$ denoting the transition elapsed time, is defined as follows:

$$\langle v, r \rangle \xrightarrow{t}_C \langle v, s \rangle \iff \begin{array}{l} s = f_v(r, t), \text{ and for each} \\ t' \in [0, t] \text{ the formula} \\ Inv(v)\,[f_v(r, t')] \text{ is true.} \end{array}$$

The *discrete reachability transition relation* $\xrightarrow{e}_D$ among admissible states is defined as follows:

$$\langle v, r \rangle \xrightarrow{e}_D \langle u, s \rangle \iff \begin{array}{l} e \in \mathcal{E}, \text{ with } v \text{ and } u \\ \text{source and destination of} \\ e, \text{ respectively, and both} \\ Act(e)[r] \text{ and } Res(e)[r, s] \text{ are} \\ \text{true.} \end{array}$$

We write $\ell \rightarrow_C \ell'$ and $\ell \rightarrow_D \ell'$ meaning respectively that there exists a $t \in \mathbb{R}_{\geq 0}$ such that $\ell \xrightarrow{t}_C \ell'$ and that there exists a $e \in \mathcal{E}$ such that $\ell \xrightarrow{e}_D \ell'$. Moreover, we write $\ell \rightarrow \ell'$ to denote that either $\ell \rightarrow_C \ell'$ or $\ell \rightarrow_D \ell'$.

Building upon a combination of both continuous and discrete transitions, we can formulate a notion of *trace* as well as a resulting notion of *reachability*. A trace is a sequence of continuous and discrete transitions. A point s is reachable from a point r if there is a trace starting from r and ending in s.

Definition 3 (Hybrid Automata - Reachability) Let $\mathcal{I}$ be either $\mathbb{N}$ or an initial finite interval of $\mathbb{N}$. A *trace* of H is a sequence of admissible states $\ell_0, \ell_1, \ldots, \ell_i, \ldots$, with $i \in \mathcal{I}$, such that $\ell_{i-1} \rightarrow \ell_i$ holds for each $i \in I$ greater than zero; such a trace is also denoted by $(\ell_i)_{i \in \mathcal{I}}$.

The automaton H *reaches* a point $s \in \mathbb{R}^{d(H)}$ (in time t) from a point $r \in \mathbb{R}^{d(H)}$ if there exists a trace $tr = \ell_0, \ldots, \ell_n$ of H such that $\ell_0 = \langle v, r \rangle$ and $\ell_n = \langle u, s \rangle$, for some $v, u \in \mathcal{V}$ (and t is the sum of the continuous transitions elapsed times). In such a case, we also say that s is *reachable* from r in H.

A trace produced by an infinite sequence of discrete transitions during a bounded amount of time is called *Zeno trace* and every hybrid automaton allowing such kind of trace is said to have a *Zeno behavior*.

Example 2 Let us consider the canonical example of a hybrid automaton, H_b modeling a *bouncing ball* whose collisions are inelastic.

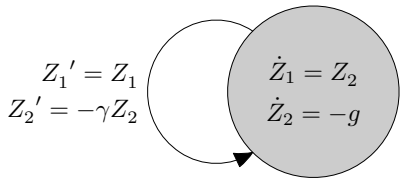

Fig. 1 Bouncing ball hybrid automaton

Such automaton is provided of two continuous variables Z_1, representing ball's height, and Z_2, representing ball's velocity. Fig. 1 presents dynamics, resets, and discrete structure of H_b, where g and γ are the standard gravity and the coefficient of restitution, respectively. The activation formula for the single edge is $Z_1 = 0$.

Fig. 2 represents the evolution of ball's elevation, Z_1, along time assuming starting height $h_0 = 10m$ and $\gamma = 0.86$. It is easy to see that the peak of bounces decreases at each iteration and eventually it will become arbitrarily small. Moreover, the overall bouncing time converges to $\sqrt{\frac{2h_0}{g}}\left(\frac{1+\gamma}{1-\gamma}\right)$ even if the ball bounces forever and, thus, the automaton H_b has a Zeno behavior.

Given a hybrid automaton H and trace, tr, of H, a *corresponding path* of tr is a path ph obtained by considering the discrete component of tr.

We are interested in the reachability problem for hybrid automata, namely, given a hybrid automaton H, an initial set of points $I \subseteq \mathbb{R}^{d(H)}$, and a final set of

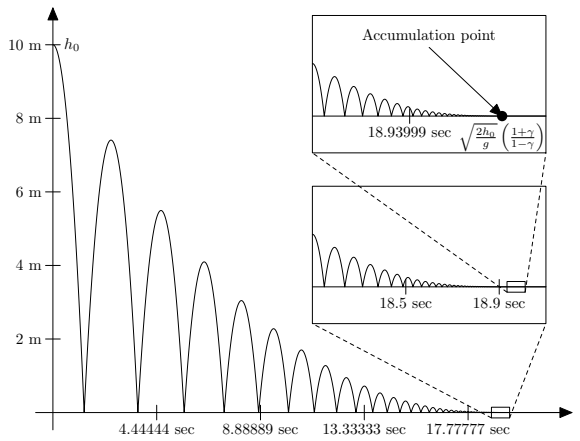

Fig. 2 Zeno behavior of a bouncing ball.

points $F \subseteq \mathbb{R}^{d(H)}$ we wish to decide whether there exists a point in I from which a point in F is reachable. This problem is undecidable on hybrid automata (see, e.g., [11]). Hence, one could try to identify classes of hybrid automata over which such problem can be decided. Many non-trivial (or non-degenerate) classes of hybrid automata for which reachability problem is decidable have been proposed. *Multirate automata* have been introduced in [38] as an extensions of *timed automata* [39]. Such hybrid automata are characterized by resets which are either identity or constant function zero. Moreover, their continuous variables evolve like clocks with rational rates (i.e., x becomes $c \cdot t + x$, where $c \in \mathbb{Q}$, in time t). Decidability of reachability problem for such class had been shown by imposing a restriction on dynamics called *simplicity condition*. Puri and Varaiya in [40] introduced *rectangular hybrid automata* whose dynamics can be characterized by a differential inclusion of the type $\dot{x} \in [l, u]$, where l and u are rational numbers. Even if Kopke proved in [41] that reachability is, in general, undecidable for such classes of hybrid automata and that three dimensional rectangular automata have infinite simulation quotient, they showed that, under a condition called *initialized condition*, reachability can be decided.

