Abstract—The ergodicity and the output-controllability of stochastic reaction networks have been shown to be essential properties to fulfill to enable their control using, for instance, antithetic integral control (Briat, Gupta, Khammash, “Antithetic integral feedback ensures robust perfect adaptation in noisy biomolecular networks,” Cell Syst., vol. 2, pp. 17–28, 2016). We propose here to extend those properties to the case of uncertain networks. To this aim, the notions of interval, robust, sign, and structural ergodicity/output-controllability are introduced. The obtained results lie in the same spirit as those obtained in [1], where those properties are characterized in terms of control theoretic concepts, linear algebraic conditions, linear programs, and graph-theoretic/algebraic conditions. An important conclusion is that all those properties can be characterized by linear programs. Two examples are given for illustration.

Index Terms—Antithetic integral control, cybergenetics, ergodicity, output-controllability, robustness, stochastic reaction networks.

I. INTRODUCTION

REACTION networks is a powerful formalism that can represent a wide variety of real-world processes [2]. When the dynamics of those processes is subject to randomness, as in biology [3], [4], stochastic reaction networks have been proven to play an essential role for their modeling, analysis, filtering, and control (see e.g., [1], [5]–[7]). Indeed, it is now well-known that stochastic reaction networks can exhibit several interesting properties that are absent for their deterministic counterparts [1], [8]–[10]. Under the well-mixed assumption, the dynamics of a stochastic reaction network can be described by a continuous-time jump Markov process evolving on an integer lattice [5]. Sufficient conditions for checking the ergodicity of open unimolecular and bimolecular stochastic reaction networks have been proposed in [6] 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 stochastic reaction networks and, consequently, 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, would establish that the closed-loop network is well-behaved (e.g., globally converging 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 global stability of a closed-loop system in the deterministic setting (see e.g., [11]). Additionally, designing synthetic circuits 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 [1] that has been shown to induce an ergodic closed-loop network when the open-loop network is both ergodic and output-controllable—a closed-loop property that holds regardless the values of the controller parameters. However, a major limitation of the ergodicity and output-controllability conditions obtained in [1], [6] is their limited scope to networks with fixed and known rate parameters only—an assumption rarely met in practice. This has motivated the consideration of stochastic reaction networks with uncertain rate parameters in [12]–[14].

The objective of this article is to provide a global picture of all the obtained results in [1], [6], [12], [13] by unifying and generalizing them, by providing comparisons between them, and by emphasizing their connections with results in systems theory, control theory, linear algebra, and optimization. This unified picture is obtained through the introduction of the concepts of interval-, robust-, sign-, and structural-ergodicity (respectively, output controllability) for uncertain stochastic reaction networks (respectively for uncertain linear positive systems). Unlike in [12] and [13], all the results are stated with their proof. Novel results are also provided as a way to consolidate the structure of this unifying viewpoint.

The interval-approach considers classes of networks described by interval matrices [15]. We show that checking the ergodicity and the output controllability of the entire network family reduces to checking the ergodicity of a single network and the output controllability of a single linear positive system, two problems, which naturally reformulate as simple linear programs. Unlike the interval-approach, the robust approach considers the explicit dependence on the rate parameters
of the matrices describing the network. In this regard, this approach may be conclusive whenever the interval-approach fails, a scenario plausible to happen when the considered network involves conversion reactions. The price to pay, however, is a higher computational cost for establishing the robust ergodicity property. Checking the output-controllability property remains the same as in the interval approach.

The sign-approach, more qualitative in nature, is based on sign-matrices [14], [16]–[18], which have been extensively studied and considered for the qualitative analysis of dynamical systems, including reaction networks, albeit much more sporadically (see e.g., [12], [14], [19], [20]). In this case, again, the ergodicity and output-controllability conditions can be stated as simple linear programs (see e.g., [12], [14]). The computational complexity is, hence, the same as in the interval approach. Finally, the structural-approach considers the exact parameter dependence, as the robust one. Ergodicity and output-controllability conditions are also formulated as simple linear programs under some realistic assumptions. When those conditions are not met, more expensive solutions can be obtained in the same flavor as in the robust case.

Outline. We recall in Section II several definitions and results related to reaction networks and antithetic integral control. Those concepts are extended to uncertain networks in Section III. Sections IV, V, VI, and VII extend the results of Section II to the interval, robust, sign, and structural cases, respectively. Examples are treated in Section VIII.

Notations. The standard basis for \( \mathbb{R}^d \) is denoted by \( \{e_i\}_{i=1}^d \). The sets of integers, nonnegative 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 \( 1_d \) (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 \( x_1, \ldots, x_d \) is denoted by \( \text{col}(x_1, \ldots, x_d) \). 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 \( \rho(M) = \max(|\lambda| : \det(\lambda I - M) = 0) \).

II. PRELIMINARIES

A. SISO Linear Positive Systems

SISO linear systems are systems of the form

\[
\begin{align*}
\dot{x}(t) &= Mx(t) + bu(t) \\
y(t) &= c^T x(t) \\
x(0) &= x_0,
\end{align*}
\]

where \( x, x_0 \in \mathbb{R}^d \), \( u \in \mathbb{R} \), and \( y \in \mathbb{R} \) are the state of the system, the initial condition, the input, and the output of the system. We also have that \( M \in \mathbb{R}^{d \times d} \) and \( b, c \in \mathbb{R}^d \). The above system is said to be internally positive if for any nonnegative initial condition and any nonnegative input, the state and the output are nonnegative. A necessary and sufficient condition for the internal positivity of (1) is that \( M \) is Metzler\(^1\) and \( b, c \) are nonnegative.

We have the following result [21].

**Proposition 1:** Assume that the system (1) is internally positive. Then, the following statements are equivalent.

a) The system (1) with \( u \equiv 0 \) is asymptotically stable.

b) The matrix \( M \) is Hurwitz stable.

c) There exists a vector \( v \in \mathbb{R}^d_{>0} \) such that \( v^T M < 0 \).

d) \( M \) is nonsingular and \( M^{-1} \leq 0 \).

We will also need the following result on the output controllability of linear SISO positive systems which is an extension of the results in [1], [12], [13] to the case of unnecessarily stable systems.

