

Michaelis-Menten Networks are Structurally Stable

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Abstract

We consider a class of biological networks where the nodes are associated with first-order linear dynamics and their interactions, which can be either activating or inhibitory, are modelled by nonlinear Michaelis-Menten functions (i.e., Hill functions with unitary Hill coefficient), possibly in the presence of external constant inputs. We show that all the systems belonging to this class admit at most one strictly positive equilibrium, which is stable; this property is structural, i.e., it holds for any possible choice of the parameter values, and topology-independent, i.e., it holds for any possible topology of the interaction network. When the network is strongly connected, the strictly positive equilibrium is the only equilibrium of the system if and only if the network includes either at least one inhibiting function, or a strictly positive external input (otherwise, the zero vector is an equilibrium). The proposed stability results hold also for more general classes of interaction functions, and even in the presence of arbitrary delays in the interactions.

Key words: Biological networks; Hill functions; Michaelis-Menten functions; Structural analysis; Systems biology.

1 Introduction

Why are biological networks so remarkably well-behaved, notwithstanding their huge complexity? The networked systems observed in nature at all scales, ranging from genetic and metabolic networks to ecological networks, are typically composed of myriads of interactions; still, they exhibit an astounding robustness (Cosentino and Bates 2011; Del Vecchio and Murray 2014) in spite of the uncertainties and the variability of parameter values, induced for instance by environmental fluctuations.

The structural analysis of biological systems (see for instance the survey by Blanchini and Giordano 2021 and the references therein) aims at answering such questions by assessing properties that hold structurally, i.e., regardless of parameter values, for a whole, qualitatively specified, family of systems. The structural stability analysis of chemical reaction networks, which dates back to the early seventies (Horn 1973), has been approached by means of Lyapunov techniques and D-stability theory by Clarke (1980) and Reder (1988), leading to remarkable results. The well renowned deficiency zero theorem by Feinberg (1987) employs entropy as a Lyapunov function to prove that weakly reversible chemical reaction networks governed by mass-action kinetics have a unique locally stable positive equilibrium in each stoichiometric compatibility class if their defi-

ciency (an integer that can be immediately computed based on the network structure) is equal to zero; see the book by Feinberg (2019) for a thorough overview of structural stability results for classes of chemical reaction networks, focused on the mass-action kinetics case. Nonlinear compartmental systems are structurally stable, because they admit the 1-norm as a structural Lyapunov function (Maeda et al. 1978). More in general, the structural stability of biochemical networks with arbitrary reaction rates has been studied by adopting piecewise linear (Blanchini and Giordano 2014, 2017) as well as piecewise linear in rates (Al-Radhawi and Angeli 2016; Al-Radhawi et al. 2020) structural Lyapunov functions.

Establishing the structural stability of a family of systems is very challenging. Here, we focus on a commonly encountered type of biological networks: activation-inhibition networks, where an arbitrary number of species, or components, interact pairwise through either activating or inhibitory actions. This is, for instance, the case of gene regulatory networks (Chen and Aihara 2002; Chen et al. 2010; Chesi and Hung 2008; Del Vecchio and Murray 2014), where gene expression levels are regulated through DNA, RNA and proteins, often by means of kinetic mechanisms for activation and inhibition based on enzymatic reactions.

Consider a regulatory network involving n key players,

whose concentrations at time t are denoted by the real non-negative variables $x_i(t)$, $i = 1, \dots, n$. The time evolution of the species concentrations can be described by the system of ordinary differential equations

$$\dot{x}_i = \sum_{j=1}^n h_{ij}(x_j) + u_i, \quad i = 1, \dots, n, \quad (1)$$

where the function h_{ij} describes how the concentration of species j affects the temporal evolution of the concentration of species i , while $u_i \geq 0$ are constant external inputs. The expression of h_{ij} is typically derived based on fundamental principles of chemical kinetics (such as the law of mass action, see Feinberg 2019, resulting in polynomial functions, $h_{ij}(x_j) = \mu_{ij}x_j^m$, $m \in \mathbb{N}$, $\mu_{ij} \in \mathbb{R}_+$) or enzymatic kinetics (resulting in rational functions): Michaelis-Menten functions or, typically in the presence of cooperativity, Hill functions (Alon 2020; Cao 2011; Del Vecchio and Murray 2014; Gómez-Gardeñes et al. 2005b; Krishnan et al. 2020; Youseph et al. 2015). Inhibiting (non-increasing) and activating (non-decreasing) Hill functions respectively take the form

$$g(x_j; \beta, p) := \frac{1}{1 + \left(\frac{x_j}{\beta}\right)^p}, \quad (2)$$

$$f(x_k; \delta, p) := \frac{\left(\frac{x_k}{\delta}\right)^p}{1 + \left(\frac{x_k}{\delta}\right)^p}, \quad (3)$$

where p is the Hill coefficient, which quantifies the ultrasensitivity of the response curve (for $p \rightarrow \infty$, Hill functions tend to ideal threshold functions) and may describe cooperativity of binding, while the threshold β (respectively, δ) is the value at which the function $g(x_j; \beta, p)$ (resp., $f(x_k; \delta, p)$) is equal to half of its initial (resp., final) value. Higher values of p correspond to sharper thresholds, as shown in Fig. 1; the most commonly used values of p range from 1 to 4 (Alon, 2020, Section 2.3.3). The functions in (2)-(3) with $p = 1$ are known as Michaelis-Menten functions. Their expression is achieved through an approximation based on time-scale separation (Gunawardena 2012, 2014; Palsson 1987; Wong et al. 2018). Although sometimes questioned (Belgacem and Gouze 2013; Kim and Tyson 2020; Naka 2020), Michaelis-Menten functions are still very broadly used and accepted, and they are considered in several contributions on the stability analysis of biochemical systems (Angeli and Sontag 2008; Chen and Aihara 2002; Chen et al. 2010; Chesi and Hung 2008; Rao 2018; Sueyoshi and Naka 2017).

Our main result is that any network of interacting elements (see e.g. Fig. 2), with linear dissipative terms and interactions modelled by Michaelis-Menten functions, is stable for any possible value of the parameters regardless of the topology of the interaction network; we refer to this property as *topology-independent structural stability*. In particular, we prove that:

- Michaelis-Menten networks admit at most one positive

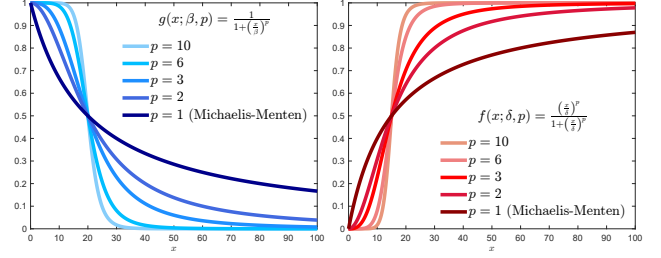


Figure 1. Left: inhibiting Hill functions of the form (2) with $\beta = 20$ and different values of p . Right: activating Hill functions of the form (3) with $\delta = 15$ and different values of p .

