

Study of Piecewise Multi-affine models for Genetic Regulatory Networks via a Lyapunov approach: an LMI framework

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Abstract: In this work we study convergence properties of Piecewise Multi-Affine models of genetic regulatory networks, by means of a Lyapunov approach. These models, quantitatively more accurate than their Piecewise Affine counterpart, are obtained by a Piecewise Linear approximation of sigmoidal regulation functions. In this work, using a linear matrix inequalities framework, we are able to find, if one exists subject to a box partitioning of the state space, a Piecewise Quadratic Lyapunov function, which is non-increasing along any system trajectory. In the first part of the paper we describe the considered model, defining and motivating the hyper-rectangular partition of the state space, while in the second part, using a result on the expression of multi-affine functions on an hyper-rectangle, we can define a set of linear matrix inequalities, whose solution gives the description of a piecewise quadratic Lyapunov function for the system. Convergence properties based on such functions are discussed and a numerical example will show the applicability of the results.

Keywords: Lyapunov methods, Piecewise Multi-affine Systems, Genetic Regulatory Networks, Systems Biology, LMIs

1. INTRODUCTION

Systems and synthetic biology have seen an ever increasing use of control theoretic tools to respectively analyse natural biological systems or design new ones to perform particular tasks (Blanchini et al., 2018). In these areas the concept of Genetic Regulatory Network (GRN) is ubiquitous, as they describe the intricate set of transcriptional interactions, inside a cell, between proteins and genes. Using tools from Chemical Reaction Networks theory and considerations on reactions timescales, one is able to model the dynamics of a GRN via a set of differential equations, which in general involve Hill functions to describe the strength of regulation interactions (Murray and Del Vecchio, 2014). GRNs are known to exhibit a large range of behaviors, such as: chaos, oscillations, monostability, multistability and bifurcations and so it is crucial to be able to study and predict their dynamical properties, and in order to do this many approaches have been developed in literature. One important class of these analysis methods are the qualitative ones. Considering the usual On/Off characteristic of regulation functions, boolean networks have been proposed as a model for GRN dynamics, with a set of boolean rules that allow to identify interactions responsible for particular system behaviors (Tournier and Chaves, 2009). While boolean networks are able to capture

their main qualitative properties, many authors proposed and studied Piecewise Affine (PWA) models for GRNs (Casey et al. (2006) and references therein), arising from a step approximation of regulation functions, in order to capture more fine-grained aspects of the network dynamics, otherwise lost in the boolean setting (Chaves et al., 2010). Despite being very useful, as many questions in systems biology have a qualitative nature, sometimes a more quantitative and accurate analysis is required (Batt et al., 2007). In Belta et al. (2002), the authors proposed the use of piecewise linear functions – which are known to have universal approximation properties – to approximate sigmoid functions. Given the existence of possible multiple complex interactions in a GRN, this solution gives rise, in general, to a Piecewise Multi-affine (PMA) model. Dynamical properties of PMA systems have been studied in many cases using reachability analysis tools and discrete abstractions of the multi-affine dynamics (Kloetzer and Belta, 2006; Collins et al., 2011; Turnip and Tamba, 2015; Barnat et al., 2017). Another important method to study the system dynamics is the use of Lyapunov functions, which can give information on equilibria landscape, their stability and possibly domains of attraction. Although Lyapunov methods have been extensively used in the study of biochemical networks (Chesi and Hung, 2008; Blanchini and Giordano, 2014; Al-Radhawi and Angeli, 2016; Pasquini and Angeli, 2019), not many results are available on Lyapunov functions constructions for PMA systems, presenting multistability and complex behaviors.

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In Nguyen et al. (2017), the authors described an LMI framework to study asymptotic stability of PMA models arising in fuzzy control applications, via Lyapunov functions. The authors used Finsler lemma and \mathcal{S} -procedure to derive a set of LMIs that can prove the stability of the origin. In the present work we will use polyhedra representation tools and conewise copositivity conditions (Iervolino et al., 2017), to search for a Piecewise quadratic Lyapunov function through an LMI feasibility problem. Differently from Nguyen et al. (2017) we can drop positivity constraints of the Lyapunov function because of boundedness properties of the trajectories and, as multistability is a fundamental properties in many biological systems, we allow this possibility by not explicitly taking advantage of information on equilibria and discussing convergence properties of the system trajectories. Considerations to improve the result significance and to expand the feasible set of solutions, are remarked and discussed as well. The paper is structured as follow: in Section 2 we introduce the Piecewise Multi-affine model to study, formally describing a state space partition, and discussing properties of multiaffine functions which will be useful in the following. Section 3 contains the main contribution of the paper, discussing how the Lyapunov function is defined and how monotonicity and continuity constraints can be enforced through the use of LMIs and Matrix Equalities. We then discuss how the state space partition can be refined to get more informative results and we prove the non-increasing property of the Lyapunov function along system trajectories. Finally, in Section 4, we analyse the example of a Self-Activating Toggle Switch showing how the framework can be applied and how convergence properties can be inferred. Section 5 concludes the work and provide final remarks on possible future developments.