**Proposition 2:** Assume that the system (1) is internally positive. Then, the following statements are equivalent.

a) The system \((M, b, c^T)\) defined in (1) is output controllable.

b) \( \text{rank}\left[c^T b \ c^T Mb \ldots c^T M^{d-1}b\right] = 1 \).

c) There exists a vector \( w \in \mathbb{R}^d_{>0} \) and a scalar \( \mu \in \mathbb{R}_{>0} \) such that \( w^T b > 0 \) and \( w^T(M - \mu I_d) + c^T = 0 \).

d) There exists a scalar \( \mu \geq 0 \) such that \( -c^T(M - \mu I_d)^{-1}b > 0 \) holds or, equivalently, the static-gain of the system \((M - \mu I, b, c^T)\) is positive.

When \( b = e_i \) and \( c = e_j \), the above statements are equivalent to

e) There is a path from node \( i \) to node \( j \) in the directed graph \( G_M = (V,E) \) defined with \( V := \{1, \ldots, d\} \) and
\[
E := \{(m,n) : e_n^T M e_m \neq 0, m,n \in V, m \neq n\}.
\]

Moreover, when the matrix \( M \) is Hurwitz stable, then, the statements (c) and (d) hold with \( \mu = 0 \).

**Proof:** The equivalence between the statements (a) and (b) follows from the definition. The equivalence with (e) can be found in [1]. The equivalence between (c) and (d) follows from choosing \( \mu \geq 0 \) such that \( M - \mu I \) is Hurwitz stable and \( w^T = -c^T(M - \mu I)^{-1} \geq 0 \), where the nonnegativity follows from the fact that the matrix \( M - \mu I \) is Metzler and Hurwitz stable. Finally, the equivalence between (a) and (c) follows from the fact that the system \((M, b, c^T)\) is output-controllable if and only if \((M - \mu I, b, c^T)\) is output-controllable.

B. General Stochastic Reaction Networks With Mass-Action Kinetics

We consider here a reaction network with \( d \) molecular species \( X_1, \ldots, X_d \) that interacts through \( K \) reaction channels \( \mathcal{R}_1, \ldots, \mathcal{R}_K \) defined as follows:

\[
\mathcal{R}_k : \sum_{i=1}^{d} \zeta_{k,i}^l X_i \ \xrightarrow{\rho^k} \ \sum_{i=1}^{d} \zeta_{k,i}^c X_i, \ k = 1, \ldots, K
\]

where \( \rho^k \in \mathbb{R}_{>0} \) is the reaction rate parameter and \( \zeta_{k,i}^l, \zeta_{k,i}^c \in \mathbb{Z}_{\geq 0} \). Each reaction is additionally described by a stoichiometric vector and a propensity function. Each reaction rate parameter is distinct and independent from the others. The stoichiometric vector of reaction \( \mathcal{R}_k \) is given by \( \zeta_k := \zeta_k^l - \zeta_k^c \in \mathbb{Z}^d \) where \( \zeta_k^l = \text{col}(\zeta_{k,1}^l, \ldots, \zeta_{k,d}^l) \) and \( \zeta_k^c = \text{col}(\zeta_{k,1}^c, \ldots, \zeta_{k,d}^c) \). In this regard, when the reaction \( \mathcal{R}_k \) fires, the state jumps from \( x \) to

\(^1\)A square matrix is Metzler if all its off-diagonal elements are nonnegative.
$x + \zeta_k$. We define the stoichiometry matrix $S \in \mathbb{Z}^{d \times K}$ as $S := [\zeta_1 \ldots \zeta_K]$. When the kinetics is mass-action, the propensity function of reaction $R_k$ 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 $x \in \mathbb{Z}^{d > 0}$ and $x + \zeta_k \notin \mathbb{Z}^{d > 0}$. We denote this reaction network by $(X, R)$. Under the well-mixed assumption, this network can be described by a continuous-time Markov process $(X_1(t), \ldots, X_d(t))_{t \geq 0}$ with state-space $\mathbb{Z}^{d > 0}$ (see e.g., [22]). This Markov process is fully described by the Chemical Master Equation or Forward Kolmogorov Equation given by [22]

$$\frac{\partial p_{x_0}(x, t)}{\partial t} = \sum_{i=1}^K \lambda_i(x)(p_{x_0}(x + \zeta_i, t) - p_{x_0}(x, t))$$  \hspace{1cm} (3)

where $p_{x_0}(x, t)$ is the probability for the Markov process to be in state $x$ at time $t$, starting from the initial state $X(0) = x_0$. Knowing the probability distribution provides a lot of information about the behavior of the Markov process and the associated reaction network. Unfortunately, this equation is difficult to solve in general and alternative ways to study its behavior need to be considered (see e.g., [23]). In particular, it is interesting to know whether there is a unique attractive stationary distribution. This leads to the following definition:

**Definition 3 (Ergodicity of a Reaction Network):** The Markov process associated with the reaction network $(X, R)$ is said to be ergodic if its probability distribution $p_{x_0}(x, \cdot)$ globally converges to a unique stationary distribution $\pi$; i.e., for every $x_0 \in \mathbb{Z}_{d > 0}$, we have that $p_{x_0}(x, t) \to \pi$ as $t \to \infty$. The network is exponentially ergodic if the convergence to the stationary distribution is exponential.

This definition is the stochastic analogue of a globally attracting equilibrium point for deterministic dynamics.

**Definition 4 (Irreducible Reaction Network):** A stochastic reaction network is said to be irreducible, if the state-space of the underlying Markov process is irreducible.

**Definition 5 (Open Reaction Network):** A reaction network is said to be open if there is no set of conserved species in the network; i.e., $z \in \mathbb{R}_{d > 0}^S$ and $z^T S = 0 \Rightarrow z = 0$.

### C. Bimolecular Stochastic Reaction Networks

Let us assume here that the network $(X, R)$ 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

$$\lambda(x) = \begin{bmatrix} w_0(\rho_0) \\ W(\rho_0)x \\ W_b(\rho_b, x) \end{bmatrix}$$  \hspace{1cm} (4)

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

**Definition 6:** The characteristic matrix $A(\rho_a)$ and the offset vector $b_0(\rho)$ of a bimolecular reaction network $(X, R)$ are defined as

$$A(\rho_a) := S_u W(\rho_a)$$

and

$$b_0(\rho) := S_0 w_0(\rho_0).$$  \hspace{1cm} (5)

Moreover, the matrix $A(\rho_a)$ is Metzler and the vector $b_0(\rho)$ is nonnegative for all positive rate parameters.