- equilibrium (i.e., with all positive components);
- this positive equilibrium (if it exists) is stable;
- if the network is strongly connected (i.e., any node is connected by an oriented path to any other node) and *non-degenerate* (i.e., there is either at least one inhibition interaction or a nonzero external constant input), the positive equilibrium does exist and there are no other equilibria;
- *degenerate* networks admit an equilibrium at zero, which can be unstable; if it is unstable, then a positive stable equilibrium exists.

We show that the results hold even in the presence of linear positive off-diagonal terms, or of arbitrary delays in the interaction functions, and also when generalised vector-type Michaelis-Menten functions are considered.

We conclude with some examples taken from the literature on systems biology and a discussion on the nature and the limitations of our results.

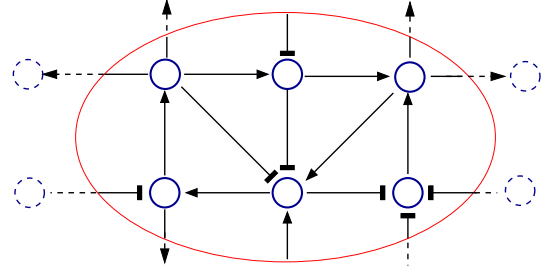


Figure 2. Portion of a generic interaction network with activating (pointed-arrow arcs) and inhibitory (hammer-headed arcs) interactions among the key players (nodes). Negative self-loops at each node, denoting self-inhibition of each species, are not visualised.

2 Model Description and Preliminaries

Consider a class of interaction networks of the form (1) with both inhibitory and activating interactions (Alon 2020; Del Vecchio and Murray 2014; Youseph et al. 2015):

$$\begin{aligned} \dot{x}_i(t) = & -\mu_i x_i(t) + \sum_{j \in R_i} \alpha_{ij} g(x_j(t); \beta_{ij}) \\ & + \sum_{k \in A_i} \gamma_{ik} f(x_k(t); \delta_{ik}) + u_i, \quad i = 1, \dots, n, \end{aligned} \quad (4)$$

where non-increasing (inhibitory) functions g and non-decreasing (activating) functions f have the Michaelis-Menten form:

$$g(x_j; \beta) := g(x_j; \beta, 1) = \frac{1}{1 + \frac{x_j}{\beta}}, \quad (5)$$

$$f(x_k; \delta) := f(x_k; \delta, 1) = \frac{\frac{x_k}{\delta}}{1 + \frac{x_k}{\delta}}, \quad (6)$$

while the term $-\mu_i x_i(t)$, $\mu_i > 0$, denotes self-inhibition of each species. The set R_i indexes all the species that inhibit species i (repressors of i) and the set A_i indexes all the species that activate species i (activators of i); we assume that $R_i \cap A_i = \emptyset$, $i \notin A_i$ and $i \notin R_i$.

The coefficients $\alpha_{ij} > 0$ and $\gamma_{ik} > 0$ quantify the interaction intensity, while $u_i \geq 0$ are constant external input flows.

We denote by $x(t)$ the vector whose components are $x_i(t)$, the state variables of the equations in (4), and by \bar{x} an equilibrium vector, with components \bar{x}_i .

The system in (4) can be associated with a graph, such as the one in Fig. 2, where:

- each node corresponds to a variable x_i ;
- each arc corresponds to an interaction, which can be either activating or inhibitory. An activating interaction is represented by a pointed-arrow arc, while an inhibitory interaction is represented by a hammer-headed arc. Although not explicitly drawn, self-inhibitions due to degradation terms are assumed to be always present for all variables.

Example 1 The system

$$\begin{aligned} \dot{m}_1(t) &= -\mu_1 m_1(t) + \frac{\alpha_{11}}{1 + \frac{p_1(t)}{\beta_{11}}} + \frac{\alpha_{1N}}{1 + \frac{p_N(t)}{\beta_{1N}}} + u_1, \\ \dot{m}_i(t) &= -\mu_i m_i(t) + \frac{\alpha_{ii}}{1 + \frac{p_i(t)}{\beta_{ii}}} + \frac{\gamma_{i,i-1} \frac{p_{i-1}(t)}{\delta_{i,i-1}}}{1 + \frac{p_{i-1}(t)}{\delta_{i,i-1}}}, \quad i = 2, \dots, N, \\ \dot{p}_j(t) &= -\mu_j p_j(t) + \frac{\gamma_{jj} \frac{m_j(t)}{\delta_{jj}}}{1 + \frac{m_j(t)}{\delta_{jj}}}, \quad j = 1, 2, \dots, N, \end{aligned}$$

can model a chain of N mRNA-protein subsystems, in which each protein activates the production of the next one, while the production of the first protein is negatively fed back by the concentration of the N th protein. The system is associated with the graph in Fig. 3, with $n = 2N$ nodes corresponding to the variables m_i and p_i , $i = 1, \dots, N$, and the presence of both activating and inhibitory arcs. How does a system of this type behave? We know that a long enough negative loop involving N mRNA-protein subsystems can yield an oscillatory behaviour. May the resulting oscillations drive the

system to instability? In principle, the situation could become even worse if also explicit delays were present (as they typically are) in the process. Surprisingly, we will show that this network admits a single stable equilibrium structurally (i.e., no matter how the parameter values are chosen) and regardless of the length N of the chain. This is no longer true if we replace Michaelis-Menten interactions with Hill interactions.

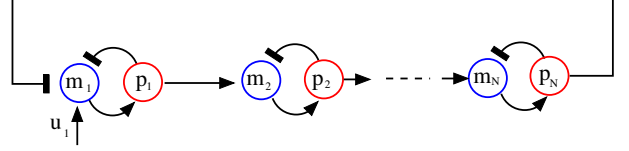


Figure 3. A chain of mRNA-protein subsystems: pointed-arrow arcs are activating, hammer-headed arcs are inhibitory.

We always assume nonnegative initial conditions $x(0) \geq 0$, componentwise, so that $x(t) \geq 0$ for all $t \geq 0$ (system (4) is positive: if $x_i = 0$, then $\dot{x}_i \geq 0$).

We introduce the following definitions.

Definition 1 (Strong-connectedness.) The networked system (4) is strongly connected if the associated graph is strongly connected, i.e., for each ordered pair of nodes (i, j) there exists an oriented path that starts from node i and reaches node j through activating or inhibitory arcs.

