



**HAL**  
open science

# Reachability analysis of a class of hybrid gene regulatory networks

Honglu Sun, Maxime Folschette, Morgan Magnin

► **To cite this version:**

Honglu Sun, Maxime Folschette, Morgan Magnin. Reachability analysis of a class of hybrid gene regulatory networks. 17th International Conference on Reachability Problems (RP'23), Oct 2023, Nice, France. pp.56-69, 10.1007/978-3-031-45286-4\_5 . hal-04180870

**HAL Id: hal-04180870**

**<https://hal.science/hal-04180870v1>**

Submitted on 14 Aug 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

# Reachability analysis of a class of hybrid gene regulatory networks<sup>\*</sup>

Honglu Sun<sup>1</sup>[0000-0002-8265-0984], Maxime Folschette<sup>2</sup>[0000-0002-3727-2320], and Morgan Magnin<sup>1</sup>[0000-0001-5443-0506]

<sup>1</sup> Nantes Université, École Centrale Nantes, CNRS, LS2N, UMR 6004, F-44000 Nantes, France

<sup>2</sup> Univ. Lille, CNRS, Centrale Lille, UMR 9189 CRISTAL, F-59000 Lille, France

**Abstract.** In this work, we study the reachability analysis method of a class of hybrid system called HGRN which is a special case of hybrid automata. The reachability problem concerned in this work is, given a singular state and a region (a set of states), to determine whether the trajectory from this singular state can reach this region. This problem is undecidable for general hybrid automata, and is decidable only for a restricted class of hybrid automata, but this restricted class does not include HGRNs. A priori, reachability in HGRNs is not decidable; however, we show in this paper that it is decidable in certain cases, more precisely if there is no chaos. Based on this fact, the main idea of this work is that if the decidable cases can be determined automatically, then the reachability problem can be solved partially. The two major contributions are the following: firstly, we classify trajectories into different classes and provide theoretical results about decidability; then based on these theoretical results, we propose a reachability analysis algorithm which always stops in finite time and answers the reachability problem partially (meaning that it can stop with the inconclusive result, for example with the presence of chaos).

**Keywords:** Reachability · Hybrid system · Decidability · Gene regulatory networks · Limit cycle.

## 1 Introduction

Reachability problem of dynamical system has been investigated on different formalisms, majorly on discrete systems [14,23,6] and hybrid systems [19,2,3,15,8,25]. In this work, we study a reachability analysis method on a class of hybrid system called hybrid gene regulatory network (HGRN) [7,4], which is an extension of Thomas' discrete modeling framework [27,28]. This hybrid system is proposed to model gene regulatory networks, which are networks of genes describing the regulation relations between genes.

HGRNs are similar to piecewise-constant derivative systems (PCD systems) [2] which is a special case of hybrid automata [1]. The major difference between

---

<sup>\*</sup> Supported by China Scholarship Council.

HGRNs and PCD systems of the works [2,3,25] is the existence of sliding mode, which means that when a trajectory reaches a black wall (a boundary of the discrete state which can be reached but cannot be crossed by trajectories), it is forced to move along the black wall. There exist other methods to define behaviors of trajectories on a black wall [17,24] which are different from the sliding mode in HGRNs.

The reachability problem concerned in this work is to determine whether the trajectory from certain state can reach a certain region (a set of states). We mainly focus on the decidability problem, that is, whether we can find an algorithm to determine the reachability problem such that this algorithm always stops in finite time and gives a correct answer.

The decidability problem among hybrid systems that are close to HGRNs is already studied in the literature. It has been proved that, for PCD systems, it is decidable in 2 dimensions [21] but it is undecidable in 3 dimensions [2]. For general hybrid automata, there exists a restricted class called initialized rectangular automata which is decidable in any dimension [19], but this class does not include HGRNs.

Up to now, there is no theoretical results of the decidability of this problem on HGRNs. A priori, we can expect that it is not decidable because of the existence of chaos. However, if we can show that it is decidable in certain cases, for example, when the trajectory considered in a reachability problem converges asymptotically to a  $n$ -dimensional limit cycle, and if these cases can be identified automatically, then the reachability problem can be answered partially, which is the main idea of this work. In order to prove the existence of chaos in HGRNs, we exhibit a HGRN with a chaotic attractor based on a different pre-existing hybrid system [18]. This work has the following contributions:

- We classify trajectories of HGRNs into three classes: trajectories halting in finite time, trajectories attracted by regularly oscillating cycles and chaotic trajectories. For the first two classes, we prove that the reachability problem is decidable and we provide methods to determine automatically their classes. For the third class, a priori, it is undecidable, and we provide a necessary condition for that a trajectory is chaotic.
- Based on the above theoretical results, we propose a reachability analysis algorithm for HGRNs which always stops in finite time and once it stops, it returns whether the set of target states is reached, not reached or if the result is unknown. The unknown result is related to the existence of chaos. To our knowledge, this is the first reachability analysis algorithm for HGRNs and it can be applied to HGRNs in any dimension.

This paper is organized as follows. In Section 2, we introduce basic notions of HGRNs. In Section 3, we present our reachability analysis method, including theoretical results and the reachability analysis algorithm. And finally in Section 4, we make a conclusion by discussing the merits and limits of this method and our future work.

## 2 Preliminary Definitions

In this section, we present HGRNs and its basic notions. Consider a gene regulatory network with  $N$  genes; the set of genes is denoted  $G = \{G_1, G_2, \dots, G_N\}$ . A *discrete state* is an integer vector of length  $N$ , noted by  $d_s$ , which assigns the discrete level  $d_s^i$  to gene  $G_i$ , where  $i \in \{1, 2, 3, \dots, N\}$  and  $d_s^i$  is the  $i^{\text{th}}$  component of  $d_s$ . The set of all discrete states is denoted by  $E_d$ .

A *hybrid gene regulatory network* (HGRN) is noted  $\mathcal{H} = (E_d, c)$ .  $c$  is a function from  $E_d$  to  $\mathbb{R}^N$ . For each  $d_s \in E_d$ ,  $c(s)$ , also noted  $c_s$ , is called the *celerity* of discrete state  $d_s$  and describes the temporal derivative of the system in  $d_s$ . A 2-dimensional HGRN is shown in Fig 1. In this system, each of these two genes ( $A = G_1, B = G_2$ ) has two discrete levels: 0 and 1, so there are 4 discrete states: 00, 01, 10, 11. Black arrows represent the celerities (temporal derivatives) of each discrete state.

In HGRNs, a *state* is also called a *hybrid state*, which is a couple  $h = (\pi, d_s)$  containing a *fractional part*  $\pi$ , which is a real vector  $[0, 1]^N$ , and a discrete state  $d_s$ . The set of all hybrid states is denoted by  $E_h$ .

A (*hybrid*) *trajectory*  $\tau$  of HGRN is a function from a time interval  $[0, t_0]$  to  $E_\tau = E_h \cup E_{sh}$ , where  $t_0 \in \mathbb{R}^+ \cup \{\infty\}$ , and  $E_{sh}$  is the set of all finite or infinite sequences of states:  $E_{sh} = \{(h_0, h_1, \dots, h_m) \in (E_h)^{m+1} \mid m \in \mathbb{N} \cup \{\infty\}\}$ . A trajectory  $\tau$  is called a *closed trajectory* if it is defined on  $[0, \infty[$  and  $\exists T > 0, \forall t \in [0, \infty[, \tau(t) = \tau(t+T)$ . In Fig 1, red arrows represent a possible trajectory of this system, which happens, in this particular case, to be a closed trajectory.

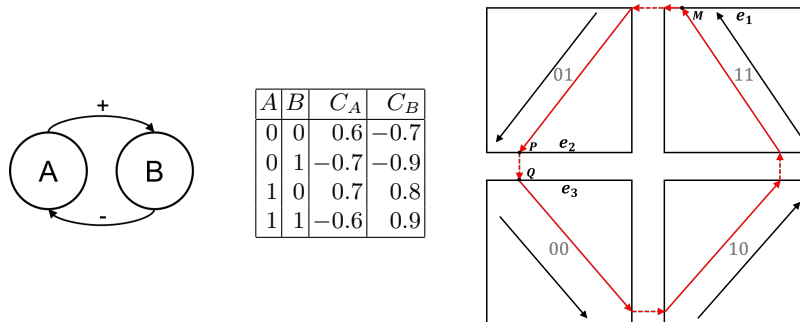


Fig. 1: Example of a HGRN in 2 dimensions. Left: Influence graph (negative feedback loop with 2 genes). Middle: Example of corresponding parameters (celerities). Right: Corresponding example of dynamics; abscissa represents gene A and ordinate represents gene B.

A *boundary* in a discrete state  $d_s$  is a set of states defined by  $e(G_i, \pi_0, d_s) = \{(\pi, d_s) \in E_h \mid \pi^i = \pi_0\}$ , where  $i \in \{1, 2, \dots, N\}$ ,  $d_s \in E_d$  and  $\pi_0 \in \{0, 1\}$ . In the rest of this paper, we simply use  $e$  to represent a boundary.