**Definition 7:** The dynamics of the first-order moments of a stochastic bimolecular reaction network $(X, R)$ is described by the internally positive system

$$\frac{d\mathbb{E}[X(t)]}{dt} = A(\rho_a)\mathbb{E}[X(t)] + b_0(\rho_0) + S_0 \mathbb{E}[W_b(\rho_b, X(t))]$$  \hspace{1cm} (6)

where $\mathbb{E}[X(0)] = x_0$.

Note that when the network is unimolecular, then the moments dynamics is described by a linear internally positive system; i.e. $A(\rho_a)$ is Metzler and $b_0(\rho)$ is nonnegative.

### D. Ergodicity of Unimolecular and Bimolecular Reaction Networks

We have the following result which is a slight extension of a result in [6].

**Theorem 8 (Ergodicity of Unimolecular Networks):** Let us consider an open irreducible unimolecular reaction network $(X, R)$ with fixed rate parameters; i.e., $A = A(\rho_a)$ and $b_0 = b_0(\rho_0)$. Then, the following statements are equivalent.

a. The reaction network $(X, R)$ is exponentially ergodic and all the moments are bounded and converging.

b. There exists a vector $v \in \mathbb{R}_{d > 0}$ such that $v^T A < 0$.

c. The matrix $A$ is Hurwitz stable.

**Proof:** The equivalence between the two last statements follows from Proposition 2. We also note that for ergodic unimolecular networks all moments globally converge to their unique fixed point (see [6]). Now assume that (a) holds. Using the fact that there is no conserved set of species, this implies that (6) with $S_0 = 0$ globally converges to a unique equilibrium point. A necessary and sufficient condition for that is that $A$ be Hurwitz stable; i.e., (c) holds. To prove the converse, we assume that the network is nonergodic. Since the state space is irreducible then the network can only be nonergodic if its trajectories grow unboundedly or, equivalently, the first-order moments diverge. This implies that $A$ must not be Hurwitz stable. This proves the result.

We then have the following generalization to bimolecular networks [6].

**Theorem 9 (Ergodicity of Bimolecular Networks):** Let us consider an open irreducible bimolecular reaction network $(X, R)$ with fixed rate parameters; i.e., $A = A(\rho_a)$ and $b_0 = b_0(\rho_0)$. Assume that there exists a vector $v \in \mathbb{R}_{d > 0}$ such that $v^T S_0 = 0$ and $v^T A < 0$. Then, the reaction network $(X, R)$ is exponentially ergodic and all the moments are bounded and converging.
E. Antithetic Integral Control of Unimolecular Networks

Antithetic integral control has been first proposed in [1] for solving the perfect adaptation problem in stochastic reaction networks. The underlying idea is to augment the open-loop network \((X, R)\) 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 \(X_1\) (the actuated species) in order to steer the mean value of the controlled species \(X_\ell, \ell \in \{1, \ldots, d\}\), to a desired set-point (the reference) and ensure perfect adaptation for the controlled species. As proved in [1], the antithetic integral control motif \((Z, R^c)\) defined with

\[
\theta \xrightarrow{\mu} Z_1, \theta \xrightarrow{\theta X_1} Z_2, Z_1 + Z_2 \xrightarrow{\eta} \theta \xrightarrow{k Z_1} X_1
\]  

(7)
solves this control problem with the set-point being equal to \(\mu/\theta\). Above, \(Z_1\) and \(Z_2\) 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 \(\mu/\theta\) as its own rate. The second one is the measurement reaction that produces the species \(Z_2\) at a rate proportional to the current population of the controlled species \(X_\ell\). 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 reaction network resulting in transport the factored part of the dynamics of the open loop network is therefore given by (1) with \(M = A(\rho_0), b = e_1, c = e_\ell\).

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

Theorem 10 (see [1]): Let us consider an open unimolecular reaction network \((X, R)\) with fixed characteristic matrix \(A = A(\rho_0^*)\) and offset vector \(b_0 = b_0(\rho_0^*)\) for some nominal parameter values \(\rho_0^*\) and \(\rho_0\). Assume further that the closed-loop reaction network \((\{X, Z\}, R \cup R^c)\) is irreducible. Then, the following statements are equivalent:

a) The open-loop reaction network \((X, R)\) is ergodic and the system \((A, e_1, e_T^f)\) is output controllable.

b) There exist vectors \(v \in \mathbb{R}^d_{>0}, w \in \mathbb{R}^d_{>0}, w_1 > 0\), such that

\[v^T A < 0 \text{ and } w^T A + e_T^f = 0.\]

Moreover, when one of the above statements holds, then the closed-loop reaction network \((\{X, Z\}, R \cup R^c)\) is ergodic and we have that \(E[X_\ell(t)] \xrightarrow{\mu/\theta} \) as \(t \to \infty\) for any values for the controller rate parameters \(\eta, k > 0\) provided that

\[
\frac{\mu}{\theta} > \frac{v^T b_0}{\alpha e_T^f v}
\]

(8)

where \(\alpha > 0\) and \(v \in \mathbb{R}^d_{>0}\) verify \(v^T (A + \alpha I) \leq 0\).

Remark 11: Interestingly, the conditions stated in the above result can be numerically verified by checking the feasibility of the following linear program:

Find \(v \in \mathbb{R}^d_{>0}, w \in \mathbb{R}^d_{>0}\), such that

\[
\begin{align*}
v^T e_1 &> 0, & v^T A &< 0, & w^T A + e_T^f &= 0.
\end{align*}
\]

(9)

III. NOTIONS OF ERGODICITY AND OUTPUT-CONTROLLABILITY FOR UNCERTAIN UNIMOLECULAR NETWORKS

We address two main families of parameters. The first one is that of bounded parameter values

\[\mathcal{P}_u \subset \mathbb{R}_{\geq 0}^n\]

(10)

where \(\mathcal{P}_u\)’s is the cartesian product of connected intervals, which are not necessarily closed. The second type is that of unbounded parameter values

\[\mathcal{P}_u^{\infty} := \mathbb{R}_{>0}^n.\]

(11)

Depending on the considered type of parameters, different concepts can be defined. Those concepts are summarized in Table I.

