

# Appendix of 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. Appendix of Reachability Analysis of a Class of Hybrid Gene Regulatory Networks. 2023. hal-04182253

## HAL Id: hal-04182253 https://hal.science/hal-04182253

Preprint submitted on 17 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.

### Appendix of Reachability Analysis of a Class of Hybrid Gene Regulatory Networks

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

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

 $^2\,$  Univ. Lille, CNRS, Centrale Lille, UMR 9189 CRIStAL, F-59000 Lille, France

#### 1 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
- 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<sup>i</sup><sub>s</sub> = 0, then the trajectory from the current state will slide along the boundary e, which is then called a *neutral boundary* of d<sub>s</sub>. dτ(t<sup>+</sup>)/dt = dτ(t<sup>-</sup>)/dt = c<sub>s</sub> and τ(t) = (π, d<sub>s</sub>).
    If c<sup>i</sup><sub>s</sub> > 0, and either d<sup>i</sup><sub>s</sub> is the maximal discrete level of the i<sup>th</sup> gene, or d<sup>i</sup><sub>s</sub>
  - If  $c_s^i > 0$ , and either  $d_s^i$  is the maximal discrete level of the  $i^{th}$  gene, or  $d_s^i$  is not the maximal discrete level of the  $i^{th}$  gene but the  $i^{th}$  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:  $\frac{d\tau(t^+)}{dt}^k = c_s^k$  for all  $k \neq i$ ,  $\frac{d\tau(t^+)}{dt}^k = 0$ ,  $\frac{d\tau(t^-)}{dt} = c_s$  and  $\tau(t) = (\pi, d_s)$ . If  $\tau$  reaches e at  $t_0 < t$ , then:  $\frac{d\tau(t)}{dt}^k = c_s^k$  for all  $k \neq i$ ,  $\frac{d\tau(t)}{dt}^k = c_s^k$  for all  $k \neq i$ ,  $\frac{d\tau(t)}{dt}^i = 0$ , and  $\tau(t) = (\pi, d_s)$ .
  - $\frac{d\tau(t)}{dt}^{i} = 0, \text{ and } \tau(t) = (\pi, d_s).$  If  $c_s^i > 0, d_s^i$  is not the maximal discrete level of the  $i^{th}$  gene, and the  $i^{th}$  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  $\pi'^i = 0$ .

2 H. Sun et al.

- 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.

#### 2 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  $C_{\tau} = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, ..., \mathcal{D}_p, \mathcal{D}_0)$  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  $[t_0, \infty]$ .

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  $Pre_{d_{s_2}}(R_2) = \bigcup_{i \in \{1,2,...,q\}} Z_i$ . If  $\forall i \in \{0,1,2,...,p\}, \forall j \in \{1,2,3,...,q\}, Z_j \not\subseteq \mathcal{D}_i$ , then  $Pre_{d_{s_2}}(R_2)$  is not reachable. Otherwise, if  $\exists i_0 \in \{0,1,2,...,p\}$  and  $\exists j_0 \in \{1,2,3,...,q\}$ , 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  $(h_{p1}, h_{p2}, ...)$  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  $(h_{p1}, h_{p2}, ...)$  converges asymptotically to a state or reaches a state which belongs to the closure of the compatible zone of  $C_{\tau}$ . 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  $(h_{p_1}, h_{p_2}, ...)$  converges asymptotically to  $h_{\infty}$  without reaching 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  $(h_{p1}, h_{p2}, ...)$  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  $(h_{p1}, h_{p2}, ..., h_{pn_0})$  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.