In Fig 1, the state  $h_M = ((\pi_M^1, 1), (1, 1))$  of point  $M$  belongs to  $e_1 = (B, 1, (1, 1))$ , that is, the upper boundary in the second dimension (the dimension of gene  $B$ ) of the discrete state 11. Since there is no other discrete state on the other side of  $e_1$ , the trajectory from  $h_M$  cannot cross  $e_1$  and has to slide along  $e_1$  ( $e_1$  can be called a black wall). The existence of such sliding mode is a speciality of HGRNs. Boundaries like  $e_1$ , which can be reached by trajectories but cannot be crossed, are defined as *attractive boundaries*. The state  $h_P = ((\pi_P^1, 0), (0, 1))$  of point  $P$  belongs to  $e_2 = (B, 0, (0, 1))$ , the lower boundary in the second dimension of the discrete state 01. The trajectory from  $h_P$  reaches instantly  $h_Q = ((\pi_Q^1, 1), (0, 0))$ , which belongs to  $e_3 = (B, 1, (0, 0))$ , the upper boundary in the second dimension of discrete state 00, because the celerities on both sides allow this (instant) discrete transition.  $e_2$  is called an *output boundary* of 01 and  $e_3$  is called an *input boundary* of 00.

When a trajectory reaches several output boundaries at the same time (Fig 2 left), it can cross any of them but can only cross one boundary at a time, which causes non-deterministic behaviors. The simulation of HGRNs is presented more formally in Appendix A.

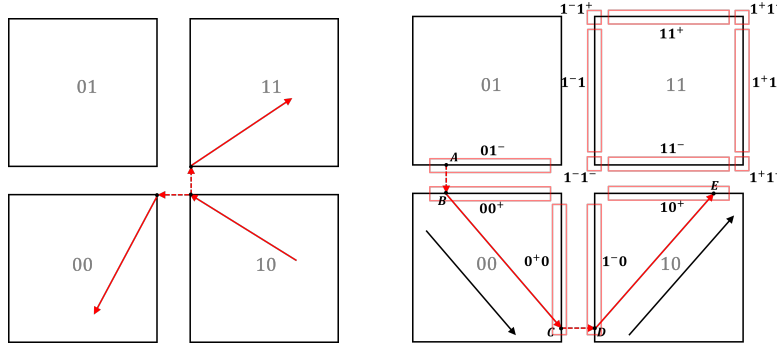


Fig. 2: Left: Illustration of a non-deterministic behavior. Right: Illustration of all discrete domains of state 11, and a sequence of discrete domains in the other states.

In order to analyze dynamical properties of HGRNs, the concepts of *discrete domain*, *transition matrix* and *compatible zone* are introduced in [26]. A *discrete domain*  $\mathcal{D}(d_s, S_-, S_+)$  is a set of states inside one discrete state  $d_s$ , defined by:

$$\mathcal{D}(d_s, S_-, S_+) = \{(\pi, d_s) \mid \forall i \in \{1, 2, \dots, N\}, \pi^i \in \begin{cases} \{1\} & \text{if } i \in S_+ \\ \{0\} & \text{if } i \in S_- \\ ]0, 1[ & \text{if } i \notin S_- \cup S_+ \end{cases} \}$$

where  $S_+$  and  $S_-$  are power sets of  $\{1, 2, \dots, N\}$  such that  $S_+ \cap S_- = \emptyset$  and  $S_+ \cup S_- \neq \emptyset$ . In fact,  $S_+$  ( $S_-$ ) represents the dimensions in which the upper (lower) boundaries are reached by any state  $h \in \mathcal{D}(d_s, S_-, S_+)$ . In the rest of

this paper, we simply use  $\mathcal{D}$  to represent a discrete domain when there is no ambiguity.

Some discrete domains are illustrated in Fig 2 right. For example,  $11^+$  denotes the discrete domain inside discrete state 11 where the upper boundary is reached for the second dimension and no boundary is reached for the first dimension, that is:  $\mathcal{D}((1, 1), \emptyset, \{2\}) = \{(\pi, (1, 1)) \mid \pi^1 \in ]0, 1[ \wedge \pi^2 = 1\}$ . The state  $D$  in this figure belongs to the discrete domain  $1^-0$ . The discrete state 11 contains 8 discrete domains:  $1^-1^-$ ,  $11^-$ ,  $1^+1^-$ ,  $1^-1^+$ ,  $11^+$ ,  $1^+1^+$ ,  $1^-1$  and  $1^+1$ , which are depicted in Fig 2 right. Note that, for instance,  $1^+1^+$  is represented by a small red rectangle for readability, but in fact it only contains one singular hybrid state  $((1, 1), (1, 1))$ .

To order to introduce the concepts of *transition matrix* and *compatible zone*, consider a sequence of discrete domains  $\mathcal{T} = (\mathcal{D}_i, \mathcal{D}_{i+1}, \mathcal{D}_{i+2}, \dots, \mathcal{D}_j)$  in the rest of this section and assume that there is a trajectory  $\tau$  which starts from  $h_i = (\pi_i, d_{s_i}) \in \mathcal{D}_i$ , reaches all discrete domains of  $\mathcal{T}$  in order without reaching any other discrete domain, and finally reaches  $h_j = (\pi_j, d_{s_j}) \in \mathcal{D}_j$ . In this case, we say that  $\tau$  is inside  $\mathcal{T}$ . For example, in Fig 2 right, the red trajectory is inside the sequence of discrete domains  $(01^-, 00^+, 0^+0, 1^-0, 10^+)$ .

The relation between  $\pi_i$  and  $\pi_j$  can be described by a *transition matrix*  $M$ :  $\pi_j = s^{-1}(Ms(\pi_i))$ , where  $s$  is a function that adds an extra dimension and the value in the extra dimension is always 1:  $s((a_1, a_2, \dots, a_N)) = (a_1, a_2, \dots, a_N, 1)$ . The transition matrix  $M$  only depends on  $\mathcal{T}$ . The transition  $\pi_j = s^{-1}(Ms(\pi_i))$  can be reformulated by another affine application  $x_j = Ax_i + b$ , where  $x_i$  (resp.  $x_j$ ) is the short version of  $\pi_i$  (resp.  $\pi_j$ ) by only considering the dimensions where boundaries are not reached in  $\mathcal{D}_i$  (resp.  $\mathcal{D}_j$ ). The matrix  $A$  is called the *reduction matrix* of  $\mathcal{T}$ ,  $b$  is called the *constant vector* of  $\mathcal{T}$  and the vector  $x_i$  is called the *reduction vector* of  $h_i$ , which is noted by  $x_i = r(h_i)$ . For example, for the state  $h_M = ((\pi_M^1, 1), (1, 1))$  in Fig 1,  $r(h_M) = (\pi_M^1)$  which is a 1-dimensional vector.

A priori, not all trajectories from  $\mathcal{D}_i$  stay inside  $\mathcal{T}$ . The maximal subset of  $\mathcal{D}_i$  from which the trajectories stay inside  $\mathcal{T}$  is called the *compatible zone* of  $\mathcal{T}$ , noted by  $\mathcal{S}$ . The compatible zone can also be described by  $\mathcal{S} = \{(\pi, d_{s_i}) \in \mathcal{D}_i \mid r(\pi) \in \mathcal{S}_r\}$  where  $\mathcal{S}_r$  is a set of reduction vectors of states in  $\mathcal{D}_i$  and  $\mathcal{S}_r$  is called the *reduction compatible zone*.

### 3 Reachability analysis method

In this section, we firstly define the reachability problem concerned in this work.

*Problem 1 (Reachability).* Consider a hybrid state  $h_1 = (\pi_1, d_{s_1})$  and a region  $R_2 = \{(\pi, d_{s_2}) \mid \pi^i \in [a_i, b_i], i \in \{1, 2, \dots, N\}\}$ , where  $a_i, b_i \in \mathbb{R}$  and  $0 \leq a_i \leq b_i \leq 1, \forall i \in \{1, 2, \dots, N\}$ . Does the trajectory  $\tau$  from  $h_1$  enter the region  $R_2$ ? In other words, does there exist  $t_0$  such that  $\tau(t_0) \in R_2$ ?

Problem 1 is illustrated in the examples of Fig 3, where the initial state of the trajectory (red arrows) is  $h_1$  and the blue rectangle represents  $R_2$ .

The following assumptions are made in this work.

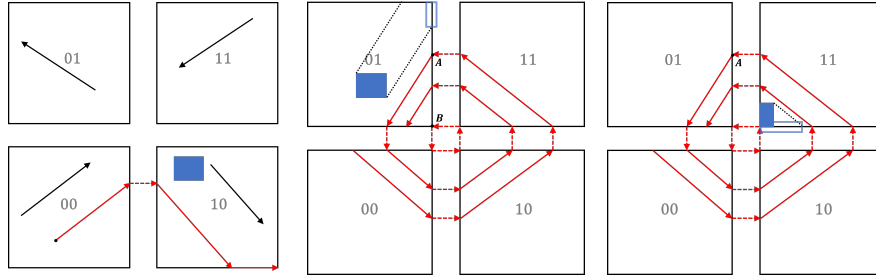


Fig. 3: Left: Illustration of Problem 1 and trajectory halting in finite time. Blue rectangle represents  $R_2$  of Problem 1. Middle and right: Illustration of trajectories attracted by cycles of discrete domains and predecessor in the same discrete state. Blue rectangles represent  $R_2$  of Problem 1 and blue boxes represent their predecessors in the same discrete state.

**Assumption 1** For any sequence of discrete domains  $\mathcal{T}$  of which the compatible zone is not empty, we assume that all eigenvalues of the reduction matrix of  $\mathcal{T}$  are real.

For now, we have not found such reduction matrix with complex eigenvalues.

**Assumption 2** The trajectory from  $h_1$  has no non-deterministic behavior.

Generally, trajectories with non-deterministic behaviors exist, but among state-of-the-art HGRNs of gene regulatory networks, the probability of a randomly chosen initial state that leads to non-deterministic behaviors is almost 0. Therefore, we ignore this kind of trajectory in this work. In fact, the method of this work could also be adapted for non-deterministic trajectories (each time when a non-deterministic state is reached, the current trajectory splits into two or several trajectories, and same method is applied on each of these new trajectories).

