

# Limit cycle analysis of a class of hybrid gene regulatory networks

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## Abstract

- Our objective: Find **limit cycles** and analyze their **stability** in a **hybrid modeling framework** of gene regulatory networks [Cornillon et al. 2016] [Behaegel, Comet, Bernot, et al. 2016] [Behaegel, Comet, and Folschette 2017] which extends René Thomas' discrete modeling.
- Our idea: Extend **Poincaré map** to this hybrid framework.
- Our contribution: We search for potential cycles by **abstracting** the continuous trajectory into a succession of visited **discrete domains**. Then we introduce **transition matrices** and **stable zones** to analyze the concrete continuous dynamics and find the actual cycles that are stable.

## Hybrid gene regulatory networks (HGRN)

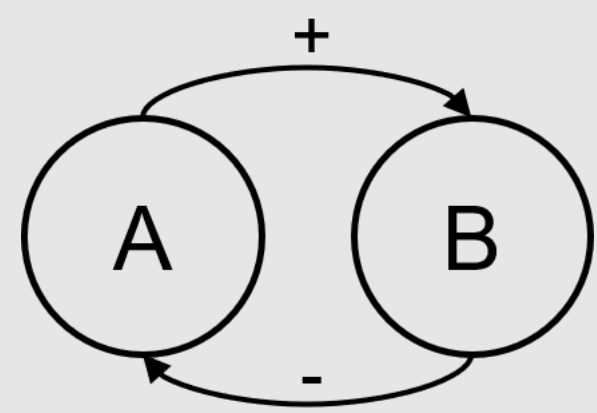


Figure 1. Influence graph of a simple gene regulatory networks in 2 dimensions

- A discrete state  $d_s$  is an integer vector which describes the discrete levels of all genes.
- A celerity  $c_s$  is a real vector assigned to  $d_s$  which describes the temporal derivative of the system in  $d_s$ . It is constant in all  $d_s$ .
- A (hybrid) state of a HGRN, noted  $h = (\pi, d_s)$ , contains a fractional part  $\pi$  and a discrete state  $d_s$ . The fractional part  $\pi$  is a real vector bounded in  $[0, 1]^N$  with  $N$  the number of genes in the system.

