

Robust and Structural Ergodicity Analysis and Antithetic Integral Control of a Class of Stochastic Reaction Networks*

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Abstract

Controlling stochastic reactions networks is a challenging problem with important implications in various fields such as systems and synthetic biology. Various regulation motifs have been discovered or posited over the recent years, a very recent one being the so-called Antithetic Integral Control (AIC) motif [3]. Several appealing properties for the AIC motif have been demonstrated for classes of reaction networks that satisfy certain irreducibility, ergodicity and output controllability conditions. Here we address the problem of verifying these conditions for large sets of reaction networks with time-invariant topologies, either from a robust or a structural viewpoint, using three different approaches. The first one adopts a robust viewpoint and relies on the notion of interval matrices. The second one adopts a structural viewpoint and is based on sign properties of matrices. The last one is a direct approach where the parameter dependence is exactly taken into account and can be used to obtain both robust and structural conditions. The obtained results lie in the same spirit as those obtained in [3] where properties of reaction networks are independently characterized in terms of control theoretic concepts, linear programs, and graph-theoretic/algebraic conditions. Alternatively, those conditions can be cast as convex optimization problems that can be checked efficiently using modern optimization methods. Several examples are given for illustration.

Keywords. Cybergenetics; Antithetic Integral Control; Stochastic reaction networks; Robustness

*This paper is the combined version of the following conference papers [1, 2]. Some results are new and complete proofs are now given.

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1 Introduction

The main objective of synthetic biology is the rational and systematic design of biological networks that can achieve de-novo functions such as the heterologous production of a metabolite of interest [4]. Besides the obvious necessity of developing experimental methodologies allowing for the reliable implementation of synthetic networks, tailored theoretical and computational tools for their design, simulation, analysis and control also need to be developed. Indeed, theoretical tools that could predict certain properties (e.g. a stable/oscillatory/switching behavior, controllable trajectories, etc.) of a synthetic biological network from an associated model formulated, for instance, in terms of a reaction network [5–7], could pave the way to the development of reliable iterative procedures for the systematic design of efficient synthetic biological networks. Such an approach would allow for a faster design procedure than those involving fastidious experimental steps, and would give insights on how to adapt the current design in order to improve a certain design criterion. This way, synthetic biology would become conceptually much closer to existing theoretically-driven engineering disciplines, such as control engineering. However, while such methods are well-developed

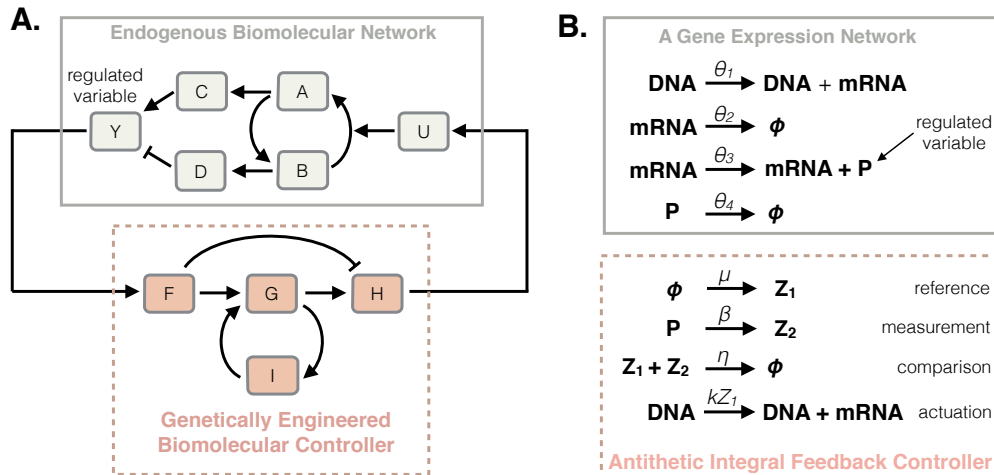


Figure 1: **A.** A synthetic feedback loop involving an endogenous network controlled with a synthetic feedback controller. **B.** A gene expression network (top) and an antithetic integral feedback controller (bottom) as examples of endogenous and synthetic networks.

for deterministic models (i.e. deterministic reaction networks), they still lag behind in the stochastic setting. This lack of tools is quite problematic since it is now well-known that stochastic reaction networks [7] are versatile modeling tools that can capture the inherent stochastic behavior of living cells [8,9] and can exhibit several interesting properties that are absent for their deterministic counterparts [3, 10–12]. Under the well-mixed assumption, it is known [13, 14] that such random dynamics can be well represented as a continuous-time jump Markov process evolving on the d -dimensional nonnegative integer lattice where d is

the number of distinct molecular species involved in the network. Sufficient conditions for checking the ergodicity of open unimolecular and bimolecular stochastic reaction networks has have been proposed in [15] and formulated in terms of linear programs. The concept of ergodicity is of fundamental importance as it can serve as a basis for the development of a control theory for biological systems. Indeed, verifying the ergodicity of a control system, consisting for instance of an endogenous biomolecular network controlled by a synthetic controller (see Fig. 1A), would prove that the closed-loop system is well-behaved (e.g. ergodic with bounded first- and second-order moments) and that the designed control system achieves its goal (e.g. set-point tracking and perfect adaptation properties). This procedure is analogous to that of checking the stability of a closed-loop system in the deterministic setting; see e.g. [16]. Additionally, designing synthetic circuits achieving a given function that are provably ergodic could allow for the rational design of synthetic networks that can exploit noise in their function. A recent example is that of the antithetic integral feedback controller proposed in [3] (see also Fig. 1B) that has been shown to induce an ergodic closed-loop network when some conditions on the endogenous network to be controlled are met; see also [17, 18].

A major limitation of the ergodicity conditions obtained in [3, 15, 19] is that they only apply to networks with fixed and known rate parameters – an assumption that is rarely met in practice as the rate parameters are usually poorly known and context dependent. This motivates the consideration of networks with uncertain rate parameters [1, 2]. Three approaches are discussed in this paper. The first one is quantitative and considers networks having an interval matrix [20] as characteristic matrix. We show that checking the ergodicity and the output controllability of the entire network class reduces to checking the Hurwitz stability of a single matrix and the output controllability of a single positive linear system. We also show that these conditions exactly write as a simple linear program having the same complexity as the program associated with the nominal case; i.e. in the case of constant and fixed rate parameters. The second approach is qualitative and is based on the theory of sign-matrices [21–24] which has been extensively studied and considered for the qualitative analysis of dynamical systems. Sign-matrices have also been considered in the context of reaction networks, albeit much more sporadically; see e.g. [1, 23, 25–28]. In this case, again, the conditions obtained in [1, 27] can be stated as a very simple linear program that can be shown to be equivalent to some graph theoretical conditions. A different approach relying on reaction network theory [5, 29] is also proposed in [30].

However, these approaches can be very conservative when the entries of the characteristic matrix of the network are not independent – a situation that appears when conversion reactions are involved in the networks or when reaction rates are functions of some hyper-parameters. In order to solve this problem, the actual parameter dependence needs to be exactly captured and many approaches exist to attack this problem such as, to cite a few, μ -analysis [31, 32], small-gain methods [32, 33], eigenvalue and perturbation methods [34, 35], Lyapunov methods [36–40], etc. Unfortunately, it is well-known that checking whether a general parameter-dependent matrix is Hurwitz stable for all the parameter values is NP-Hard. In this regard, it seems important to develop an approach that is tailored to our problem

by exploiting its inherent properties. By exploiting the structure of the problem at hand, several conditions for the robust ergodicity of unimolecular and biomolecular networks are first obtained in terms of a sign switching property for the determinant of the upper-bound of the characteristic matrix of the network. This condition also alternatively formulates as the existence of a positive vector depending polynomially on the uncertain parameters and satisfying certain inequality conditions. The complexity of the problem is notably reduced by exploiting the Metzler structure¹ of the matrices involved and through the use of various algebraic results such as the Perron-Frobenius theorem. The structural ergodicity of unimolecular networks is also considered and shown to reduce to the analysis of constant matrices when some certain realistic assumptions are met. It is notably shown in the examples that this latter result can be applied to bimolecular networks in some situations.

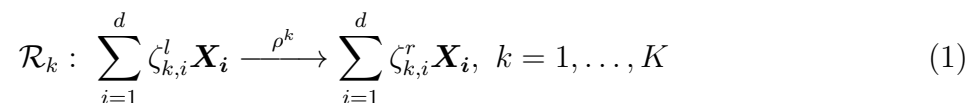
Outline. We recall in Section 2 several definitions and results related to reaction networks and antithetic integral control. Section 3 is concerned with the extension of the results in [3] to characteristic interval-matrices whereas Section 4 addresses the same problem using a parametric approach. Section 5 is concerned with the structural case where only the sign pattern of the characteristic matrix is known whereas Section 6 is devoted to the same problem using a parametric approach. Examples are treated in Section 7.

Notations. The standard basis for \mathbb{R}^d is denoted by $\{e_i\}_{i=1}^d$. The sets of integers, non-negative integers, nonnegative real numbers and positive real numbers are denoted by \mathbb{Z} , $\mathbb{Z}_{\geq 0}$, $\mathbb{R}_{\geq 0}$ and $\mathbb{R}_{> 0}$, respectively. The d -dimensional vector of ones is denoted by $\mathbf{1}_d$ (the index will be dropped when the dimension is obvious). For vectors and matrices, the inequality signs \leq and $<$ act componentwise. Finally, the vector or matrix obtained by stacking the elements x_1, \dots, x_d is denoted by $\text{col}_{i=1}^d(x_i)$ or $\text{col}(x_1, \dots, x_d)$. The diagonal operator $\text{diag}(\cdot)$ is defined analogously. The spectral radius of a matrix $M \in \mathbb{R}^{n \times n}$ is defined as $\rho(M) = \max\{|\lambda| : \det(\lambda I - M) = 0\}$.