In general, the reachability problem for $\mathcal{T}$ hybrid automata can be reduced to the satisfiability of a numerable disjunction of formulæ of $\mathcal{T}$ itself. In particular, if H is a $\mathcal{T}$ hybrid automaton, then $q \in \mathbb{R}^{d(H)}$ in location v' is reachable from $p \in \mathbb{R}^{d(H)}$ in location v by H through a trace whose corresponding path begins in v, ends in v', and has length at most i, if and only if the formula $Reach^i_H(v, v')[p, q]$ holds (e.g., $Reach^0_H(v, v)$ characterizes continuous reachability in location v, $Reach^1_H(v, v')$ denotes automaton evolutions which begin in location v, end in location v', and cross at most one discrete edge from v to v', etc.). However, even if $\mathcal{T}$ is decidable (i.e., there exists an algorithm to decide whether a formula in $\mathcal{T}$ is valid or not), the reachability problem for $\mathcal{T}$ hybrid automata may be undecidable (see [42]).

Given the above undecidability results, natural questions arise:

- *What is the meaning of these undecidability results when we model biological systems?*
- *What happens to our undecidability results if we add to the semantics natural hypothesis which are consequence of the fact that we are modeling biological systems?*

Let us consider the first question. In the modeling of biological systems each variable represents the quantity of a reactant (e.g., protein level, gene expression, ...), hence it is reasonable to assume that each variable ranges over a bounded interval. When we consider hybrid automata with bounded invariants, undecidability is a consequence of the possibility, usually related with the presence of a Zeno behavior, of characterizing regions of arbitrarily small size. In applications this corresponds to the ability of measuring with infinite precision. This is not only unrealistic, but misleading. First, the continuous quantities used in hybrid automata are mainly an abstraction of the discrete (large) quantities involved in biological systems, hence it makes no sense to use infinite precision. Moreover, one of the most important features of biological systems is robustness. This means that small fluctuations have no effects on the global behavior. Hence, again infinite precision is unnecessary. Keeping these considerations in mind we can now turn to our second question.

First we have to consider bounded regions. Boundedness immediately calls into play the notion of compactness. In particular, the set of points reachable from I by H, denoted by $RSet_H(I)$, is characterized by

$$RSet_H(I) = \bigcup_{i \in \mathbb{N}} RSet^i_H(I) = \lim_{i \to +\infty} RSet^i_H(I)$$

where $RSet^i_H(I)$ is defined as $RSet^i_H(I) = \{q \in \mathbb{R}^{d(H)} \mid \exists p \in I\, \exists v, v' \in \mathcal{V}$ s.t. $Reach^i_H(v, v')[p, q]\}$, i.e., the sets of points reachable from I in at most i discrete steps provide a covering of $RSet_H(I)$. If $RSet_H(I)$ were compact and for each i the set $RSet^i_H(I)$ had a non-empty interior, then we would have obtained the decidability of reachability. In fact, from each open covering of a compact set it is possible to extract a finite covering. Unfortunately, even if we use only closed and bounded sets we cannot ensure that $RSet_H(I)$ is closed. Here, our considerations about measuring precision come into play. Even if we do not have compact sets, the boundedness hypothesis together with finite precision provide the following result. Given a set S, let $B(S, \epsilon) = \{q \mid \exists p \in S$ s.t. $d(p, q) < \epsilon\}$, where $d(p, q)$ is the standard Euclidean distance.

Lemma 1 *Let $S \subseteq \mathbb{R}^{d(H)}$ be a bounded set such that $S = \cup_{i\in\mathbb{N}} D_i$, with either $D_i = D_j$ or $D_i \cap D_j = \emptyset$. If there exists $\epsilon > 0$ such that for each $i \in \mathbb{N}$ there exists $a_i \in \mathbb{R}^{d(H)}$ such that $B(\{a_i\}, \epsilon) \subseteq D_i$, then there exists $j \in \mathbb{N}$ such that $S = \bigcup_{i\leq j} D_i$ holds.*

Proof Let us assume by contradiction that $\cup_{i\leq j} D_i \subset S$ holds for each $j \in \mathbb{N}$. Since $S = \cup_{i\in\mathbb{N}} D_i$, for each $j \in \mathbb{N}$ and each $i \leq j$, there exists $k > j$ such that $D_k \neq D_i$ and $D_k \cap D_i = \emptyset$. Let $B_k = B(\{a_k\}, \epsilon) \subseteq D_k$. We consider the succession $(s_n)_{n\in\mathbb{N}}$ defined as $s_0 = B_0$ and $s_j = B_k$, with j and k as previously described. The above considerations ensure that s_n is properly defined for all $n \in \mathbb{N}$. By construction, all the sets s_n's are disjoint and $\cup_{n\in\mathbb{N}} s_n \subseteq S$. Let μ be the Lebesgue measure over $\mathbb{R}^{d(H)}$, we have that $\mu(\cup_{n\in\mathbb{N}} s_n) = \sum_{n\in\mathbb{N}} \mu(s_n) = \sum_{n\in\mathbb{N}} b$, where $b = \mu(B(\{a_k\}, \epsilon)) > 0$ for all $k \in \mathbb{N}$. Hence, $\mu(S) \geq \mu(\cup_{n\in\mathbb{N}} s_n) = +\infty$ which contradicts the fact that S is bounded. Hence, the thesis holds.

Intuitively this means that if we cannot measure sets which are "smaller" than ϵ and we are working on bounded regions, then only a finite number of measurements is necessary.

Embedding the above lemma into our context we get the following theorem.

Theorem 1 *Let $\mathcal{T}$ be a decidable first-order theory over the reals and H be a $\mathcal{T}$ hybrid automaton with bounded invariants. If there exists $\epsilon > 0$, such that, for each $I \subseteq \mathbb{R}^{d(H)}$ and for each $i \in \mathbb{N}$, either $RSet_H^{i+1}(I) = RSet_H^i(I)$ or there exists a $a_i \in \mathbb{R}^{d(H)}$ such that $B(\{a_i\}, \epsilon) \subseteq RSet_H^{i+1}(I) \setminus RSet_H^i(I)$, then there exists j such that $RSet_H(I) = RSet_H^j(I)$ and the reachability problem over H is decidable.*

Proof It is not restrictive to assume that the invariants are pairwise disjoint. This can be simply realized by adding one dummy continuous variable whose value represents the current location.