**Assumption 3** Any non-instant transition on a limit cycle does not reach more than one new boundary at the same time.

In real-life systems, it is indeed very unlikely for parameters to be that constrained due to the existence of noise.

### 3.1 Different classes of hybrid trajectories

In this section, we classify trajectories of HGRNs into three classes: trajectories halting in finite time, trajectories attracted by cycles of discrete domains and chaotic trajectories. And we provide some theoretical results regarding this reachability problem.

**Trajectories halting in finite time** A trajectory  $\tau$  is a *trajectory halting in finite time* if  $\exists t_0$  such that the derivative of  $\tau(t_0)$  is 0 in any dimension, in other words  $\tau(t_0)$  is a fixed point. The trajectory in Fig 3 left is a trajectory halting in finite time. We can easily see that Problem 1 is decidable if the trajectory from  $h_1$  is a trajectory halting in finite time, because, in this case, the trajectory is a composition of a finite number of  $n$ -dimensional “straight lines”; to verify if this trajectory reaches  $R_2$ , we only need to verify if any of these “straight lines” cross  $R_2$ , which can be verified in finite time.

**Trajectories attracted by cycles of discrete domains** A trajectory  $\tau$  is a *trajectory attracted by a cycle of discrete domains* if  $\exists t_0$  such that after  $t_0$ ,  $\tau$  always stays inside a cycle of discrete domains  $\mathcal{C}_\tau = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p, \mathcal{D}_0)$ , meaning that  $\tau$  crosses this cycle an infinite number of times without leaving it. Intuitively, if a trajectory  $\tau$  is attracted by a cycle of discrete domains, then  $\tau$  converges to or reaches a limit cycle. In Fig 3 middle and right, both trajectories are attracted by a cycle of discrete domains: indeed, these trajectories converge to the limit cycle in the center of the figure (which only has instant transitions).

To prove the decidability of trajectories attracted by cycles of discrete domains, we introduce the notion of *predecessor in the same discrete state*: for any set of hybrid states in the same discrete state defined by  $R = \{(\pi, d_s) \mid \pi \in E\}$  where  $E \subseteq [0, 1]^N$  is a closed set, the predecessor of  $R$  in the same discrete state, noted by  $Pre_{d_s}(R)$ , is the union of sets of hybrid states:  $Pre_{d_s}(R) = \bigcup_{i \in \{1, 2, \dots, q\}} Z_i$ , such that: 1) each  $Z_i$  belongs to a different discrete domain on an input boundary of  $d_s$ , 2) any trajectory from  $Pre_{d_s}(R)$  reaches  $R$  directly (“reach  $R$  directly” means that reach  $R$  before reaching a new discrete state), 3) any trajectory from an input boundary of  $d_s$  but not from  $Pre_{d_s}(R)$  does not reach directly  $R$ . For Problem 1, we can see that if the trajectory  $\tau$  from  $h_1$  has already crossed at least one discrete state (we say  $\tau$  has already crossed a discrete state at  $t_0$  if there exists  $t < t_0$  such that  $\tau(t_0)$  and  $\tau(t)$  do not belong to the same discrete state) without reaching the region  $R_2$ , then Problem 1 is equivalent to “Does  $\tau$  reach  $Pre_{d_{s_2}}(R_2)$ ?”.

Examples of predecessors in the same discrete state are illustrated in Fig 3 middle and right where blue rectangles represent  $R_2$  and blue boxes present their predecessors in the same discrete state.

**Theorem 1.** *Problem 1 is decidable if the trajectory from  $h_1$  is a trajectory attracted by a cycle of discrete domains.*

The proof of Theorem 1 is given in Appendix B. The idea of this proof can be explained intuitively by 2-dimensional examples in Fig 3 middle and right. In Fig 3 middle, the trajectory which reaches state A, noted by  $\tau$ , can be considered as two trajectories: the first one is the part of  $\tau$  before reaching A and the second one is the part of  $\tau$  after reaching A. This first one can be considered as a trajectory halting in finite time so whether it reaches  $R_2$  is decidable, and in this example it does not reach  $R_2$ . For the second one, these two following statements can be verified: 1. The intersection points between this trajectory



and the “right” boundary of discrete state 01 must be located in the line segment AB. 2. The line segment AB does not intersect with the predecessor of  $R_2$  in the same discrete state. Based on these two statements, we can prove that this second part cannot reach  $R_2$  either. In this way, we prove theoretically that  $R_2$  is not reached by  $\tau$ , and since this process can be done automatically in finite time, the problem is decidable. Note that in the general case, this “line segment AB” is a  $(n-1)$ -dimensional region such that the trajectory always returns to this region and this region does not intersect the predecessor of  $R_2$  in the same discrete state. In Fig 3 right, it can be verified automatically in finite time that the limit cycle with only instant transitions (at the center) reaches  $R_2$ , and that  $\tau$  converges to this limit cycle, so we can prove that  $\tau$  finally reaches  $R_2$ , and this case is thus decidable too.

We also develop the following theorem to determine if a trajectory is attracted by a cycle of discrete domains. In order to simplify this theorem, for the cycle of discrete domains  $\mathcal{C}_{\mathcal{T}} = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p, \mathcal{D}_0)$  and the hybrid state  $h_0 \in \mathcal{D}_0$  considered in this theorem, we note that:

- The reduction matrix and the constant vector of  $\mathcal{C}_{\mathcal{T}}$  are  $A$  and  $b$  respectively.
- The reduction compatible zone of  $\mathcal{C}_{\mathcal{T}}$  is described by linear constraints  $\{x \mid Wx > c\}$  where  $c$  is a vector and  $W$  is a matrix.  $W$  is of size  $n_0 \times n_1$ , where  $n_1$  is the number of dimensions of  $r(h_0)$ .  $W_i$  is the  $i^{\text{th}}$  line of matrix  $W$  ( $W_i$  is of size  $1 \times n_1$ ) and  $c_i$  is the  $i^{\text{th}}$  component of vector  $c$ .
- $r_{\infty} = \lim_{n \rightarrow \infty} f^n(r(h_0))$  where  $f(x) = Ax + b$ .
- The eigenvalues and eigenvectors of  $A$  are  $\{\lambda_i \mid i \in \{1, 2, \dots, n_1\}\}$  and  $\{v_i \mid i \in \{1, 2, \dots, n_1\}\}$  respectively.  $\lambda_1$  is chosen as the eigenvalue with the maximum absolute value among the eigenvalues that differ from 1.
- The decomposition of  $r(h_0) - r_{\infty}$  in the directions of eigenvectors of the reduction matrix  $A$  is noted as  $r(h_0) - r_{\infty} = \sum_{i=1}^{n_1} \alpha_i v_i$ .

**Theorem 2.** *A trajectory  $\tau$  is attracted by a cycle of discrete domains if and only if  $\tau$  reaches  $h_0$  which belongs to the compatible zone of a cycle of discrete domains  $\mathcal{C}_{\mathcal{T}} = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p, \mathcal{D}_0)$  such that  $\mathcal{D}_0$  has no free dimension (meaning that, in  $\mathcal{D}_0$ , boundaries are reached in all dimensions) or the following conditions are satisfied.*

- $\mathcal{D}_0$  has at least one free dimension.
- $\forall i \in \{1, 2, \dots, n_1\}, |\lambda_i| \leq 1 \wedge \lambda_i \neq -1$ .
- $\forall i \in \{1, 2, \dots, n_0\}$ , we have either  $W_i r_{\infty} = c_i$  or  $W_i r_{\infty} > c_i$ . We use  $I_e$  to represent the maximum set of integers such that  $\forall i \in I_e, W_i r_{\infty} = c_i$  and we use  $I_n$  to represent the maximum set of integers such that  $\forall i \in I_n, W_i r_{\infty} > c_i$ .
- If  $\lambda_1 \neq 0$  (we assume that  $\lambda_1$  is unique if  $\lambda_1 \neq 0$ ) and  $I_e$  is not empty, then  $\lambda_1$  is positive.
- If  $\lambda_1 \neq 0$ , then  $\forall i \in I_e, \forall j \in \{2, \dots, n_1\}, |W_i v_1 \alpha_1| > n_1 |W_i v_j \alpha_j|$  (we ignore the case that  $\exists i \in I_e, W_i v_1 = 0$ ).
- If  $\lambda_1 \neq 0$ , then  $\forall i \in I_n, \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{j=1}^{n_1} \beta_j \alpha_j v_j\|_2 < \frac{W_i r_{\infty} - c_i}{\|W_i\|_2}$ .

The proof of Theorem 2 is given in Appendix C. The main idea of Theorem 2 is illustrated in Fig 4 where the huge rectangle represents a discrete domain  $\mathcal{D}$  which has two free dimensions and the zone surrounded by dashed lines represents the compatible zone  $\mathcal{S}$  (which is a open set) of a certain cycle of discrete domains  $\mathcal{C}_{\mathcal{T}}$ . Each dashed line  $l_{ci}$  represents a linear constraint of the form  $w^T x > c$  where  $w, x$  are vectors and  $c$  is a real number. The fact that a trajectory  $\tau$  is attracted by  $\mathcal{C}_{\mathcal{T}}$  is equivalent to the fact that the intersection points between  $\tau$  and  $\mathcal{D}$ , noted by the sequence  $(h_1, h_2, \dots)$ , always stay inside  $\mathcal{S}$  and converge to  $(\lambda_1 \neq 0)$  or reach  $(\lambda_1 = 0)$   $h_{\infty}$ , which belongs to the closure of  $\mathcal{S}$ . Need to mention that this idea of using the intersection points between a trajectory and a hyperplan to study the properties of this trajectory is based on the idea of Poincaré map. Similar ideas have been widely used in the literature to study limit cycles of other hybrid systems [5,12,29,13,11,16,20,10,22] and also have been applied to analyze the stability of limit cycles of HGRNs in [26].

