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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)

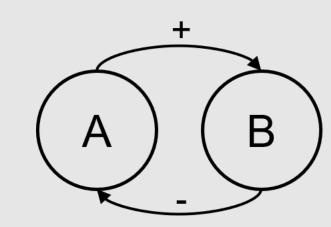


Figure 1. Influence graph of a simple gene regulatory networks in 2 dimensions

- 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 π and a discrete state d_s . The fractional part π is a real vector bounded in $[0,1]^N$ with N the number of genes in the system.

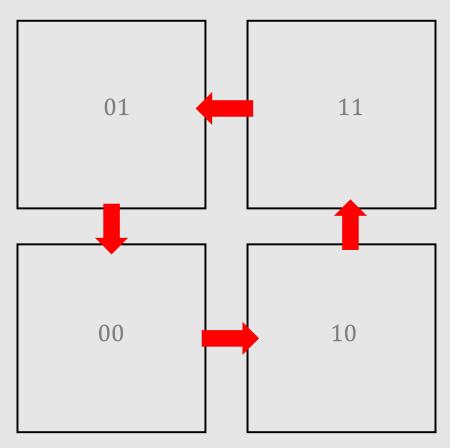


Figure 2. Example of dynamics of a discrete model (depending on discrete parameters)

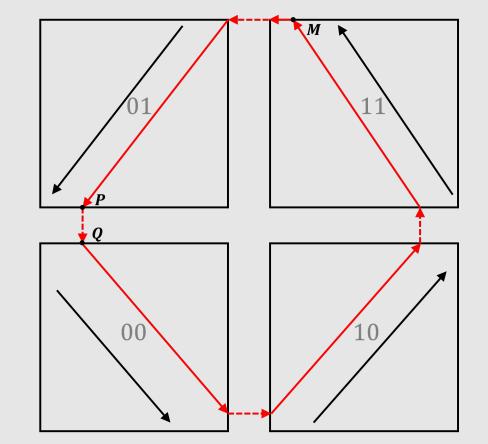


Figure 3. Example of dynamics of a HGRN (depending on real parameters); the black arrows represent the celerities

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:

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.