A. Interval Ergodicity and Output-Controllability

In this case, we assume that the characteristic matrix of the network belongs to the set

\[A := \{M \in \mathbb{R}^{d \times d} : A^- \leq M \leq A^+\}, \quad A^- \leq A^+\]

(12)

where the matrices \(A^-\) and \(A^+\) verify \(A^- \leq A(\rho_u) \leq A^+\) holds for all \(\rho_u \in \mathcal{P}_u\). In other words, we have that

\[\{A(\rho_u) : \rho_u \in \mathcal{P}_u\} \subset A.\]

(13)

Alternatively, we can define the interval matrix \([A]\) such as \(e_T^f [A] e_j = [a_{ij}^-, a_{ij}^+]; i.e., its (i, j)\’s element is an interval.

We can then define the concepts of interval ergodicity and interval output-controllability

Definition 12 (Interval Ergodicity): The unimolecular network \((X, R)\) with interval characteristic matrix \([A]\) is interval (exponentially) ergodic if for each \(A \in A\), the network with characteristic matrix \(A(\rho_u)\) is (exponentially) ergodic.

Definition 13 (Interval Output-Controllability): The linear interval system \(([A], e_i, e_T^f)\) is interval output-controllable if for each \(A \in A\), the system \((A, e_i, e_T^f)\) is output-controllable.

B. Robust Ergodicity and Output-Controllability

The robust case considers the exact parameter dependence of the characteristic matrix. This leads to the following concepts of robust ergodicity and robust output-controllability.

Definition 14 (Robust Ergodicity): The unimolecular network \((X, R)\) with parameter-dependent characteristic matrix \(A(\rho_u), \rho_u \in \mathcal{P}_u\), is robustly (exponentially) ergodic if for each \(\theta \in \mathcal{P}_u\), the network with characteristic matrix \(A(\theta)\) is (exponentially) ergodic.

Definition 15 (Robust Output-Controllability): The linear system \((A(\rho_u), e_i, e_T^f), \rho_u \in \mathcal{P}_u\), is robustly output-controllable.

| TABLE I |
| --- |
| List of the Considered Different Concepts With Their Exactness and Domain of Definition |
| | Bounded parameters | Unbounded parameters |
| Approximated model | Interval concepts | Sign concepts |
| Exact model | Robust concepts | Structural concepts |
if for each \( \theta \in \mathcal{P}_u \), the system \( (A(\theta), e_i, e_j^T) \) is output-controllable.

### C. Sign Ergodicity and Output-Controllability

The sign ergodicity addresses the ergodicity of all the reaction networks having a characteristic matrix sharing the same given sign pattern. We define now the set of sign symbols \( \Sigma := \{0, \oplus, \ominus\} \). A sign-matrix is a matrix with entries in \( \Sigma \) and the qualitative class \( \mathcal{Q}(\Sigma) \) of a sign-matrix \( \Sigma \in \mathbb{S}^{m \times n} \) is defined as

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

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

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

Starting from \( A(\rho_u) \), we can build the associated sign-pattern as \( S_A = A(\oplus) \) where \( A(\oplus) \) stands for the matrix where we have replaced all the parameters by \( \oplus \) and used the arithmetic rules \( -\ominus = \ominus \) and \( \ominus + \ominus = \ominus \). Under the assumption that the network does not involve any conversion nor autocatalytic reactions, we have that

\[
\{ A(\rho_u) : \rho_u \in \mathcal{P}_u^\infty \} \subset \mathcal{Q}(S_A).
\]

This leads to the following concepts of sign ergodicity and sign output-controllability.

**Definition 16:** Assume that the unimolecular network \((X, \mathcal{R})\) with characteristic sign-matrix \( S_A \) does not contain any conversion reaction. Then, it is sign (exponentially) ergodic if for each \( A \in \mathcal{Q}(S_A) \), the network with characteristic matrix \( A \) is (exponentially) ergodic.

**Definition 17:** The linear sign system \((S_A, e_i, e_j^T)\) is sign output controllable if for each \( A \in \mathcal{Q}(S_A) \), the system \((A, e_i, e_j^T)\) is output-controllable.

### D. Structural Ergodicity and Output-Controllability

The structural case considers the exact parameter dependence of the characteristic matrix. This leads to the following concepts of structural ergodicity and structural output-controllability.

**Definition 18:** The unimolecular network \((X, \mathcal{R})\) with parameter-dependent characteristic matrix \( A(\rho_u), \rho_u \in \mathcal{P}_u^\infty \), is structurally (exponentially) ergodic if for each \( \theta \in \mathcal{P}_u^\infty \), the network with characteristic matrix \( A(\theta) \) is (exponentially) ergodic.

**Definition 19:** The linear parameter-dependent system \((A(\rho_u), e_i, e_j^T), \rho_u \in \mathcal{P}_u^\infty \), is structurally output-controllable if for each \( \theta \in \mathcal{P}_u^\infty \), the system \((A(\theta), e_i, e_j^T)\) is output-controllable.

### E. Equivalence Between the Concepts

It seems interesting to start with some illustrative examples. The first one illustrates the impact of conversion reactions on the tightness of the interval and sign approximation.

**Example 20 (Hurwitz Stability):** Let us consider the matrix

\[
A(\rho_u) = \begin{bmatrix} -\rho^1 - \rho^2 & \rho^4 \\ \rho^2 & -\rho^3 - \rho^4 \end{bmatrix}, \rho_u = (\rho^1, \rho^2, \rho^3, \rho^4)
\]

where the rates \( \rho^2 \) and \( \rho^4 \) are rates of conversion reactions. This matrix is Hurwitz stable for all positive parameter values, hence it is structurally stable. It is also robustly stable provided the diagonal elements are bounded away from 0. However, if we pick \( \rho^1 = \rho^3 = 1 \) and \( \rho_2, \rho_4 \in [1,3] \), then it is not interval stable since

\[
A^+ = \begin{bmatrix} -2 & 4 \\ 4 & -2 \end{bmatrix}
\]

is not Hurwitz stable. Similarly, the sign representation given by

\[
A(\oplus) = \begin{bmatrix} \oplus & \oplus \\ \oplus & \oplus \end{bmatrix}
\]

is not sign-stable.