Let us consider the sets $D_0 = RSet_H^0(I)$ and $D_{i+1} = RSet_H^{i+1}(I) \setminus RSet_H^i(I)$. We have that the sets D_i are disjoint. Moreover, $\cup_{i\in\mathbb{N}} D_i = RSet_H(I)$ is bounded, since it is included in bounded invariants. By Lemma 1, there exists j such that $RSet_H(I) = \bigcup_{i\leq j} D_i$. As a consequence, we get that the set $RSet_H(I)$ is equal to $\bigcup_{i\leq j} RSet_H^i(I)$. Moreover, since, by definition, $RSet_H^k(I)$ is the set of points reachable from I with at most k discrete transitions, $RSet_H^k(I) \subseteq RSet_H^{k+1}(I)$ for each $k \in \mathbb{N}$ and $RSet_H^j(I)$ is such that $RSet_H(I) = RSet_H^j(I)$.

As far as decidability is concerned, we have that the sets $RSet_H^i(I)$ are computable since $\mathcal{T}$ is decidable and H is a $\mathcal{T}$ hybrid automaton. Moreover, since we assumed disjoint invariants, it is easy to see that $RSet_H(I) = RSet_H^k(I)$ if and only if $RSet_H^k(I) = RSet_H^{k+1}(I)$. Hence, to compute $RSet_H(I)$, we compute all the $RSet_H^i(I)$ until we reach the fix-point $RSet_H^j(I)$.

The above result finds interesting applications when it makes no sense to distinguish measurements which differ for less than ϵ. In such cases we have the decidability of reachability, even though a full-precision analysis could lead to (Zeno behavior and) undecidability. On the one hand, biological systems can somehow naturally produce such situations when, for example, bi-stability is expected. On the other hand, bi-stability is a typical situation in which the continuous/discrete modeling capability of hybrid systems is most effectively used (see [43,44]). A paradigmatic example of Zeno behavior arising in a context of a bi-stable system eliminated through the use of ϵ-semantics, is given in Section 6.

4 Finite Precision Semantics

We are interested in distinguishing only between sets which differ for "at least ϵ". The hybrid automaton characterization based on formulæ enables us to change the semantics of semi-algebraic automata by modifying semantics of first-order formulæ defining them. Hence, we can achieve our goal by giving to each formula a semantics "of dimension at least ϵ".

Let us consider the following general semantics.

Definition 4 (ϵ-Semantics) Let $\mathcal{T}$ be a first order theory and let $\epsilon \in \mathbb{R}_{>0}$. For each formula ψ on $\mathcal{T}$ let $\left\{\!\left\{\psi\right\}\!\right\}_\epsilon \subseteq \mathbb{R}^d$, where d is the number of free variables of ψ, be such that:

(ϵ) either $\left\{\!\left\{\psi\right\}\!\right\}_\epsilon = \emptyset$ or there exists $p \in \mathbb{R}^d$ such that $B(\{p\}, \epsilon) \subseteq \left\{\!\left\{\psi\right\}\!\right\}_\epsilon$;
($\cap$) $\left\{\!\left\{\psi_1 \wedge \psi_2\right\}\!\right\}_\epsilon \subseteq \left\{\!\left\{\psi_1\right\}\!\right\}_\epsilon \cap \left\{\!\left\{\psi_2\right\}\!\right\}_\epsilon$;
($\cup$) $\left\{\!\left\{\psi_1 \vee \psi_2\right\}\!\right\}_\epsilon = \left\{\!\left\{\psi_1\right\}\!\right\}_\epsilon \cup \left\{\!\left\{\psi_2\right\}\!\right\}_\epsilon$;
($\forall$) $\left\{\!\left\{\forall X \psi[X, Z]\right\}\!\right\}_\epsilon = \left\{\!\left\{\bigwedge_{r\in\mathbb{R}} \psi[r, Z]\right\}\!\right\}_\epsilon$;
($\exists$) $\left\{\!\left\{\exists X \psi[X, Z]\right\}\!\right\}_\epsilon = \left\{\!\left\{\bigvee_{r\in\mathbb{R}} \psi[r, Z]\right\}\!\right\}_\epsilon$;
($\neg$) $\left\{\!\left\{\psi\right\}\!\right\}_\epsilon \cap \left\{\!\left\{\neg\psi\right\}\!\right\}_\epsilon = \emptyset$.

Any semantics satisfying the above conditions is said to be an *ϵ-semantics for $\mathcal{T}$*.

We can now use such a general semantics to guide our reachability algorithm. The idea is that, since the semantics of our formulæ is either empty or it contains at least a set of the form $B(\{p\}, \epsilon)$, our algorithm terminates when the formula characterizing the new reached points has empty semantics, i.e., when we do not reach enough new points. Let I be a set of points included

in the invariants and characterized by the first-order formula $\psi[Z]$, i.e., $I = \left\{\!\left|\psi[Z]\right|\!\right\}_\epsilon$. Consider Algorithm 3 whose goal is to determine the the points reachable from I with respect to the ϵ-semantics $\{\!|\cdot|\!\}_\epsilon$.