2 Preliminaries

2.1 Reaction networks

We consider here a reaction network with d molecular species $\mathbf{X}_1, \dots, \mathbf{X}_d$ that interacts through K reaction channels $\mathcal{R}_1, \dots, \mathcal{R}_K$ defined as



where $\rho^k \in \mathbb{R}_{> 0}$ is the reaction rate parameter and $\zeta_{k,i}^l, \zeta_{k,i}^r \in \mathbb{Z}_{\geq 0}$. Each reaction is additionally described by a stoichiometric vector and a propensity function. The stoichiometric vector of reaction \mathcal{R}_k is given by $\zeta_k := \zeta_k^r - \zeta_k^l \in \mathbb{Z}^d$ where $\zeta_k^r = \text{col}(\zeta_{k,1}^r, \dots, \zeta_{k,d}^r)$ and $\zeta_k^l = \text{col}(\zeta_{k,1}^l, \dots, \zeta_{k,d}^l)$. In this regard, when the reaction \mathcal{R}_k fires, the state jumps from x to $x + \zeta_k$. We define the stoichiometry matrix $S \in \mathbb{Z}^{d \times K}$ as $S := [\zeta_1 \dots \zeta_K]$. When the kinetics

¹A Metzler matrix is a square matrix with nonnegative off-diagonal elements.

is mass-action, the propensity function of reaction \mathcal{R}_k is given by $\lambda_k(x) = \rho^k \prod_{i=1}^d \frac{x_i!}{(x_i - \zeta_{k,i})!}$ and is such that $\lambda_k(x) = 0$ if $x \in \mathbb{Z}_{\geq 0}^d$ and $x + \zeta_k \notin \mathbb{Z}_{\geq 0}^d$. We denote this reaction network by $(\mathbf{X}, \mathcal{R})$. Under the well-mixed assumption, this network can be described by a continuous-time Markov process $(X_1(t), \dots, X_d(t))_{t \geq 0}$ with state-space $\mathbb{Z}_{\geq 0}^d$; see e.g. [13].

2.2 Ergodicity of unimolecular and bimolecular reaction networks

Let us assume here that the network $(\mathbf{X}, \mathcal{R})$ is at most bimolecular and that the reaction rates are all independent of each other. In such a case, the propensity functions are polynomials of at most degree 2 and we can write the propensity vector as

$$\lambda(x) = \begin{bmatrix} w_0(\rho_0) \\ W(\rho_u)x \\ Y(\rho_b, x) \end{bmatrix} \quad (2)$$

where $w_0(\rho_0) \in \mathbb{R}_{\geq 0}^{n_0}$, $W(\rho_u)x \in \mathbb{R}_{\geq 0}^{n_u}$ and $Y(\rho_b, x) \in \mathbb{R}_{\geq 0}^{n_b}$ are the propensity vectors associated the zeroth-, first- and second-order reactions, respectively. Their respective rate parameters are also given by ρ_0 , ρ_u and ρ_b , and according to this structure, the stoichiometric matrix is decomposed as $S =: [S_0 \ S_u \ S_b]$. Before stating the main results of the section, we need to introduce the following terminology:

Definition 1 *The characteristic matrix $A(\rho_u)$ and the offset vector $b_0(\rho)$ of a bimolecular reaction network $(\mathbf{X}, \mathcal{R})$ are defined as*

$$A(\rho_u) := S_u W(\rho_u) \text{ and } b_0(\rho_0) := S_0 w_0(\rho_0). \quad (3)$$

A particularity is that the matrix $A(\rho_u)$ is Metzler (i.e. all the off-diagonal elements are nonnegative) for all $\rho_u \geq 0$. This property plays an essential role in the derivation of the results of [3] and will also be essential for the derivation of the main results of this paper. It is also important to define the property of ergodicity:

Definition 2 *The Markov process associated with the reaction network $(\mathbf{X}, \mathcal{R})$ is said to be ergodic if its probability distribution globally converges to unique stationary distribution. It is exponentially ergodic if the convergence to the stationary distribution is exponential.*

We then have the following result:

Theorem 3 ([15]) *Let us consider an irreducible² bimolecular reaction network $(\mathbf{X}, \mathcal{R})$ with fixed rate parameters; i.e. $A = A(\rho_u)$ and $b_0 = b_0(\rho_0)$. Assume that there exists a vector $v \in \mathbb{R}_{> 0}^d$ such that $v^T S_b = 0$ and $v^T A < 0$. Then, the reaction network $(\mathbf{X}, \mathcal{R})$ is exponentially ergodic and all the moments are bounded and converging.*

We also have the following immediate corollary pertaining on unimolecular reaction networks:

²Computationally tractable conditions for checking the irreducibility of reaction networks are provided in [41].

Corollary 4 *Let us consider an irreducible unimolecular reaction network $(\mathbf{X}, \mathcal{R})$ with fixed rate parameters; i.e. $A = A(\rho_u)$ and $b_0 = b_0(\rho_0)$. Assume that there exists a vector $v \in \mathbb{R}_{>0}^d$ such that $v^T A < 0$. Then, the reaction network $(\mathbf{X}, \mathcal{R})$ is exponentially ergodic and all the moments are bounded and converging.*

2.3 Antithetic integral control of unimolecular networks

Antithetic integral control has been first proposed in [3] for solving the perfect adaptation problem in stochastic reaction networks. The underlying idea is to augment the open-loop network $(\mathbf{X}, \mathcal{R})$ with an additional set of species and reactions (the controller). The usual set-up is that this controller network acts on the production rate of the molecular species \mathbf{X}_1 (the *actuated species*) in order to steer the mean value of the *controlled species* \mathbf{X}_ℓ , $\ell \in \{1, \dots, d\}$, to a desired set-point (the reference). To the regulation problem, it is often sought to have a controller that can ensure perfect adaptation for the controlled species. As proved in [3], the antithetic integral control motif $(\mathbf{Z}, \mathcal{R}^c)$ defined with



solves this control problem with the set-point being equal to μ/θ . Above, \mathbf{Z}_1 and \mathbf{Z}_2 are the *controller species*. The four controller parameters $\mu, \theta, \eta, k > 0$ are assumed to be freely assignable to any desired value. The first reaction is the *reference reaction* as it encodes part of the reference value μ/θ as its own rate. The second one is the *measurement reaction* that produces the species \mathbf{Z}_2 at a rate proportional to the current population of the controlled species \mathbf{X}_ℓ . The third reaction is the *comparison reaction* as it compares the populations of the controller species and annihilates one molecule of each when these populations are both positive. Finally, the fourth reaction is the *actuation reaction* that produces the actuated species \mathbf{X}_1 at a rate proportional to the controller species \mathbf{Z}_1 .

The following fundamental result states conditions under which a unimolecular reaction network can be controlled using an antithetic integral controller:

Theorem 5 ([3]) *Suppose that the open-loop reaction network $(\mathbf{X}, \mathcal{R})$ is unimolecular and that the state-space of the closed-loop reaction network $((\mathbf{X}, \mathbf{Z}), \mathcal{R} \cup \mathcal{R}^c)$ is irreducible. Let us assume that ρ_0 and ρ_u are fixed and known (i.e. $A = A(\rho_u)$ and $b_0 = b_0(\rho_0)$) and assume, further, that there exist vectors $v \in \mathbb{R}_{>0}^d$, $w \in \mathbb{R}_{\geq 0}^d$, $w_1 > 0$, such that*

$$v^T A < 0, w^T A + e_\ell^T = 0 \text{ and } \frac{\mu}{\theta} > \frac{v^T b_0}{c e_\ell^T v} \quad (5)$$

where $c > 0$ verifies $v^T(A + cI) \leq 0$.

Then, for any values for the controller rate parameters $\eta, k > 0$, (i) the closed-loop network is ergodic, (ii) $\mathbb{E}[X_\ell(t)] \rightarrow \mu/\theta$ as $t \rightarrow \infty$ and (iii) $\mathbb{E}[X(t)X(t)^T]$ is bounded over time.

We can see that the conditions above consist of the combination of an ergodicity condition ($v^T A < 0$) and an output controllability condition for Hurwitz stable matrices A ($w^T A + e_\ell^T =$

0 with $w_1 > 0$), which are fully consistent with the considered control problem. Note, however, that unlike in the deterministic case, the above result proves that the closed-loop network cannot be unstable; i.e. have trajectories that grow unboundedly with time. This is illustrated in more details in the supplemental material of [3].

We will also need the following result on the output controllability of linear SISO positive systems:

Lemma 6 ([3]) *Let $M \in \mathbb{R}^{d \times d}$ be a Metzler matrix. Then, the following statements are equivalent:*

(a) *The linear system*

$$\begin{aligned} \dot{x}(t) &= Mx(t) + e_i u(t) \\ y(t) &= e_j^T x(t) \end{aligned} \quad (6)$$

is output controllable.

(b) $\text{rank} [e_j^T e_i \quad e_j^T M e_i \quad \dots \quad e_j^T M^{d-1} e_i] = 1$.

(c) *There is a path from node i to node j in the directed graph $\mathcal{G}_M = (\mathcal{V}, \mathcal{E})$ defined with $\mathcal{V} := \{1, \dots, d\}$ and*

$$\mathcal{E} := \{(m, n) : e_n^T M e_m \neq 0, m, n \in \mathcal{V}, m \neq n\}. \Delta$$

Moreover, when the matrix M is Hurwitz stable, then the above statements are also equivalent to:

(e) *The inequality $e_j^T M^{-1} e_i \neq 0$ holds or, equivalently, the static-gain of the system (6) is nonzero.* Δ

Before stating the main result, it is convenient to define here the following properties:

- P1.** the closed-loop reaction network $((\mathbf{X}, \mathbf{Z}), \mathcal{R} \cup \mathcal{R}^c)$ is ergodic,
- P2.** the mean of the controlled species satisfies $\mathbb{E}[X_\ell(t)] \rightarrow \mu/\theta$ as $t \rightarrow \infty$,
- P3.** the second-order moment matrix $\mathbb{E}[X(t)X(t)^T]$ is uniformly bounded and globally converges to its unique stationary value.