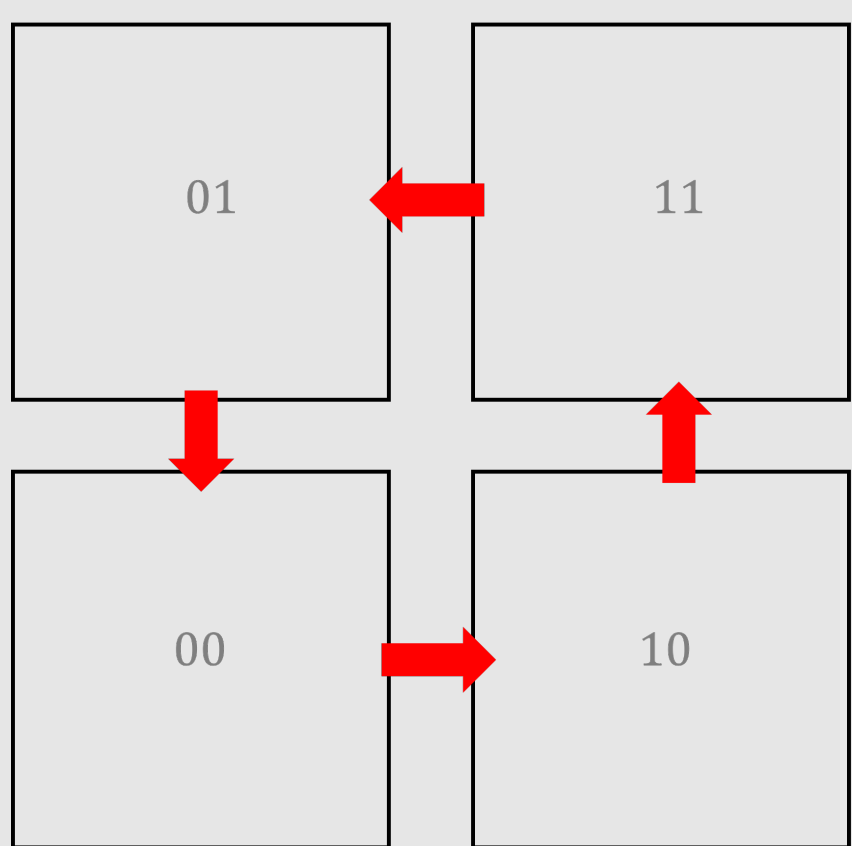


Figure 2. Example of dynamics of a discrete model (depending on discrete parameters)

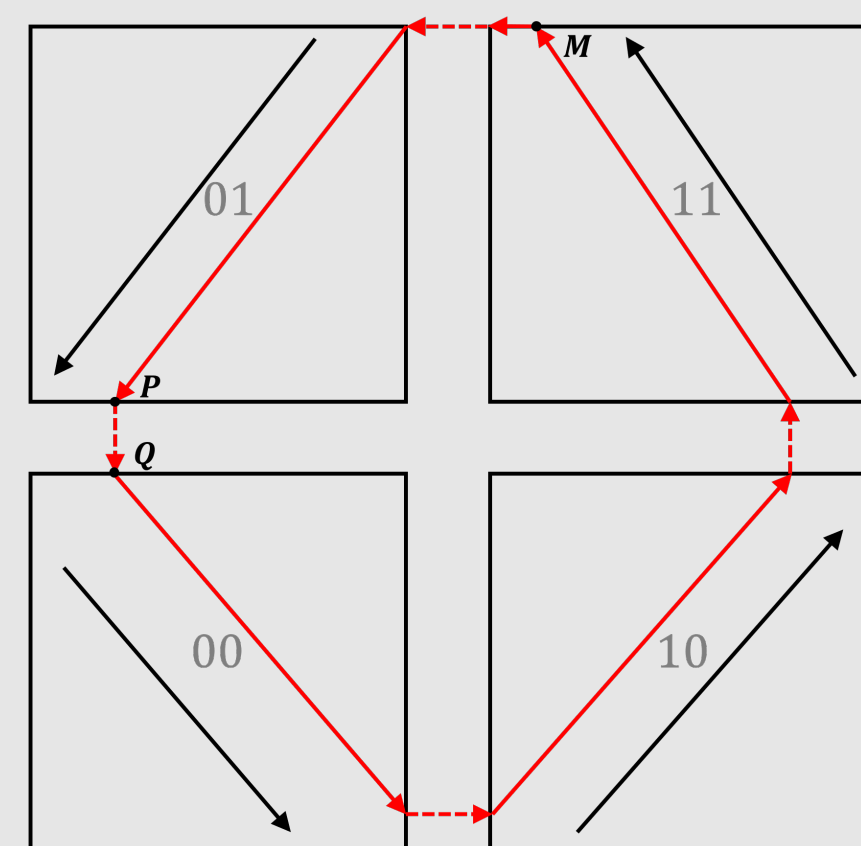


Figure 3. Example of dynamics of a HGRN (depending on real parameters); the black arrows represent the celerities

Compared with discrete models (Figure 2), HGRNs model a continuous dynamics inside each discrete state (Figure 3). [Cornillon et al. 2016]

## 1. Abstraction of a HGRN into discrete domains

A discrete domain is a set of hybrid states that touch the same boundaries. For example, discrete state  $(1, 1)$  has 8 discrete domains (see Figure 4), among which:

- $(1^+, 1^+) = \{(\pi, (1, 1)) \mid \pi^1 = 1, \pi^2 = 1\}$ ,
- $(1, 1^+) = \{(\pi, (1, 1)) \mid \pi^1 \in ]0, 1[, \pi^2 = 1\}$ , ...