Algorithm 1 Init($H, \psi[Z]$)

Ensure: $R(v)[Z] = \psi[Z] \wedge Inv(v)[Z]$ and $N(v) = \bot$.
1: **for all** $v \in \mathcal{V}$ **do**
2: $\quad R(v)[Z] \leftarrow \psi[Z] \wedge Inv(v)[Z]$
3: $\quad N(v) \leftarrow \bot$
4: **end for**
5: **return** $\langle R, N\rangle$

The variables $R(v)[Z]$, $N(v)[Z]$, and $C(v)[Z]$ maintain the formulæ denoting the reach set from begin of the computation, the reach set from $\left\{\!\left|R(v)[Z]\right|\!\right\}_\epsilon$ admitting at most one discrete step, and the set of points which are reached for the first time by the last iteration in location v, respectively. At the beginning of the computation, the points reachable by H from $\left\{\!\left|\psi[Z]\right|\!\right\}_\epsilon$ are the points which both satisfy invariants and are "reachable" with neither discrete nor continuous transitions. Hence, Algorithm 1 sets $\psi[Z]$ to $\psi[Z] \wedge Inv(v)[Z]$, while poses the newly reached points to $\{\!|\bot|\!\}_\epsilon$, i.e., to the empty set. At the i-th iteration of the algorithm, the reach set is added of the points which are reachable from $\psi[Z]$ through a sequence of transitions containing at most $i-1$ discrete transitions. In particular, $\left\{\!\left|R(v)[Z]\right|\!\right\}_\epsilon$ is augmented by the points which are denoted by $N(v)$ at the $(i-1)$-th iteration (line 2 of Algorithm 2). After that, $N(v)[Z]$ is assigned by line 5 of Algorithm 2 to represent the points reachable from the set $\left\{\!\left|R(v)[Z]\right|\!\right\}_\epsilon$ with at most one discrete transition, i.e., the set of points reachable from $\psi[Z]$ by using at most i discrete transitions. Finally, the **repeat-until** condition at line 7 imposes to increase the number of allowed discrete transitions used during the reachability evolution until a fixed point is reached.

Algorithm 2 ReachStep(H, R, N)

Require: $\left\{\!\left|N(v)[Z]\right|\!\right\}_\epsilon \cup \left\{\!\left|R(v)[Z]\right|\!\right\}_\epsilon \subseteq \left\{\!\left|Inv(v)[Z]\right|\!\right\}_\epsilon$.
Ensure: $\left\{\!\left|N(v)[Z]\right|\!\right\}_\epsilon \cup \left\{\!\left|R(v)[Z]\right|\!\right\}_\epsilon \subseteq \left\{\!\left|Inv(v)[Z]\right|\!\right\}_\epsilon$.
1: **for all** $v \in \mathcal{V}$ **do**
2: $\quad R(v)[Z] \leftarrow R(v)[Z] \vee N(v)[Z]$
3: **end for**
4: **for all** $v \in \mathcal{V}$ **do**
5: $\quad N(v)[Z] \leftarrow \bigvee_{v' \in \mathcal{V}} \left(\exists Z' \left(R(v')[Z'] \wedge Reach^1_H(v', v)[Z', Z]\right)\right)$
6: **end for**
7: **return** $\langle R, N\rangle$

Notice that, in all the presented algorithms, the right hand sides of assignments are variables representing formulæ and the assignments are syntactic operations. Namely, they consist in building the formula at the right side of the assignments themselves. For instance, the instruction at line 5 of Algorithm 3 assigns the formula $\left(\phi_1 \wedge \neg\phi_2\right)$, where ϕ_1 and ϕ_2 are the formulæ in $N(v)[Z]$ and $R(v)[Z]$, respectively, to the variable $C(v)[Z]$. The only formula evaluation performed by the algorithm is at line 7 and, for such a reason, the semantics $\{\!|\cdot|\!\}_\epsilon$ is not a parameter of either Algorithm 1 or Algorithm 2.

Algorithm 3 Reachability($H, \psi[Z], \{\!|\cdot|\!\}_\epsilon$)

Ensure: $\left\{\!\left|R(v)[Z]\right|\!\right\}_\epsilon \subseteq \left\{\!\left|Inv(v)[Z]\right|\!\right\}_\epsilon$ for all $v \in \mathcal{V}$.
1: $\langle R, N\rangle \leftarrow$Init($H, \psi[Z]$)
2: **repeat**
3: $\quad \langle R, N\rangle \leftarrow$ ReachStep(H, R, N)
4: $\quad$ **for all** $v \in \mathcal{V}$ **do**
5: $\quad\quad C(v)[Z] \leftarrow (N(v)[Z] \wedge \neg R(v)[Z])$
6: $\quad$ **end for**
7: **until** $\left\{\!\left|\bigvee_{v\in\mathcal{V}} C(v)[Z]\right|\!\right\}_\epsilon = \emptyset$
8: **return** R

All sets characterized by the formulæ occurring in our algorithm are included in the invariants and are monotonically growing in size of at least ϵ at each iteration. Hence, our algorithm always terminates, if the invariants are bounded. We recall that a semantics $\mathcal{M}$ is decidable, if $\mathcal{T}(\mathcal{M})$ is decidable.

Theorem 2 *Let $\mathcal{T}$ be a first-order theory over the reals, H be a $\mathcal{T}$ hybrid automaton, and let $\{\!|\cdot|\!\}_\epsilon$ be a decidable ϵ-semantics for $\mathcal{T}$. If H has bounded invariants, i.e., $\{\!|\bigvee_{v\in\mathcal{V}} Inv(v)[Z]|\!\}_\epsilon$ is bounded, then Algorithm 3 always terminates and computes the reachability set of H from $\left\{\!\left|\psi\right|\!\right\}_\epsilon$ with respect to $\{\!|\cdot|\!\}_\epsilon$.*

Proof If we prove that $\{\!|\bigvee_{v\in\mathcal{V}} C(v)[Z]|\!\}_\epsilon$ is a covering of a subset of $\{\!|\bigvee_{v\in\mathcal{V}} Inv(v)[Z]|\!\}_\epsilon$, then we can exploit Lemma 1 and Theorem 1 to prove termination.

It is not restrictive to assume that the invariants are pairwise disjoint, i.e., $\{\!|Inv(v)[Z]|\!\}_\epsilon \cap \{\!|Inv(v')[Z]|\!\}_\epsilon$ is empty set for all $v, v' \in \mathcal{V}$ with $v \neq v'$. This can be simply realized by adding one dummy continuous variable whose value represents the current location.