We are now ready to state the main result of [3] on unimolecular networks:

Theorem 7 ([3]) *Assume that the open-loop reaction network $(\mathbf{X}, \mathcal{R})$ is unimolecular and that the state-space of the closed-loop reaction network $((\mathbf{X}, \mathbf{Z}), \mathcal{R} \cup \mathcal{R}^c)$ is irreducible. Let us also assume that the vector of reaction rates ρ is fixed and equal to some nominal value ρ_0^0 and ρ_u^0 for the zeroth- and first-order reactions, respectively. In this regard, we set $A = A(\rho_u^0)$ and $b_0 = b_0(\rho_0^0)$. Then, the following statements are equivalent:*

(a) There exist vectors $v \in \mathbb{R}_{>0}^d$, $w \in \mathbb{R}_{\geq 0}^d$, $w_1 > 0$, such that $v^T A < 0$ and $w^T A + e_\ell^T = 0$.

(b) The positive linear system describing the dynamics of the first-order moments given by

$$\begin{aligned} \frac{d\mathbb{E}[X(t)]}{dt} &= A\mathbb{E}[X(t)] + e_1 u(t) + b_0(\rho_0) \\ y(t) &= e_\ell^T \mathbb{E}[X(t)] \end{aligned} \quad (7)$$

is asymptotically stable and output controllable; i.e. the characteristic matrix A of the network $(\mathbf{X}, \mathcal{R})$ is Hurwitz stable and

$$\text{rank} [e_\ell^T e_1 \quad e_\ell^T A e_1 \quad \dots \quad e_\ell^T A^{d-1} e_1] = 1. \quad (8)$$

Moreover, when one of the above statements holds, then for any values for the controller rate parameters $\eta, k > 0$, the properties **P1.**, **P2.** and **P3.** hold provided that

$$\frac{\mu}{\theta} > \frac{v^T b_0}{c e_\ell^T v} \quad (9)$$

where $c > 0$ and $v \in \mathbb{R}_{>0}^d$ verify $v^T (A + cI) \leq 0$. △

Interestingly, the conditions stated in the above result can be numerically verified by checking the feasibility of the following linear program

$$\begin{aligned} \text{Find} \quad & v \in \mathbb{R}_{>0}^d, \quad w \in \mathbb{R}_{\geq 0}^d \\ \text{s.t.} \quad & w^T e_1 > 0 \\ & v^T A < 0 \\ & w^T A + e_\ell^T = 0 \end{aligned} \quad (10)$$

which involves $2d$ variables, $3d$ inequality constraints and d equality constraints.

3 Robust ergodicity of reaction networks - Interval matrices

3.1 Preliminaries

The results obtained in the previous section apply when the characteristic matrix $A = A(\rho_u^0)$ is fixed as the linear programming problem (10) can only be solved for that characteristic matrix. The goal is to generalize these results to the case where the characteristic matrix $A(\rho)$ and the offset vector $b_0(\rho)$ are uncertain and belong to the sets

$$\mathcal{A} := \{M \in \mathbb{R}^{d \times d} : A^- \leq M \leq A^+\}, \quad A^- \leq A^+, \quad (11)$$

and

$$\mathcal{B} := \{b \in \mathbb{R}_{\geq 0}^d : b_0^- \leq b \leq b_0^+\}, \quad 0 \leq b_0^- \leq b_0^+, \quad (12)$$

where the inequality signs are componentwise and the extremal Metzler matrices A^+, A^- and vectors b_0^-, b_0^+ are known. These bounds can be determined such that the inequalities

$$A^- \leq A(\rho_u) \leq A^+ \text{ and } b_0^- \leq b_0(\rho_0) \leq b_0^+ \quad (13)$$

hold for all $\rho_0 \in \mathcal{P}_0 \subset \mathbb{R}_{>0}^{n_0}$ and $\rho_u \in \mathcal{P}_u \subset \mathbb{R}_{>0}^{n_u}$ where \mathcal{P}_0 and \mathcal{P}_u are compact sets containing all the possible values for the rate parameters. We have the following preliminary result:

Lemma 8 *The following statements are equivalent:*

(a) *All the matrices in \mathcal{A} are Hurwitz stable;*

(b) *The matrix A^+ is Hurwitz stable.* △

Proof : The proof that (a) implies (b) is immediate. The converse can be proved using the fact that for two Metzler matrices $M_1, M_2 \in \mathbb{R}^{d \times d}$ verifying the inequality $M_1 \leq M_2$, we have that $\lambda_F(M_1) \leq \lambda_F(M_2)$ where $\lambda_F(\cdot)$ denotes the Frobenius eigenvalue (see e.g. [42]). Hence, we have that $\lambda_F(M) \leq \lambda_F(A^+) < 0$ for all $M \in \mathcal{A}$. The conclusion then readily follows. \diamond

3.2 Main result

We are now in position to state the following generalization of Theorem 7:

Theorem 9 *Let us consider a unimolecular reaction network $(\mathbf{X}, \mathcal{R})$ with characteristic matrix A in \mathcal{A} and offset vector b_0 in \mathcal{B} . Assume also that the state-space of the closed-loop reaction network $((\mathbf{X}, \mathbf{Z}), \mathcal{R} \cup \mathcal{R}^c)$ is irreducible. Then, the following statements are equivalent:*

(a) *All the matrices in \mathcal{A} are Hurwitz stable and for all $A \in \mathcal{A}$, there exists a vector $w \in \mathbb{R}_{\geq 0}^d$ such that $w_1 > 0$ and $w^T A + e_\ell^T = 0$.*

(b) *There exist two vectors $v_+ \in \mathbb{R}_{>0}^d$, $w_- \in \mathbb{R}_{\geq 0}^d$ such that $v_+^T A^+ < 0$, $w_-^T e_1 > 0$ and $w_-^T A^- + e_\ell^T = 0$.*

*Moreover, when one of the above statements holds, then for any values for the controller rate parameters $\eta, k > 0$ and any $(A, b_0) \in \mathcal{A} \times \mathcal{B}$, the properties **P1.**, **P2.** and **P3.** hold provided that*

$$\frac{\mu}{\theta} > \frac{q^T (A^+ - \Delta)^{-1} b^+}{c q^T (A^+ - \Delta)^{-1} e_\ell} \quad (14)$$

and

$$q^T (c(A^+ - \Delta)^{-1} + I_d) \geq 0 \quad (15)$$

for some $c > 0$, $q \in \mathbb{R}_{>0}^d$ and for all $\Delta \in [0, A^+ - A^-]$. △

Proof : The proof that (a) implies (b) is immediate. So let us focus on the reverse implication. Define, with some slight abuse of notation, the matrix $A(\Delta) := A^+ - \Delta$, $\Delta \in \mathbf{\Delta}^+ := [0, A^+ - A^-]$, where the set membership symbol is componentwise. The Hurwitz-stability of all the matrices in \mathcal{A} directly follows for the theory of linear positive systems and Lemma 8. We need now to construct a suitable positive vector $v(\Delta) \in \mathbb{R}_{>0}^d$ such that $v(\Delta)^T A(\Delta) < 0$ for all $\Delta \in \mathbf{\Delta}^+$ provided that $v_+^T A^+ < 0$. We prove now that such a $v(\Delta)$ is given by $v(\Delta) = (I_d + \Delta(A^+ - \Delta)^{-1})^T v_+$. Since $A(\Delta) = A^+ - \Delta$, then we immediately get that $v(\Delta)^T A(\Delta) = v_+^T A^+ < 0$. Hence, it remains to prove the positivity of the vector $v(\Delta)$ for all $\Delta \in \mathbf{\Delta}^+$. The difficulty here is that the product $\Delta(A^+ - \Delta)^{-1}$ is a nonnegative matrix since $\Delta \geq 0$ and $(A^+ - \Delta)^{-1} \leq 0$, the latter being the consequence of the fact that $A^+ - \Delta$ is Metzler and Hurwitz stable (see e.g. [42]). Therefore, there may exist values for $v_+ \in \mathbb{R}_{>0}^d$ for which we have $v(\Delta) \not\geq 0$. To rule out this possibility, we restrict the analysis to all those $v_+ \in \mathbb{R}_{>0}^d$ for which we have $v_+^T A^+ < 0$. We can parameterize all these v_+ as $v_+(q) = -(A^+)^{-T} q$ where $q \in \mathbb{R}_{>0}^d$ is arbitrary. We prove now that the vector $v(\Delta) = -(I_d + \Delta(A^+ - \Delta)^{-1})^T (A^+)^{-T} q > 0$ is positive for all $q \in \mathbb{R}_{>0}^d$ and for all $\Delta \in \mathbf{\Delta}^+$. This is done by showing below that the matrix $\mathcal{M} := -(I_d + \Delta(A^+ - \Delta)^{-1})^T (A^+)^{-T}$ is nonnegative and invertible. Indeed, we have that

$$\begin{aligned} \mathcal{M} &= -(I_d + \Delta(A^+ - \Delta)^{-1})^T (A^+)^{-T} \\ &= -((A^+)^{-1} + (A^+)^{-T} \Delta (A^+ - \Delta)^{-1})^T \\ &= -((A^+)^{-1} + (A^+)^{-T} \Delta (I_d - (A^+)^{-1} \Delta)^{-1} A^+)^T \\ &= -(A^+ - \Delta)^{-T} \end{aligned} \tag{16}$$

where the latter expression follows from the Woodbury matrix identity. Since $(A^+ - \Delta) = A(\Delta)$ is Metzler and Hurwitz stable for all $\Delta \in \mathbf{\Delta}^+$, then $A^+ - \Delta$ is invertible and we have $-(A^+ - \Delta)^{-1} \geq 0$, which proves the result.