Whether  $h_{\infty}$  belongs to the closure of  $\mathcal{S}$  or not can be easily verified by using these linear constraints. A necessary condition for this sequence to always satisfy these linear constraints is that the absolute values of all eigenvalues of the reduction matrix of  $\mathcal{C}_{\mathcal{T}}$  are less than or equal to 1. In case that these eigenvalues satisfy this necessary condition, to verify if this sequence always satisfies these linear constraints, we separate these constraints on two classes: the first class contains all constraints which are not reached by  $h_{\infty}$ :  $l_{c2}, l_{c3}, l_{c4}$ , the second class contains all constraints which are reached by  $h_{\infty}$ :  $l_{c1}, l_{c5}$ . To verify if  $l_{c2}, l_{c3}, l_{c4}$  are always satisfied, we can verify if this sequence enters and stays in a circle centered by  $h_{\infty}$  which only contains states satisfying constraints  $l_{c2}, l_{c3}, l_{c4}$  (this is related to the condition: if  $\lambda_1 \neq 0$ , then  $\forall i \in I_n, \max_{\beta \in \{-1,1\}^{n_1}} \|\sum_{j=1}^{n_1} \beta_j \alpha_j v_j\|_2 < \frac{W_i r_{\infty} - c_i}{\|W_i\|_2}$ ), such circle can always be found if it is sufficiently small, for example, the circle in Fig 4. To verify if  $l_{c1}, l_{c5}$  are always satisfied, we can verify if this sequence is sufficiently "close" to  $v_1$  which is the eigenvector related to the eigenvalue with the maximum absolute value among the eigenvalues that differ from 1 and which also "points into"  $\mathcal{S}$  (this is related to the condition: if  $\lambda_1 \neq 0$ , then  $\forall i \in I_e, \forall j \in \{2, \dots, n_1\}, |W_i v_1 \alpha_1| > n_1 |W_i v_j \alpha_j|$ ). Here, sufficiently "close" to  $v_1$  means intuitively that the angle between  $\overrightarrow{h_{\infty} h_i}$  and  $v_1$  is sufficiently small.

**Chaotic trajectories** In this work, a trajectory of HGRN is called a chaotic trajectory if it does not reach a fixed point and it is not attracted by a cycle of discrete domains. So all trajectories which are not included in the previous two classes are chaotic trajectories. Need to mention that the dynamics of chaotic trajectories, a priori, can be different from the chaotic dynamics of classic non-linear dynamical systems. The reason why we still use the terminology "chaotic" is that similar concept of chaos has been used in some pre-existing works of other hybrid systems[9,18].

To prove such chaotic trajectories exist, we have constructed a HGRN with chaotic trajectories based on a pre-existing model of circuit with a chaotic attractor [18]. Parameters of this HGRN are given in the code of our work.

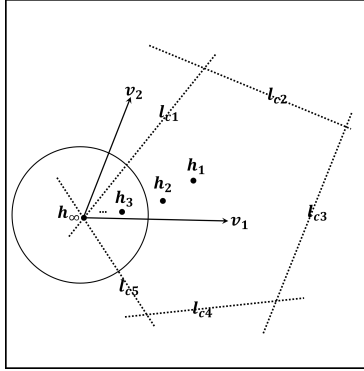


Fig. 4: Illustration of the idea of Theorem 2.

In our work, we have not yet found a method to check reachability for chaotic trajectories, which, a priori, can be undecidable. So, in this subsection, we only introduce a method to predict whether a trajectory is chaotic, based on a necessary condition.

For a chaotic trajectory  $\tau$ , there exist  $t_0$  and a finite set of discrete domains  $L_D$ , such that after  $t_0$ ,  $\tau$  cannot reach any discrete domain which does not belong to  $L_D$ , and for any discrete domain  $\mathcal{D}_0 \in L_D$ ,  $\mathcal{D}_0$  is reached by  $\tau$  an infinite number of times. This is a result of the fact that the number of discrete domains is finite and the trajectory does not stay in a particular discrete domain.

For any  $\mathcal{D}_0 \in L_D$ , we can find  $t_1 > t_0$  such that, from  $t_1$ ,  $\tau$  returns to  $\mathcal{D}_0$  an infinite number of times, and each time it stays inside a sequence of discrete domains of the form  $(\mathcal{D}_0, \dots, \mathcal{D}_0)$ . The set of all such sequences of discrete domains is noted by  $L_T$ . We assume that  $L_T$  is a finite set, which is based on the fact that the number of discrete domains is limited and the dynamics in the discrete states is simple (a constant vector). Based on this, if  $t_1$  is sufficiently big, then we can derive that from  $t_1$ ,  $\forall \mathcal{T} \in L_T$  is crossed by  $\tau$  an infinite number of times.

Now the sequence of discrete domains crossed by  $\tau$  from  $t_1$  can be described by the infinite sequence  $(\mathcal{T}_1, \mathcal{T}_2, \mathcal{T}_3, \dots)$ , where  $\forall i \in \mathbb{N}, \mathcal{T}_i \in L_T$ . And we can get the following property of chaotic trajectories, which is used in the following section to predict whether a trajectory is chaotic.

*Property 1.*  $\exists i \in \mathbb{N}, \exists k \in \mathbb{N}, k \neq 1$ , such that  $\mathcal{T}_i \neq \mathcal{T}_{i+1}$  and  $\mathcal{T}_i = \mathcal{T}_{i+k}$ .

*Proof.* This can be derived from the two facts: 1)  $\exists i \in \mathbb{N}$ , such that  $\mathcal{T}_i \neq \mathcal{T}_{i+1}$ ; 2)  $\forall i \in \mathbb{N}, \exists k \in \mathbb{N}$ , such that  $\mathcal{T}_i = \mathcal{T}_{i+k}$ . The first one is a direct result of the fact that all elements of  $L_T$  must appear in the sequence  $(\mathcal{T}_1, \mathcal{T}_2, \mathcal{T}_3, \dots)$  and  $L_T$  has at least two elements. If the second one is not true, then  $\mathcal{T}_i$  is crossed by  $\tau$  for finite times, which contradicts with the result that  $\forall \mathcal{T} \in L_T$  is crossed by  $\tau$  an infinite number of times.  $\square$

### 3.2 Reachability analysis algorithm

In this section, we present our reachability analysis algorithm, see Algorithm 1, where we call a *transition from  $h$  to  $h'$* , noted  $h \rightarrow h'$ , a minimal trajectory from state  $h$  that reaches a new boundary in state  $h'$ . In other words,  $h \rightarrow h'$  can be considered an atomic step of simulation, either instant (change of discrete state) or not (with continuous time elapsed).

---

#### Algorithm 1 Reachability analysis algorithm

---

**Input 1:** A hybrid state  $h_1 = (\pi_1, d_{s_1})$   
**Input 2:** A region  $R_2 = \{(\pi, d_{s_2}) \mid \pi^i \in [a_i, b_i], i \in \{1, 2, \dots, N\}\}$   
**Output:** “ $R_2$  is reached”, “ $R_2$  is not reached” or “unknown result”

- 1: Current state  $h := h_1$
- 2: **while**  $h$  is not a fixed point **do**
- 3:    $h' :=$  next state so that  $h \rightarrow h'$  is a transition
- 4:   **if** Transition  $h \rightarrow h'$  reaches  $R_2$  **then**
- 5:     **return** “ $R_2$  is reached”
- 6:   **else**
- 7:      $h := h'$
- 8:     **if** Current simulation is attracted by a cycle of discrete domains **then**
- 9:       **if**  $Stop\_condition(Cycle_h, Cycle_{\mathcal{D}}, R_2)$  returns Yes **then**
- 10:         **return** “ $R_2$  is not reached”
- 11:       **else if**  $Stop\_condition(Cycle_h, Cycle_{\mathcal{D}}, R_2)$  returns Reached **then**
- 12:         **return** “ $R_2$  is reached”
- 13:       **end if**
- 14:     **else if** Current simulation is probably a chaotic trajectory **then**
- 15:       **return** “unknown result”
- 16:     **end if**
- 17:   **end if**
- 18: **end while**
- 19: **return** “ $R_2$  is not reached”

---

To determine if the current simulation is attracted by a cycle of discrete domains (line 8) or if the current simulation is probably a chaotic trajectory (line 14), we use Theorem 2 or Property 1 respectively.

The objective of the function  $Stop\_condition$  is, knowing that this trajectory is attracted by a cycle of discrete domains, to determine if the trajectory can reach  $R_2$  after an infinite number of transitions (see Fig 3 right). If it is the case, the function returns “Reached”. Otherwise, if from the current state, there is no more chance to reach  $R_2$  (see Fig 3 middle), then the function returns “Yes”. For both cases, this function can give the right answer in finite time, and the result stops the algorithm. However, if both cases do not apply, the function returns “No” and the algorithm continues. The idea of the function  $Stop\_condition$  is similar to the proof of Theorem 1. Details about the function  $Stop\_condition$  are given in Appendix D.