In the graph of discrete domains (see Figure 5), a discrete domain  $\mathcal{D}_j$  is a successor of  $\mathcal{D}_i$  if, considering only the signs of celerities, a simple trajectory (straight line) could exist from  $\mathcal{D}_i$  to  $\mathcal{D}_j$ . We ignore the case of trajectories that reach more than one boundary at the same time.

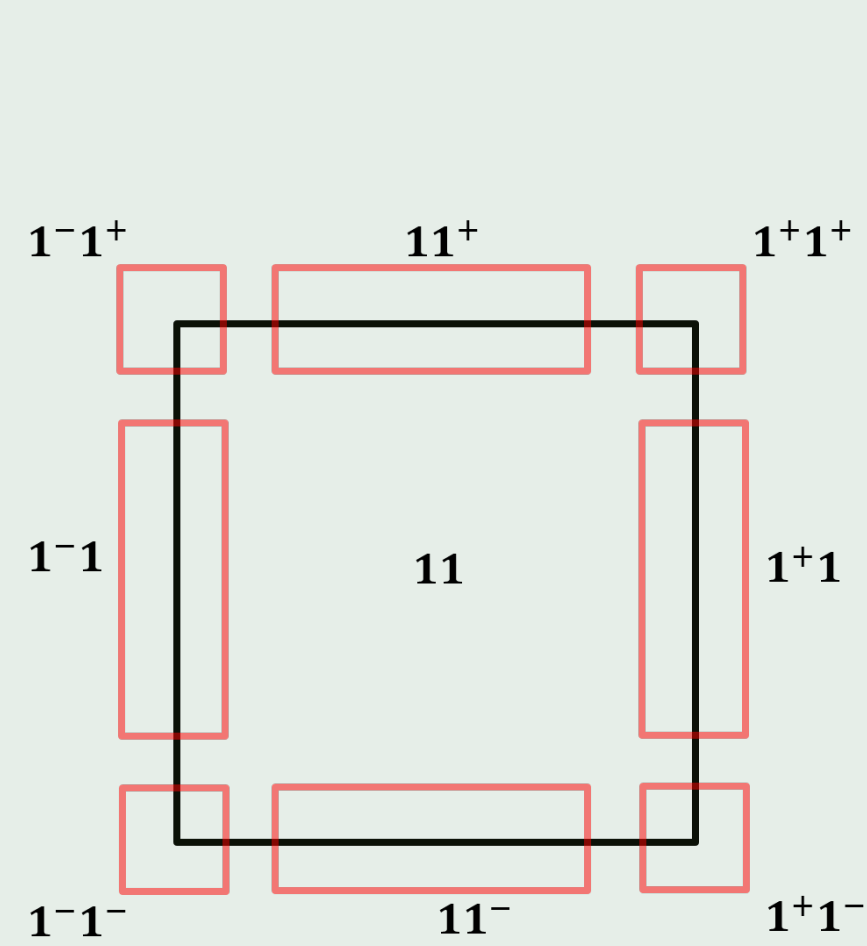


Figure 4. Discrete domains of the discrete state  $(1, 1)^T$

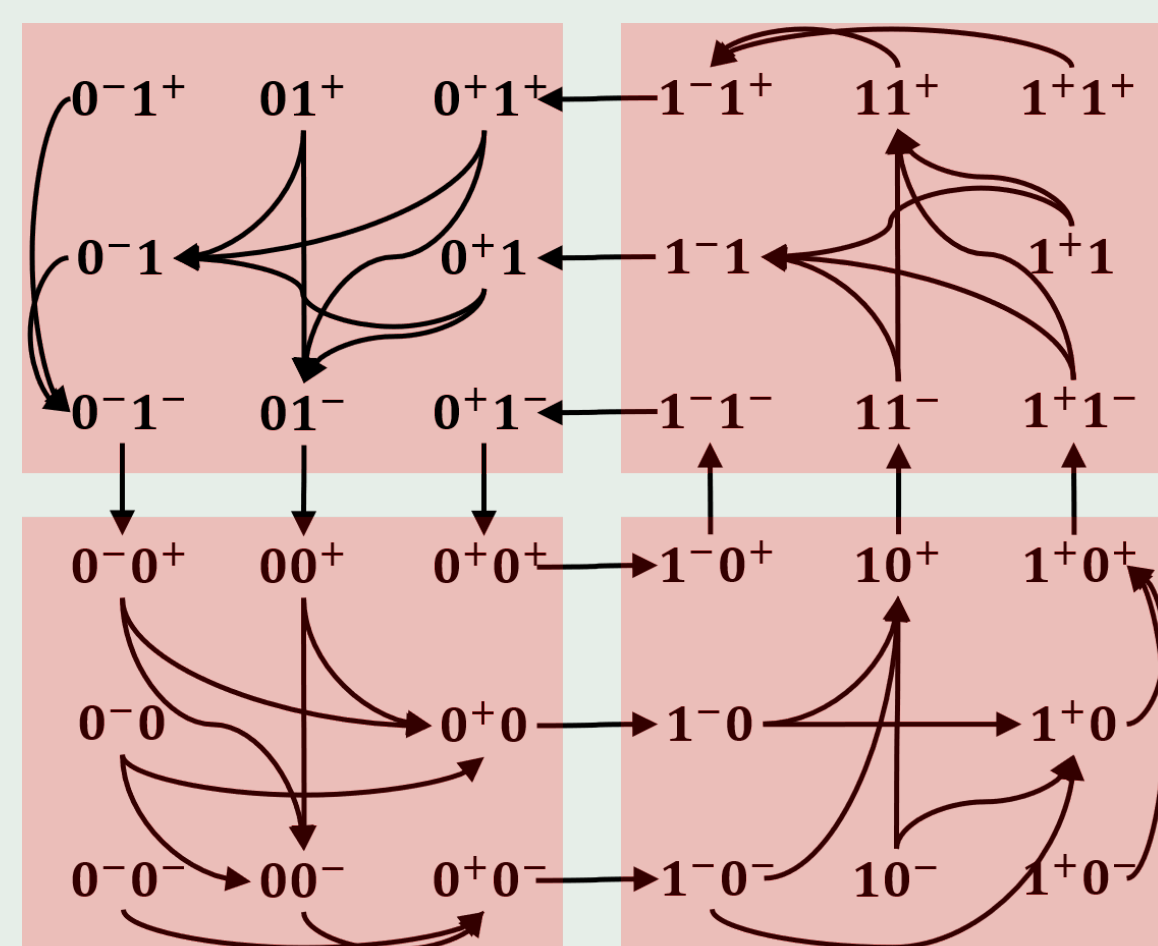


Figure 5. Graph of discrete domains of the HGRN

## 2. Find closed discrete trajectories

- The stable zone  $\mathcal{S}$  of a sequence of discrete domains  $\mathcal{T} = (\mathcal{D}_0, \mathcal{D}_1, \dots, \mathcal{D}_m)$  is the maximal subset of  $\mathcal{D}_0$  such that any trajectory starting from  $\mathcal{S}$  stays inside  $\mathcal{T}$  (begins from  $\mathcal{D}_0$  and reaches by order all discrete domains of  $\mathcal{T}$ ).
- If the stable zone  $\mathcal{S}$  of  $\mathcal{T}$  is not empty, then  $\mathcal{T}$  is called a discrete trajectory.
- For a discrete trajectory  $\mathcal{T} = (\mathcal{D}_0, \mathcal{D}_1, \dots, \mathcal{D}_m)$ , if  $\mathcal{D}_0 = \mathcal{D}_m$ , then  $\mathcal{T}$  is a closed discrete trajectory.

In order to find limit cycles, we find closed discrete trajectories at first, because a limit cycle must be inside a closed discrete trajectory.

A depth first algorithm is used to find closed discrete trajectories (see Figure 6). The HGRN of Figure 5 has 5 closed discrete trajectories (see Figure 7).