The second one addresses the case where the set of values of the parameters is not closed.

**Example 21:** Let us consider the following matrix:

\[
A = \begin{bmatrix} -1 & 0 \\ \rho_1 & 0 \end{bmatrix}, \quad b = e_1, c = e_2.
\]

Clearly, the system \((A, b, c)\) is structurally output-controllable. However, it is not interval observable if one considers that \( \rho \in (0,1) \), since the matrix \( A^+ \) will have 0 as bottom-left entry.

The above remarks are formalized below as follows.

**Proposition 22:** Assume that the network \((X, \mathcal{R})\) is unimolecular. Then, the following statements are equivalent:

a) There is no conversion reactions in the network \((X, \mathcal{R})\) and the set \( \mathcal{P}_u \) is closed.

b) We have that \( A = \{ A(\rho_u) : \rho_u \in \mathcal{P}_u \} \).

**Proof:** Clearly, if there are conversion reactions, then the sets do not match since the bounds \( A^- \), \( A^+ \) will not be tight due to the presence of the same parameters in different entries, i.e., both on the diagonal and in the corresponding columns. Indeed, in such a case, there is no \( \rho_u \in \mathcal{P}_u \) such that \( A(\rho_u) = A^- \) or \( A(\rho_u) = A^+ \). Additionally, if the set \( \mathcal{P}_u \) is not closed, the bounds are never attained. This proves the result.

The following result provides conditions under which the sign formulation is exact.

**Proposition 23:** Assume that the network \((X, \mathcal{R})\) is unimolecular. The following statements are equivalent:

a) There is no conversion nor autocatalytic reaction in the reaction network \((X, \mathcal{R})\).

b) We have that \( \{ A(\rho_u) : \rho_u \in \mathbb{R}^n_{>0} \} = \mathcal{Q}(S_A) \).

**Proof:** If there is no conservation reaction, then all the entries in the matrix are independent and, therefore, the sign approach becomes nonconservative.

### F. Extensions to More General Networks

It is interesting to discuss whether those concepts extend to some bimolecular networks. The robust and structural definitions can be extended to any type of reaction networks as
those definitions lie at the level of the reaction rates. The other definitions can be adapted to a class of bimolecular networks through the use of Theorem 9. Note that the sign-ergodicity of bimolecular networks has been addressed in [14, Proposition 8.8] through the concept of $\text{Ker}_+ (B)$-sign-stability.

IV. INTERVAL RESULTS

The objective of this section is to develop interval-analogues of the ergodicity and output-controllability results of Section II.

A. Interval Ergodicity of Unimolecular Reaction Networks

Let us consider set of matrices (12) where the bounds $A^-, A^+$ have been determined such that (13) holds. Then, we have the following result:

**Proposition 24:** Let us consider an irreducible open unimolecular reaction network $(X, R)$ with interval characteristic matrix $[A]$. Then, the following statements are equivalent:

a) The network $(X, R)$ is interval exponentially ergodic;

b) All the matrices in $A$ are Hurwitz stable or, equivalently, for any $M \in A$, there exists a $v = v(M) \in \mathbb{R}^d_{>0}$ such that $v^T M < 0$;

c) The matrix $A^+$ is Hurwitz stable or, equivalently, there exists a vector $v_+ \in \mathbb{R}^d_{>0}$ such that $v_+^T A^+ < 0$.

Moreover, when one of the above statements holds, then the reaction network $(X, R)$ is robustly ergodic.

**Proof:** The proof that (a) is equivalent to (b) simply follows from Theorem 8. The proof that (b) implies (c) is immediate. The converse can be proved using the fact that for two Metzler matrices $M_1, M_2 \in \mathbb{R}^{d,d}$ 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. [25]). Hence, we have that $\lambda_F (M) \leq \lambda_F (A^+) < 0$ for all $M \in A$. The conclusion then readily follows.

B. Interval Ergodicity of Bimolecular Reaction Networks

We now provide an extension of the conditions of Theorem 9 for bimolecular networks to the case of uncertain networks described by uncertain matrices:

**Proposition 25:** Let us consider an uncertain open irreducible bimolecular reaction network $(X, R)$ with interval characteristic matrix $[A]$ and assume that there exists a vector $v \in \mathbb{R}^d_{>0}$ such that

$$v^T A^+ < 0 \text{ and } v^T S_b = 0.$$  \hspace{1cm} (21)

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

**Proof:** The result immediately follows from Theorem 9 and Proposition 24.

C. Interval Output-Controllability of Unimolecular Reaction Networks

Let us consider the set of matrices (12) where the bounds $A^-, A^+$ have been determined such that (13) holds. Then, we have the following result:

**Proposition 26:** The following statements are equivalent.

a) The interval system $([A], e_1, e_T^2)$ is interval output-controllable.

b) For all $A \in A$, there exists a vector $w \in \mathbb{R}^d_{>0}$ and a scalar $\mu \geq 0$ such that $w^T e_1 > 0$ and $w^T (A - \mu I_d) + e_T^2 = 0$.

c) There exists a vector $w_+ \in \mathbb{R}^d_{>0}$ and a scalar $\mu_- \geq 0$ verifying $w_+^T e_1 > 0$ and $w_+^T (A^+ - \mu_- I_d) + e_T^2 = 0$. \hspace{1cm} \triangle

Moreover, if all the matrices in $A$ are Hurwitz stable, then the above statements hold with $\mu = \mu_- = 0$.