Let us now consider then the output controllability condition and define $A(\Delta)$ as $A(\Delta) := A^- + \Delta$ where $\Delta \in \mathbf{\Delta}^- := [0, A^+ - A^-]$. We use a similar approach as previously and we build a $w(\Delta)$ that verifies the expression $w(\Delta)^T A(\Delta) + e_\ell^T = 0$ for all $\Delta \in \mathbf{\Delta}^-$ provided that $w_-^T A^- + e_\ell^T = 0$. We prove that such a $w(\Delta)$ is given by $w(\Delta) := (A^- (A^- + \Delta)^{-1})^T w_-$. We first prove that this $w(\Delta)$ is nonnegative and that it verifies $e_1^T w(\Delta) > 0$ for all $\Delta \in \mathbf{\Delta}^-$. To show this, we rewrite this $w(\Delta)$ as $w(\Delta) = (I_d - \Delta(A^- + \Delta)^{-1})^T w_-$ and using the fact that $(A^- + \Delta)^{-1} \leq 0$ since $(A^- + \Delta)$ is a Hurwitz stable Metzler matrix for all $\Delta \in \mathbf{\Delta}^-$, then we can conclude that $w(\Delta) \geq w_- \geq 0$ for all $\Delta \in \mathbf{\Delta}^-$. An immediate consequence is that $w(\Delta)^T e_1 \geq w_-^T e_1 > 0$ for all $\Delta \in \mathbf{\Delta}^-$. This proves the first part. We now show that this $w(\Delta)$ verifies the output controllability condition. Evaluating then $w(\Delta)^T (A^- + \Delta)$ yields

$$\begin{aligned} w(\Delta)^T (A^- + \Delta) &= w_-^T (A^- (A^- + \Delta)^{-1}) (A^- + \Delta) \\ &= w_-^T A^- \\ &= -e_\ell^T \end{aligned} \tag{17}$$

where the last row has been obtained from the assumption that $w_-^T A^- + e_\ell^T = 0$. This proves the second part. Finally, the condition (14) is obtained by substituting the expression for

$v(\Delta)$ defined above in (9). This completes the proof. \diamond

As in the nominal case, the above result can be exactly formulated as the linear program

$$\begin{aligned} \text{Find} \quad & v \in \mathbb{R}_{>0}^d, \quad w \in \mathbb{R}_{\geq 0}^d \\ \text{s.t.} \quad & w^T e_1 > 0 \\ & v^T A^+ < 0 \\ & w^T A^- + e_\ell^T = 0 \end{aligned} \tag{18}$$

which has exactly the same complexity as the linear program (10). Hence, checking the possibility of controlling a family of networks defined by a characteristic interval-matrix is not more complicated than checking the possibility of controlling a single network.

3.3 A robust ergodicity result for bimolecular networks

We now provide an extension of the conditions of Theorem 3 for bimolecular networks to the case of uncertain networks described by uncertain matrices:

Proposition 10 *Let us consider the reaction network $(\mathbf{X}, \mathcal{R})$ and assume it is mass-action with at most reaction of order two. Assume further that the state-space of the underlying Markov process is irreducible and that there exists a vector $v \in \mathbb{R}_{>0}^d$ such that*

$$v^T A^+ < 0 \text{ and } v^T S_b = 0. \tag{19}$$

Then, the stochastic reaction network $(\mathbf{X}, \mathcal{R})$ is robustly exponentially ergodic for all $A \in [A^-, A^+]$.

Proof : The result immediately follows from Theorem 3 and Theorem 9. \diamond
Once again, the conditions can be efficiently checked by solving a linear program.

4 Robust ergodicity of reaction networks - Parametric approach

The approach based on interval matrices has the advantage of being very simple at the expense of some potentially high conservatism when the upper-bound A^+ is not tight. This is the case when conversion reactions are involved. This may also be the case when some entries in the characteristic matrix are not independent; e.g. reaction rates are functions of some hyper-parameters. In this regard, the ergodicity test based on interval matrices may fail even if the characteristic matrix is Hurwitz stable for all possible values for the reaction rates. This motivates the consideration of a parametric approach tackling the problem in its primal form. Note that since the output observability test based on interval matrices is non-conservative, we only address here the problem of accurately checking the Hurwitz stability of the characteristic matrix for all admissible values for the reaction rates.

4.1 Preliminaries

The following lemma will be useful in proving the main results of this section:

Lemma 11 *Let us consider a matrix $M(\theta) \in \mathbb{R}^{d \times d}$ which is Metzler and bounded for all $\theta \in \Theta \subset \mathbb{R}_{\geq 0}^N$ and where Θ is assumed to be compact and connected. Then, the following statements are equivalent:*

- (a) *The matrix $M(\theta)$ is Hurwitz stable for all $\theta \in \Theta$.*
- (b) *The coefficients of the characteristic polynomial of $M(\theta)$ are positive Θ .*
- (c) *The conditions hold:*
 - (c1) *there exists a $\theta^* \in \Theta$ such that $M(\theta^*)$ is Hurwitz stable, and*
 - (c2) *for all $\theta \in \Theta$ we have that $(-1)^d \det(M(\theta)) > 0$.*

Proof: The proof of the equivalence between (a) and (b) follows, for instance, from [43] and is omitted. It is also immediate to prove that (b) implies (c) since if $M(\theta)$ is Hurwitz stable for all $\theta \in \Theta$ then (c1) holds and the constant term of the characteristic polynomial of $M(\theta)$ is positive on $\theta \in \Theta$. Using now the fact that that constant term is equal to $(-1)^d \det(M(\theta))$ yields the result.

To prove that (c) implies (a), we use the contraposition. Hence, let us assume that there exists at least a $\theta_u \in \Theta$ for which the matrix $M(\theta_u)$ is not Hurwitz stable. If such a θ_u can be arbitrarily chosen in Θ , then this implies the negation of statement (c1) (i.e. for all $\theta^* \in \Theta$ the matrix $M(\theta^*)$ is not Hurwitz stable) and the first part of the implication is proved.

Let us consider now the case where there exists some $\theta_s \in \Theta$ such that $M(\theta_s)$ is Hurwitz stable. Let us then choose a θ_u and a θ_s such that $M(\theta_u)$ is not Hurwitz stable and $M(\theta_s)$ is. Since Θ is connected, then there exists a path $\mathcal{P} \subset \Theta$ from θ_s and θ_u . From Perron-Frobenius theorem, the dominant eigenvalue, denoted by $\lambda_{PF}(\cdot)$, is real and hence, we have that $\lambda_{PF}(M(\theta_s)) < 0$ and $\lambda_{PF}(M(\theta_u)) \geq 0$. Hence, from the continuity of eigenvalues then there exists a $\theta_c \in \mathcal{P}$ such that $\lambda_{PF}(M(\theta_c)) = 0$, which then implies that $(-1)^d \det(M(\theta_c)) = 0$, or equivalently, that the negation of (c2) holds. This concludes the proof. \diamond

Before stating the next main result of this section, let us assume that S_u in Definition 1 has the following form

$$S_u = \begin{bmatrix} S_{dg} & S_{ct} & S_{cv} \end{bmatrix} \quad (20)$$

where $S_{dg} \in \mathbb{R}^{d \times n_{dg}}$ is a matrix with nonpositive columns, $S_{ct} \in \mathbb{R}^{d \times n_{ct}}$ is a matrix with nonnegative columns and $S_{cv} \in \mathbb{R}^{d \times n_{cv}}$ is a matrix with columns containing at least one negative and one positive entry. Also, decompose accordingly ρ_u as $\rho_u =: \text{col}(\rho_{dg}, \rho_{ct}, \rho_{cv})$ and define

$$\rho_{\bullet} \in \mathcal{P}_{\bullet} := [\rho_{\bullet}^-, \rho_{\bullet}^+], \quad 0 \leq \rho_{\bullet}^- \leq \rho_{\bullet}^+ < \infty$$

where $\bullet \in \{dg, ct, cv\}$ and let $\mathcal{P}_u := \mathcal{P}_{dg} \times \mathcal{P}_{ct} \times \mathcal{P}_{cv}$.

In this regard, we can alternatively rewrite the matrix $A(\rho_u)$ as $A(\rho_{dg}, \rho_{ct}, \rho_{cv})$. We then have the following result:

Lemma 12 *The following statements are equivalent:*

(a) *The matrix $A(\rho_u)$ is Hurwitz stable for all $\rho_u \in \mathcal{P}_u$.*

(b) *The matrix*

$$A^+(\rho_{cv}) := A(\rho_{dg}^-, \rho_{ct}^+, \rho_{cv}) \quad (21)$$

is Hurwitz stable for all $\rho_{cv} \in \mathcal{P}_{cv}$.