First we prove that, at each iteration of Algorithm 3, $\{\!|\bigvee_{v\in\mathcal{V}} C(v)[Z]|\!\}_\epsilon$ is a subset of $\{\!|\bigvee_{v\in\mathcal{V}} Inv(v)[Z]|\!\}_\epsilon$. Algorithm 2 is called at line 3 of Algorithm 3. It assigns the formulæ $R(v)[Z] \vee N(v)[Z]$ and $\vee_{v'\in\mathcal{V}}(\exists Z'(R(v')[Z'] \wedge Reach^1_H(v', v)[Z', Z]))$ to $R(v)[Z]$ and $N(v)[Z]$, respectively. By items ($\exists$) and ($\cap$) of Definition 4, $\{\!|N(v)[Z]|\!\}_\epsilon$ is subset of $\bigcup_{v'\in\mathcal{V}} \bigcup_{r\in\mathbb{R}} \{\!|R(v')[r]|\!\}_\epsilon$ and, by item ($\cup$), the set $\{\!|R(v)[Z]|\!\}_\epsilon$ is equal to $\{\!|R(v)[Z]|\!\}_\epsilon \cup \{\!|N(v)[Z]|\!\}_\epsilon$.

Thus, if both $\{\!|R(v)\,[Z]|\!\}_\epsilon$ and $\{\!|N(v)\,[Z]|\!\}_\epsilon$ are subset of $\{\!|Inv(v)\,[Z]|\!\}_\epsilon$ before the execution of the Algorithm 2, then they are its subsets also after the execution. Since the execution of Algorithm 1 sets $R(v)\,[Z]$ and $N(v)\,[Z]$ to $\psi[Z] \wedge Inv(v)\,[Z]$ and $\bot$, respectively, after the execution of Algorithm 1, $\{\!|R(v)\,[Z]|\!\}_\epsilon$ is a subset of $\{\!|Inv(v)\,[Z]|\!\}_\epsilon$, by item ($\cap$) of Definition 4, and $\{\!|N(v)\,[Z]|\!\}_\epsilon = \{\!|\bot|\!\}_\epsilon = \emptyset \subseteq \{\!|Inv(v)\,[Z]|\!\}_\epsilon$. Thus, by induction on the number i of iterations, along the execution of the **repeat-until** of Algorithm 3, $\{\!|R(v)\,[Z]|\!\}_\epsilon \subseteq \{\!|Inv(v)\,[Z]|\!\}_\epsilon$ and $\{\!|N(v)\,[Z]|\!\}_\epsilon \subseteq \{\!|Inv(v)\,[Z]|\!\}_\epsilon$. In particular, at each execution of line 5, $\{\!|C(v)\,[Z]|\!\}_\epsilon$ becomes a subset of $\{\!|Inv(v)\,[Z]|\!\}_\epsilon$ by item ($\cap$) of Definition 4 and, finally, the set $\{\!|\vee_{v\in\mathcal{V}} C(v)\,[Z]|\!\}_\epsilon$ is included $\{\!|\vee_{v\in\mathcal{V}} Inv(v)\,[Z]|\!\}_\epsilon$ by item ($\cup$). It follows that the set $\{\!|\vee_{v\in\mathcal{V}} C(v)\,[Z]|\!\}_\epsilon$ is a covering of a subset of $\{\!|\vee_{v\in\mathcal{V}} Inv(v)\,[Z]|\!\}_\epsilon$ and, since $\{\!|\vee_{v\in\mathcal{V}} Inv(v)\,[Z]|\!\}_\epsilon$ is bounded by hypothesis, $\{\!|\vee_{v\in\mathcal{V}} C(v)\,[Z]|\!\}_\epsilon$ is bounded also.

Let us denote $\{\!|C(v)\,[Z]|\!\}_\epsilon$, $\{\!|N(v)\,[Z]|\!\}_\epsilon$, $\{\!|R(v)\,[Z]|\!\}_\epsilon$, and $\{\!|\vee_{v\in Loc} C(v)\,[Z]|\!\}_\epsilon$ at the i-th iteration of the Algorithm 3 with $C_i(v)$, $N_i(v)$, $R_i(v)$, and C_i, respectively. In order to satisfy the hypothesis of both Lemma 1 and Theorem 1, we have now to prove that (1) C_i is either empty set or includes a ball of radius $\epsilon > 0$ for all $i \in \mathbb{N}$ and (2) $C_i \cap C_j$ is empty for all $j > i$. Statement (1) holds because of item (ϵ) of Definition 4. Concerning statement (2), by line 5 of Algorithm 3 and by both items ($\cap$) and ($\neg$) of Definition 4, $C_j(v)$ is included into $N_j(v)$ and is disjoint from $R_j(v)$. However, by line 2 of Algorithm 2 and item ($\cup$) of Definition 4, it is easy to prove by induction on $j - i$ that $R_j(v) \supseteq R_i(v) \cup N_i(v)$ for all $j > i$. Hence, $C_j(v)$ is disjoint from $R_i(v) \cup N_i(v)$ and $C_i(v) \cap C_j(v)$ is empty set for all $j > i$. Moreover, since $\{\!|C(v)\,[Z]|\!\}_\epsilon$ is subset of $\{\!|Inv(v)\,[Z]|\!\}_\epsilon$ as proved above and $\{\!|Inv(v)\,[Z]|\!\}_\epsilon$ and $\{\!|Inv(v')\,[Z]|\!\}_\epsilon$ are disjoint by assumption for all $v, v' \in \mathcal{V}$ with $v \neq v'$, it follows that $C_i(v)$ and $C_j(v')$ are pairwise disjoint for all $j > i \in \mathbb{N}$ and $v, v' \in \mathcal{V}$ with $v \neq v'$. The sets $\cup_{v\in\mathcal{V}} C_i(v)$ and $\cup_{v\in\mathcal{V}} C_j(v)$ are disjoint and $C_i \cap C_j = \emptyset$ for all $j > i$. Thus, we can apply Lemma 1 and Theorem 1 and deduce both termination and correctness of Algorithm 3.

Since we are going to propose a new semantics, it is important to recall that, even if $>$, $\leq$, and $\geq$ are all definable in any theory having as relational symbol $<$, they are actually syntactic shortcuts and are not provided of a real stand-alone semantics. In particular, $x > y$ is syntactically equivalent to $y < x$, $x \leq y$ stands for $\neg(x > y)$, and $x \geq y$ is used in place of $y \leq x$.