Definition 2 (Non-degeneracy.) The networked system (4) is non-degenerate if it includes at least one nonzero inhibiting function g , or if it includes at least one strictly positive external input $u_i > 0$. It is degenerate otherwise.

3 Structural Stability of Michaelis-Menten Networks

In this section, we show that a strongly connected networked system of the form (4) can admit exclusively equilibria that are strictly positive if and only if it is non-degenerate (Proposition 1); a degenerate networked system always admits the trivial equilibrium at zero. All positive equilibria are asymptotically stable (Proposition 2). In the non-degenerate case, the equilibrium is unique, hence the system is monostable (Proposition 3). In the degenerate case, if the equilibrium at zero is unstable, then there exists a unique positive stable equilibrium (Proposition 4).

We start by determining a closed hyper-rectangle that is positively invariant for the networked system in (4); this property ensures the existence of an equilibrium point.

Lemma 1 (Existence of an equilibrium.) The set

$$\mathcal{S} := \left\{ x: 0 \leq x_i \leq \hat{x}_i^+ := \frac{\sum_{j \in R_i} \alpha_{ij} + \sum_{k \in A_i} \gamma_{ik} + u_i}{\mu_i}, \quad \forall i \right\}$$

is positively invariant for the networked system (4), i.e., $x(t_0) \in \mathcal{S}$ implies $x(t) \in \mathcal{S}$ for $t \geq t_0$. Therefore, the system admits at least one equilibrium point.

Proof If x_i is at its lower bound, $x_i = 0$, then $\dot{x}_i \geq 0$. If x_i is at its upper bound, $x_i = \hat{x}_i^+$, then, since all Michaelis-Menten functions are bounded as $0 \leq g \leq 1$ and $0 \leq f \leq 1$, from (4) we have that

$$\dot{x}_i \leq -\mu_i \hat{x}_i^+ + \sum_{k \in \mathcal{R}_i} \alpha_{ij} + \sum_{k \in \mathcal{A}_k} \gamma_{ik} + u_i = 0. \quad (7)$$

Since the two inequalities are verified for all i , \mathcal{S} is positively invariant (Abate et al. 2009; Blanchini and Miani 2015).

Positive invariance of the compact set \mathcal{S} implies that \mathcal{S} includes an equilibrium point (Richeson and Wiseman 2002, 2004; Szrednicki 1985), thus ensuring existence of at least one equilibrium point. ■

Under strong connectedness assumptions, non-degeneracy of the system is equivalent to the fact that all its equilibria are strictly positive.

Proposition 1 (Strictly positive equilibria.) *Consider the networked system (4) and assume it is strongly connected. Then, all non-negative equilibria are strictly positive if and only if (4) is non-degenerate. Moreover, all non-negative equilibria necessarily lie in \mathcal{S} .*

Proof If the network is degenerate, $\bar{x}_i = 0 \forall i$ is an equilibrium, because $f(0; \delta_{ik}) = 0$. The zero equilibrium is in \mathcal{S} .

Conversely, if the network is non-degenerate, then there exists one node, say x_i , whose equation includes a positive input $u_i > 0$ or an inhibiting function $g(x_j; \beta_{ij}) > 0$. The guaranteed presence of a positive term at the equilibrium, which can be either $K_i = \alpha_{ij}g(\bar{x}_j; \beta_{ij})$ or $K_i = u_i$, implies that $\bar{x}_i > 0$, because

$$0 = -\mu_i \bar{x}_i + K_i + \text{non-negative terms} \geq -\mu_i \bar{x}_i + K_i,$$

hence $\bar{x}_i \geq K_i/\mu_i > 0$. Possibly rearranging the indices, let us label this node as node 1. Now, by contradiction, assume that the steady-state sign pattern is $\bar{x}_p > 0$ for $p = 1, \dots, k-1$ and $\bar{x}_q = 0$ for $q = k, \dots, n$, for some $k \in \{2, \dots, n\}$. Being the network strongly connected, one of the $k-1$ nodes in the former subset, say node h , with $h < k$, is connected to at least one of the nodes in the latter subset, say node ℓ , with $\ell \geq k$. Hence, there is an inhibitory steady-state interaction $\kappa = \alpha_{\ell h}g(\bar{x}_h; \beta_{\ell h}) > 0$ or an activating steady-state interaction $\kappa = \gamma_{\ell h}f(\bar{x}_h; \delta_{\ell h}) > 0$, and therefore

$$0 = -\mu_\ell \bar{x}_\ell + \kappa + \text{non-negative terms},$$

meaning that $\bar{x}_\ell > 0$, a contradiction. Hence, $\bar{x}_i > 0 \forall i$.

Finally, this positive equilibrium lies in \mathcal{S} , because, if we assume $x_i > \hat{x}_i^+$, then the strict inequality (7) holds and guarantees $\dot{x}_i < 0$; therefore, no equilibrium can exist out of \mathcal{S} , since the equilibrium condition requires $\dot{x}_i = 0$. ■

Before investigating uniqueness of the equilibrium, we prove that any positive equilibrium is stable.

To this aim, we introduce a normalisation with respect to the equilibrium value \bar{x}_i and replace all variables x_i by their normalised value $z_i := x_i/\bar{x}_i$. The equilibrium values in the new variables are $\bar{z}_i = 1$. This transformation just requires scaling all coefficients as $\bar{\alpha}_{ij} := \alpha_{ij}/\bar{x}_i$, $\bar{\beta}_{ij} := \beta_{ij}/\bar{x}_j$, $\bar{\gamma}_{ik} := \gamma_{ik}/\bar{x}_i$ and $\bar{\delta}_{ik} := \delta_{ik}/\bar{x}_k$, to have the same type of equations for $\frac{d}{dt}(x_i(t)/\bar{x}_i) = \dot{z}_i(t)$:

$$\begin{aligned} \dot{z}_i(t) = & -\mu_i z_i(t) + \sum_{j \in \mathcal{R}_i} \bar{\alpha}_{ij} g(z_j(t); \bar{\beta}_{ij}) \\ & + \sum_{k \in \mathcal{A}_i} \bar{\gamma}_{ik} f(z_k(t); \bar{\delta}_{ik}) + \bar{u}_i, \quad i = 1, \dots, n, \end{aligned} \quad (8)$$

where $\bar{u}_i := u_i/\bar{x}_i$. To keep the notation simple, we drop all the bars on the coefficients and we assume, without restriction, that the equilibrium point is $\bar{x} = [1 \ 1 \ \dots \ 1]^T =: \bar{x}_1$.