Mathematical notation: We consider any vector $v \in \mathbb{R}^n$ to be a column, except for the gradient ∇f of a function $f : \Omega \subseteq \mathbb{R}^n \rightarrow \mathbb{R}$, which we consider to be a row. If v is a vector, with $\|v\|$ we indicate its norm. With \mathbb{R}_+^n we denote the set of all the entrywise non-negative vectors in \mathbb{R}^n . With $\text{int}(D)$, $\text{cl}(D)$ and ∂D we denote the interior, the closure and the boundary of the set D , respectively. If $M \in \mathbb{R}^{n \times n}$ is a symmetric matrix, then with $M \succeq 0$ ($M \preceq 0$) we denote the fact that $x^T M x \geq 0$ ($x^T M x \leq 0$), $\forall x \in \mathbb{R}^n$. ◀

2. PIECEWISE MULTIAFFINE MODEL

We consider a piecewise linear approximation of Hill regulation functions (see Fig. 1), formally described by:

$$r^+(x_i, \theta_i^k, \theta_i^l) = \begin{cases} 0 & \text{if } x_i < \theta_i^k \\ a_i x_i + b_i & \text{if } \theta_i^k \leq x_i \leq \theta_i^l \\ 1 & \text{if } x_i > \theta_i^l \end{cases} \quad (1)$$

$$r^-(x_i, \theta_i^k, \theta_i^l) = 1 - r^+(x_i, \theta_i^k, \theta_i^l)$$

where $\theta_i^k < \theta_i^l$ and a_i and b_i are univocally defined given that r^+ is continuous.

This approximation is often considered in modelling biological systems (Belta et al. (2002); Belta and Habets (2006); Batt et al. (2007)), as opposed to a step-like one

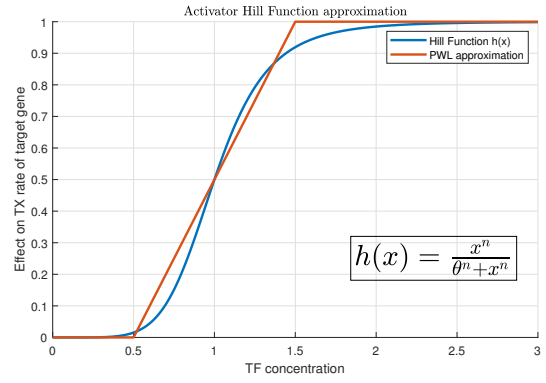


Fig. 1. Approximation of a sigmoid using a piecewise linear function. The tuning parameters are θ_i^k and θ_i^l in Eq. (1). In theory one can consider more breakpoints (i.e. θ s) in order to get a better approximation, as the whole analysis will still be valid. Techniques to choose optimally such parameters are available (Grosu et al., 2011).

(Casey et al. (2006) and references therein). In fact, even if the latter present monotonicity properties well suited in a qualitative analysis of gene networks, the former is able to give more valid quantitative information, while still displaying mathematical properties that can be exploited in the system analysis (Batt et al., 2007).

Given the approximation (1), and the fact that complex transcription regulation can occur, in which more than one transcription factor has effect on the target gene, Piecewise Multi-Affine functions defined on a box partition of the positive orthant, will be present in the dynamics of the system describing the GRN.

To formalize this, the following definitions will be used.