Proof : The proof that (a) implies (b) is immediate. To prove that (b) implies (a), first note that we have

$$A(\rho_{dg}, \rho_{ct}, \rho_{cv}) \leq A^+(\rho_{cv}) = A(\rho_{dg}^-, \rho_{ct}^+, \rho_{cv}) \quad (22)$$

since for all $(\rho_{dg}, \rho_{ct}, \rho_{cv}) \in \mathcal{P}_u$. Using the fact that for two Metzler matrices B_1, B_2 , the inequality $B_1 \leq B_2$ implies $\lambda_{PF}(B_1) \leq \lambda_{PF}(B_2)$ [42], then we can conclude that $A(\rho_{dg}^-, \rho_{ct}^+, \rho_{cv})$ is Hurwitz stable for all $\rho_{cv} \in \mathcal{P}_{cv}$ if and only if the matrix $A(\rho_{dg}, \rho_{ct}, \rho_{cv})$ is Hurwitz stable for all $(\rho_{dg}, \rho_{ct}, \rho_{cv}) \in \mathcal{P}_u$. This completes the proof. \diamond

4.2 Unimolecular networks

The following theorem states the main result on the robust ergodicity of unimolecular reaction networks:

Theorem 13 *Let $A(\rho_u) \in \mathbb{R}^{d \times d}$ be the characteristic matrix of some unimolecular network and $\rho_u \in \mathcal{P}_u$. Then, the following statements are equivalent:*

(a) *The matrix $A(\rho_u)$ is Hurwitz stable for all $\rho_u \in \mathcal{P}_u$.*

(b) *The matrix*

$$A^+(\rho_{cv}) := A(\rho_{dg}^-, \rho_{ct}^+, \rho_{cv}) \quad (23)$$

is Hurwitz stable for all $\rho_{cv} \in \mathcal{P}_{cv}$.

(c) *There exists a $\rho_{cv}^s \in \mathcal{P}_{cv}$ such that the matrix $A^+(\rho_{cv}^s)$ is Hurwitz stable and the polynomial $(-1)^d \det(A^+(\rho_{cv}))$ is positive for all $\rho_{cv} \in \mathcal{P}_{cv}$.*

(d) *There exists a polynomial vector-valued function $v : \mathcal{P}_{cv} \mapsto \mathbb{R}_{>0}^d$ of degree at most $d - 1$ such that $v(\rho_{cv})^T A^+(\rho_{cv}) < 0$ for all $\rho_{cv} \in \mathcal{P}_{cv}$.*

Proof : The equivalence between the statement (a), (b) and (c) directly follows from Lemma 11 and Lemma 12. To prove the equivalence between the statements (b) and (d), first remark that (b) is equivalent to the fact that for any $q(\rho_{cv}) > 0$ on \mathcal{P}_{cv} , there exists a unique parameterized vector $v(\rho_{cv}) \in \mathbb{R}^d$ such that $v(\rho_{cv}) > 0$ and $v(\rho_{cv})^T A^+(\rho_{cv}) = -q(\rho_{cv})^T$ for

all $\rho_{cv} \in \mathcal{P}_{cv}$. Choosing $q(\rho_{cv}) = -\mathbf{1}_n(-1)^d \det(A^+(\rho_{cv}))$, we get that such a $v(\rho_{cv})$ is given by

$$\begin{aligned} v(\rho_{cv})^T &= -\mathbf{1}_d^T (-1)^d \det(A^+(\rho_{cv})) A^+(\rho_{cv})^{-1} \\ &= (-1)^{d+1} \mathbf{1}_d^T \text{Adj}(A^+(\rho_{cv})) > 0 \end{aligned} \quad (24)$$

for all $\rho_{cv} \in \mathcal{P}_{cv}$. Since the matrix $A^+(\rho_{cv})$ is affine in ρ_{cv} , then the adjugate matrix $\text{Adj}(A^+(\rho_{cv}))$ contains entries of at most degree $d - 1$ and the conclusion follows. \diamond

Checking the condition (c) amounts to solving two problems. The first one is concerned with the construction of a stabilizer $\rho_{cv} \in \mathcal{P}_{cv}$ for the matrix $A^+(\rho_{cv})$ whereas the second one is about checking whether a polynomial is positive on a compact set. The first problem can be easily solved by checking whether $A^+(\rho_{cv})$ is Hurwitz stable for some randomly chosen point in \mathcal{P}_{cv} . For the second one, optimization-based methods can be used such as those based on the Handelman's Theorem combined with linear programming [44, 45] or Putinar's Positivstellensatz combined with semidefinite programming [46, 47]. Note also that the degree $d - 1$ is a worst case degree and that, in fact, polynomials of lower degree will in general be enough for proving the Hurwitz stability of the matrix $A^+(\rho_{cv})$ for all $\rho_{cv} \in \mathcal{P}_{cv}$. For instance, the matrices $A(\rho)$ and $A^+(\rho_{cv})$ are very sparse in general due to the particular structure of biochemical reaction networks. The sparsity property is not considered here but could be exploited to refine the necessary degree for the polynomial vector $v(\rho_{cv})$.

It is important to stress here that Theorem 13 can only be considered when the rate parameters are time-invariant (i.e. constant deterministic or drawn from a distribution). When they are time-varying (e.g. time-varying stationary random variables), a possible workaround relies on the use of a constant vector v as formulated below:

Proposition 14 (Constant v) *Let $A(\rho_u) \in \mathbb{R}^{d \times d}$ be the characteristic matrix of some unimolecular network and $\rho_u \in \mathcal{P}_u$. Then, the following statements are equivalent:*

- (a) *There exists a vector $v \in \mathbb{R}_{>0}^d$ such that $v^T A^+(\rho_{cv}) < 0$ holds for all $\rho_{cv} \in \mathcal{P}_{cv}$.*
- (b) *There exists a vector $v \in \mathbb{R}_{>0}^d$ such that $v^T A^+(\theta) < 0$ holds for all $\theta \in \text{vert}(\mathcal{P}_{cv})$ where $\text{vert}(\mathcal{P}_{cv})$ denotes the set of vertices of the set \mathcal{P}_{cv} .*

Proof: The proof exploits the affine, hence convex, structure of the matrix $A^+(\rho_{cv})$. Using this property, it is indeed immediate to show that the inequality $v^T A^+(\rho_{cv}) < 0$ holds for all $\rho_{cv} \in \mathcal{P}_{cv}$ if and only if $v^T A^+(\theta) < 0$ holds for all $\theta \in \text{vert}(\mathcal{P}_{cv})$ (see e.g. [36] for a similar arguments in the context of quadratic Lyapunov functions). \diamond

The above result is connected to the existence of a linear copositive Lyapunov function for a linear positive switched system with matrices in the family $\{A(\theta) : \theta \in \text{vert}(\mathcal{P}_{cv})\}$ for which many characterizations exist; see e.g. [48, 49].

4.3 Bimolecular networks

In the case of bimolecular networks, we have the following result:

Proposition 15 *Let $A(\rho_u) \in \mathbb{R}^{d \times d}$ be the characteristic matrix of some bimolecular network and $\rho_u \in \mathcal{P}_u$. Then, the following statements are equivalent:*

(a) *There exists a polynomial vector-valued function $v : \mathcal{P}_u \mapsto \mathbb{R}_{>0}^d$ of degree at most $d - 1$ such that*

$$v(\rho_u) > 0, \quad v(\rho_u)^T S_b = 0 \quad \text{and} \quad v(\rho_u)^T A(\rho_u) < 0 \quad (25)$$

for all $\rho_u \in \mathcal{P}_u$.

(b) *There exists a polynomial vector-valued function $\tilde{v} : \mathcal{P}_{cv} \mapsto \mathbb{R}^{d-n_b}$ of degree at most $d - 1$ such that*

$$\tilde{v}(\rho_{cv})^T S_b^\perp > 0 \quad \text{and} \quad \tilde{v}(\rho_{cv})^T S_b^\perp A^+(\rho_{cv}) < 0 \quad (26)$$

for all $\rho_{cv} \in \mathcal{P}_{cv}$ and where $n_b := \text{rank}(S_b)$ and $S_b^\perp S_b = 0$, S_b^\perp full-rank.

Proof : It is immediate to see that (a) implies (b). To prove the converse, first note that we have that $v(\rho_{cv}) = (S_b^\perp)^T \tilde{v}(\rho_{cv})$ verifies $v(\rho_{cv})^T S_b = 0$ and $v(\rho_{cv}) > 0$ for all $\rho_{cv} \in \mathcal{P}_{cv}$. This proves the equality and the first inequality in (25). Observe now that for any $\rho_u \in \mathcal{P}_u$, there exists a nonnegative matrix $\Delta(\rho_{dg}, \rho_{ct}) \in \mathbb{R}_{\geq 0}^{d \times d}$ such that $A(\rho_u) = A^+(\rho_{cv}) - \Delta(\rho_{dg}, \rho_{ct})$. Hence, we have that

$$\begin{aligned} v(\rho_{cv})^T A(\rho_u) &= v(\rho_{cv})^T (A^+(\rho_{cv}) - \Delta(\rho_{dg}, \rho_{ct})) \\ &\leq v(\rho_{cv})^T A^+(\rho_{cv}) < 0 \end{aligned} \quad (27)$$

which proves the result. \diamond

As in the unimolecular case, we have been able to reduce the number of parameters by using an upper-bound on the characteristic matrix. It is also interesting to note that the condition $\tilde{v}(\rho_{cv})^T S_b^\perp A^+(\rho_{cv}) < 0$ can be sometimes brought back to a problem of the form $\tilde{v}(\rho_{cv})^T M(\rho_{cv}) < 0$ for some square, and often Metzler, matrix $M(\rho_{cv})$ which can be dealt in the same way as in the unimolecular case.

The following result can be used when the parameters are time-varying and is the bimolecular analogue of Proposition 14:

Proposition 16 (Constant v) *Let $A(\rho_u) \in \mathbb{R}^{d \times d}$ be the characteristic matrix of some bimolecular network and $\rho_u \in \mathcal{P}_u$. Then, the following statements are equivalent:*

(a) *There exists a vector $v \in \mathbb{R}_{>0}^d$ such that $v^T S_b = 0$ and $v^T A^+(\rho_{cv}) < 0$ hold for all $\rho_{cv} \in \mathcal{P}_{cv}$.*

(b) *There exists a vector $v \in \mathbb{R}_{>0}^d$ such that $v^T S_b = 0$ and $v^T A^+(\theta) < 0$ hold for all $\theta \in \text{vert}(\mathcal{P}_{cv})$.*

5 Structural ergodicity of reaction networks network - Sign matrices

In the previous section, we were interested in uncertain networks characterized in terms of a characteristic interval-matrix. We consider here a different approach based on the qualitative analysis of matrices where we simply assume that we only know the sign-pattern of the characteristic matrix. We are then looking for criteria assessing whether all the characteristic matrices sharing the same sign-pattern verify the conditions of Theorem 7.