It can be proved that Algorithm 1 always stops in finite time. Firstly, if the trajectory from  $h_1$  is a trajectory halting in finite time, then the algorithm stops after a finite number of transitions. Secondly, if the trajectory is a chaotic trajectory, then Property 1 will be satisfied after a finite number of transitions, and once it is satisfied, the algorithm stops. Thirdly, if the trajectory is attracted by a cycle of discrete domains, then there are three cases: 1. The trajectory reaches  $R_2$  in finite time; 2. The trajectory reaches  $R_2$  after an infinite number of transitions; 3. The trajectory does not reach  $R_2$ . We assume here that Property 1 is not satisfied before the trajectory reaching the attractive cycle of discrete domains (the cycle of discrete domains which attracts the trajectory from  $h_1$ ). For case 1, the algorithm must stop in finite time, as the trajectory will eventually reach  $R_2$ . For case 2, the function *Stop\_condition* returns "Reached" in finite time. For case 3, the function *Stop\_condition* returns "Yes" in finite time. Need to mention that, since Property 1 is a necessary condition for that a trajectory is chaotic, the algorithm might return inconclusive results ("unknown result") even in the cases that are decidable (trajectories are non-chaotic). In fact, among HGRNs of gene regulatory networks, the cases that satisfy this necessary condition are likely to be very rare: there is no identified HGRN of a gene regulatory network with either chaos or non-chaotic trajectory that satisfies this condition. So, for now, this algorithm is sufficient for checking reachability in practice.

## 4 Conclusion

In this work, we propose a reachability analysis method for HGRNs. In the first part of this work, we classify trajectories of HGRNs into different classes: trajectories halting in finite time, trajectories attracted by cycles of discrete domains and chaotic trajectories, and provide some theoretical results about these trajectories regarding the reachability problem. Then, based on these theoretical results, we provide the first reachability analysis algorithm for HGRNs.

This algorithm always stops, and it returns the correct answer to the reachability problem if it does not stop with the inconclusive result ("unknown result"). In the presence of chaos, the algorithm always stops with this inconclusive result. However, so far, no model with such chaotic behavior has been identified in the model repositories we use from real-life case studies. But the fact that a HGRN with a chaotic trajectory has been identified is a motivation to investigate more.

In our future work, we will try to find other applications of this reachability analysis method and mainly focus on the development of control strategies of gene regulatory networks. Moreover, we are interested in improving the current method to analyze reachability problems in chaotic trajectories.

## ADDITIONAL INFORMATION

Link to the code of this work: [https://github.com/Honglu42/Reachability\\_HGRN/](https://github.com/Honglu42/Reachability_HGRN/).

## References

1. Alur, R., Courcoubetis, C., Henzinger, T.A., Ho, P.H.: Hybrid automata: An algorithmic approach to the specification and verification of hybrid systems. Tech. rep., Cornell University (1993)
2. Asarin, E., Maler, O., Pnueli, A.: Reachability analysis of dynamical systems having piecewise-constant derivatives. *Theoretical computer science* **138**(1), 35–65 (1995)
3. Asarin, E., Mysore, V.P., Pnueli, A., Schneider, G.: Low dimensional hybrid systems—decidable, undecidable, don’t know. *Information and Computation* **211**, 138–159 (2012)
4. Behaegel, J., Comet, J.P., Bernot, G., Cornillon, E., Delaunay, F.: A hybrid model of cell cycle in mammals. *Journal of bioinformatics and computational biology* **14**(01), 1640001 (2016)
5. Belgacem, I., Gouzé, J.L., Edwards, R.: Control of negative feedback loops in genetic networks. In: 2020 59th IEEE Conference on Decision and Control (CDC). pp. 5098–5105. IEEE (2020)
6. Chai, X., Ribeiro, T., Magnin, M., Roux, O., Inoue, K.: Static analysis and stochastic search for reachability problem. *Electronic Notes in Theoretical Computer Science* **350**, 139–158 (2020)
7. Cornillon, E., Comet, J.P., Bernot, G., Enée, G.: Hybrid gene networks: a new framework and a software environment. *advances in Systems and Synthetic Biology* (2016)
8. Dang, T., Testylier, R.: Reachability analysis for polynomial dynamical systems using the bernstein expansion. *Reliab. Comput.* **17**(2), 128–152 (2012)
9. Edwards, R., Glass, L.: A calculus for relating the dynamics and structure of complex biological networks. *Advances in chemical physics* **132**, 151–178 (2006)
10. Edwards, R.: Analysis of continuous-time switching networks. *Physica D: Nonlinear Phenomena* **146**(1-4), 165–199 (2000)
11. Edwards, R., Glass, L.: A calculus for relating the dynamics and structure of complex biological networks. *Adventures in Chemical Physics: A Special Volume of Advances in Chemical Physics* **132**, 151–178 (2005)
12. Firippi, E., Chaves, M.: Topology-induced dynamics in a network of synthetic oscillators with piecewise affine approximation. *Chaos: An Interdisciplinary Journal of Nonlinear Science* **30**(11), 113128 (2020)
13. Flieller, D., Riedinger, P., Louis, J.P.: Computation and stability of limit cycles in hybrid systems. *Nonlinear Analysis: Theory, Methods & Applications* **64**(2), 352–367 (2006)
14. Folschette, M., Paulevé, L., Magnin, M., Roux, O.: Sufficient conditions for reachability in automata networks with priorities. *Theoretical Computer Science* **608**, 66–83 (2015)
15. Frehse, G., Le Guernic, C., Donzé, A., Cotton, S., Ray, R., Lebeltel, O., Ripado, R., Girard, A., Dang, T., Maler, O.: Spaceex: Scalable verification of hybrid systems. In: *Computer Aided Verification: 23rd International Conference, CAV 2011, Snowbird, UT, USA, July 14-20, 2011. Proceedings* 23. pp. 379–395. Springer (2011)
16. Girard, A.: Computation and stability analysis of limit cycles in piecewise linear hybrid systems. *IFAC Proceedings Volumes* **36**(6), 181–186 (2003)
17. Gouzé, J.L., Sari, T.: A class of piecewise linear differential equations arising in biological models. *Dynamical systems* **17**(4), 299–316 (2002)

18. Hamatani, S., Tsubone, T.: Analysis of a 3-dimensional piecewise-constant chaos generator without constraint. *IEICE Proceedings Series* **48**(A2L-B-3) (2016)
19. Henzinger, T.A., Kopke, P.W., Puri, A., Varaiya, P.: What’s decidable about hybrid automata? In: *Proceedings of the twenty-seventh annual ACM symposium on Theory of computing*. pp. 373–382 (1995)
20. Hiskens, I.A.: Stability of hybrid system limit cycles: Application to the compass gait biped robot. In: *Proceedings of the 40th IEEE Conference on Decision and Control (Cat. No. 01CH37228)*. vol. 1, pp. 774–779. IEEE (2001)
21. Maler, O., Pnueli, A.: Reachability analysis of planar multi-linear systems. In: *Computer Aided Verification: 5th International Conference, CAV’93 Elounda, Greece, June 28–July 1, 1993 Proceedings 5*. pp. 194–209. Springer (1993)
22. Mestl, T., Lemay, C., Glass, L.: Chaos in high-dimensional neural and gene networks. *Physica D: Nonlinear Phenomena* **98**(1), 33–52 (1996)
23. Paulevé, L.: Reduction of qualitative models of biological networks for transient dynamics analysis. *IEEE/ACM transactions on computational biology and bioinformatics* **15**(4), 1167–1179 (2017)
24. Plahte, E., Kjøglum, S.: Analysis and generic properties of gene regulatory networks with graded response functions. *Physica D: Nonlinear Phenomena* **201**(1-2), 150–176 (2005)
25. Sandler, A., Tveretina, O.: Deciding reachability for piecewise constant derivative systems on orientable manifolds. In: *Reachability Problems: 13th International Conference, RP 2019, Brussels, Belgium, September 11–13, 2019, Proceedings 13*. pp. 178–192. Springer (2019)
26. Sun, H., Folschette, M., Magnin, M.: Limit cycle analysis of a class of hybrid gene regulatory networks. In: *Computational Methods in Systems Biology: 20th International Conference, CMSB 2022, Bucharest, Romania, September 14–16, 2022, Proceedings*. pp. 217–236. Springer (2022)
27. Thomas, R.: Boolean formalization of genetic control circuits. *Journal of theoretical biology* **42**(3), 563–585 (1973)
28. Thomas, R.: Regulatory networks seen as asynchronous automata: a logical description. *Journal of theoretical biology* **153**(1), 1–23 (1991)
29. Znegui, W., Gritli, H., Belghith, S.: Design of an explicit expression of the poincaré map for the passive dynamic walking of the compass-gait biped model. *Chaos, Solitons & Fractals* **130**, 109436 (2020)

## A Simulation of HGRNs

This appendix formally describes the simulation of HGRNs.

Consider a state  $h = (\pi, d_s)$  and a trajectory  $\tau$  which reaches  $h$  at  $t > 0$ .