Definition 1. (Kloetzer and Belta, 2006) A *multi-affine* function $f : \Omega \rightarrow \mathbb{R}^n$, $\Omega \subseteq \mathbb{R}^n$ is a polynomial in the variables x_1, \dots, x_n , in which every variable has at most degree 1, namely:

$$f(x) = \sum_{i_1, \dots, i_n \in \{0,1\}} b_{i_1, \dots, i_n} x_1^{i_1} x_2^{i_2} \dots x_n^{i_n}$$

where $b_{i_1, \dots, i_n} \in \mathbb{R}^n$. ◀

Definition 2. Let \mathcal{P}_i be the partition of the positive i -th axis induced by the thresholds $\theta_i^1, \dots, \theta_i^{m_i} \in \mathbb{R}_+$, formally:

$$\mathcal{P}_i = \{[0, \theta_i^1), [\theta_i^1, \theta_i^2), \dots, [\theta_i^{m_i}, \infty)\}$$

The set $\mathcal{D} = \{D_1, \dots, D_m\}$ is called *hyper-rectangular (or box) partition of \mathbb{R}_+^n* , induced by the axis partitions $\mathcal{P}_1, \dots, \mathcal{P}_n$, if:

$$\mathbb{R}_+^n = D_1 \cup D_2 \cup \dots \cup D_m$$

$$\text{int}(D_i) \cap \text{int}(D_j) = \emptyset, \quad \forall i \neq j, \quad i, j \in \{1, \dots, m\}$$

$$D_k = d_k^1 \times \dots \times d_k^n, \quad d_k^l \in \mathcal{P}_l, \quad k \in \{1, \dots, m\}$$

Any element D_i of the set \mathcal{D} is referred to as domain in the following. ◀

Definition 3. Let \mathcal{D} be a box partition of the positive orthant as in Definition 2 and let $\sigma(x, k)$ be the function:

$$\sigma(x, k) = \begin{cases} 1 & \text{if } x \in D_k, \\ 0 & \text{otherwise} \end{cases}$$

Let $f^1(x), \dots, f^m(x)$ be multi-affine functions as in Definition 1. Then a *Piecewise Multi-Affine (PMA)* function $f : \mathbb{R}_+^n \rightarrow \mathbb{R}^n$ on the partition \mathcal{D} , is a function defined as:

$$f(x) = \sum_{k=1}^m \sigma(x, k) \cdot f^k(x)$$

In this work we consider the following model for a gene regulatory network:

$$\dot{x} = f(x) - Cx \quad (2)$$

in which $x \in \mathbb{R}_+^n$ is a vector of protein concentrations, $f : \mathbb{R}_+^n \rightarrow \mathbb{R}_+^n$ is a PMA function defined on a box partition of the positive orthant, representing transcriptional regulation and C is a diagonal matrix with strictly positive diagonal entries, representing the protein degradation rates.

Remark 1. Being Cx a linear contribution to the dynamics, the entire right-hand side of Eq. (2) is a piecewise multi-affine function. This means that, while keeping in mind the structure of the model we are considering, every result that applies to PMA functions, can be applied to the entire right-hand side of Eq. (2) and not just to $f(x)$. ◀

Given that, in our model, $f(x)$ will be a continuous combination of bounded piecewise linear functions as in Eq. (1), representing genetic transcriptional interactions, then it is not restrictive to ask for the following assumption:

Assumption 1. For the function $f(x)$ in Eq. (2):

$$\exists M > 0 \quad \text{s.t.} \quad \|f(x)\| \leq M, \quad \forall x \in \mathbb{R}_+^n$$

Assumption 1 implies the existence of an attractive and positively invariant box to which the analysis of the system can be restricted.

Finally we recall the following result from Kloetzer and Belta (2006), on multi-affine functions defined on an hyper-rectangle.

Proposition 1. Let D be a bounded hyper-rectangle in \mathbb{R}^n and let $V(D) = \{v_{D,1}, \dots, v_{D,2^n}\}$ be the set of its vertices. Let $f : cl(D) \rightarrow \mathbb{R}^n$ be a multi-affine function as in Definition 1. Then $f(x)$ is a convex combination of the values assumed by f at the vertices of D , for any $x \in D$, formally:

$$\begin{cases} f(x) = \sum_{i=1}^{2^n} \lambda_i(x) f(v_{D,i}), & \forall x \in D \\ \sum_{i=1}^{2^n} \lambda_i(x) = 1, \lambda_i(x) \geq 0, & \forall i \in \{1, \dots, 2^n\} \\ & \forall x \in D \end{cases}$$