To this aim, let us consider the set of *sign symbols* $\mathbb{S} := \{0, \oplus, \ominus\}$ and define a *sign-matrix* as a matrix with entries in \mathbb{S} . The qualitative class $\mathcal{Q}(\Sigma)$ of a sign-matrix $\Sigma \in \mathbb{S}^{m \times n}$ is defined as

$$\mathcal{Q}(\Sigma) := \{M \in \mathbb{R}^{m \times n} : \text{sgn}(M) = \text{sgn}(\Sigma)\} \quad (28)$$

where the signum function $\text{sgn}(\cdot)$ is defined as

$$[\text{sgn}(\Sigma)]_{ij} := \begin{cases} 1 & \text{if } \Sigma_{ij} \in \mathbb{R}_{>0} \cup \{\oplus\}, \\ -1 & \text{if } \Sigma_{ij} \in \mathbb{R}_{<0} \cup \{\ominus\}, \\ 0 & \text{otherwise.} \end{cases} \quad (29)$$

The following result proved in [27] will turn out to be a key ingredient for deriving the main result of this section:

Lemma 17 ([27]) *Let $\Sigma \in \mathbb{S}^{d \times d}$ be a given Metzler sign-matrix. Then, the following statements are equivalent:*

- (a) *All the matrices in $\mathcal{Q}(\Sigma)$ are Hurwitz stable.*
- (b) *The matrix $\text{sgn}(\Sigma)$ is Hurwitz stable.*
- (c) *The diagonal elements of Σ are negative and the directed graph $\mathcal{G}_\Sigma = (\mathcal{V}, \mathcal{E})$ defined with*
 - $\mathcal{V} := \{1, \dots, d\}$ and
 - $\mathcal{E} := \{(m, n) : e_n^T \Sigma e_m \neq 0, m, n \in V, m \neq n\}$.

is an acyclic directed graph.

△

We are now ready to state the main result of this section:

Theorem 18 *Let $S_A \in \mathbb{S}^{d \times d}$ be Metzler and $S_b \in \{0, \oplus\}^d$ be some given sign patterns for the characteristic matrix and the offset vector of some unimolecular reaction network $(\mathbf{X}, \mathcal{R})$. Assume that $\ell \neq 1$ and that the state-space of the closed-loop reaction network $((\mathbf{X}, \mathbf{Z}), \mathcal{R} \cup \mathcal{R}^c)$ is irreducible. Then, the following statements are equivalent:*

- (a) *All the matrices in $\mathcal{Q}(S_A)$ are Hurwitz stable and, for all $A \in \mathcal{Q}(S_A)$, there exists a vector $w \in \mathbb{R}_{\geq 0}^d$ such that $w_1 > 0$ and $w^T A + e_\ell^T = 0$.*

(b) The diagonal elements of S_A are negative and the directed graph \mathcal{G}_{S_A} is acyclic and contains a path from node 1 to node ℓ .

(c) There exist vectors $v_1 \in \mathbb{R}_{>0}^d$, $v_2, v_3 \in \mathbb{R}_{\geq 0}^d$, $\|v_2 + v_3\|_1 = 1$, such that the conditions

$$v_1^T \operatorname{sgn}(S_A) < 0 \quad (30)$$

and

$$v_2 - \operatorname{sgn}(\operatorname{sgn}(S_A) + e_1 e_\ell^T) v_3 = 0 \quad (31)$$

hold.

Moreover, when one of the above statements holds, then for any values for the controller rate parameters $\eta, k > 0$ and any $(A, b_0) \in \mathcal{Q}(S_A) \times \mathcal{Q}(S_b)$, the properties **P1.**, **P2.** and **P3.** hold provided that

$$\frac{\mu}{\theta} > \frac{v^T b_0}{c e_\ell^T v} \quad (32)$$

where $c > 0$ and $v \in \mathbb{R}_{>0}^d$ verify $v^T(A + cI) \leq 0$. \triangle

Proof: The equivalence between the statement (a) and statement (b) follows from Lemma 6 and Lemma 17. Hence, we simply have to prove the equivalence between statement (c) and statement (b).

The equivalence between the Hurwitz-stability of $\operatorname{sgn}(S_A)$ and all the matrices in $\mathcal{Q}(S_A)$ directly follows from Lemma 17. Note that if \mathcal{G}_{S_A} has a cycle, then there exists an unstable matrix in $\mathcal{Q}(S_A)$. Let us assume then for the rest of the proof that there is no cycle in \mathcal{G}_{S_A} and let us focus now on the statement equivalent to the output controllability condition. From Lemma 17, we know that since all the matrices in $\mathcal{Q}(S_A)$ are Hurwitz stable, then the graph \mathcal{G}_{S_A} is an acyclic directed graph and S_A has negative diagonal entries. From Lemma 6, we know that the network is output controllable if and only if there is a path from node 1 to node ℓ in the graph \mathcal{G}_A . To algebraically formulate this, we introduce the sign matrix $S_C \in \mathbb{S}^{d \times d}$ for which the associated graph $\mathcal{G}_{S_C} := (\mathcal{V}, \mathcal{E} \cup (\ell, 1))$, where $\ell \neq 1$ by assumption, consists of the original graph to which we add an edge from node ℓ to node 1. Note that if $(\ell, 1) \in \mathcal{E}$, then $S_A = S_C$. The output controllability condition then equivalently turns into the existence of a cycle in the graph \mathcal{G}_{S_C} (recall the no cycle assumption for \mathcal{G}_{S_A} as, otherwise, some matrices in $\mathcal{Q}(S_A)$ would not be Hurwitz stable). Considering again Lemma 6, we can turn the existence condition of a cycle in \mathcal{G}_{S_C} into an instability condition for some of the matrices in $\mathcal{Q}(S_C)$. Since S_C is a Metzler sign-matrix, then there exist some unstable matrices in $\mathcal{Q}(S_C)$ if and only if $v^T \operatorname{sgn}(S_C) \not\leq 0$ for all $v > 0$. Using Farkas' lemma [50], this is equivalent to saying that there exist $v_2, v_3 \in \mathbb{R}_{\geq 0}^d$, $\|v_2 + v_3\|_1 = 1$ such that $v_2 - \operatorname{sgn}(S_C) v_3 = 0$. Therefore, the existence of v_2, v_3 verifying the conditions above is equivalent to saying that for all $A \in \mathcal{Q}(S_A)$, there exists a $w \geq 0$, $w_1 > 0$, such that $w^T A + e_\ell^T = 0$. Noting, finally, that $\operatorname{sgn}(S_C) = \operatorname{sgn}(\operatorname{sgn}(S_A) + e_\ell e_1^T)$ yields the result. \diamond

Remark 19 *In the case $\ell = 1$, the output controllability condition is trivially satisfied as the actuated species coincides with the controlled species and hence we only need to check the Hurwitz stability condition $v^T \text{sgn}(S_A) < 0$ for some $v \in \mathbb{R}_{>0}^d$.*

As in the nominal and robust cases, the above result can also be naturally reformulated as the linear feasibility problem:

$$\begin{aligned} \text{Find} \quad & v_1 \in \mathbb{R}_{>0}^d, v_2, v_3 \in \mathbb{R}_{\geq 0}^d \\ \text{s.t.} \quad & v_1^T \text{sgn}(A) < 0 \\ & \mathbf{1}_d^T (v_2 + v_3) = 1 \\ & v_2 - \text{sgn}(\text{sgn}(S_A) + e_1 e_\ell^T) v_3 = 0 \end{aligned} \tag{33}$$

where $\mathbf{1}_d$ the d -dimensional vector of ones. The computational complexity of this program is slightly higher (i.e. $3d$ variables, $4d$ inequality constraints and $2d + 1$ equality constraints) but is still linear in d and, therefore, this program will remain tractable even when d is large.

6 Structural ergodicity of reaction networks - Parametric approach

We are interesting in this section in the structural stability of the characteristic matrix of given unimolecular network. Hence, we have in this case $\mathcal{P}_\bullet := \mathbb{R}_{>0}^{n_\bullet}$, $\bullet \in \{u, dg, ct, cv\}$ where n_\bullet is the dimension of the vector ρ_\bullet .

6.1 A preliminary result

Lemma 20 *Let $A(\rho_u) \in \mathbb{R}^{d \times d}$ be the characteristic matrix of some unimolecular network and $\rho_u \in \mathcal{P}_u$. Then, the following statements are equivalent:*

- i. For all $\rho_{dg} \in \mathcal{P}_{dg}$ and a $\rho_{cv} \in \mathcal{P}_{cv}$, the matrix $A(\rho_{dg}, \rho_{cv}, 0)$ is Hurwitz stable.*
- ii. The matrix $A(\mathbf{1}, \rho_{cv}, 0)$ is Hurwitz stable for all $\rho_{cv} \in \mathcal{P}_{cv}$.*

Proof : The proof that (a) implies (b) is immediate. To prove the reverse implication, we use contraposition and we assume that there exist a $\rho_{dg} \in \mathcal{P}_{dg}$ and a $\rho_{cv} \in \mathcal{P}_{cv}$ such that $A(\rho_{dg}, \rho_{cv}, 0)$ is not Hurwitz stable. Then, we clearly have that

$$A(\rho_{dg}, \rho_{cv}, 0) \leq A(\theta \mathbf{1}, \rho_{cv}, 0) \tag{34}$$

where $\theta = \min(\rho_{dg})$ and hence $A(\theta \mathbf{1}, \rho_{cv}, 0)$ is not Hurwitz stable. Since $A(\theta \mathbf{1}, \rho_{cv}, 0)$ is affine in θ and ρ_{cv} , then we have that $\theta A(\mathbf{1}, \rho_{cv}/\theta, 0)$ and since θ is independent of ρ_{cv} , then we get that the matrix $A(\mathbf{1}, \tilde{\rho}_{cv}, 0)$ is not Hurwitz stable for some $\tilde{\rho}_{cv} \in \mathcal{P}_{cv}$. The proof is complete.