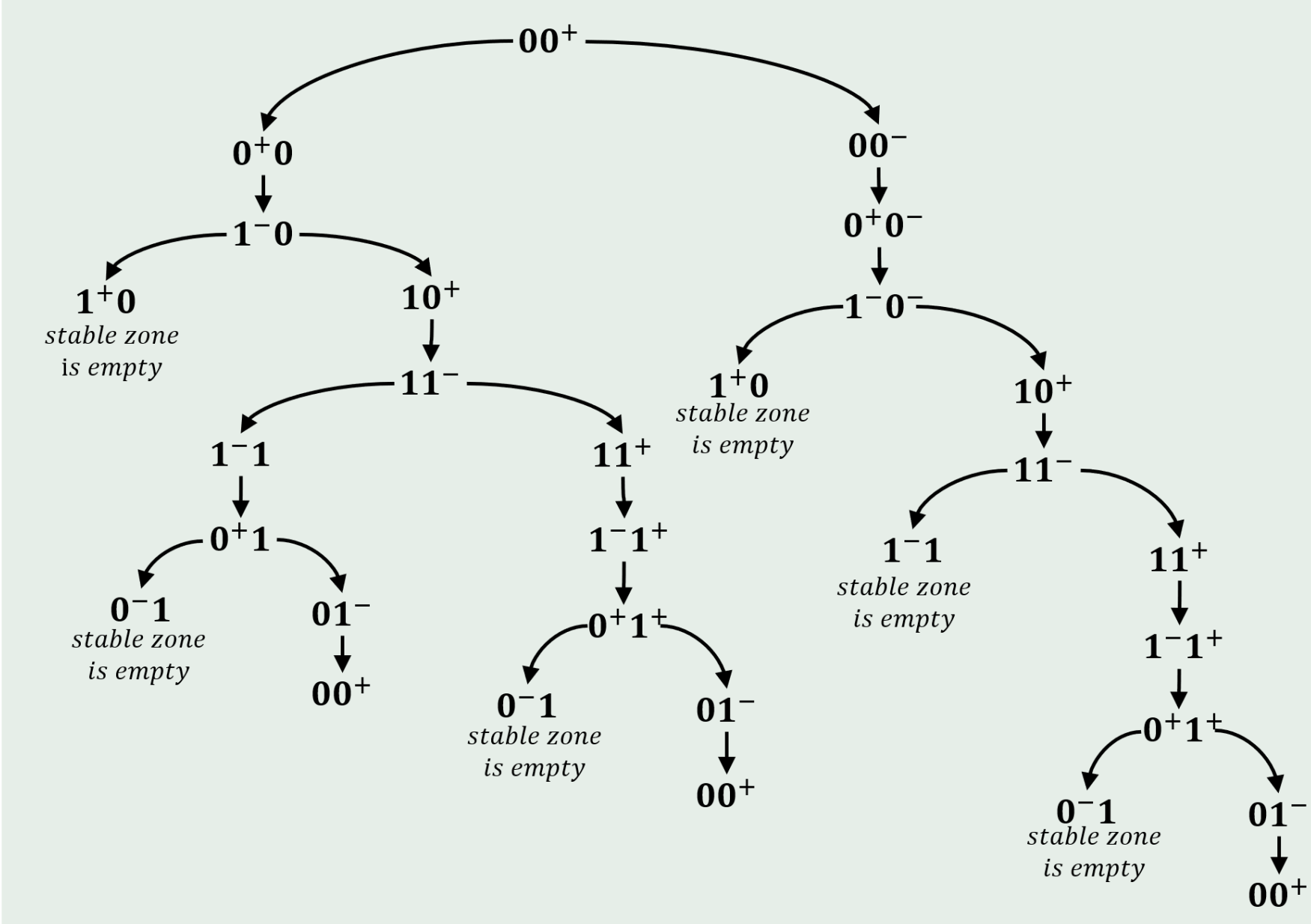


Figure 6. Illustration of the depth first algorithm starting from discrete domain  $(0, 0^+)^T$