3. MAIN CONTRIBUTION

3.1 PWQ Lyapunov function - LMI Feasibility Problem

Our goal is to find a Lyapunov function V for the system, with the property of being non-increasing along any trajectory of system (2). We choose V to be a Piecewise Quadratic (PWQ) function, defined on the same partition \mathcal{D} on which $f(x)$ in Eq. (2) is defined, formally:

$$\begin{aligned} V(x) &= \sum_{k=1}^m \sigma(x, k) \cdot V_{D_k}(x) \\ V_{D_k}(x) &= x^T P_{D_k} x + 2d_{D_k}^T x + \omega_{D_k} = \\ &= [x^T \ 1] \begin{bmatrix} P_{D_k} & d_{D_k} \\ d_{D_k}^T & \omega_{D_k} \end{bmatrix} \begin{bmatrix} x \\ 1 \end{bmatrix} = \\ &= \bar{x}^T \bar{P}_{D_k} \bar{x} \end{aligned} \quad (3)$$

In the following we will define an LMI feasibility problem, in which the decision variables are the matrices \bar{P}_{D_k} of (3). The method we are going to use is similar to Pasquini and Angeli (2019) and Iervolino et al. (2017), which are specifically designed for Piecewise Affine systems, here adapted for PMA models. The following constraints are asked on V :

- Continuity of V on the intersection between adjacent domains;
- Monotonicity of V inside any domain.

Remark 2. There are no constraints on the positivity of V , as the system trajectories are bounded given Assumption 1. Continuity of V is asked everywhere to avoid singular behaviors in the Lyapunov function evolution along particular trajectories (e.g. limit cycles). However many results are available in literature on discrete abstractions of PMA systems and qualitative dynamics (see Kloetzer and Belta (2006); Collins et al. (2011); Turnip and Tamba (2015); Benes et al. (2018)). Such discrete abstraction can be used to reduce the number of continuity constraints. ◀

Remark 3. From Assumption 1, and the following discussion on the existence of an attractive and positively invariant box, we restrict our analysis to the intersection between the positive orthant \mathbb{R}_+^n and such box \mathcal{B} (which can be easily constructed). As a result any domain considered from now on will be bounded. ◀

3.2 Continuity constraints

The first type of constraint we want to satisfy, is the continuity of V on the whole state space. Let D_i and D_j be two adjacent domains. In order to have continuity of V on $\partial D_i \cap \partial D_j$, i.e.:

$$\lim_{\substack{y_i \rightarrow x, \\ y_i \in D_i}} V_{D_i}(y_i) = \lim_{\substack{y_j \rightarrow x, \\ y_j \in D_j}} V_{D_j}(y_j), \quad \forall x \in \partial D_i \cap \partial D_j$$

the following equivalent Matrix Equality (ME) condition can be asked (Iervolino et al., 2017; Pasquini and Angeli, 2019):

$$\Gamma_{ij}^T (\bar{P}_{D_i} - \bar{P}_{D_j}) \Gamma_{ij} = 0 \quad (4)$$

where Γ_{ij} is the ray matrix of the homogenization cone of $\partial D_i \cap \partial D_j$ (see Iervolino et al. (2017) for further details on what an homogenization cone is and how to compute Γ_{ij}) and \bar{P}_{D_k} is defined in Eq. (3). Condition (4) should be asked for any couple D_i, D_j of domains such that $\partial D_i \cap \partial D_j \neq \emptyset$.

3.3 Monotonicity constraints

The second kind of constraint we need to ask is the monotonicity of V , which converts in asking the monotonicity of V_D in Eq. (3), inside the domain D , for all $D \in \mathcal{D}$. In particular, this constraint is expressed as:

$$\dot{V}_D(x) = \nabla V_D(x) \cdot f(x) \leq 0, \quad \forall x \in D \quad (5)$$

Being D a bounded box (Remark 3) and taking advantage of Proposition 1, condition (5) can be satisfied by asking:

$$\begin{aligned} \nabla V_D(x) \cdot (f(v_{D,i}) - Cv_{D,i}) = \\ = \nabla V_D(x) \cdot \bar{f}(v_{D,i}) \leq 0, \quad \forall i \in \{1, \dots, 2^n\} \end{aligned} \quad (6)$$

where $v_{D,i}$ is the i -th vertex of D and the first equality is motivated by Remark 1. The set of conditions (6) can be satisfied by asking the following set of LMIs:

$$\Gamma_D^T \bar{P}_{D,i} \Gamma_D + M_{D,i} \preceq 0, \quad \forall i \in \{1, \dots, 2^n\} \quad (7)$$

where Γ_D is the ray matrix of the homogenization cone of D , $M_{D,i}$ can be any entrywise-non-negative and symmetric matrix and:

$$\bar{P}_{D,i} = \begin{bmatrix} 0 & P_D \bar{f}(v_{D,i}) \\ \bar{f}^T(v_{D,i}) P_D & 2d_D^T \bar{f}(v_{D,i}) \end{bmatrix} \quad (8)$$