- If  $h$  does not belong to any boundary, then  $\frac{d\tau(t)}{dt} = c_s$  (the temporal derivative of a hybrid state  $h = (\pi, d_s)$  is defined as  $\frac{dh}{dt} = \frac{d\pi}{dt}$ ).
- If  $h$  only belongs to one boundary  $e$ , let us consider that  $e$  is the upper boundary in  $i^{th}$  dimension (the result is easily adapted when  $e$  is the lower boundary). In case  $d_s^i$  is not the maximal discrete level of  $i^{th}$  gene, the discrete state on the other side of  $e$  is noted as  $d_r$ , where  $d_s^k = d_r^k$  for all  $k \neq i$ , and  $d_s^i + 1 = d_r^i$ . There are four possible cases:

- If  $c_s^i < 0$ , then the trajectory from the current state will enter the interior of the current discrete state.  $e$  called an *input boundary* of  $d_s$ .  $\frac{d\tau(t^+)}{dt} = c_s$ ,  $\frac{d\tau(t^-)}{dt} = c_r$  and  $\tau(t) = ((\pi', d_r), (\pi, d_s))$ , where  $\pi'^k = \pi^k$  for all  $k \neq i$ , and  $\pi'^i = 0$ , which means that there is an instant transition from  $(\pi', d_r)$  to  $(\pi, d_s)$  at  $t$ .
- If  $c_s^i = 0$ , then the trajectory from the current state will slide along the boundary  $e$ , which is then called a *neutral boundary* of  $d_s$ .  $\frac{d\tau(t^+)}{dt} = \frac{d\tau(t^-)}{dt} = c_s$  and  $\tau(t) = (\pi, d_s)$ .
- If  $c_s^i > 0$ , and either  $d_s^i$  is the maximal discrete level of the  $i^{\text{th}}$  gene, or  $d_s^i$  is not the maximal discrete level of the  $i^{\text{th}}$  gene but the  $i^{\text{th}}$  component of  $c_r$  is negative, then the trajectory from the current state will slide along the boundary  $e$ , which is called an *attractive boundary* of  $d_s$ . If  $\tau$  reaches  $e$  at  $t$ , then:  $\frac{d\tau(t^+)}{dt} = c_s^k$  for all  $k \neq i$ ,  $\frac{d\tau(t^+)}{dt} = 0$ ,  $\frac{d\tau(t^-)}{dt} = c_s$  and  $\tau(t) = (\pi, d_s)$ . If  $\tau$  reaches  $e$  at  $t_0 < t$ , then:  $\frac{d\tau(t)}{dt} = c_s^k$  for all  $k \neq i$ ,  $\frac{d\tau(t)}{dt} = 0$ , and  $\tau(t) = (\pi, d_s)$ .
- If  $c_s^i > 0$ ,  $d_s^i$  is not the maximal discrete level of the  $i^{\text{th}}$  gene, and the  $i^{\text{th}}$  component of  $c_r$  is positive, then the trajectory from the current state will cross instantly the boundary  $e$  and enter the discrete state  $d_r$ .  $e$  is called an *output boundary* of  $d_s$ .  $\frac{d\tau(t^+)}{dt} = c_r$ ,  $\frac{d\tau(t^-)}{dt} = c_s$  and  $\tau(t) = ((\pi, d_s), (\pi', d_r))$ , where  $\pi'^k = \pi^k$  for all if  $k \neq i$ , and  $\pi'^i = 0$ .
- If  $h$  belongs to several boundaries, then the previous cases can be mixed:
  - If in these boundaries there is no output boundary, then the trajectory from the current state will exit all input boundaries and slide along all attractive or neutral boundaries.
  - If in these boundaries there is only one output boundary, then the trajectory from the current state will cross this output boundary.
  - If in these boundaries there are several output boundaries, then the trajectory from the current state can cross any of them, but can only cross one boundary at one time, which causes non-deterministic behavior.

## B Proof of Theorem 1

*Proof.* For a trajectory  $\tau$  attracted by a cycle of discrete domains,  $\exists t_0$  such that after  $t_0$ ,  $\tau$  always stays in a cycle of discrete domains  $\mathcal{C}_\tau = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p, \mathcal{D}_0)$  and before  $t_0$ ,  $\tau$  has already crossed at least one discrete state.  $\tau$  can be separated on two trajectories by  $t_0$ : the restriction of  $\tau$  on time interval  $[0, t_0]$ , noted by  $\tau_{[0, t_0]}$ , and the restriction of  $\tau$  on time interval  $[t_0, \infty]$ , noted by  $\tau_{[t_0, \infty]}$ .

For the trajectory  $\tau_{[0, t_0]}$ , whether it reaches  $R_2$  is decidable. If it reaches  $R_2$ , then it is reachable. And if it does not reach  $R_2$ , then we need to consider  $\tau_{[t_0, \infty]}$ .

For the trajectory  $\tau_{[t_0, \infty]}$ , in case that  $\tau_{[0, t_0]}$  does not reach  $R_2$ , whether  $\tau_{[t_0, \infty]}$  reaches  $R_2$  is equivalent to whether it reaches  $Pre_{d_{s_2}}(R_2) = \bigcup_{i \in \{1, 2, \dots, q\}} Z_i$ . If  $\forall i \in \{0, 1, 2, \dots, p\}$ ,  $\forall j \in \{1, 2, 3, \dots, q\}$ ,  $Z_j \not\subseteq \mathcal{D}_i$ , then  $Pre_{d_{s_2}}(R_2)$  is not



reachable. Otherwise, if  $\exists i_0 \in \{0, 1, 2, \dots, p\}$  and  $\exists j_0 \in \{1, 2, 3, \dots, q\}$ , such that  $Z_{j_0} \subseteq \mathcal{D}_{i_0}$ , then to verify if  $Z_{j_0}$  is reachable, we need to consider the relation between the intersection points of  $\tau_{[t_0, \infty]}$  with  $\mathcal{D}_{i_0}$  noted by a infinite sequence  $(h_{p1}, h_{p2}, \dots)$  and  $Z_{j_0}$  as following. (Need to mention that when a trajectory reaches a discrete domain, it might slide inside this discrete domain, in this case, based on the general meaning of "intersection", the intersection points of this trajectory and this discrete domain are not singular points. In this paper, we define that the intersection points between a trajectory and a discrete domain are the points where the trajectory just reaches the discrete domain.)

Since  $\tau$  always stays inside this cycle of discrete domains, the sequence  $(h_{p1}, h_{p2}, \dots)$  converges asymptotically to a state or reaches a state which belongs to the closure of the compatible zone of  $\mathcal{C}_{\mathcal{T}}$ . For both cases, this particular state is noted by  $h_{\infty}$ .

If  $h_{\infty} \in Z_{j_0}$ , then  $Pre_{d_{s_2}}(R_2)$  is reachable. Need to mention that, in case that  $h_{\infty}$  is on the boundary of  $Z_{j_0}$  and the sequence  $(h_{p1}, h_{p2}, \dots)$  converges asymptotically to  $h_{\infty}$  without reaching directly  $Z_{j_0}$ ,  $Z_{j_0}$  is also considered as reachable, which in fact is reached after an infinite times of intersections.

If  $h_{\infty} \notin Z_{j_0}$ , then we can find a small neighborhood of  $h_{\infty}$  inside  $\mathcal{D}_{i_0}$ , noted by  $\mathcal{N}_{h_{\infty}}$ , such that  $\forall h \in \mathcal{N}_{h_{\infty}}, h \notin Z_{j_0}$ . Since the sequence  $(h_{p1}, h_{p2}, \dots)$  converges to  $h_{\infty}$  or finally reaches  $h_{\infty}$ , we can find  $n_0$  such that  $\forall n > n_0, h_{pn} \in \mathcal{N}_{h_{\infty}}$ . This means that after that  $\tau_{[t_0, \infty]}$  reaches  $h_{pn_0}$ , it will never reach  $Z_{j_0}$ . So, in this case, to verify if  $Z_{j_0}$  is reached, we only need to verify if the finite sequence  $(h_{p1}, h_{p2}, \dots, h_{pn_0})$  ever reaches  $Z_{j_0}$ , which is decidable.

Now we see that, for a certain  $Z_i$ , whether  $\tau_{[t_0, \infty]}$  reaches  $Z_i$  or not is decidable. Since  $Pre_{d_{s_2}}(R_2)$  has a finite number of such  $Z_i$ , whether  $\tau_{[t_0, \infty]}$  reaches  $Pre_{d_{s_2}}(R_2)$  is also decidable.  $\square$

## C Proof of Theorem 2

*Proof.* Firstly, we prove that it is a sufficient condition:

In the case that a trajectory  $\tau$  is attracted by a cycle of discrete domains, then after certain moment,  $\tau$  will always stay in the same cycle of discrete domains, noted by  $\mathcal{C}_{\mathcal{T}} = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p, \mathcal{D}_0)$ .

We consider at first the case that there is one  $\mathcal{D}_i$  of  $\mathcal{C}_{\mathcal{T}}$  such that  $\mathcal{D}_i$  has at least one free dimension (meaning that there exists one dimension such that the boundaries are not reached in this dimension), without loss of generality we assume that  $\mathcal{D}_0$  has at least one free dimension, so the first condition is satisfied.

A priori, we cannot ensure the second condition, because the decomposition of  $r(h_0) - r_{\infty}$  in the directions of certain eigenvectors of the reduction matrix of  $\mathcal{C}_{\mathcal{T}}$  can be zero and these eigenvectors happen to be associated to eigenvalues of which the absolute values are greater than 1, however this is extremely rare. So in this paper we ignore this case, and based on this assumption, we must have that for any eigenvalue  $\lambda_i$ ,  $|\lambda_i| \leq 1$ , otherwise we cannot ensure that  $\tau$  always stays inside this cycle, because if there exists an eigenvalue such that  $|\lambda_i| > 1$ , then  $r_{\infty}$  is infinitely far away from  $r(h_0)$ . If there exists  $\lambda_i = -1$ ,

we can double this cycle of discrete domains (the doubled cycle of discrete domains is  $(\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p, \mathcal{D}_0, \mathcal{D}_1, \dots, \mathcal{D}_p, \mathcal{D}_0)$ ) to eliminate this eigenvalue. So the second condition is satisfied.