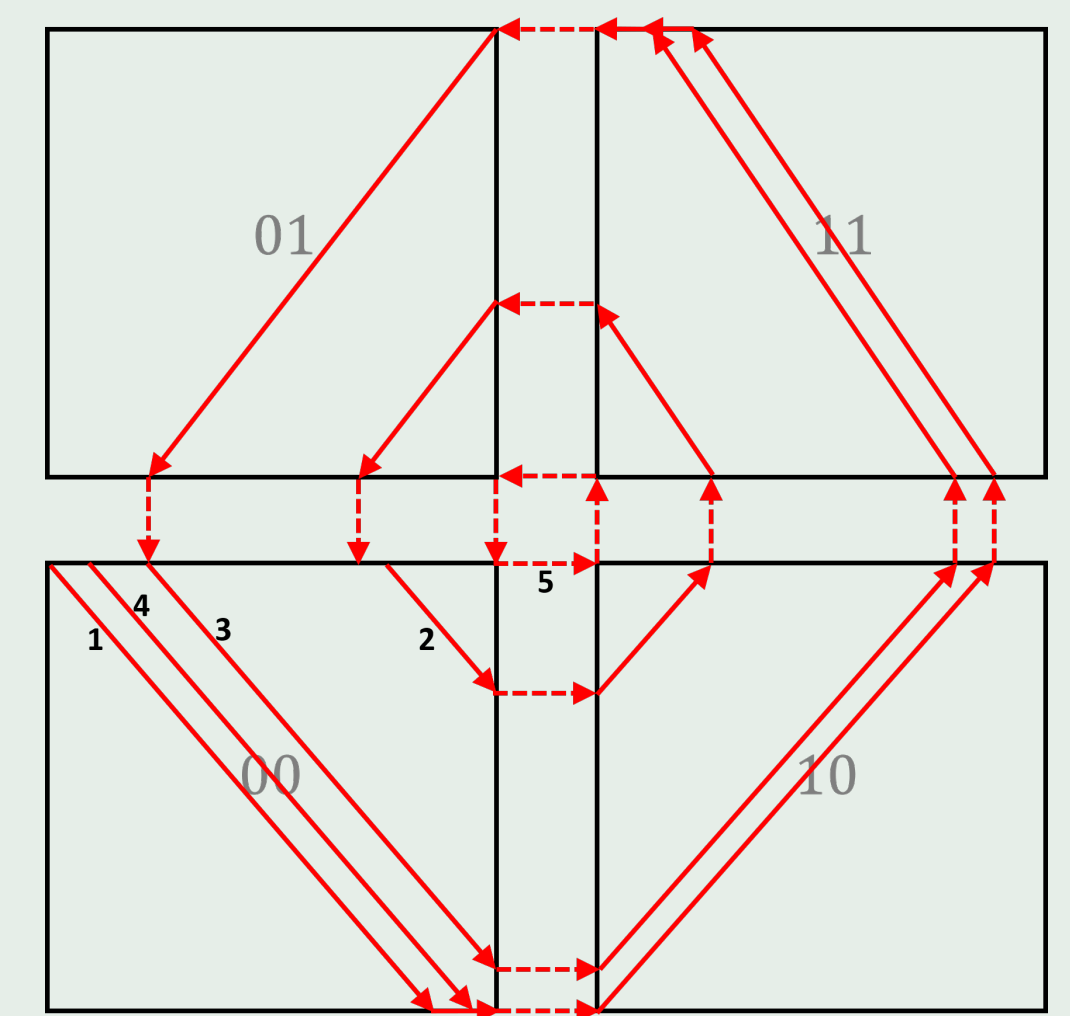


Figure 7. Examples of hybrid trajectories contained inside 5 different discrete trajectories

For example, in Figure 7, trajectory number 3 is contained in sequence:  $(0, 0^+) \rightarrow (0^+, 0) \rightarrow (1^-, 0) \rightarrow (1, 0^+) \rightarrow (1, 1^-) \rightarrow (1, 1^+) \rightarrow (1^-, 1^+) \rightarrow (0^+, 1^+) \rightarrow (0, 1^-) \rightarrow (0, 0^+)$ , which is also a closed discrete trajectory.