Using the notation above, we want to solve the following: *Feasibility Problem 1.* Consider the system (2). Find a Piecewise quadratic function $V : \mathbb{R}_+^n \rightarrow \mathbb{R}$, of the form (3), subject to:

$$\Gamma_{ij}^T (\bar{P}_{D_i} - \bar{P}_{D_j}) \Gamma_{ij} = 0, \quad \forall D_i, D_j | \partial D_i \cap \partial D_j \neq \emptyset$$

$$\Gamma_D^T \bar{P}_{D,i} \Gamma_D + M_{D,i} \preceq 0, \quad \forall i \in \{1, \dots, 2^n\}, \forall D \in \mathcal{D}$$

A solution of the Feasibility Problem 1 is referred to as a Lyapunov function for system (2).

Remark 4. To solve Feasibility problem 1 amounts to find a feasible solution of a set of LMIs. The decision variables of this problem are: the matrices \bar{P}_{D_k} , describing the function (3) in any domain D_k , and the matrices $M_{D,i}$ in (7), constrained only by the fact of being symmetric and entrywise non-negative. Available numerical solvers for semidefinite programming are used to find a numerical solution.

Remark 5. The number of domains increases exponentially with the dimension of the state space and consequently it increases, in the same way, the complexity of the feasibility problem. For this reason, techniques that can exclude particular domains from the computation (Collins et al., 2011) should be exploited.

Remark 6. Condition (6) asks for the function V to be non-increasing, inside a certain domain D , along all the directions $f(v_{D,i})$. There can be some configurations of these directions – usually near equilibria – such that the only possibility for V is to be constant in D . If this happens, we lose the information given from V on how the system behaves in such domain. To overcome this problem we can re-partition the positive orthant with a finer grid, by adding thresholds θ . The new partition obtained by adding other thresholds to the axis partition (see Definition 3), applies only to the search of a Lyapunov function as the system dynamics is still defined on the original partition, given by the structure of the PMA function $f(x)$. This kind of procedure can be applied more than once, at the cost of computational efficiency (as the number of constraints to ask, as well as the number of decision variables, will increase).

3.4 Formal properties of the Lyapunov function

We make the following assumption, implied by mild conditions on the set of times when the system switches between two different domains, conditions that are generally true for the considered class of systems.

Assumption 2. Let $x(\cdot)$ be a solution of (2). Then for all times t , with the possible exception of a countable set, it holds:

$$\exists \epsilon > 0, \exists D_t \in \mathcal{D} \quad \text{s.t.} \quad x(\tau) \in D_t, \quad \forall \tau \in (t - \epsilon, t + \epsilon)$$

The following formal result can be stated for the function V , solution of the Feasibility Problem 1.

Theorem 1. Consider the system (2) and let $V(x)$ be a solution of Feasibility Problem 1. Then $V(x(t))$ is non-increasing along any trajectory $x(\cdot)$ of system (2), satisfying Assumption 2.

Proof. We can prove that, given a solution $x(t)$ of (2), $V(x(t))$ is an absolutely continuous function of t , by using arguments similar to the ones we used in the proof of [Theorem 1, Pasquini and Angeli (2019)].

Let $t_1, t_2 \in \mathbb{R}_+$ be such that $t_1 \leq t_2$. Then :

$$V(t_2) - V(t_1) = \int_{t_1}^{t_2} \frac{dV(x(\tau))}{d\tau} d\tau$$

where the integral is intended in the sense of Lebesgue. Because of Assumption 2 then, apart from a zero measure set of times, $x(t)$ belongs to a uniquely specified domain D and because V is a solution of Feasibility Problem 1, hence satisfying (4) and (7) in every domain, it is guaranteed that $\frac{dV(x(t))}{dt} \leq 0$ for a.e. t and so it holds:

$$\int_{t_1}^{t_2} \frac{dV(x(\tau))}{d\tau} d\tau \leq 0$$

which concludes the proof. \square

Because of Theorem 1, the following proposition from Pasquini and Angeli (2019) – to which the reader is referred for a formal proof – holds:

Proposition 2. Let V be a solution of Feasibility Problem 1 and let $x(\cdot)$ be a solution of (2). Then:

$$\lim_{\tau \rightarrow \infty} \mu(\{t \geq \tau : \frac{dV(x(t))}{dt} < -\epsilon\}) = 0, \quad \forall \epsilon > 0 \quad (9)$$

where $\mu(E)$ denotes the measure of the set E . ◀

Proposition 2 is a consequence of the monotonicity of V and gives a useful tool to study the convergence set of the system, as shown in the following example.

4. EXAMPLE: SELF-ACTIVATING TOGGLE SWITCH

Consider the genetic regulatory network in Fig. 2, and the corresponding PMA system:

$$\begin{cases} \dot{x}_1 = b_{10} + b_1 r^-(x_2, \theta_2^1, \theta_2^3) r^+(x_1, \theta_1^2, \theta_1^4) - c_1 x_1 \\ \dot{x}_2 = b_{20} + b_2 r^-(x_1, \theta_1^1, \theta_1^3) r^+(x_2, \theta_2^2, \theta_2^4) - c_2 x_2 \end{cases} \quad (10)$$

with $b_{10} = 0.05$, $b_{20} = 0.12$, $b_1 = 7.5$, $b_2 = 10$, $c_1 = 0.7$, $c_2 = 1.2$, $\theta_1^1 = 2$, $\theta_1^2 = 3$, $\theta_1^3 = 5$, $\theta_1^4 = 6$, $\theta_2^1 = 4$, $\theta_2^2 = 6$, $\theta_2^3 = 7$, $\theta_2^4 = 8$ and the functions $r^+(\cdot)$ and $r^-(\cdot)$ defined as in (1). Self-activating toggle switches have been

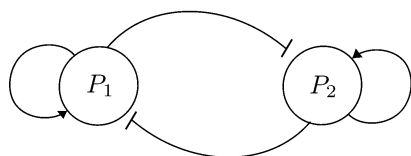


Fig. 2. Genetic regulatory network of the self-activating toggle switch.

studied in literature (Lu et al., 2013) as they may have an important role in cell-fate decision in cancer cells and are known to show tristability. Simulations of (10) (Fig. 3) show this kind of tristable behavior. By formulating the

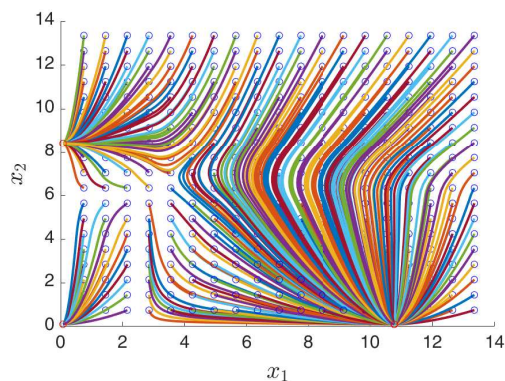


Fig. 3. Trajectories of system (10) from a grid of initial points (blue), showing a tristable behavior

LMI's Feasibility problem described in Section 3.1, we can find the description of a Piecewise Quadratic Lyapunov function for the system, the contour plot of which is shown in Fig. 4a. In many domains the function V is constant, as explained in Remark 6, and so a finer partition of the state space can be defined and a new feasibility problem can be formulated on it. By solving this new problem we obtain the function in Fig. 4b. The plot in Fig. 5 shows how the Lyapunov function is non-increasing along system trajectories, in accordance to Theorem 1. Because of Proposition 2, by studying the level sets of \dot{V} we can describe the convergence set of the system. In Fig. 6 we

can see that the three areas containing the stable equilibria are highlighted. Other regions are highlighted as well, due to the existence of unstable equilibria in the system. Local analysis should then be performed to determine the nature of the equilibria in these regions.

5. CONCLUSION

In this paper we constructed an LMI feasibility problem, whose solution describes a piecewise quadratic Lyapunov function for a piecewise multi-affine model of genetic regulatory networks. Constraints on the function derivative along the system vector field at domains vertices, and continuity along domains boundaries, are imposed. After discussing how the state space partition can be refined, to get a more informative Lyapunov function, we proved that the function is non-increasing along any system trajectory and consequently a Lasalle-like result holds. These results are used to study a self-activating toggle switch system, highlighting its convergence regions.