In order to prove our next result, we need to consider the derivatives of the functions g and f computed at \bar{x}_1 :

$$g'(1; \beta_{ij}) = -g(1; \beta_{ij}) \frac{1}{1 + \frac{1}{\beta_{ij}}}, \quad (9)$$

$$f'(1; \delta_{ik}) = f(1; \delta_{ik}) \frac{1}{1 + \frac{1}{\delta_{ik}}}. \quad (10)$$

The derivative computed at 1 is strictly less, in absolute value, than the function itself evaluated at 1. This noteworthy property allows us to prove the stability of all positive equilibria of the system, by showing that the corresponding Jacobian matrix is strictly row-diagonally dominant with negative diagonal entries, and hence it is Hurwitz.

Proposition 2 (Stability.) *Each positive equilibrium of the networked system (4) is locally asymptotically stable.*

Proof Considering the variable normalisation, the system Jacobian evaluated at the generic positive equilibrium is

$$J = \begin{bmatrix} -\mu_1 & a_{12} & \dots & a_{1n} \\ a_{21} & -\mu_2 & \dots & a_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1} & a_{n2} & \dots & -\mu_n \end{bmatrix},$$

where each term a_{ij} is equal to: zero, if species j has no effect on species i ; α_{ij} times the term (9), if species j is a

repressor of species i ; γ_j times a term of the form (10) with k replaced by j , if species j is an activator of species i .

Matrix J is row-diagonally dominant, namely,

$$\mu_i > \sum_{j \in \mathcal{R}_i} |a_{ij}| + \sum_{k \in \mathcal{A}_i} |a_{ik}|,$$

because, adopting expressions (9) and (10),

$$\begin{aligned} & -\mu_i + \sum_{j \in \mathcal{R}_i} |a_{ij}| + \sum_{k \in \mathcal{A}_i} |a_{ik}| \\ = & -\mu_i + \sum_{j \in \mathcal{R}_i} \alpha_{ij} g(1; \beta_{ij}) \frac{1}{1 + \frac{1}{\beta_{ij}}} + \sum_{k \in \mathcal{A}_i} \gamma_{ik} f(1; \delta_{ik}) \frac{1}{1 + \frac{1}{\delta_{ik}}} \\ < & -\mu_i + \sum_{j \in \mathcal{R}_i} \alpha_{ij} g(1; \beta_{ij}) + \sum_{k \in \mathcal{A}_i} \gamma_{ik} f(1; \delta_{ik}) + u_i = 0, \quad \forall i, \end{aligned}$$

where the inequality holds because the fractions are strictly less than 1, while the subsequent equality is the equilibrium condition computed at \bar{x}_i . Considering that any strictly diagonally dominant matrix with negative diagonal entries is Hurwitz, as it can be shown by directly applying the first Gershgorin circle theorem, concludes the proof. ■

Remark 1 (Structural Lyapunov function.) *Since the Jacobian is strictly row-diagonally dominant, as shown in the proof of Proposition 2, no matter how the system parameters are chosen, the system (4) structurally admits the polyhedral norm $V(x) = \|x\|_\infty$ as a local (but not global, as we discuss later, in Section 5.3) Lyapunov function (Blanchini and Miani 2015).*

We can now provide conditions to have a unique equilibrium.

Proposition 3 (Uniqueness of the equilibrium.) *If system (4) is strongly connected and non-degenerate, then it has a unique equilibrium, which is positive.*

Proof Proposition 1 guarantees that all (non-negative) equilibria are necessarily in the set \mathcal{S} and, in view of the non-degeneracy assumption, $\bar{x}_i > 0 \forall i$. On the other hand, in view of Proposition 2, all positive equilibria (in \mathcal{S}) are locally asymptotically stable. To show uniqueness, assume by contradiction that there are r equilibrium points, e_1, e_2, \dots, e_r . According to Brouwer's degree theory (Lloyd 1978; see also Hofbauer 1990, Theorem 2), we have that

$$\sum_{k=1}^r \text{sign det}[-J(e_k)] = 1, \quad (11)$$

where $J(e_k)$ is the Jacobian computed at the equilibrium e_k . Being $J(e_k)$ Hurwitz, $\text{det}[-J(e_k)] > 0$, hence $\text{sign det}[-J(e_k)] = 1$. Then, from (11), we conclude that it must be $r = 1$, and hence the equilibrium is unique. ■

Therefore, for a strongly-connected non-degenerate system of the form (4), we have monostability. The unique equilib-

rium in Proposition 3 is positive, in view of Proposition 1, and asymptotically stable, in view of Proposition 2.

When the network is degenerate, namely, there are no external inputs and all the interactions are activating, $\bar{x}_0 := [0 \ 0 \ \dots \ 0]^\top$ is an equilibrium point, as shown in the proof of Proposition 1. Relying on the theory of monotone systems (Hirsch and Smith 2006; Smith 1988; Sontag 2007), we can assess the stability properties of the zero equilibrium, as well as the existence and stability of other equilibria: the zero equilibrium is either attractive, and there are no other equilibria, or repulsive, and there is also one positive, and stable, equilibrium.

Proposition 4 (Degenerate systems.) *Consider a strongly connected and degenerate networked system (4) and its zero equilibrium \bar{x}_0 . The following mutually exclusive cases are the only possible ones:*

- \bar{x}_0 is the only equilibrium and is asymptotically stable;
- \bar{x}_0 is unstable and there exists a unique nontrivial equilibrium \bar{x} , which is strictly positive and locally asymptotically stable.

Proof In the absence of inhibitory interactions, the system is monotone: its Jacobian, computed at any point, is a Metzler matrix (i.e., it has non-negative off-diagonal entries). Assume that \bar{x}_0 is the only equilibrium; then, since the system solutions are bounded within a compact set (viz. set \mathcal{S} defined in Lemma 1) including \bar{x}_0 , it must be stable (Hirsch and Smith 2006; Sontag 2007). Conversely, if \bar{x}_0 is not the only equilibrium, then there exists another equilibrium \bar{x} with some non-zero components. Since the network is strongly connected, we can show that any nonzero equilibrium must have *all* nonzero components by reasoning as in the proof of Proposition 1. Therefore, \bar{x} is strictly positive, and hence it is locally asymptotically stable in view of Proposition 2. The equilibrium \bar{x} is also unique as a nontrivial equilibrium. Indeed, a second one would be again strictly positive and locally asymptotically stable, which would imply the existence of a third nontrivial and unstable equilibrium, between the two component-wise (Smith, 1988, Proposition 2.9, p. 98), which is impossible in view, again, of Proposition 2. For the same reason \bar{x}_0 is unstable. ■

All the presented results are *structural*, because they hold regardless of the values of the parameters $\mu, \alpha, \beta, \gamma, \delta$ in the system. They are also *topology-independent*, because they hold regardless of the topology and of the size (number of nodes/arcs) of the networked system.