## 3. Find a limit cycle and analyze its stability

We note  $G(\cdot)$  the Poincaré map on the stable zone of  $\mathcal{T}$  which is calculated based on the transition matrix. The Poincaré map, which is widely used to study periodic trajectories in nonlinear dynamical systems, is the intersection of periodic trajectories with a certain lower-dimensional subspace, called the Poincaré section.

To verify if there is a **limit cycle** inside a closed discrete trajectory  $\mathcal{T} = (\mathcal{D}_0, \mathcal{D}_1, \dots, \mathcal{D}_m, \mathcal{D}_0)$ , we only need to verify:

- $\exists (\pi_0, d_0) \in \mathcal{D}_0$  such that  $G(\pi_0) = \pi_0$ , and
- $(\pi_0, d_0)$  belongs to the stable zone of  $\mathcal{T}$ .

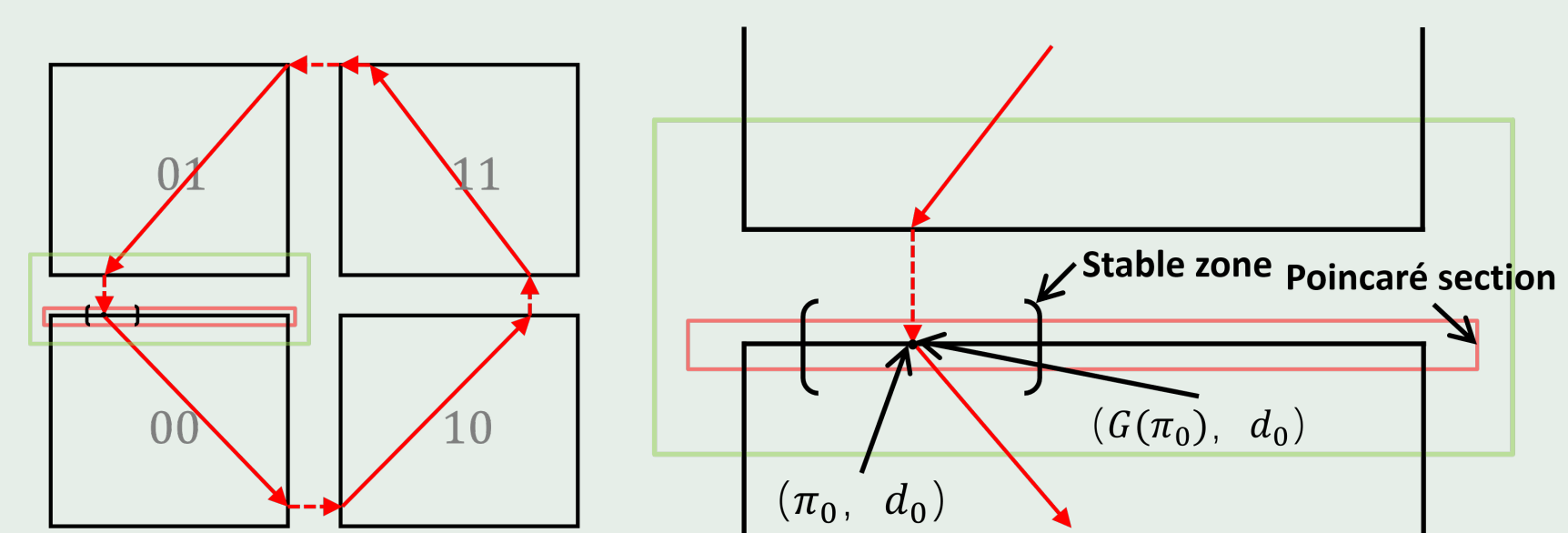


Figure 8. Illustration of the method to find limit cycle

To verify if the limit cycle inside  $\mathcal{T} = (\mathcal{D}_0, \dots, \mathcal{D}_m, \mathcal{D}_0)$  that crosses  $(\pi_0, d_0)$  is **stable**, we only need to verify whether  $\max_{i \in \{1, 2, \dots, p\}} |\lambda_i| < 1$ , where:

- $\lambda_1, \lambda_2, \dots, \lambda_p$  are the eigenvalues of  $A$ , and
- $x = Ax + b$  is equivalent to  $G(\pi_0) = \pi_0$ ,

where  $x$  is the reduction of  $\pi_0$  which only contains the dimensions in which the boundaries are not reached and  $A$  is the same reduction on the transition matrix.