**Proof:** The equivalence between the two first statements follows from Proposition 2. Clearly, (b) implies (c). We prove that the converse is also true. To this aim, define $A(\Delta)$ as $A(\Delta) := A^+ - \Delta$ for $\Delta \in \Delta := [0, A^+ - A^-]$. The key idea is to build a $w(\Delta) \geq 0$ and a $\mu(\Delta) \geq 0$ that verify the expressions $w(\Delta)^T (A(\Delta) - \mu(\Delta) I_d) + e_T^2 = 0$ and $w(\Delta)^T e_1 > 0$ for all $\Delta \in \Delta$ provided that $w(\Delta)^T (A^+ - \mu_- I_d) + e_T^2 = 0$ and $w^T e_1 > 0$. We prove that such a $w(\Delta)$ is given by $w(\Delta) := [(A^+ - \mu_- I_d) (A(\Delta) - \mu(\Delta) I_d)]^{1/2} w_+$. With some large enough $\mu_- \geq 0$ such that $\mu_- \geq \mu(\Delta)$ with $A(\Delta) - \mu(\Delta) I_d$ Hurwitz stable. Note that such a $\mu(\Delta)$ always exists.

We first prove that this $w(\Delta)$ is nonnegative and that it verifies $w(\Delta)^T e_1 > 0$ for all $\Delta \in \Delta$. To show this, let us rewrite it as $w(\Delta) = [I_d + ((\mu(\Delta) - \mu_-) I_d - \Delta)] (A(\Delta) - \mu(\Delta) I_d)^{-1} w_+$ and $\mu(\Delta) \leq \mu(\Delta)$ under the considered assumptions for $\mu(\Delta)$ and $\mu_-$. We get that $(A(\Delta) - \mu(\Delta) I_d)^{-1} \leq 0$. This together with $\Delta \geq 0$ and $\mu_- - \mu(\Delta) \geq 0$, we obtain that $w(\Delta)^T e_1 \geq w_+^T e_1 > 0$ for all $\Delta \in \Delta$ and, therefore, that $w(\Delta)^T e_1 \geq w_+^T e_1 > 0$ for all $\Delta \in \Delta$.

We now show that this $w(\Delta)$ verifies the equality condition. Substituting the expression for $w(\Delta)$ in $w(\Delta)^T (A(\Delta) - \mu(\Delta) I_d)$ yields

$$w(\Delta)^T (A(\Delta) - \mu(\Delta) I_d) = w_+^T (A^+ - \mu_- I_d) = -e_T^2$$ \hspace{1cm} (22)

where the last equality has been obtained from the assumption that $w_+^T (A^+ - \mu_- I_d) + e_T^2 = 0$. This proves that (c) implies (b). The final statement follows from the same reasons as in Proposition 2.

D. Antithetic Integral Control of Interval Reaction Networks

We are now in position to state the following generalization of Theorem 10.

**Theorem 27:** Let us consider an open unimolecular reaction network $(X, R)$ with interval characteristic matrix $[A]$ and interval offset vector $[b] = [b_0, b_0^r]$. Assume also that the closed-loop reaction network $(X, Z, R \cup R^r)$ is irreducible. Then, the following statements are equivalent.

a) The open-loop reaction network $(X, R)$ is interval ergodic and the system $([A], e_1, e_T^2)$ is interval output-controllable.

b) There exist two vectors $v_+ \in \mathbb{R}^d_{>0}$, $v_- \in \mathbb{R}^d_{>0}$ such that $v_+^T (A^+ - e_T^2) = 0$, $v_-^T (A^+ - e_T^2) = 0$.

Moreover, when one of the above statements holds, then the closed-loop reaction network $(X, Z, R \cup R^r)$ is interval ergodic and we have that $F_{X(t)} \rightarrow \mu/\theta$ as $t \rightarrow \infty$ for any
values for the controller rate parameters $\eta, k > 0$ provided that
\[
\frac{\mu}{\theta} > \frac{q^T (A^+ - \Delta)^{-1} b^+}{\alpha q^T (A^+ - \Delta)^{-1} e^T}
\]  
(23)
and
\[
q^T (\alpha (A^+ - \Delta)^{-1} + I_d) \geq 0
\]  
(24)
for some $\alpha > 0$, $q \in \mathbb{R}^d_{>0}$ and for all $\Delta \in [0, A^+ - A^-]$. △

Proof: The proof of the equivalence between (a) and (b) follows from the notion of interval ergodicity and interval output controllability as well as Propositions 25 and 26. The conclusion of the theorem is an adaptation of that of Theorem 10. To prove (23), let us define, with some slight abuse of notation, the matrix $A(\Delta) := A^+ - \Delta$, $\Delta \in \Delta := [0, A^+ - A^-]$. This (Metzler) matrix is Hurwitz stable for all $\Delta \in \Delta$ and, therefore, its inverse is nonpositive. We need now to construct a suitable positive vector $v(\Delta) \in \mathbb{R}^d_{>0}$ such that $v(\Delta)^T A(\Delta) < 0$ for all $\Delta \in \Delta$ provided that $v^T_d A^+ < 0$. We prove now that such a $v(\Delta)$ is given by $v(\Delta) = (A^+ + \Delta)^{-1} T v$. To prove its positivity for all $\Delta \in \Delta$, first rewrite $v(\Delta)$ as $v(\Delta) = (A^+ - \Delta)^{-1} (v^T_d A^+)^T$ and note that we both have $(A^+ - \Delta)^{-1} \leq 0$ and $v^T_d A^+$, hence the resulting vector is strictly positive for all $\Delta \in \Delta$. We show now that this vector verifies $v(\Delta)^T A(\Delta) < 0$ for all $\Delta \in \Delta$. Direct substitution yields $v(\Delta)^T A(\Delta) = v^T_d A^+ < 0$, which proves the desired result. To obtain a more explicit expression for $v(\Delta)$, note that since $A^+$ is Metzler and Hurwitz stable, then for any $q \in \mathbb{R}^d_{>0}$, there exists a $v_q \in \mathbb{R}^d_{>0}$ such that $v^T_q A^+ = -q^T$. Substituting the expression $v_q^T = -q^T (A^+)^{-1}$ in the above formula for $v(\Delta)$ and substituting into (8) yields (23).

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

\[
\begin{aligned}
& \text{Find} & & u \in \mathbb{R}^d_{>0}, v \in \mathbb{R}^d_{>0} \\
& \text{s.t.} & & v^T c_1 > 0, v^T A^+ < 0, w^T A^- + e^T = 0
\end{aligned}
\]  
(25)
which has exactly the same complexity as the linear program (9). Hence, checking the possibility of controlling a family of networks defined by a characteristic interval-matrix is not more complicated that checking the possibility of controlling a single network.