The intersection points of  $\tau$  with  $\mathcal{D}_0$  will converge to or reach certain state  $h_\infty = (\pi_\infty, d_{s_0})$  which belongs to the closure of the compatible zone. We have that  $r_\infty$  is the short version of  $\pi_\infty$  by only considering the dimensions where boundaries are not reached in  $\mathcal{D}_0$ . Based on Assumption 3, the reduction compatible zone can be described by  $\{x \mid Wx > c\}$ . If  $h_\infty$  belongs to the compatible zone, then we have  $\forall i \in \{1, 2, \dots, n_0\}, W_i r_\infty > c_i$ , else if  $h_\infty$  does not belong to the compatible zone but belongs to the closure of the compatible zone, then we have that for some  $i \in \{1, 2, \dots, n_0\}, W_i r_\infty = c_i$ , meaning that some "boundaries" of the reduction compatible zone are reached, and for other  $i \in \{1, 2, \dots, n_0\}$ , we have  $W_i r_\infty > c_i$ . So the third condition is satisfied.

We note the intersection states of  $\tau$  and  $\mathcal{D}_0$  as the sequence  $(h_0, h_1, h_2, \dots)$ . We have that  $r(h_n) = r_\infty + \sum_{i=1}^{n_1} \lambda_i^n \alpha_i v_i$  where  $v_i$  are eigenvectors of the reduction matrix of  $\mathcal{C}_\tau$  and  $r(h_0) - r_\infty = \sum_{i=1}^{n_1} \alpha_i v_i$ , by choosing  $\lambda_1$  as the eigenvalue with maximum absolute eigenvalue among the eigenvalues that differ from 1, if  $\lambda_1 \neq 0$ , then we have:  $\lim_{n \rightarrow \infty} |\lambda_1^n \alpha_1| \gg |\lambda_i^n \alpha_i|$  where  $i \neq 1$ , and  $\lim_{n \rightarrow \infty} \sum_{i=1}^{n_1} \lambda_i^n \alpha_i v_i \rightarrow 0$ . This proves that the fifth and the sixth conditions are satisfied.

Supposing that  $\lambda_1 \neq 0$ . Since the sequence  $(h_0, h_1, h_2, \dots)$  is inside the compatible zone, if  $I_e$  is not empty, then for any  $j \in I_e$ , we should have  $\forall n \in \mathbb{N}, W_j \sum_{i=1}^{n_1} \lambda_i^n \alpha_i v_i > 0$ . When  $n$  is sufficiently big, for any  $j \in I_e$ , the sign of  $W_j \sum_{i=1}^{n_1} \lambda_i^n \alpha_i v_i$  is dominated only by  $W_j \lambda_1^n \alpha_1 v_1$ , meaning that  $W_j \sum_{i=1}^{n_1} \lambda_i^n \alpha_i v_i$  and  $W_j \lambda_1^n \alpha_1 v_1$  have the same sign, in fact, when  $n$  is sufficiently big, we have  $|W_j \lambda_1^n \alpha_1 v_1| > \sum_{i=2}^{n_1} |W_j \lambda_i^n \alpha_i v_i|$ , this means that adding  $\sum_{i=2}^{n_1} W_j \lambda_i^n \alpha_i v_i$  to  $W_j \lambda_1^n \alpha_1 v_1$  does not change the sign of  $W_j \lambda_1^n \alpha_1 v_1$ . So the sign of  $\lambda_1$  is positive, otherwise we can not ensure that  $\forall j \in I_e, \forall n \in \mathbb{N}, W_j \sum_{i=1}^{n_1} \lambda_i^n \alpha_i v_i > 0$ , which is equivalent to  $\forall j \in I_e, \forall n \in \mathbb{N}, W_j \lambda_1^n \alpha_1 v_1 > 0$  when  $n$  is sufficiently big. This proves that the fourth condition is satisfied.

In the case that any  $\mathcal{D}_i$  of  $\mathcal{C}_\tau$  has no free dimension, we can easily see that it is a sufficient condition.

Secondly, we prove that it is a necessary condition.

If  $\mathcal{D}_0$  has no free dimension, then  $\tau$  reaches a limit cycle which is a special case of that  $\tau$  is attracted by a cycle of discrete domains.

If these six conditions are satisfied, to prove that  $\tau$  is attracted by a cycle of discrete domains, we only need to prove that  $\tau$  always returns to the compatible zone of  $\mathcal{C}_\tau$ . This can be easily proved if  $\lambda_1 = 0$ . From now on, we suppose the  $\lambda_1 \neq 0$ . We note that trajectory from  $h_0$  returns to  $\mathcal{D}_0$  at  $h_1$ . We have that  $r(h_1) - r_\infty = \sum_{i=1}^{n_1} \lambda_i \alpha_i v_i$ . A sufficient condition for " $h_0$  belongs to the compatible zone" is  $(\forall j \in I_e, W_j \sum_{i=1}^{n_1} \alpha_i v_i > 0) \wedge (\forall j \in I_n, \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{i=1}^{n_1} \beta_i \alpha_i v_i\|_2 < \frac{W_j r_\infty - c_j}{\|W_j\|_2})$  which is satisfied in this case. In fact, the first part of this sufficient condition is a necessary condition for that  $h_0$  belongs to the compatible zone and the second part is ensured by the sixth condition. Now we want to prove that this sufficient condition is also

satisfied for  $h_1$ . The fifth condition indicates that for any  $j \in I_e$  the sign of  $W_j \sum_{i=1}^{n_1} \alpha_i v_i$  is dominated by the sign of  $W_j \alpha_1 v_1$ , so  $W_j \alpha_1 v_1$  is also positive. Since  $\forall i \neq 1$ , we have either  $|\lambda_1| > |\lambda_i|$  or  $|\lambda_1| < |\lambda_i| \wedge \alpha_i = 0$ , so we have  $\forall j \in I_e, \forall i \in \{2, \dots, n_1\}, |W_j v_1 \lambda_1 \alpha_1| > n_1 |W_j v_i \lambda_i \alpha_i|$ . This means that for any  $j \in I_e$  the sign of  $W_j \sum_{i=1}^{n_1} \alpha_i \lambda_i v_i$  is also dominated by the sign of  $W_j \alpha_1 \lambda_1 v_1$ . Since  $\lambda_1$  is positive if  $I_e$  is not empty, we have  $\forall j \in I_e, W_j \sum_{i=1}^{n_1} \lambda_i \alpha_i v_i > 0$ , because the sign of  $W_j \sum_{i=1}^{n_1} \lambda_i \alpha_i v_i$  is same as the sign of  $W_j \alpha_1 \lambda_1 v_1$  which is same as the sign of  $W_j \alpha_1 v_1$  of which the sign is positive. Since  $\forall \lambda_i, |\lambda_i| \leq 1$ , we have  $\max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{i=1}^{n_1} \beta_i \lambda_i \alpha_i v_i\|_2 \leq \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{i=1}^{n_1} \beta_i \alpha_i v_i\|_2$ . So we also have  $\forall j \in I_n, \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{i=1}^{n_1} \beta_i \lambda_i \alpha_i v_i\|_2 < \frac{W_j r_\infty - c_i}{\|W_j\|_2}$ . By now we prove that  $h_1$  also belongs to the compatible zone. By mathematical induction, we can prove that  $\tau$  always returns to the compatible zone of  $\mathcal{C}_T$ . So  $\tau$  is attracted by a cycle of discrete domains.  $\square$

## D Details about the function *Stop\_condition* in Algorithm 1

The details of the function *Stop\_condition* are presented in Algorithm 2. Its objective is, knowing that a trajectory is attracted by a cycle of discrete domains, to determine if the trajectory can reach  $R_2$  after an infinite number of transitions (see Fig 3 right), in this case, return “Reached”, or if from the current moment, there is no more chance to reach  $R_2$  (see Fig 3 middle), in this case, return “Yes”, otherwise return “No”. The cases other than “No” mean that the main algorithm for reachability analysis can be stopped.

In order to describe the Non-intersection condition in Algorithm 2, we note the predecessor in the same discrete state of  $R_2$  as  $Pre_{d_{s_2}}(R_2) = \bigcup_{i \in \{1, 2, \dots, q\}} Z_i$ . We note  $r(Z_i)$  as the set of the reduction vectors of all states of  $Z_i$ .

This Non-intersection condition (its formal definition will be given later) is a sufficient condition for that  $\forall j \in \{1, 2, \dots, q\}$ , if  $Z_j \subset \mathcal{D}_i$ , then  $\{x \in \mathcal{S}_r(\mathcal{D}_i) \mid \|x - r(h_i^\infty)\|_2 \leq \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{k=1}^{n_1} \beta_k \alpha_k v_k\|_2\} \cap r(Z_j) = \emptyset$  where  $\mathcal{S}_r(\mathcal{D}_i)$  is the reduction compatible zone of this cycle inside  $\mathcal{D}_i$ ,  $n_1$  is the dimension of  $\mathcal{S}_r(\mathcal{D}_i)$ ,  $r(h_i) - r(h_i^\infty) = \sum_{k=1}^{n_1} \alpha_k v_k$ ,  $v_k$  are the eigenvectors of the reduction matrix of this cycle  $(\mathcal{D}_i, \dots, \mathcal{D}_i)$ .