#### 3 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  $C_{\tau} = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, ..., \mathcal{D}_p, \mathcal{D}_0).$ 

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  $C_{\mathcal{T}}$  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  $(\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, ..., \mathcal{D}_p, \mathcal{D}_0, \mathcal{D}_1, ..., \mathcal{D}_p, \mathcal{D}_0)$ ) 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  $\forall i \in \{1, 2, ..., n_0\}, W_i r_{\infty} > c_i$ , 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  $i \in \{1, 2, ..., n_0\}, W_i r_{\infty} = c_i$ , meaning that some "boundaries" of the reduction compatible zone are reached, and for other  $i \in \{1, 2, ..., n_0\}$ , 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  $(h_0, h_1, h_2, ...)$ . 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  $\mathcal{C}_{\mathcal{T}}$  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:  $\lim_{n\to\infty} |\lambda_1^n \alpha_1| \gg |\lambda_i^n \alpha_i|$  where  $i \neq 1$ , and  $\lim_{n\to\infty} \sum_{i=1}^{n_1} \lambda_i^n \alpha_i v_i \to 0$ . This proves that the fifth and the sixth conditions are satisfied. 4 H. Sun et al.

Supposing that  $\lambda_1 \neq 0$ . Since the sequence  $(h_0, h_1, h_2, ...)$  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 forth condition is satisfied.

In the case that any  $\mathcal{D}_i$  of  $\mathcal{C}_{\mathcal{T}}$  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  $\mathcal{C}_{\mathcal{T}}$ . 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  $(\forall j \in I_e, W_j \sum_{i=1}^{n_1} \alpha_i v_i > 0) \land (\forall j \in I_e, W_j \sum_{i=1}^{n_1} \alpha_i v_i > 0)$  $I_n, \max_{\beta \in \{-1,1\}^{n_1}} \|\sum_{i=1}^{n_1} \beta_i \alpha_i v_i\|_2 < \frac{W_j r_\infty - c_i}{\|W_j\|_2}$  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  $|\lambda_1| < |\lambda_i| \land \alpha_i = 0$ , so we have  $\forall j \in I_e, \forall i \in \{2, ..., n_1\}, |W_j v_1 \lambda_1 \alpha_1| > n_1 |W_j v_i \lambda_i \alpha_i|.$  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  $\max_{\beta \in \{-1,1\}^{n_1}} \|\sum_{i=1}^{n_1} \beta_i \lambda_i \alpha_i v_i\|_2 \le \max_{\beta \in \{-1,1\}^{n_1}} \|\sum_{i=1}^{n_1} \beta_i \alpha_i v_i\|_2$ . 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  $\mathcal{C}_{\mathcal{T}}$ . So  $\tau$  is attracted by a cycle of discrete domains. 

#### 4 Details about the function *Stop* condition

The details of the function  $Stop\_condition$  are presented in Algorithm 1. 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 1, we note the predecessor in the same discrete state of  $R_2$  as  $Pre_{d_{s_2}}(R_2) = \bigcup_{i \in \{1,2,\ldots,q\}} Z_i$ . 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  $\forall j \in \{1, 2, ..., q\}$ , 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  $(\mathcal{D}_i, ..., \mathcal{D}_i)$ .

idea of the Non-intersection condition is illustrated The by Fig 1. Firstly, we want to verify  $\forall j$  $\{1, 2, ..., q\}$ , if  $Z_j$  $\in$  $\subset$  $\mathcal{D}_{i}, \text{ then } \left\{ x \in \mathcal{S}_{r}(\mathcal{D}_{i}) \mid \|x - r(h_{i}^{\infty})\|_{2} \le \max_{\beta \in \{-1,1\}^{n_{1}}} \|\sum_{k=1}^{n_{1}} \beta_{k} \alpha_{k} v_{k}\|_{2} \right\}$  $\cap$  $r(Z_i) = \emptyset$  where  $S_r(\mathcal{D}_i)$  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 1 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  $\left\{h \in \mathcal{S}(\mathcal{D}_i) \mid \|r(h) - r(h_i^{\infty})\|_2 \le \max_{\beta \in \{-1,1\}^{n_1}} \|\sum_{k=1}^{n_1} \beta_k \alpha_k v_k\|_2\right\} \text{ (black box)}$ by the red zone in Fig 1 middle (need to mention that Fig 1 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 1 right. Now to verify if Condition is satisfied, we only need to verify if the red trajectory in Fig 1 right reaches the blue and red zone, which can be done automatically and is called Non-intersection condition.