Remark 2 (More general classes of functions.) *Can f and g in system (4) belong to more general classes of functions, not necessarily of the Michaelis-Menten type? It can be proven that our results still hold if we consider, for instance, activating functions such that $f'(x) \leq f(x)/x$ and inhibiting functions such that $-g'(x) \leq g(x)/x$. For example, these conditions are satisfied by functions (2)-(3) whenever $p \leq 1$,*

while they are not satisfied when $p > 1$ because, in this latter case, the functions have an inflection point, hence they are neither convex (when decreasing) nor concave (when increasing).

Remark 3 (The Hill case: A counterexample.) The considered functions f and g in system (4) are special cases of (2)-(3), with $p = 1$. This is a key aspect in our results. For functions (2)-(3) with $p > 1$, no structural stability result can be achieved in general. The simplest counterexample is provided by the second order system with $p = 2$

$$\dot{x}_1 = -x_1 + \frac{5}{1 + (2x_2)^2}, \quad \dot{x}_2 = -x_2 + \frac{5}{1 + (2x_1)^2},$$

having an unstable equilibrium at $[1 \ 1]^\top$: the Jacobian evaluated at this point,

$$J = \begin{bmatrix} -1 & -8/5 \\ -8/5 & -1 \end{bmatrix},$$

has a positive real eigenvalue. This system is bistable; it has three positive equilibria, two of which are stable: $[\bar{x}_H \ \bar{x}_L]^\top$ and $[\bar{x}_L \ \bar{x}_H]^\top$, where $\bar{x}_H \approx 4.9495$ and $\bar{x}_L \approx 0.0505$. Analogous counterexamples can be found with $p > 1$ and real.

Hence, in the absence of sharp thresholds ($p \leq 1$) stability is guaranteed regardless of the network topology and parameters, while in the presence of sharper thresholds ($p > 1$) stability does depend on the parameters in general and instability may well arise.

4 Extensions to More General Models

In this section we consider several generalisations of the model (4), for which our results still hold.

4.1 Michaelis-Menten networks with positive linear and mixed terms

A first generalisation of the model (4) includes, besides increasing and decreasing Michaelis-Menten functions, functions that are the ratio of two first-order polynomials:

$$\ell(x; \alpha, \gamma, \delta) := \frac{\alpha + \gamma x / \delta}{1 + x / \delta} = \frac{\alpha}{1 + x / \delta} + \frac{\gamma x / \delta}{1 + x / \delta}. \quad (12)$$

We can see function ℓ as a *mixed* Michaelis-Menten function, because it can be decomposed as the sum of a decreasing and an increasing Michaelis-Menten function: therefore, it is useful to capture situations when a system variable has two incoherent effects (one inhibitory, the other activating) on another variable. Considering *mixed* Michaelis-Menten functions amounts to assuming that the sets R_i and A_i in (4) are not disjoint. This generalisation does not alter the diagonal dominance of the system Jacobian, and hence all our results remain valid.

We can also consider a more general class of models that includes linear positive terms, as follows:

$$\begin{aligned} \dot{x}_i(t) = & -\mu_i x_i(t) + \sum_{j \in R_i} \alpha_{ij} g(x_j(t); \beta_{ij}) \\ & + \sum_{k \in A_i} \gamma_{ik} f(x_k(t); \delta_{ik}) + \sum_{h \in L_i} \phi_{ih} x_h + u_i, \end{aligned} \quad (13)$$

$i = 1, \dots, n$, where the set L_i ($i \notin L_i$) indexes all the species that linearly activate species i , with a coefficient $\phi_{ih} > 0$.

For this new model, we have no guarantee that an equilibrium exists. However, a structural condition for the boundedness of the solutions, and hence for the existence of an equilibrium, is that the graph formed by the nodes and the arcs associated with the linear positive terms has no cycles (Blanchini and Franco 2014). In general, to ensure the existence of an equilibrium, we need the next condition.

Proposition 5 (Existence of an equilibrium.) Write system (13) as

$$\dot{x} = \Phi x + N(x), \quad (14)$$

where Φx is the linear part and $N(x)$ includes all the non-linear terms. If the Metzler matrix Φ is Hurwitz, then system (13) has bounded solutions, and therefore it admits an equilibrium.

Proof The result follows immediately since $N(x)$ is a globally bounded term for $x \geq 0$.

The existence of an equilibrium can be concluded from boundedness of solutions in view of the results by Richeson and Wiseman (2002, 2004); Szrednicki (1985). ■

The condition of Φ being Hurwitz in Proposition 5 is “almost necessary” for stability: if the linear system is unstable (Φ is not Hurwitz), then the system trajectories diverge.

Proposition 6 (Uniqueness and stability of the equilibrium.) If system (14) is strongly connected and non-degenerate and Φ is Hurwitz, then there is a unique equilibrium, which is strictly positive and asymptotically stable.

Proof We first prove that any positive equilibrium is locally asymptotically stable. We normalise the variables so that the positive equilibrium has all components equal to 1. Therefore, at the equilibrium,

$$\begin{aligned} \mu_i &= \sum_{j \in R_i} \alpha_{ij} \underbrace{g(1; \beta_{ij})}_{\geq |g'|} + \sum_{k \in A_i} \gamma_{ik} \underbrace{f(1; \delta_{ik})}_{\geq |f'|} + \sum_{h \in L_i} \phi_{ih} + u_i \\ &\geq \sum_{j \in R_i} \alpha_{ij} |g'(1; \beta_{ij})| + \sum_{k \in A_i} \gamma_{ik} |f'(1; \delta_{ik})| + \sum_{h \in L_i} \phi_{ih} \\ &\geq \sum_{j \neq i} |a_{ij}|, \quad i = 1, \dots, n, \end{aligned}$$

where a_{ij} , $i \neq j$, denotes an off-diagonal entry of the Jacobian matrix at steady state, as in the proof of Proposition 2.

Hence, the Jacobian at the equilibrium is row-diagonally dominant, with negative diagonal entries, which ensures local asymptotic stability. The positivity and uniqueness of the equilibrium can be proven exactly as in the proofs of Proposition 1 and Proposition 3. ■

The degenerate case, also for system (13) in the presence of positive linear terms, can be dealt with along the same lines as in Proposition 4.

4.2 Michaelis-Menten networks with explicit delays

An important property of Michaelis-Menten networks is that structural stability can be ensured even in the presence of delays in the interactions, thus modifying system (4) as

$$\begin{aligned} \dot{x}_i(t) = & -\mu_i x_i(t) + \sum_{j \in \mathbb{R}_i} \alpha_{ij} g(x_j(t - \tau_{ij}); \beta_{ij}) \\ & + \sum_{k \in \mathbb{A}_i} \gamma_{ik} f(x_k(t - \tau_{ik}); \delta_{ik}) + u_i, \quad i = 1, \dots, n, \end{aligned} \quad (15)$$

where functions f and g are of the same type as in (4), but explicit delay times $\tau_{ij} > 0$ and $\tau_{ik} > 0$ are included.