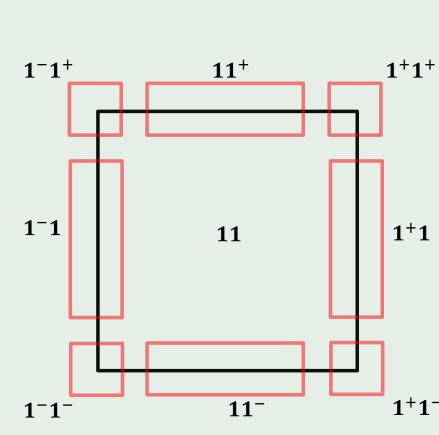


Figure 4. Discrete domains of the discrete state $(1,1)^T$

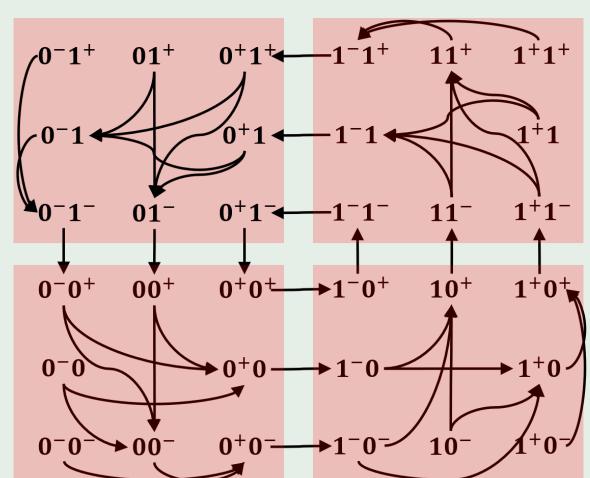


Figure 5. Graph of discrete domains of the HGRN

References

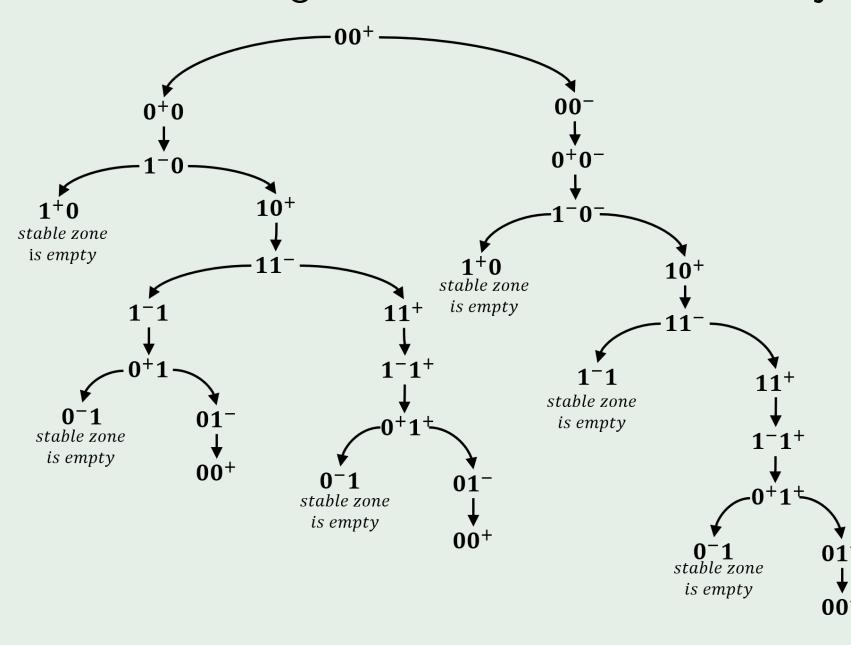
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2. Find closed discrete trajectories

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



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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: $(0,0^+) \to (0^+,0) \to (1^-,0) \to (1,0^+) \to (1,1^-) \to (1,1^+) \to (1^-,1^+) \to (0^+,1^+) \to (0,1^-) \to (0,0^+)$, which is also a closed discrete trajectory.

3. Find a limit cycle and analyze its stability

We note G(.) 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

 $\mathcal{T} = (\mathcal{D}_0, \mathcal{D}_1, ... \mathcal{D}_m, \mathcal{D}_0)$, we only need to verify:

- $lacksquare \exists (\pi_0,d_0)\in \mathcal{D}_0 ext{ such that } G(\pi_0)=\pi_0 ext{, and }$
- \blacksquare (π_0, d_0) belongs to the stable zone of \mathcal{T} .

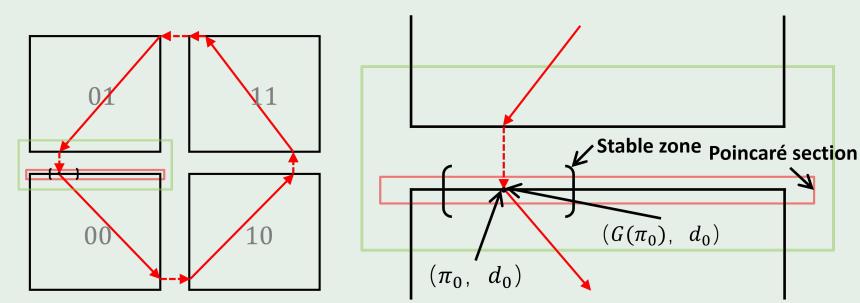


Figure 8. Illustration of the method to find limit cycle

To verify if the limit cycle inside $\mathcal{T} = (\mathcal{D}_0, ... \mathcal{D}_m, \mathcal{D}_0)$ that crosses (π_0, d_0) is **stable**, we only need to verify whether $\max_{i \in \{1, 2, ..., p\}} |\lambda_i| < 1$, where:

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

where x is the reduction of π_0 which only contains the dimensions in which the boundaries are not reached and A is the same reduction on the transition matrix.

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.

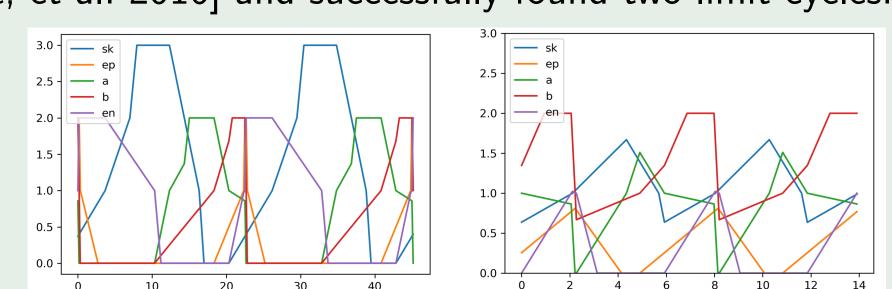


Figure 9. Simulation of limit cycles. Left: stable limit cycle. Right: unstable limit cycle.