\section{V. Robust Results}

To palliate the potential lack of accuracy of the interval approach, the robust approach captures the exact parameter dependence is developed in this section.

\subsection{A. Preliminaries}

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

Lemma 28: Let us consider a matrix $M(\theta) \in \mathbb{R}^{d \times d}$ which is Metzler and bounded for all $\theta \in \Theta \subset \mathbb{R}^N_{>0}$ and where $\Theta$ 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 for all $\theta \in \Theta$.

c) The conditions hold:
\[\begin{aligned}
& c1) \text{there exists a } \theta^* \in \Theta \text{ such that } M(\theta^*) \text{ is Hurwitz stable}, \\
& c2) \text{for all } \theta \in \Theta \text{ we have that } (-1)^d \text{det}(M(\theta)) > 0.
\end{aligned}\]

Proof: The proof of the equivalence between (a) and (b) follows, for instance, from [26] 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 this constant term is equal to $(-1)^d \text{det}(M(\theta))$ yields the result.

To prove that (c) implies (a), we use the contraposition. Hence, let us assume that there exists at least a $\theta_u \in \Theta$ such that the matrix $M(\theta_u)$ is not Hurwitz stable. If such a $\theta_u$ can be arbitrarily chosen in $\Theta$, 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 $\theta \in \Theta$ such that $M(\theta)$ is Hurwitz stable. Let us then choose a $\theta_u$ and a $\theta_s$ such that $M(\theta_u)$ is not Hurwitz stable and $M(\theta_s)$ is. Since $\Theta$ is connected, then there exists a path $\mathcal{P} \subset \Theta$ from $\theta_u$ and $\theta_s$. From Perron–Frobenius theorem, the dominant eigenvalue, denoted by $\lambda_{PF}$, 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 $\theta \in \mathcal{P}$ such that $\lambda_{PF}(M(\theta)) = 0$, which then implies that $(-1)^d \text{det}(M(\theta)) = 0$, or equivalently, that the negation of (c2) holds. This concludes the proof.

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

\[
\begin{aligned}
& \text{Find} & & u \in \mathbb{R}^d_{>0}, v \in \mathbb{R}^d_{>0} \\
& \text{s.t.} & & v^T c_1 > 0, v^T A^+ < 0, w^T A^- + e^T = 0
\end{aligned}
\]  
(25)
which has exactly the same complexity as the linear program (9). Hence, checking the possibility of controlling a family of networks defined by a characteristic interval-matrix is not more complicated that checking the possibility of controlling a single network.

\section{V. Robust Results}

Before stating the next main result of this section, let us assume that $S_u$ in Definition 6 has the following form:

\[
S_u = [S_{dg} \ S_{ct} \ S_{cv}]
\]  
(26)
where $S_{dg} \in \mathbb{R}^{d \times n_{dv}}$ 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 $\rho_u$ as $\rho_u =: \text{col}(\rho_{dg, ct, cv})$ and define

\[
\rho_u \in \mathcal{P}_u := [\rho_{\bullet} \rho_{\bullet}^+] > 0 \leq \rho_{\bullet}^+ < \infty
\]  

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 29: The following statements are equivalent.

a) The matrix $A(\rho_{dg})$ is Hurwitz stable for all $\rho_{dg} \in \mathcal{P}_{dg}$.

b) The matrix

\[
A^{+}(\rho_{cv}) := A(\rho_{dg}^{+}, \rho_{ct}^{+}, \rho_{cv})
\]  
(27)

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

\[
A(\rho_{dg}, \rho_{ct}, \rho_{cv}) \leq A^{+}(\rho_{cv}) = A(\rho_{dg}^{+}, \rho_{ct}^{+}, \rho_{cv})
\]  
(28)

since for all $\rho_{dg, ct, cv} \in \mathcal{P}_{u}$. Using the fact that for two Metzler matrices $B_1, B_2$, the inequality $B_1 \leq B_2$ implies $\lambda_{PF}(B_1) \leq \lambda_{PF}(B_2)$ [25], 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.

**B. Robust Ergodicity of Unimolecular Networks**

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

**Proposition 30:** Let us consider an irreducible open unimolecular reaction network $(\mathbf{X}, \mathcal{R})$ with parameter-dependent characteristic matrix $A(\rho_u), \rho_u \in \mathcal{P}_u$. Then, the following statements are equivalent.

a) The reaction network $(\mathbf{X}, \mathcal{R})$ is robustly ergodic.

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

c) The matrix

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

(29)

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

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

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

$$v(\rho_u)^T A^+(\rho_{cv}) < 0$$

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

**Proof:** The equivalence between the statement (a), (b) and (c) directly follows from Lemmas 28 and 29. 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

$$v(\rho_{cv})^T = -\mathbf{1}_d^T (-1)^d \det(A^+(\rho_{cv})) A^+(\rho_{cv})^{-1}$$

$$= (-1)^d \mathbf{1}_d \text{Adj}(A^+(\rho_{cv})) > 0$$

(30)

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

**C. Robust Ergodicity of Bimolecular Networks**

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

**Proposition 31:** Let us consider an irreducible open bimolecular reaction network $(\mathbf{X}, \mathcal{R})$ with parameter-dependent characteristic matrix $A(\rho_u), \rho_u \in \mathcal{P}_u$. Then, the following statements are equivalent.

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

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

(31)

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

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

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

(32)

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

Moreover, when one of the above statements holds, then the network $(\mathbf{X}, \mathcal{R})$ is robustly ergodic.