Under strong-connectedness and non-degeneracy assumptions, it can be shown that the positive equilibrium, which is invariant with respect to the delay values, remains stable.

Indeed, the linearised system around the equilibrium is

$$\dot{y}_i(t) = -\mu_i y_i(t) + \sum_{j \neq i} a_{ij} y_j(t - \tau_{ij}), \quad i = 1, \dots, n, \quad (16)$$

where $y_i = x_i - \bar{x}_i$, and its characteristic equation reads

$$\det[sI - J(s)] = 0, \quad (17)$$

with

$$J(s) := \begin{bmatrix} -\mu_1 & a_{12}e^{-\tau_{12}s} & \dots & a_{1n}e^{-\tau_{1n}s} \\ a_{21}e^{-\tau_{21}s} & -\mu_2 & \dots & a_{2n}e^{-\tau_{2n}s} \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1}e^{-\tau_{n1}s} & a_{n2}e^{-\tau_{n2}s} & \dots & -\mu_n \end{bmatrix}. \quad (18)$$

The asymptotic stability of the linearised system (16) is ensured if all the roots of (17) have strictly negative real part (Hofbauer and So 2000). This is indeed the case, as we show next.

Proposition 7 (Stability with delays.) *The roots of (17) have strictly negative real part.*

Proof This is a special case of the results by Hofbauer and So (2000). We sketch the proof for the sake of completeness.

Let (17) be satisfied for $s = \lambda$ and let $y \in \mathbb{C}^n \setminus \{0\}$ be such that

$$sy = J(s)y. \quad (19)$$

By contradiction, assume that $\Re(\lambda) \geq 0$. This implies $|e^{-\tau_{ij}\lambda}| \leq 1$. Let y_i be the largest in modulus (necessarily nonzero) of all the components of y . Divide all terms of the i th equation in (19) by $y_i \neq 0$ to get the equivalent equation

$$(\lambda + \mu_i) = \sum_{j \neq i} a_{ij} \frac{y_j}{y_i} e^{-\tau_{ij}\lambda}.$$

Then,

$$\begin{aligned} |\lambda + \mu_i| &= \left| \sum_{j \neq i} a_{ij} \frac{y_j}{y_i} e^{-\tau_{ij}\lambda} \right| \leq \sum_{j \neq i} \left| a_{ij} \frac{y_j}{y_i} e^{-\tau_{ij}\lambda} \right| \\ &\leq \sum_{j \neq i} |a_{ij}| \left| \frac{y_j}{y_i} \right| |e^{-\tau_{ij}\lambda}| \leq \sum_{j \neq i} |a_{ij}| < \mu_i, \end{aligned}$$

which implies that the roots λ are in the interior of a circle centered in $-\mu_i$ with radius μ_i , contradicting $\Re(\lambda) \geq 0$. ■

It is worth emphasising that our results still hold if delays are introduced in the more general model (13), where also positive linear terms are included.

4.3 Generalised Michaelis-Menten functions

Our local stability results still hold true if we consider generalised Michaelis-Menten functions (Boccaletti and al. 2006; Gómez-Gardeñes et al. 2005a,b):

$$\begin{aligned} g(x_1, x_2, \dots; \beta_1, \beta_2, \dots) &:= \frac{1}{1 + \sum_j \frac{x_j}{\beta_j}}, \\ f(x_1, x_2, \dots; \delta_1, \delta_2, \dots) &:= \frac{\sum_k \frac{x_k}{\delta_k}}{1 + \sum_k \frac{x_k}{\delta_k}}. \end{aligned} \quad (20)$$

With this generalisation, the class of systems becomes

$$\dot{x}_i(t) = -\mu_i x_i(t) + \sum_{j \in \mathbb{R}_i} \alpha_{ij} G(w^{(j)}) + \sum_{k \in \mathbb{A}_i} \gamma_{ik} F(w^{(k)}) + u_i \quad (21)$$

where

$$G(w) = \frac{1}{1+w} \quad \text{and} \quad F(w) = \frac{w}{1+w},$$

and where we denote by $w^{(j)}$ the weighted sum of variables

$$w^{(j)} := \sum_{h=1}^n \theta_{jh} x_h.$$

The coefficients θ can be either $\theta_{jh} = 0$, or $\theta_{jh} = 1/\beta_{jh}$, or $\theta_{jh} = 1/\delta_{jh}$ where β_{jh} and δ_{jh} are the thresholds of suitable

Michaelis-Menten functions. We always assume $\theta_{ii} = 0$. The sets R_i and A_i change their original meaning and now index variables $w^{(j)}$ (and no longer individual species x_j).

Any positive equilibrium can be rescaled as $\bar{x}_1 = [1 \ 1 \ \dots \ 1]^\top$ without restriction, so as to get

$$\bar{w}^{(j)} = \sum_{h=1}^n \theta_{jh}$$

at the equilibrium. To prove the stability of the equilibrium, we show that the Jacobian is still diagonally dominant. The equilibrium condition is

$$0 = \dot{x}_i = -\mu_i + \sum_{j \in R_i} \alpha_{ij} G(\bar{w}^{(j)}) + \sum_{k \in A_i} \gamma_{ik} F(\bar{w}^{(k)}) + u_i.$$

Consider all nonzero partial derivatives of function G at the equilibrium, i.e.,

$$\begin{aligned} \left. \frac{\partial(\alpha_{ij} G(w^{(j)}))}{\partial x_m} \right|_{w^{(j)} = \bar{w}^{(j)}} &= \alpha_{ij} \left. \frac{\partial G(\sum_{h=1}^n \theta_{jh} x_h)}{\partial x_m} \right|_{x_h = \bar{x}_h} = \\ \alpha_{ij} \left. \frac{\partial \left(\frac{1}{1+w^{(j)}} \right)}{\partial w^{(j)}} \right|_{w^{(j)} = \bar{w}^{(j)}} &\theta_{jm} = -\frac{\alpha_{ij}}{(1 + \bar{w}^{(j)})^2} \theta_{jm}, \end{aligned}$$

and sum their absolute values (change their sign, since they are all negative):

$$\begin{aligned} \sum_{m=1}^n \frac{\alpha_{ij}}{(1 + \bar{w}^{(j)})^2} \theta_{jm} &= \alpha_{ij} G(\bar{w}^{(j)}) \sum_{m=1}^n \theta_{jm} G(\bar{w}^{(j)}) = \\ \alpha_{ij} G(\bar{w}^{(j)}) \sum_{m=1}^n \frac{\theta_{jm}}{1 + \sum_{m=1}^n \theta_{jm}} &= \alpha_{ij} G(\bar{w}^{(j)}) \frac{\sum_{m=1}^n \theta_{jm}}{1 + \sum_{m=1}^n \theta_{jm}} \\ &< \alpha_{ij} G(\bar{w}^{(j)}). \end{aligned}$$