Many future research directions are open. First of all, while positivity constraints are already dropped, results on discrete abstraction of the system dynamics available in literature can be used to drop many continuity constraints as well. Moreover techniques to find parameter dependent Lyapunov functions may be investigated, the parameters being connected to the weight of the convex combination in Proposition 1.

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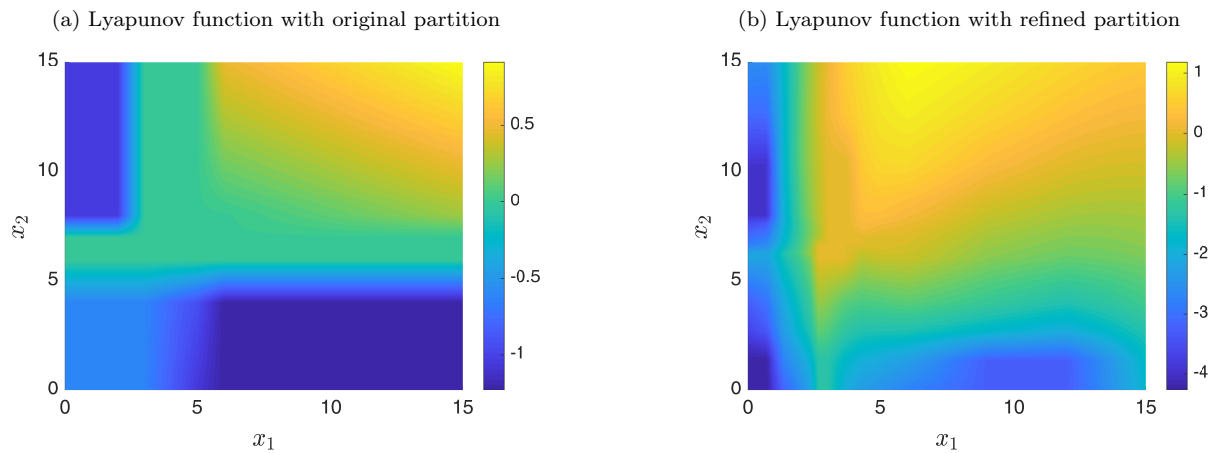


Fig. 4. Lyapunov function contour plots for system (10). As explained in Remark 6, with the original partition (a) there are many areas in which the Lyapunov function is constant, while with a refined partition (b) these areas become smaller and the LF more informative.

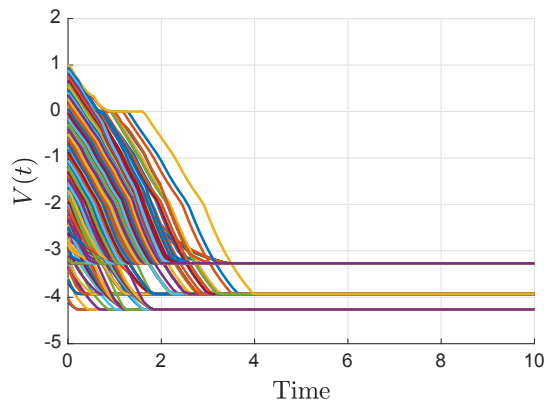


Fig. 5. Evolution in time of the Lyapunov function.

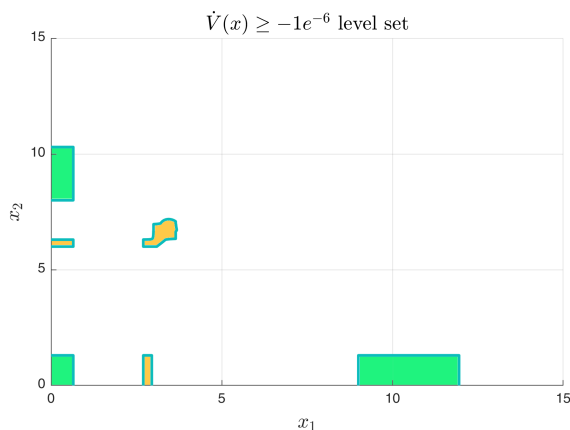


Fig. 6. Level set of the Lyapunov function derivative along the system field ($\dot{V} \geq 1e^{-6}$). Green regions contain asymptotically stable equilibria, while the orange ones contain unstable equilibria.

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