## References

- Behaegel, J., J.-P. Comet, and M. Folschette (2017). "Constraint identification using modified Hoare logic on hybrid models of gene networks". In: *24th International Symposium on Temporal Representation and Reasoning (TIME 2017)*. Schloss Dagstuhl-Leibniz-Zentrum fuer Informatik.
- Behaegel, J., J.-P. Comet, G. Bernot, E. Cornillon, and F. Delaunay (2016). "A hybrid model of cell cycle in mammals". In: *Journal of bioinformatics and computational biology* 14.01, p. 1640001.
- Cornillon, E., J.-P. Comet, G. Bernot, and G. Enée (2016). "Hybrid gene networks: a new framework and a software environment". In: *advances in Systems and Synthetic Biology*.

## Application

We applied our method on a HGRN of the cell cycle in 5 dimensions [Behaegel, Comet, Bernot, et al. 2016] and successfully found two limit cycles.

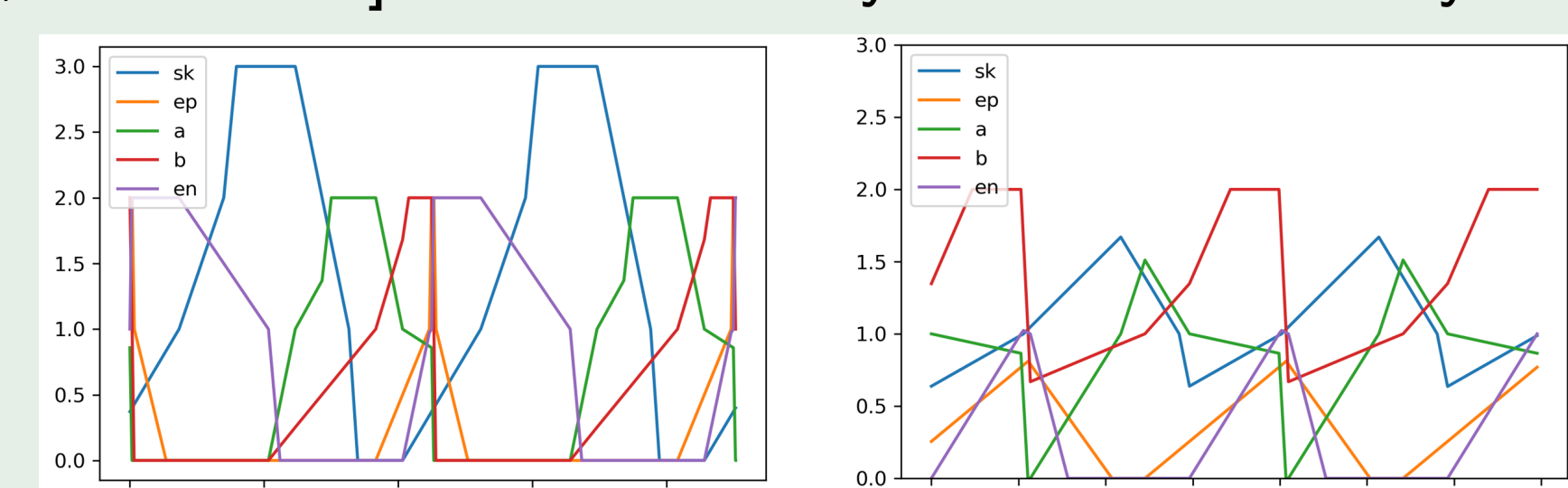


Figure 9. Simulation of limit cycles. Left: stable limit cycle. Right: unstable limit cycle.