Now consider all nonzero partial derivatives of function F at the equilibrium, i.e.,

$$\begin{aligned} \left. \frac{\partial(\gamma_{ik} F(w^{(k)}))}{\partial x_m} \right|_{w^{(k)} = \bar{w}^{(k)}} &= \gamma_{ik} \left. \frac{\partial F(\sum_{h=1}^n \theta_{kh} x_h)}{\partial x_m} \right|_{x_h = \bar{x}_h} = \\ \gamma_{ik} \left. \frac{\partial \left(\frac{w^{(k)}}{1+w^{(k)}} \right)}{\partial w^{(k)}} \right|_{w^{(k)} = \bar{w}^{(k)}} &\theta_{km} = +\frac{\gamma_{ik}}{(1 + \bar{w}^{(k)})^2} \theta_{km}, \end{aligned}$$

and sum their absolute values (take them as they are, since they are all positive):

$$\begin{aligned} \sum_{m=1}^n \frac{\gamma_{ik}}{(1 + \bar{w}^{(k)})^2} \theta_{km} &= \gamma_{ik} \frac{\sum_{m=1}^n \theta_{km}}{(1 + \bar{w}^{(k)})^2} = \gamma_{ik} \frac{\bar{w}^{(k)}}{(1 + \bar{w}^{(k)})^2} \\ &= \gamma_{ik} F(\bar{w}^{(k)}) \frac{1}{1 + \bar{w}^{(k)}} < \gamma_{ik} F(\bar{w}^{(k)}). \end{aligned}$$

Now consider the sum of the absolute values of all nonzero partial derivatives in the i th row:

$$\sum_{c=1, c \neq i}^n |a_{ic}| < \sum_{j \in R_i} \alpha_{ij} G(\bar{w}^{(j)}) + \sum_{k \in A_i} \gamma_{ik} F(\bar{w}^{(k)}) = \mu_i - u_i \leq \mu_i,$$

where the equality holds in view of the equilibrium condition, thus showing row-diagonal dominance. This ensures that all our results hold in this generalised case as well.

5 Examples and Discussion

In this section, we analyse some examples taken from the systems biology literature and then we discuss our results, their scope and their limitations.

5.1 Examples of biological systems

Example 2 (Delayed negative-feedback loop.) *The system*

$$\begin{aligned} \dot{x}_1(t) &= \frac{\alpha_{1n}}{1 + x_n/\beta_{1n}} - \mu_1 x_1(t) \\ \dot{x}_2(t) &= \phi_1 x_1(t) - \mu_2 x_2(t) \\ &\vdots \\ \dot{x}_n(t) &= \phi_{n-1} x_{n-1}(t - \tau) - \mu_n x_n(t) \end{aligned}$$

generalises the biological model of testosterone dynamics presented in Section 7.6, p. 246 by Murray (2002), for which $n = 3$. In the case $n = 3$, its stability has been proven by DasGupta et al. (2007); Enciso and Sontag (2004). The generalised model falls into the class we are considering: it is a strongly connected and non-degenerate Michaelis-Menten network that includes positive linear terms and delays. Hence we can confirm those stability results and extend their validity to any $n \geq 3$ (and any choice of the parameters). Indeed, the linear part of the system is triangular (lower bidiagonal) and is Hurwitz, as is required by Proposition 6. It is worth stressing that stability holds for any n as long as the term in the equation of x_1 is a Michaelis-Menten function (i.e., a first-order Hill function). When a higher order Hill function is adopted, persistent oscillations cannot be excluded.

Example 3 (Generalised repressilator.) *Consider the loop of N subsystems of the form*

$$\begin{aligned} \dot{x}_{i-1}(t) &= g_{i-1,i-2}(x_{i-2}(t)) - \mu_{i-1} x_{i-1}(t) \\ \dot{x}_i(t) &= \phi_{i,i-1} x_{i-1}(t) - \mu_i x_i(t), \quad i = 2, 4, \dots, 2N, \end{aligned}$$

where $i-2 := 2N$ when $i = 2$ and all functions $g_{i-1,i-2}$ are decreasing Hill functions: $g_{i-1,i-2}(x_{i-2}) = \frac{\alpha_{i-1,i-2}}{1 + (x_{i-2}/\beta_{i-1,i-2})^p}$. If the number N of subsystems is even, then we have a positive-feedback loop; while, if N is odd, we have a negative-feedback loop. For $N = 3$, the system corresponds

to the well-studied repressilator (Del Vecchio and Murray, 2014, Section 5.4), which is known to give rise to oscillations for suitable choices of the parameter values, when $p > 1$. However, as long as $p = 1$ (Michaelis-Menten case), our results rule out undamped oscillations and guarantee structural stability of the unique equilibrium, for all possible parameter values, even when delays are introduced, regardless of the number N of subsystems.

Example 4 (Network of mRNAs and proteins.) Consider the generic network formed by mRNA-protein production elements described by Chen and Aihara (2002):

$$\begin{aligned}\dot{m}(t) &= H(p(t - \tau_p)) - \Lambda m(t) \\ \dot{p}(t) &= K(m(t - \tau_m)) - \Sigma p(t),\end{aligned}$$

where the vectors $m = [m_1, \dots, m_N]$ and $p = [p_1, \dots, p_N]$ respectively stack mRNA and protein concentrations, the diagonal matrices Λ and Σ include the degradation rates respectively for mRNAs and proteins, while the vectors τ_m and τ_p include all the time delays for mRNAs and proteins respectively. The components of the vector function K are nonlinear activation terms $K_i(m_i) = \frac{(m_i/\delta_i)^{k_i}}{1+(m_i/\delta_i)^{k_i}}$ (the Jacobian of K is a diagonal matrix), since in the translation process each protein is assumed to be associated with a single mRNA, while mRNA transcription is typically regulated (activated or repressed) by multiple proteins and therefore the nonlinear components of the vector function H are the sum of Hill functions:

$$H_i(p) = \sum_j h_{ij}(p_j),$$

where h_{ij} is the inhibitory or activating regulation of the transcription of mRNA i due to protein j . Chen and Aihara (2002) perform a local stability analysis for this class of systems under suitable assumptions. Our results ensure that, as long as $k_i = 1$ for all i and all functions h_{ij} are Michaelis-Menten functions, the system enjoys structural topology-independent stability: it admits a unique equilibrium, which is positive and asymptotically stable, regardless of the parameter values and of the topology of the interaction network (as long as it is strongly connected and non-degenerate).