In the following, given a first-order theory over the reals, $\mathcal{T}$, and any formula ψ in $\mathcal{T}$, $\left\|\psi[Z]\right\|$ will denote the set of points satisfying $\psi[Z]$ in the standard semantics, i.e., $\left\|\psi[Z]\right\| = \{p \mid \psi[p] \in \mathcal{T}\}$. Let us now try to instantiate our general schema.

Definition 5 (Sphere Semantics) Let $\mathcal{T}$ be a first-order theory over the reals and let $\epsilon > 0$. The set $\left\|\psi\right\|_\epsilon$ is defined by structural induction on ψ as follows:

- $[\![t_1 \circ t_2]\!]_\epsilon = B([\![t_1 \circ t_2]\!], \epsilon)$, for $\circ \in \{=, <\}$;
- $\left\|\psi_1 \wedge \psi_2\right\|_\epsilon = \cup_{B(\{p\},\epsilon)\subseteq [\![\psi_1]\!]_\epsilon \cap [\![\psi_2]\!]_\epsilon} B(\{p\}, \epsilon)$;
- $\left\|\psi_1 \vee \psi_2\right\|_\epsilon = \left\|\psi_1\right\|_\epsilon \cup \left\|\psi_2\right\|_\epsilon$;
- $\left\|\forall X \psi\,[X, Z]\right\|_\epsilon = \left\|\wedge_{r\in\mathbb{R}} \psi\,[r, Z]\right\|_\epsilon$;
- $\left\|\exists X \psi\,[X, Z]\right\|_\epsilon = \left\|\vee_{r\in\mathbb{R}} \psi\,[r, Z]\right\|_\epsilon$;
- $\left\|\neg\psi\right\|_\epsilon = \cup_{B(\{p\},\epsilon)\cap [\![\psi]\!]_\epsilon = \emptyset} B(\{p\}, \epsilon)$.

Example 3 Let us consider the formula $1 < X < 5$ and $\epsilon = 0.1$. We have that $[\![1 < X < 5]\!]_\epsilon = [\![1 < X \wedge X < 5]\!]_\epsilon = (0.9, 5.1)$, hence, in this case the sphere semantics over approximates the standard one. If we consider the formula $\neg(1 < X \wedge X < 5)$ we get that $[\![\neg(1 < X \wedge X < 5)]\!]_\epsilon = (-\infty, 0.9) \cup (5.1, +\infty)$ which is an under approximation of the standard semantics.

Notice that, if $t_1 \leq t_2$ was a shortcut for $(t_1 < t_2) \wedge (t_1 = t_2)$, the above formula would not be "sphere equivalent" to the formula $X \leq 1 \vee 5 \leq X$, as the sphere semantics of the latter would be $[\![X \leq 1 \vee 5 \leq X]\!]_\epsilon = (-\infty, 1.1) \cup (4.9, +\infty)$. However, since as argued above $t_1 \leq t_2$ stands for $\neg(t_2 < t_1)$, the formula $X \leq 1 \vee 5 \leq X$ is a shortcut for $\neg(1 < X) \vee \neg(X < 5)$ and its semantics is $(-\infty, 0.9) \cup (5.1, +\infty)$ which is precisely the semantics of $\neg(1 < X \wedge X < 5)$. Moreover, the formula $X = 5$ is syntactically equivalent to $\neg(5 < X) \wedge \neg(X < 5)$ whose ϵ sphere semantics is $\emptyset$.

At the light of above example, it is clear that the formulæ to be used in the automata have to be carefully analyzed to avoid wrong modeling due to classical assumptions which fails with respect to ϵ-semantics.

It is easy to see that sphere semantics $[\![\cdot]\!]_\epsilon$ satisfies the requirements of Definition 4 and is an ϵ-semantics.

Example 4 As already noticed above, Example 2 reports a hybrid automaton having a Zeno behavior. In particular, the height of bounces decreases at each iteration and eventually it will become arbitrarily small. By using the proposed semantics, from a certain time on, the ball will "reach" all the points in $\{y \in B(\{y'\}, \epsilon) \mid 0 \in B(\{y'\}, \epsilon)\}$. Such behavior avoids the need of further investigations on the reachable region from that time on and faithfully represents the real physics of the ball.

The accuracy of the proposed model relays on ϵ. For instance, if we choose an ϵ greater than γ, then the bounce's height would increase and, hence, this would not be a proper model. The smaller is ϵ the tighter is the model behavior to the real world physics. Nevertheless, to avoid Zeno behaviors, ϵ must be greater 0.

A different ϵ-semantics, $(\!|\cdot|\!)_\epsilon$, can be defined as:

$$\left(\!\left|\phi\right|\!\right)_\epsilon \stackrel{\text{def}}{=} \begin{cases} \cup_{B(\{p\},\epsilon)\subseteq[\![\phi]\!]} B(\{p\},\epsilon) & \text{if } \phi \text{ is } t_1 < t_2 \text{ or } t_1 = t_2 \\ \left[\!\left[\phi\right]\!\right]_\epsilon & \text{otherwise} \end{cases}$$

Such new semantics under-approximates the standard semantics of predicates like $t_1 < t_2$, whereas sphere semantics tends to over-approximate them. However, as noticed also for sphere semantics, $(\!|\cdot|\!)_\epsilon$ is neither an over-approximating nor an under-approximating semantics. For instance, the set $\left(\!\left|2 * X^2 < \epsilon^2\right|\!\right)_\epsilon = \emptyset$ is an under-approximation of $\left[\!\left[2 * X^2 < \epsilon^2\right]\!\right]$, while $\left(\!\left|\neg(2 * X^2 < \epsilon^2)\right|\!\right)_\epsilon$ over-approximates $\left[\!\left[\neg(2 * X^2 < \epsilon^2)\right]\!\right]$. We leave further investigations on the set of ϵ-semantics, i.e., on its elements and on their relationships as future work.

5 Semi-Algebraic Theory and ϵ-Semantics

The results reported in Section 4 provides an algorithm to compute the reachability set of a $\mathcal{T}$ hybrid automaton with respect to any decidable ϵ-semantics over $\mathcal{T}$. However, the most expressive first-order theory over the reals which is known to be decidable is the semi-algebraic theory, whose terms are inequalities of polynomials (see [32]), and even the decidability of the exponential theory, whose terms are inequalities of polynomials and exponential formulæ, is still an open problem [45]. Because of such considerations, one could conclude that both ϵ-semantics and Algorithm 3 cannot be used to reason about real systems whose continuous dynamics are usually represented by complex differential equations such as, for instance, Michaelis-Menten kinetics. Luckily, this is not the case.