◇

6.2 Main result

Theorem 21 *Let $A(\rho_u) \in \mathbb{R}^{d \times d}$ be the characteristic matrix of some unimolecular network and $\rho_u \in \mathbb{R}_{>0}^{n_u}$. Then, the following statements are equivalent:*

- (a) *The matrix $A(\rho_u)$ is Hurwitz stable for all $\rho_u \in \mathbb{R}_{>0}^{n_u}$.*
- (b) *There exists a polynomial vector $v(\rho_u) \in \mathbb{R}^d$ of degree at most $d - 1$ such that $v(\rho_u) > 0$ and $v^T A(\rho_u) < 0$ for all $\rho_u \in \mathbb{R}_{>0}^{n_u}$.*
- (c) *There exists a $\rho_u^s \in \mathbb{R}_{>0}^{n_u}$ such that the matrix $A(\rho_u^s)$ is Hurwitz stable and the polynomial $(-1)^d \det(A(\rho_u))$ is positive for all $\rho_u \in \mathbb{R}_{>0}^{n_u}$.*
- (d) *For all $\rho_{dg} \in \mathbb{R}_{>0}^{n_{dg}}$ and a $\rho_{cv} \in \mathbb{R}_{>0}^{n_{cv}}$, the matrix $A_\rho := A(\rho_{dg}, \rho_{cv}, 0)$ is Hurwitz stable and we have that $\varrho(W_{ct} A_\rho^{-1} S_{ct}) = 0$.*
- (e) *The matrix $A_n(\rho_{cv}) := A(\mathbf{1}, \rho_{cv}, 0)$ is Hurwitz stable for all $\rho_{cv} \in \mathbb{R}_{>0}^{n_{cv}}$ and $\varrho(W_{ct} A_n(\rho_{cv})^{-1} S_{ct}) = 0$ for all $\rho_{cv} \in \mathbb{R}_{>0}^{n_{cv}}$.*

Moreover, when S_{cv} contains exactly one entry equal to -1 and one equal to 1 , then the above statements are also equivalent to

- (f) *The matrix $A_{\mathbf{1}} := A(\mathbf{1}, \mathbf{1}, 0)$ is Hurwitz stable and $\varrho(W_{ct} A_{\mathbf{1}}^{-1} S_{ct}) = 0$.*

Proof: The equivalence between the three first statements has been proved in Theorem 13. Let us prove now that (c) implies (d). Assuming that (c) holds, we get that the existence of a $\rho_u^s = \text{col}(\rho_{dg}^s, \rho_{cv}^s, \rho_{ct}^s)$ such that the matrix $A(\rho_u^s)$ is Hurwitz stable immediately implies that the matrix $A_\rho = A(\rho_{dg}, \rho_{cv}, 0)$ is Hurwitz stable since we have that $A_\rho \leq A(\rho_u)$ and, therefore $\lambda_{PF}(A_\rho) \leq \lambda_{PF}(A(\rho_u)) < 0$. Using now the determinant formula, we have that

$$\det(A(\rho_u)) = \det(A_\rho) \det(I + D(\rho_{ct}) W_{ct} A_\rho^{-1} S_{ct}) \quad (35)$$

where $D(\rho_{ct}) := \text{diag}(\rho_{ct})$ and W_{ct} is defined such that $\text{diag}(\rho_{ct}) W_{ct} x$ is the vector of propensity functions associated with the catalytic reactions. Hence, this implies that

$$\det(I + D(\rho_{ct}) W_{ct} A_\rho^{-1} S_{ct}) > 0 \quad (36)$$

for all $\rho_{ct} \in \mathbb{R}_{>0}^{n_{ct}}$. Since the matrices W_{ct}, S_{ct} are nonnegative, the diagonal entries of $D(\rho_{ct})$ are positive and A_ρ^{-1} is nonpositive (since A_ρ is Metzler and Hurwitz stable), then it is necessary that all the eigenvalues of $W_{ct} A_\rho^{-1} S_{ct}$ be zero for the determinant to remain positive. This completes the argument.

The converse (i.e. (d) implies (c)) can be proven by noticing that if A_ρ is Hurwitz stable, then $A_\rho + \epsilon S_{ct} W_{ct}$ remains Hurwitz stable for some sufficiently small $\epsilon > 0$. This proves the existence of a $\rho_u^s \in \mathbb{R}_{>0}^{n_u}$ such that the matrix $A(\rho_u^s)$ is Hurwitz stable. Using the determinant formula, it is immediate to see that the second statement implies the determinant condition of statement (c).

The equivalence between the statements (d) and (e) comes from Lemma 20 and the fact that the sign-pattern of the inverse of a Hurwitz stable Metzler matrix is uniquely defined by its sign-pattern.

Let us now focus on the equivalence between the statements (d) and (f) under the assumption that S_{cv} contains exactly one entry equal to -1 and one equal to 1 . Assume w.l.o.g that $S_{dg} = \text{col}(-I_{n_{dg}}, 0)$. Then, we have that $\mathbf{1}_d^T A(\rho_{dg}, \rho_{cv}, 0) = [-\rho_{dg}^T \ 0]$. Hence, the function $V(z) = \mathbf{1}_d^T z$ is a weak Lyapunov function for the linear positive system $\dot{z} = A(\rho_{dg}, \rho_{cv}, 0)z$. Invoking LaSalle's invariance principle, we get that the matrix is Hurwitz stable if and only if the matrix

$$A^{22}(\rho_{dg}, \rho_{cv}) := \begin{bmatrix} 0 \\ I \end{bmatrix}^T A(\rho_{dg}, \rho_{cv}, 0) \begin{bmatrix} 0 \\ I \end{bmatrix} \quad (37)$$

is Hurwitz stable for all $(\rho_{dg}, \rho_{cv}) \in \mathbb{R}_{>0}^{n_{dg}} \times \mathbb{R}_{>0}^{n_{cv}}$. Note that this is a necessary condition for the matrix $A(\rho_{dg}, \rho_{cv}, 0)$ to be Hurwitz stable for all rate parameters values. Hence, this means that the stability of the matrix A_ρ is equivalent to the Hurwitz stability of $A_{\mathbf{1}} := A(\mathbf{1}, \mathbf{1}, 0)$. Finally, since $A^{22}(\rho_{dg}, \rho_{cv})$ is Hurwitz stable, then we have that $\mathbf{1}^T A^{22}(\mathbf{1}, \mathbf{1}) < 0$. The proof is complete. \diamond

7 Examples

7.1 Example 1: Modified stochastic switch

We propose to illustrate the results by considering a variation of the stochastic switch [51] described by the set of reactions given in Table 1, where the functions f_1 and f_2 are valid nonnegative functions (e.g. mass-action or Hill-type). Our goal is to control the mean population of \mathbf{X}_2 by actuating \mathbf{X}_1 . We further assume that $\alpha_1, \alpha_2, \gamma_1, \gamma_2 > 0$, which implies that the state-space of the open-loop network is irreducible.

Scenario 1. In this scenario, we simply assume that f_1 and f_2 are bounded functions with respective upper-bounds $\beta_1 > 0$ and $\beta_2 > 0$. Then, using the results in [15], the ergodicity of the network in Table 1 can be established by checking the ergodicity of a comparison network obtained by substituting the functions f_1 and f_2 by their upper-bound. In the current case, the comparison network coincides with a unimolecular network with mass-action kinetics defined with

$$A = \begin{bmatrix} -\gamma_1 & 0 \\ k_{12} & -\gamma_2 \end{bmatrix} \text{ and } b_0 = \begin{bmatrix} \alpha_1 + \beta_1 \\ \alpha_2 + \beta_2 \end{bmatrix}. \quad (38)$$

It is immediate to see that the characteristic matrix is Hurwitz stable and that the system is output controllable provided that $k_{12} \neq 0$ since $e_2^T A^{-1} e_1 = -k_{12}/(\gamma_1 \gamma_2)$ (see Lemma 6). Hence, tracking is achieved provided that the lower bound condition (9) in Theorem 7 is satisfied. Moreover, we can see that for any $\alpha_1, \alpha_2, \beta_1, \beta_2, \gamma_1, \gamma_2, k_{12} > 0$, we have that

$A \in \mathcal{Q}(S_A)$ and $b_0 \in \mathcal{Q}(S_b)$ where

$$S_A = \begin{bmatrix} \ominus & 0 \\ \oplus & \ominus \end{bmatrix} \text{ and } S_b = \begin{bmatrix} \oplus \\ \oplus \end{bmatrix}. \quad (39)$$

All the matrices in $\mathcal{Q}(S_A)$ are Hurwitz stable since the matrix $\text{sgn}(S_A)$ is Hurwitz stable or, equivalently, since the graph associated with S_A given by $\mathcal{G}_{S_A} = \{(1, 2)\}$ is acyclic (Lemma 17). Moreover, this graph trivially contains a path from node 1 to node 2, proving then that tracking will be ensured by the AIC motif provided that the inequality (32) is satisfied (Theorem 18). Alternatively, we can prove this by augmenting the graph \mathcal{G}_{S_A} with the edge $\{(2, 1)\}$ (see the proof of Theorem 18) to obtain the graph \mathcal{G}_{S_C} with associated sign matrix

$$S_C = \begin{bmatrix} \ominus & \oplus \\ \oplus & \ominus \end{bmatrix}, \quad (40)$$

which is not sign-stable since the matrix $\text{sgn}(S_C)$ has an eigenvalue located at 0 or, equivalently, since the graph \mathcal{G}_{S_C} has a cycle (Lemma 17). To arrive to the same result, we can also check that the vectors $v_1 = (2, 1)$, $v_2 = (0, 0)$ and $v_3 = (1/2, 1/2)$ solve the linear program (33).