The idea of the Non-intersection condition is illustrated by Fig 5. Firstly, we want to verify  $\forall j \in \{1, 2, \dots, q\}$ , if  $Z_j \subset \mathcal{D}_i$ , then  $\{x \in \mathcal{S}_r(\mathcal{D}_i) \mid \|x - r(h_i^\infty)\|_2 \leq \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{k=1}^{n_1} \beta_k \alpha_k v_k\|_2\} \cap r(Z_j) = \emptyset$  where  $\mathcal{S}_r(\mathcal{D}_i)$  is the reduction compatible zone of this cycle inside  $\mathcal{D}_i$ . This is equivalent to that the black box does not intersect the blue boxes in Fig 5 left. The reason why we want to verify this condition, noted here as Condition1, is that once it is satisfied, there is no more chance that the trajectory can reach  $R_2$  from  $\mathcal{D}_i$  inside this discrete state. However, it is complicated to compute directly the intersection of these sets. So, firstly we overestimate all states in this discrete state which can be reached by  $\{h \in \mathcal{S}(\mathcal{D}_i) \mid \|r(h) - r(h_i^\infty)\|_2 \leq \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{k=1}^{n_1} \beta_k \alpha_k v_k\|_2\}$  (black box) by the red zone in Fig 5 middle (need to mention that Fig 5 is just a illustration,

the shape of the real red zone is slightly different from the one in this figure). If this red zone does not intersect the blue rectangle, then Condition1 is satisfied. However, this intersection is still difficult to compute. So secondly, we move the "thickness" of the red zone to the blue rectangle in Fig 5 right. Now to verify if Condition1 is satisfied, we only need to verify if the red trajectory in Fig 5 right reaches the blue and red zone, which can be done automatically and is called Non-intersection condition.

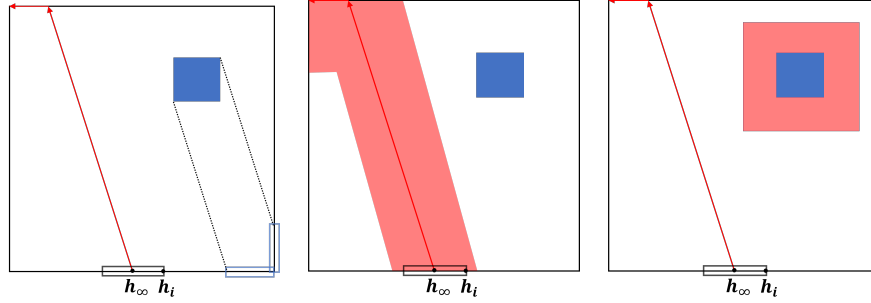


Fig. 5: Illustration of the Non-intersection condition in Algorithm 2.

The Non-intersection condition is defined formally in the following.

The trajectory from  $h_i^\infty$  can be represented by  $h_i^\infty = h_{i,0}^\infty \rightarrow h_{i,1}^\infty \rightarrow \dots \rightarrow h_{i,K}^\infty$  where  $\{h_{i,j}^\infty, j \in \{1, 2, \dots, K\}\}$  represents all states at which this trajectory reaches new boundaries and  $h_{i,K}^\infty$  represents the state at which this trajectory reaches an output boundary of  $d_{s_2}$  for the first time. We note  $u_j, j \in \{1, 2, \dots, K\}$  as the left derivative of state  $h_{i,j}^\infty$ . We use  $w_j \in \{0, 1\}^N, j \in \{1, 2, \dots, K\}$  to describe the dimension where new boundary is reached in each elementary transition, for the transition  $h_{i,j-1}^\infty \rightarrow h_{i,j}^\infty, j \in \{1, 2, \dots, K\}$ , if the new boundary is reached in  $m_j^{\text{th}}$  dimension, then  $w_j^{m_j} = 1$  and  $w_j^k = 0, k \in \{1, 2, \dots, N\} \setminus \{m_j\}$ . We associate a distance  $l_j, j \in \{1, 2, \dots, K, K+1\}$  to each transition, which is computed as following:  $l_1 = \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{k=1}^{n_1} \beta_k \alpha_k v_k\|_2$  and  $\forall j \in \{2, 3, \dots, K, K+1\}, l_j = \frac{l_{j-1}}{\frac{|u_j \cdot w_j|}{\|u_j\|_2}}$  where  $u_j \cdot w_j$  is the inner product of  $u_j$  and  $w_j$ . The Non-intersection condition is satisfied if the trajectory from  $h_{i,0}^\infty$  does not reach the region  $R'_2 = \{(\pi, d_{s_2}) \mid \pi^i \in [\max(a_i - l_{K+1}, 0), \min(b_i + l_{K+1}, 1)], i \in \{1, 2, \dots, N\}\}$  inside the discrete state  $d_{s_2}$ .

We note this trajectory  $h_i^\infty = h_{i,0}^\infty \rightarrow h_{i,1}^\infty \rightarrow \dots \rightarrow h_{i,K}^\infty$  which begins from  $h_{i,0}^\infty$  and finally reaches  $h_{i,K}^\infty$  as  $\tau_i$ . If the Non-intersection condition is satisfied, then for any state  $h_x$  which belongs to  $R_2$  and for any state  $h_y$  which belongs to  $\tau_i$ , the distance between  $h_x$  and  $h_y$  is greater than  $l_{K+1}$ . On the other hand, for any trajectory  $\tau_x$  which is inside this discrete state and begins from the region  $\{h \in \mathcal{S}(\mathcal{D}_i) \mid \|r(h) - r(h_i^\infty)\|_2 \leq \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{k=1}^{n_1} \beta_k \alpha_k v_k\|_2\}$  where  $\mathcal{S}(\mathcal{D}_i)$

---

**Algorithm 2** Stop condition

---

**Input 1:** A list of hybrid states  $Cycle_h = (h_0, h_1, h_2, \dots, h_p, h'_0)$  which describes a simulation of a model

**Input 2:** A list of discrete domains  $Cycle_{\mathcal{D}} = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p, \mathcal{D}_0)$  such that  $\forall i \in \{0, 1, 2, \dots, p\}, h_i \in \mathcal{D}_i, h'_0 \in \mathcal{D}_0$  and the trajectory from  $h_0$  is attracted by  $(\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p, \mathcal{D}_0)$

**Input 3:** A region  $R_2 = \{(\pi, d_{s_2}) \mid \pi^i \in [a_i, b_i], i \in \{1, 2, \dots, N\}\}$

**Output (three possibilities):** Yes, No, and Reached

- 1: Compute the states  $h_0^\infty, h_1^\infty, h_2^\infty, \dots, h_p^\infty$  such that the intersection states between this trajectory and  $\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, \dots, \mathcal{D}_p$  converge to or reach these states when  $t \rightarrow \infty$ .
  - 2:  $var\_stop \leftarrow True$
  - 3: **for**  $i \in \{0, 1, 2, \dots, p\}$  **do**
  - 4:   **if**  $\mathcal{D}_i$  is on an input boundary of  $d_{s_2}$  **then**
  - 5:     **if** Trajectory from  $h_i^\infty$  reaches  $R_2$  inside  $d_{s_2}$  **then**
  - 6:       **return** “Reached”
  - 7:     **else if** Non-intersection condition is satisfied **then**
  - 8:        $var\_stop \leftarrow var\_stop \wedge True$
  - 9:     **else if** Non-intersection condition is not satisfied **then**
  - 10:        $var\_stop \leftarrow var\_stop \wedge False$
  - 11:     **end if**
  - 12:   **end if**
  - 13: **end for**
  - 14: **if**  $var\_stop = True$  **then**
  - 15:   **return** “Yes”
  - 16: **else if**  $var\_stop = False$  **then**
  - 17:   **return** “No”
  - 18: **end if**
-

is the compatible zone of this cycle inside  $\mathcal{D}_i$ , for any state  $h'_x$  on  $\tau_x$ , we can find a state  $h'_y$  on  $\tau_i$ , such that the distance between  $h'_x$  and  $h'_y$  is smaller than  $l_{K+1}$ . If  $\tau_x$  crosses  $R_2$ , then there exists a state  $h''_y$  which is on  $\tau_x$  and also belongs to  $R_2$ , such that  $\exists h''_x$  on  $\tau_i$ , the distance between  $h''_x$  and  $h''_y$  is smaller than  $l_{K+1}$  which is not possible as  $h''_y$  belongs to  $R_2$ . This proves that  $\forall j \in \{1, 2, \dots, q\}$ , if  $Z_j \subset \mathcal{D}_i$ , then  $\{x \in \mathcal{S}_r(\mathcal{D}_i) \mid \|x - r(h_i^\infty)\|_2 \leq \max_{\beta \in \{-1, 1\}^{n_1}} \|\sum_{k=1}^{n_1} \beta_k \alpha_k v_k\|_2\} \cap r(Z_j) = \emptyset$ .

In fact, if  $h_i$  is sufficiently close to  $h_i^\infty$ , then the Non-intersection condition must be satisfied, because  $L_{K+1}$  is sufficiently close to 0 in this case. Based on this fact, it can be proved that if trajectory from  $h_1$  is attracted by a cycle of discrete domains and does not reach  $R_2$ , then the Non-intersection condition must be verified in finite time for all discrete domains which belong to an input boundary of the discrete state of  $R_2$  and belong to the attractive cycle of discrete domains (the cycle of discrete domains which attracts the trajectory from  $h_1$ ). In this case, this algorithm returns "Yes", meaning that the trajectory from  $h_1$  has no more chance to reach  $R_2$ .