Our main goal is to increase the fidelity of our models by avoiding the un-natural ability of distinguish too close points and, in particular, we do not want to discriminate evolutions which differ for a quantity smaller than a fixed ϵ. By Taylor's approximation, any differentiable function f can be approximated on a given interval I with a maximum error γ by a polynomial $p(I, \gamma, f)$. Hence, if we admit a limited time horizon t_h, for any ϵ, we can approximate any differentiable function $f(t)$ (e.g., Michaelis-Menten) by a polynomial $p(t)$ such that $\|f(t) - p(t)\| < \epsilon$ for all $t \in [0, t_h]$. It follows that $p(t)$ and $f(t)$ cannot be distinguished by any ϵ-semantics and we can use $p(t)$ in place of $f(t)$ to represent the its evolution for all $t \in [0, t_h]$. Practically, once we have chosen ϵ, we can replace every differentiable dynamics, f, by its Taylor approximation, p_T, whose degree is high enough to ensure that the corresponding Lagrange remainder is smaller than ϵ itself in $t \in [0, t_h]$. This guarantees us that f and p_T cannot be distinguished by any ϵ-semantics.

Let us consider the class of *semi-algebraic hybrid automata* [14,42], i.e., the class of hybrid automata definable in the Tarski theory (i.e., the theory of polynomials over the reals). As we notice above, if we adopt any ϵ-semantics, all the possible dynamics (differentiable reset functions) can be modeled by using an opportune formula in $\langle \mathbb{R}, 0, 1, +, *, < \rangle$. Hence, semi-algebraic hybrid automata are enough to model any hybrid system according the framework proposed in this paper.

Intriguingly, both $[\![\cdot]\!]_\epsilon$ and $(\!|\cdot|\!)_\epsilon$ of Tarski theory are definable in Tarski theory itself. For instance, the set $\left[\!\left[\psi_1[Z] < \psi_2[Z]\right]\!\right]_\epsilon$ is definable by the semi-algebraic formula $\exists Z'\ \psi_1[Z'] < \psi_2[Z'] \wedge d(Z, Z') < \epsilon$, while the two sets $\left(\!\left|\psi_1[Z] < \psi_2[Z]\right|\!\right)_\epsilon$ and $[\![\exists Z'(\forall Z''\ d(Z', Z'') < \epsilon \rightarrowtriangle \psi_1[Z''] < \psi_2[Z'']) \wedge Z' = Z]\!]$ are the same. Since Tarski theory is decidable, both $[\![\cdot]\!]_\epsilon$ and $(\!|\cdot|\!)_\epsilon$ on $\langle \mathbb{R}, 0, 1, +, *, < \rangle$ are also decidable and the next theorem immediately follows.

Lemma 2 *If H is a semi-algebraic hybrid automaton with bounded invariants, then Algorithm 3 on both $[\![\cdot]\!]_\epsilon$ and $(\!|\cdot|\!)_\epsilon$ terminates.*

Proof The first part is immediate. The second part is a consequence of Theorem 2.

6 Modeling of Biological Systems

In order to prove the effectiveness of ϵ-semantics, let us consider the Delta-Notch mechanism (see [46]). Delta and Notch are transmembrane proteins that are at the basis of cells differentiation and signal when cells are in direct contact. Notch production is triggered by high Delta levels in neighboring cells, while Delta production is triggered by low Notch concentrations in the same cell. High Delta concentration leads to differentiated cells and low Delta levels to undifferentiated ones. The Delta-Notch signaling mechanism has attracted the attention of many researchers, since it is the core of biological pattern formation. The mathematical model for Delta-Notch signaling, presented in [46], has been rephrased in terms of hybrid automata in [47,48] and approximated by a piecewise affine hybrid automaton in both [48] and [49]. As observed by the authors, the hybrid automaton representing the two cells model has a Zeno behavior which is "vestige of the mathematical model and not observable in nature due to noise" [47]. The one cell model has and two continuous variables, X_D and X_N, representing Delta and Notch concentrations, respectively. Moreover, it is provided with four discrete states, q_1, q_2, q_3, and q_4, characterizing all the possible combinations of high/low concentration levels for Delta and Notch. Figure 3 partially depicts the

model suggested in [47]. Invariant conditions are rectangular regions depending on concentration levels in the cell and in its neighbors and resets are identity functions. All the details, including a full description for both activations and invariants, can be found in [47].

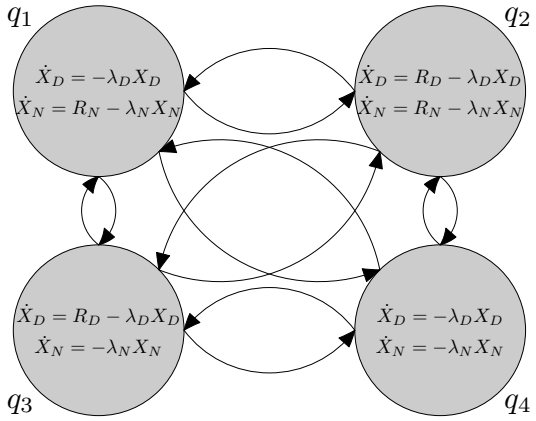

Fig. 3 One cell Delta-Notch model.

The two-cells automaton is the Cartesian product of two one-cell models. It has two feasible equilibria corresponding to high Delta in the first cell and low in the second one and vice-versa. No matter which are the dynamical laws, it also exhibits a Zeno behavior: the automaton cycles on path $\langle q_4, q_4\rangle, \langle q_3, q_3\rangle, \langle q_1, q_1\rangle, \langle q_2, q_2\rangle$ in the case of two cells with identical initial concentrations. However, this is an artifact of the mathematical model. In Nature, two cells will always reach one of the equilibrium points in a finite amount of time, since it is not reasonable to have the two cells exhibiting the same concentrations forever.