Fig. 1: Illustration of the Non-intersection condition in Algorithm 1.

6 H. Sun et al.

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

#### Algorithm 1 Stop condition

Input 1: A list of hybrid states  $Cycle_h = (h_0, h_1, h_2, ..., h_p, h'_0)$  which describes a simulation of a model Input 2: A list of discrete domains  $Cycle_{\mathcal{D}} = (\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, ..., \mathcal{D}_p, \mathcal{D}_0)$  such that  $\forall i \in \{0, 1, 2, ..., p\}, h_i \in \mathcal{D}_i, h'_0 \in \mathcal{D}_0$  and the trajectory from  $h_0$  is attracted by  $(\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, ..., \mathcal{D}_p, \mathcal{D}_0)$ Input 3: A region  $R_2 = \{(\pi, d_{s_2}) \mid \pi^i \in [a_i, b_i], i \in \{1, 2, ..., N\}\}$ Output (three possibilities): Yes, No, and Reached 1: Compute the states  $h_0^{\infty}, h_1^{\infty}, h_2^{\infty}, ..., h_p^{\infty}$  such that the intersection states between this trajectory and  $\mathcal{D}_0, \mathcal{D}_1, \mathcal{D}_2, ..., \mathcal{D}_p$  converge to or reach these states when  $t \to \infty$ . 2:  $var\_stop \leftarrow True$ 3: for  $i \in \{0, 1, 2, ..., p\}$  do if  $\mathcal{D}_i$  is on an input boundary of  $d_{s_2}$  then 4: if Trajectory from  $h_i^{\infty}$  reaches  $R_2$  inside  $d_{s_2}$  then 5:6: return "Reached" 7: else if Non-intersection condition is satisfied then 8:  $var stop \leftarrow var stop \land True$ 9: else if Non-intersection condition is not satisfied then  $var \ stop \leftarrow var \ stop \land False$ 10:11: end if 12:end if 13: end for 14: if var stop = True then 15:return "Yes" 16: else if  $var\_stop = False$  then return "No" 17:18: end if

The trajectory from  $h_i^{\infty}$  can be represented by  $h_i^{\infty} = h_{i,0}^{\infty} \to h_{i,1}^{\infty} \to \dots \to h_{i,K}^{\infty}$  where  $\{h_{i,j}^{\infty}, j \in \{1, 2, ..., K\}\}$  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  $u_j, j \in \{1, 2, ..., K\}$  as the left derivative of state  $h_{i,j}^{\infty}$ . We use  $w_j \in \{0, 1\}^N, j \in \{1, 2, ..., K\}$  to describe the dimension where new boundary is reached in each elementary transition, for the transition  $h_{i,j-1}^{\infty} \to h_{i,j}^{\infty}, j \in \{1, 2, ..., K\}$ , if the new boundary is reached in  $m_j^{th}$  dimension, then  $w_j^{m_j} = 1$  and  $w_j^k = 0, k \in \{1, 2, ..., N\} \setminus \{m_j\}$ . We associate a distance  $l_j, j \in \{1, 2, ..., K, K+1\}$  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  $\forall j \in \{2, 3, ..., K, K+1\}$ ,  $l_j = \frac{l_{j-1}}{|\frac{u_j \cdot w_j}{\|u_j\|_2|}}$  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

 $R'_{2} = \left\{ (\pi, d_{s_{2}}) \mid \pi^{i} \in [\max(a_{i} - l_{K+1}, 0), \min(b_{i} + l_{K+1}, 1)], i \in \{1, 2, ..., N\} \right\}$ inside the discrete state  $d_{s_{2}}$ .

We note this trajectory  $h_i^{\infty} = h_{i,0}^{\infty} \to h_{i,1}^{\infty} \to \dots \to h_{i,K}^{\infty}$  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  $\mathcal{S}(\mathcal{D}_i)$  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  $\forall j \in \{1, 2, ..., q\}$ , 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  $R_2$ .