Example 5 (Aggregates of monotone subsystems.) So far, we have considered networked models where each node corresponds to a single variable of the system. However, in many cases, a node stands for a complex entity, which is a whole subsystem. An interesting case is that of a network that interconnects stable input-output monotone subsystems (Blanchini et al. 2015, 2018) of the form

$$\dot{z}^{(k)} = F^{(k)} z^{(k)} + G u^{(k)}, \quad y^{(k)} = H z^{(k)}, \quad (22)$$

where $F^{(k)}$ are Hurwitz Metzler matrices, while G and H are nonnegative input and output vector matrices. Assume that an arbitrary number of systems having this form are interconnected by inhibitory or activating interactions of the

Michaelis-Menten type:

$$u^{(k)} = \sum_{j \in R_i} \alpha_{ij} g(y^{(j)}(t); \beta_{ij}) + \sum_{k \in A_i} \gamma_{ik} f(y^{(k)}(t); \delta_{ik}), \quad (23)$$

depending on the outputs of the other subsystems. If the system is strongly connected and non-degenerate, we claim that the interconnections preserve stability (as long as they do not include positive linear terms), regardless of the network topology and of the values of the system parameters.

In fact, for the whole aggregated system, the linear part is Hurwitz, because it is associated with a block diagonal matrix including as diagonal blocks the submatrices $F^{(k)}$, which are Hurwitz by assumption. Then, Proposition 5 ensures the existence of an equilibrium. Under non-degeneracy assumptions, such an equilibrium is positive and stable, in view of Proposition 6 and the results of Section 4.3. Indeed, by substituting the output $y^{(k)}$, as in (22), into the expression (23), we get exactly the generalised Michaelis-Menten functions introduced in Section 4.3.

5.2 Michaelis-Menten self-degradation terms

Throughout the paper, we have assumed that the self-degradation terms have the linear form $-\mu x_i$. Can we replace them by Michaelis-Menten functions $-\mu \frac{x_i}{1+x_i/v}$?

First of all we notice that, in this case, an equilibrium may not exist in general. When a single positive equilibrium does exist, it may not be stable, unless the parameters v_i are large enough (and hence the Michaelis-Menten self-degradation term becomes sufficiently close to a linear self-degradation term). For instance, consider the negative-feedback loop

$$\dot{x}_i = -\frac{\mu x_i/v}{1+x_i/v} + \frac{\alpha}{1+x_{i-1}/\beta},$$

with $i = 1, 2, \dots, n$, n odd (where $i = 0$ means $i = n$), where we assume that all the coefficients have the same value in all the equations. This system admits a single equilibrium, which we may assume is $[1 \ 1 \ \dots \ 1]^T$. For $v > 0$ and small, such an equilibrium can be unstable. For instance, in the case $n = 3$, the system Jacobian is

$$J(\alpha, \beta, \mu, v) = \begin{bmatrix} -\frac{\mu v}{(1+v)^2} & 0 & -\frac{\alpha \beta}{(1+\beta)^2} \\ -\frac{\alpha \beta}{(1+\beta)^2} & -\frac{\mu v}{(1+v)^2} & 0 \\ 0 & -\frac{\alpha \beta}{(1+\beta)^2} & -\frac{\mu v}{(1+v)^2} \end{bmatrix}.$$

Take $\alpha = \beta = 1$, $v = 1/4$ and pick $\mu = 5/8$ to satisfy

$$\frac{\mu/v}{1+1/v} = \frac{\alpha}{1+1/\beta} = \frac{1}{2},$$

so that $[1 \ 1 \ 1]^T$ is an equilibrium. Then, the equilibrium

is unstable: the Jacobian has eigenvalues with positive real part.

5.3 Local versus global

Our results rely on the property that the system Jacobian is row-diagonally dominant at the equilibrium. A row-diagonally dominant *linear* system admits the ∞ -norm, $\|\cdot\|_\infty$, as a Lyapunov function (Willems 1976). Indeed, as observed in Remark 1, the ∞ -norm is a structural *local* Lyapunov function for the considered systems. Then a natural question is whether the ∞ -norm is also a *global* Lyapunov function (for any non-negative initial condition); unfortunately, this is not the case in general. For instance, for the planar system

$$\dot{x}_1 = -\mu x_1 + \frac{\alpha}{1 + \frac{x_2}{\beta}}, \quad \dot{x}_2 = -\mu x_2 + \frac{\alpha}{1 + \frac{x_1}{\beta}}, \quad (24)$$

with $\alpha = 1$, $\beta = 1/2$ and $\mu = 1/3$, Fig. 4 shows that the function $\|\cdot\|_\infty$ decreases only locally, close to the equilibrium $[1 \ 1]^T$, but not in the whole positive orthant.

Other classes of weighted p -norms or entropy functions could be adopted for the *linearised* system, as shown by Willems (1976), but it is unclear whether these can be used to prove *global* stability. Still, after intensive numerical experiments, convergence has always been globally satisfied with no exceptions. However, no proofs are available so far: global stability is an open problem. Interestingly, also the deficiency zero theorem guarantees the existence of a single positive *locally stable* equilibrium, and also in that case global stability is an open research question in general.

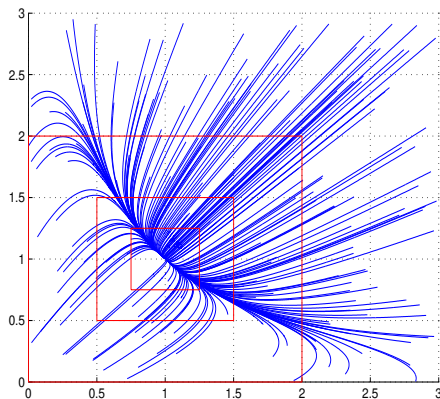


Figure 4. The norm $\|\cdot\|_\infty$ is not a global Lyapunov function for (24). The system trajectories are shown in blue and the level sets of the ∞ -norm, centred at the equilibrium $[1 \ 1]^T$, are shown in red.

6 Conclusions

We have shown that Michaelis-Menten networks, in which the interactions among nodes are governed by first-order Hill

functions, are topology-independent structurally stable under strong connectedness and non-degeneracy assumptions: they admit a single positive equilibrium, which is locally stable, regardless of parameter values and regardless of the network topology.

While our results are extremely general as far as the parameter values and the network topology are concerned, they are very specific as far as the Hill coefficient p is concerned, because it must be equal to 1: our results hold exclusively for networks with *Michaelis-Menten* interactions. Trivial counterexamples show that for $p > 1$, i.e., for generic Hill interactions of higher order, no structural result can be proven.

Future research directions, besides the investigation of global stability, concern stability conditions, in the presence of suitable assumptions on the topology and the parameters, for larger Hill coefficients p .

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