As noticed in Section 5, the dynamics of above hybrid automata can be *exactly* represented by polynomials with respect to any ϵ-semantics. In particular, if we fix t_h as maximum evolution time and, for all $t \in [0, t_h]$, it holds that $\epsilon > \frac{(-\lambda_N)^n (R_N - \lambda_N X_N)}{(n+1)!} t^{n+1}$, then $\dot{X}_N = R_N - \lambda_N X_N$ and

$$X'_N = X_N + \sum_{i=0}^{n-1} \frac{(-\lambda_N)^i (R_N - \lambda_N X_N)}{(i+1)!} T^{i+1}$$

are equivalent with respect to any ϵ-semantics, i.e., there is no ϵ-semantics which can distinguish them. Analogously, we can write polynomial dynamics which are equivalent to $\dot{X}_N = -\lambda_N X_N$, $\dot{X}_D = R_D - \lambda_D X_D$, and $\dot{X}_D = -\lambda_D X_D$. Hence, the above models can be rephrased into equivalent semi-algebraic hybrid automata whose evolutions cannot be distinguished by any ϵ-semantics (e.g., $[\![\cdot]\!]_\epsilon$ or $(\!|\cdot|\!)_\epsilon$). If we investigate the semi-algebraic hybrid automaton corresponding to the two-cells model and we endow it with ϵ-semantics, the Zeno behavior disappears. As a matter of facts, even if we start from a point, p, of the form $\langle x_D, x_N, x_D, x_N\rangle$, as soon as the first transition is taken, an ϵ-neighborhood of p is reached, and, since such kind of set always includes at least one point of the form $\langle x_D, x_N, y_D, y_N\rangle$, with $x_D \neq y_D$ and $x_N \neq y_N$, we known that from such a point we will eventually reach equilibrium. In particular, because of neighborhood symmetry, both the equilibria will be reached. This is consistent with what we would expect. Since, it is almost impossible to start with two cells with the same concentrations, this means that our measures of the concentrations are not precise enough to determine the differences in the concentrations. Hence, we only know that we will reach one of the equilibria, but not which one. Moreover, even if we assume that we can really start with the same concentrations in both cells, due to small perturbations (e.g., in the decay of the proteins), such situation will not hold forever. This again means that we do not know when, why, and which, but one of the equilibria will be eventually reached.

7 Conclusions and Discussion

Hybrid automata allow to reason on continuous quantities and to exploit a large and powerful set of techniques inherited from mathematical analysis. However, such continuous quantities are, in Systems Biology context, over approximations of a discrete (huge) number of molecules. Hence, while on the hybrid automaton we can reason with infinite precision, on the biological system we cannot go behind the precision of one molecule. This difference does not only introduce in the hybrid model unrealistic behaviors, but soon leads to undecidability. In fact, we end up with a weird model in which the more intractable behaviors are exactly the unrealistic ones. Starting from such analysis, we presented alternative semantics, called *ϵ-semantics*, which allow to give a more faithful representation of biological systems by reasoning up to limited precision.

In [50] similar considerations are posed from a different perspective: "real hybrid systems are always subject to noise". To model such noise the author introduced a disturbed variant $\widetilde{H}$ of the original automaton H and proved that all the states reachable from H are reachable in $\widetilde{H}$ after a finite number i of discrete steps. Since i is computable, the reachability problem over H can be effectively over-approximated. However, the decidability of the reachability problem over either the original automaton or on the disturbed one is not guaranteed. In Fränzle framework it is not interest-

ing to study the reachability problem on the disturbed automaton $\widetilde{H}$, since it is only functional to the over-approximation of the reachability problem on H and, hence, it is more reasonable to stop the computation of $Reach(\widetilde{H})(I, i)$ as soon as this set includes $Reach(H)(I)$. The semantics we proposed in this paper instead are neither over nor under approximating and try to introduce in our model a finite precision ingredient. Once established which ϵ-semantics is more suitable for a particular application it is necessary to reason only in terms of such ϵ-semantics and forget about the classical one. In fact, our semantics does not only affect the continuous dynamics as in the case of [50], but all the interpretations of the formulæ involved in the automaton. We start from the assumption that we are modeling robust systems and we try to embed robustness in the semantics, while Fränlzle analyzes also non-robust systems and proves that robustness is undecidable.

Many other approaches, which avoid undecidability by introducing approximations, have been proposed in the literature (see, e.g., [51,52,19]). In these works the space is a-priori discretized and such discretization is used to perform the reachability computation. Intuitively, when over approximations are concerned this can be seen as putting a grid on the space and marking as reachable a square of the grid as soon as at least a point in the square is reached. In these pictorial terms we can read our approach as follows: instead of having a fixed grid we have a lens allowing us to see only objects of size at least ϵ. The ϵ-semantics establishes the size of each object by fixing the size of the basic ones and of their combinations. Then what we have to do is to follow the dynamics with our lens and to stop looking as soon as we cannot see anything new.

There are three main reasons to adopt the proposed framework: first of all, provided the decidability of the ϵ-semantics of a theory $\mathcal{T}$, the reachability problem over $\mathcal{T}$ hybrid automata with bounded invariants with respect to the ϵ-semantics is decidable. Moreover, Zeno behaviors, which are at the ground of the difference between practice and theory in the modeling of biological systems with hybrid automata, are not possible in the proposed framework. Last, but not least, since ϵ-semantics cannot distinguish too close evolutions, semi-algebraic theory can model any kind of dynamics exactly with respect to ϵ-semantics themselves.

Such last point, together with the observation that many ϵ-semantics for semi-algebraic hybrid automata are semi-algebraic also, opens new scenarios about automatic deduction in Systems Biology and Bioinformatics analysis. In particular, it means that ϵ-semantics enable us to both model *any* biological system by using semi-algebraic hybrid automata and apply Model Checking techniques, such as reachability computation, being confident in the solvability of the investigated decision problem. Unfortunately, the most efficient known decision algorithm for Tarski theory is more that exponential with respect to both formula size and number of variables [36]. Hence, because of the chosen quantum ϵ or because of their complexity, many systems cannot be currently investigated in an efficient way by using the proposed method. However, specific ϵ-semantics decision algorithms have not been investigated yet and we hope, in the future, to identify relevant ϵ-semantics with low complexity decision methods.

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