Scenario 2. We slightly modify here the previous scenario by making the function f_1 affine in X_2 , i.e. $f_1(X_2) = k_{21}X_2 + \delta_1$, $k_{21}, \delta_1 \geq 0$. It is immediate to see that the structural result fails as the resulting characteristic matrix has the same sign pattern as the matrix S_C . Hence, the network is not structurally ergodic but it can be robustly ergodic. To illustrate this, we define the following intervals for the parameters $\gamma_1 \in [1, 2]$, $\gamma_2 \in [3, 4]$, $k_{12} \in [k_{12}^-, 2]$ and $k_{21} = [0, k_{21}^+]$, where $0 \leq k_{12}^- \leq 2$ and $k_{21}^+ \geq 0$. Hence, we have that

$$\begin{bmatrix} -2 & 0 \\ k_{12}^- & -4 \end{bmatrix} = A^- \leq A \leq A^+ = \begin{bmatrix} -1 & k_{21}^+ \\ 2 & -3 \end{bmatrix}. \quad (41)$$

The stability of all the matrices A in this interval is established through the stability of A^+ (Lemma 8), which holds provided that $k_{21}^+ < 2/3$. This can also be checked by verifying that $v^T A < 0$ for $v = (5, k_{21}^+ + 1)$ under the very same condition on k_{21}^+ . Regarding the output controllability, we need to consider the matrix A^- (Theorem 9) and observe that if $k_{12}^- = 0$ then output controllability does not hold as there is no path from node 1 to node 2 in the graph (Lemma 6). Alternatively, we can check that, in this case, $e_2^T (A^-)^{-1} e_1 = 0$ (Theorem 9) or that the linear program (18) is not feasible. To conclude, when $k_{12}^- > 0$ and $k_{21}^+ < 2/3$, then the linear program (18) is feasible with the vectors $v = (5, k_{21}^+ + 1)$ and $w = (k_{12}^-/8, 1/4)$, proving then that, in this case, the AIC motif will ensure robust tracking for the controlled network provided that the condition (14) is satisfied.

7.2 Example 2: SIR model

Let us consider the open stochastic SIR model considered in [15] described by the matrices

$$A = \begin{bmatrix} -\gamma_s & 0 & k_{rs} \\ 0 & -(\gamma_i + k_{ir}) & 0 \\ 0 & k_{ir} & -(\gamma_r + k_{rs}) \end{bmatrix}, \quad S_b = \begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix} \quad (42)$$

Table 1: Modified stochastic switch of [51]

	Reaction	Propensity
\mathcal{R}_1	$\emptyset \longrightarrow \mathbf{X}_1$	$\alpha_1 + f_1(X_2)$
\mathcal{R}_2	$\mathbf{X}_1 \longrightarrow \emptyset$	$\gamma_1 X_1$
\mathcal{R}_3	$\emptyset \longrightarrow \mathbf{X}_2$	$\alpha_2 + f_2(X_1) + k_{12} X_1$
\mathcal{R}_4	$\mathbf{X}_2 \longrightarrow \emptyset$	$\gamma_2 X_2$

where all the parameters are positive. The constraint $v^T S_b = 0$ enforces that $v = \tilde{v}^T S_b^\perp$, $\tilde{v} > 0$, where $S_b^\perp = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$. This leads to

$$\tilde{v}^T S_b^\perp A < 0 \Leftrightarrow \tilde{v}^T \begin{bmatrix} -(\gamma_i + k_{ir}) & k_{rs} \\ k_{ir} & -(\gamma_r + k_{rs}) \end{bmatrix} < 0. \quad (43)$$

Since the entries are not independent, the use of sign-matrices or interval matrices are conservative. However, if we use Theorem 21, then we can just substitute the parameters by 1 and observe that the resulting matrix is Hurwitz stable to prove the structural stability of the matrix. Alternatively, we can take $\tilde{v} = \mathbf{1}$ and obtain

$$\tilde{v}^T \begin{bmatrix} -(\gamma_i + k_{ir}) & k_{rs} \\ k_{ir} & -(\gamma_r + k_{rs}) \end{bmatrix} = [-\gamma_i \quad -\gamma_r] < 0 \quad (44)$$

from which the same result follows.

7.3 Example 3: Circadian Clock

We consider the circadian clock-model of [10] which is described by the matrices

$$A = \begin{bmatrix} -\delta_{M_A} & 0 & 0 & 0 & 0 \\ \beta_A & -\delta_A & 0 & 0 & 0 \\ 0 & 0 & -\delta_{M_R} & 0 & 0 \\ 0 & 0 & \beta_R & -\delta_R & \delta_A \\ 0 & 0 & 0 & 0 & -\delta_A \end{bmatrix}, \quad S_b = \begin{bmatrix} 0 \\ -1 \\ 0 \\ -1 \\ 1 \end{bmatrix} \quad (45)$$

where all the parameters are positive. As in the previous example, the condition reduces to

$$\tilde{v}^T S_b^\perp A < 0 \Leftrightarrow \tilde{v}^T \begin{bmatrix} -\delta_{M_A} & 0 & 0 & 0 \\ \beta_A & -\delta_A & 0 & 0 \\ 0 & 0 & -\delta_{M_R} & 0 \\ 0 & 0 & \beta_R & -\delta_R \end{bmatrix} < 0 \quad (46)$$

where $\tilde{v} > 0$. Clearly, we have four degradation reactions and two catalytic ones. Using the last statement of Theorem 21 we get that the matrix $A_{\mathbf{1}} = -I$. We also have in this case that

$$W_{ct} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix} \quad \text{and} \quad S_{ct} = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}^T \quad (47)$$

and, hence, $W_{ct}A_{\mathbb{1}}^{-1}S_{ct} = 0$. Hence, the system is structurally stable. Alternatively, the triangular structure of the matrix would also lead to the same conclusion.

7.4 Example 4: Toy model

Let us consider here the following toy network where

$$A = \begin{bmatrix} -(\gamma_1 + \alpha_1) & 0 & k_1 \\ k_2 & -(\gamma_2 + \alpha_2) & 0 \\ 0 & k_3 & -k_1 \end{bmatrix}. \quad (48)$$

Assume that $\alpha_1 = k_2$ and $\alpha_2 = k_3$. Then, we get that

$$A_{\mathbb{1}} = \begin{bmatrix} -2 & 0 & 1 \\ 1 & -2 & 0 \\ 0 & 1 & -1 \end{bmatrix} \quad (49)$$

is Hurwitz stable and hence that the matrix is structurally stable. However, if we assume now that $\alpha_1 = \alpha_2 = 0$, then we get

$$A_{\mathbb{1}} = \begin{bmatrix} -1 & 0 & 1 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix} \quad \text{and} \quad A_{\mathbb{1}}^{-1} = \begin{bmatrix} -1 & 0 & -1 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix} \quad (50)$$

where $A_{\mathbb{1}}$ is Hurwitz stable. We have in this case that

$$W_{ct} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix} \quad \text{and} \quad S_{ct} = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}^T \quad (51)$$

and hence

$$W_{ct}A_{\mathbb{1}}^{-1}S_{ct} = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix} \quad (52)$$

which has a spectral radius equal to 1. Hence, the matrix is not structurally stable. Define now

$$A^+(k_1) = \begin{bmatrix} -\gamma_1^- & 0 & k_1 \\ k_2^+ & -\gamma_2^- & 0 \\ 0 & k_3^+ & -k_1 \end{bmatrix}. \quad (53)$$

Using a perturbation argument, we can prove that the 0-eigenvalue of $A^+(0)$ locally bifurcates to the open right-half plane for some sufficiently small $k_1 > 0$ if and only if $k_2k_3 - \gamma_1\gamma_2 < 0$. Hence, there exists a $k_1 > 0$ such that $A^+(k_1)$ is Hurwitz stable if and only if $k_2k_3 - \gamma_1\gamma_2 < 0$. Noting now that

$$\det(A^+(k_1)) = k_1(k_2k_3 - \gamma_1\gamma_2) < 0 \quad (54)$$

and, hence, the determinant never switches sign, which proves that the matrix $A^+(k_1)$ is structurally stable.

8 Conclusion

Several extensions of nominal ergodicity and output controllability results initially proposed in [3, 15] have been obtained. Those extensions are based on the use of interval matrices, sign-matrices and parameter-dependent matrices, respectively. The two first approaches have the benefits of leading to conditions that are easy to check and applicable to large networks as the complexity of the conditions scales linearly with the number of species. However, they may suffer from an arbitrarily large conservatism as the interval matrix and the sign-matrix representation is not necessarily exact. This issue is palliated by the use of parameter-dependent matrix where the entries of the characteristic matrix are exactly parameterized in terms of the reaction rates. This representation is exact but is more difficult to theoretically exploit. Numerically, it is known that checking the stability of a parameter-dependent matrix is NP-Hard. However, by exploiting the Metzler structure of the matrix, it has been possible to obtain interesting simplified conditions for the robust and structural ergodicity of stochastic reaction networks with uncertain reaction rates. Possible extensions of those results would pertain on more general reaction networks or the development of efficient algorithms for the analysis and the control of reaction networks.

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