**Proof:** It is immediate to see that (a) implies (b). To prove the converse, first note that we have that $v(\rho_{cv}) = (S_b^+)^T \tilde{v}(\rho_{cv})$ verifies $v(\rho_{cv})^T S_b = 0$ and $v(\rho_{cv})^T > 0$ for all $\rho_{cv} \in \mathcal{P}_{cv}$. This proves the equality and the first inequality in (31). Observe now that for any $\rho_u \in \mathcal{P}_u$, there exists a nonnegative matrix $\Delta(\rho_{dg}, \rho_{ct}) \in \mathbb{R}_{d-0}^{d \times d}$ such that $A(\rho_u) = A^+(\rho_{cv}) - \Delta(\rho_{dg}, \rho_{ct})$. Hence, we have that

$$v(\rho_{cv})^T A(\rho_u) = v(\rho_{cv})^T (A^+(\rho_{cv}) - \Delta(\rho_{dg}, \rho_{ct}))$$

$$\leq v(\rho_{cv})^T A^+(\rho_{cv}) < 0$$

(33)

which proves the implication. □

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 $v(\rho_{cv})^T S_b^+ A^+(\rho_{cv}) < 0$ can be sometimes brought back to a problem of the form $\tilde{v}(\rho_{cv})^T M(\rho_{cv}) < 0$ for some square, and sometimes Metzler, matrix $M(\rho_{cv})$ which can be dealt in the same way as in the unimolecular case.

**D. Robust Output Controllability of Unimolecular Networks**

In this case, we have the following result.

**Proposition 32:** The following statements are equivalent.

a) The parameter-dependent system $(A(\rho_u), e_i, e_j^T), \rho_u \in \mathcal{P}_u$, is robustly output-controllable.

b) For all $\rho_u \in \mathcal{P}_u$, there exists a vector-valued function $w : \mathcal{P}_u \mapsto \mathbb{R}_{d-0}^d$ and a function $\mu : \mathcal{P}_u \mapsto \mathbb{R}_{d-0}$ verifying $w(\rho_u)^T e_i > 0$ and $w(\rho_u)^T A(\rho_u) - \mu(\rho_u) I_d + e_j^T I_d = 0$ for all $\rho_u \in \mathcal{P}_u$.

c) There exists a vector $w_\ast \in \mathbb{R}_{d-0}^d$ and a scalar $\mu_\ast \in \mathbb{R}_{d-0}$ verifying $w_\ast^T e_i > 0$ and $w_\ast^T (I_d - \mu_\ast I_d) + e_j^T I_d = 0$ where $A^- := A(\rho_{dg}, \rho_{ct}, \rho_{cv})$.

Moreover, when the matrix $A(\rho_u)$ is Hurwitz stable for all $\rho_u \in \mathcal{P}_u$, then the statement (b) holds with $\mu \equiv 0$.

**Proof:** The proof of this result follows from the same lines as the proof of Proposition 26 with the difference that the parameter $\rho_{cv}$ is now present. However, we know from Proposition 2 that only the location of the nonzero off-diagonal elements matters from the output-controllability. In this respect, the worst-case happens whenever the reaction rates of the catalytic and conversion reactions are the smallest. The final statement follows from the same reasons as in Proposition 2. □

**E. Robust Antithetic Integral Control of Unimolecular Networks**

**Theorem 33:** Let us consider an open unimolecular reaction network $(\mathbf{X}, \mathcal{R})$ with parameter-dependent characteristic matrix $A(\rho_u), \rho_u \in \mathcal{P}_u$ and parameter-dependent offset vector $b_0(\rho_u), \rho_u \in \mathcal{P}_0$. Assume further that the closed-loop reaction
network \(((X, Z), R \cup R^c)\) is irreducible. Then, the following statements are equivalent:

a) The open-loop reaction network \((X, R)\) is robustly ergodic and the system \((A(\rho_s), e_1, e_f^T)\) is robustly output controllable.

b) There exist two vector-valued functions \(v_+: \mathcal{P}_{cv} \mapsto \mathbb{R}^d_{\geq 0}, \ w_-: \mathcal{P}_{cv} \mapsto \mathbb{R}^d_{\geq 0}\) such that \(v_+(\rho_0)T A^+(\rho_0) < 0, \ w_-(\rho_0)T e_1 > 0\) and \(w_-(\rho_0)T A^- (\rho_0) + e_f^T = 0\).

Moreover, when one of the above statements holds, then the closed-loop reaction network \(((X, Z), R \cup R^c)\) is robustly ergodic and we have that \(\mathbb{E}[X(t)] \to \mu/\theta\) as \(t \to \infty\) for any values for the controller rate parameters \(\eta, k > 0\) provided that

\[
\frac{\mu}{\theta} > \frac{v_+(\rho_0)T A^+(\rho_0)}{\alpha v_+(\rho_0)T e_f} \tag{34}
\]

and

\[
v_+(\rho_0)^T (A^+(\rho_0) + \alpha I_d) \leq 0 \tag{35}
\]

for some \(\alpha > 0\) and for all \(\rho_0 \in \mathcal{P}_{cv}\).

Proof: The equivalence between the statements (a) and (b) follows from Propositions 30 and 32. The concluding statement is an adaptation of that of Theorem 10.

The above result can be exactly formulated as the following infinite-dimensional linear program

\[
\begin{align*}
\text{Find } & v: \mathcal{P}_{cv} \mapsto \mathbb{R}^d_{\geq 0}, \ w: \mathcal{P}_{cv} \mapsto \mathbb{R}^d_{\geq 0} \\
\text{s.t. } & w(\rho_0)T e_1 > 0, \ v(\rho_0)T A^+(\rho_0) < 0, \\
& w(\rho_0)T A^- (\rho_0) + e_f^T = 0, \ \text{for all } \rho_0 \in \mathcal{P}_{cv} \tag{36}
\end{align*}
\]

which has a higher complexity than the previous feasibility problems due to its infinite-dimensional nature. However, from Propositions 30 and 32, we know that it is enough to look for polynomials of degree \(d - 1\). Hence, polynomial optimization methods can be used to solve this problem (see e.g., [27]–[32]).

VI. SIGN RESULTS

The objective of this section is to prove analogues of the ergodicity and output-controllability results of Section II whenever the parameters take arbitrary positive values.

A. Sign-Ergodicity of Unimolecular Networks

The following result proved in [33] will turn out to be a key ingredient for deriving the main result of this section.

Proposition 34 (see [33]): Let us consider an irreducible open unimolecular reaction network \((X, R)\) with sign characteristic matrix \(S_A\) and sign offset vector \(S_0\). Assume further that the closed-loop reaction network \(((X, Z), R \cup R^c)\) is irreducible. Then, the following statements are equivalent:

a) The open-loop reaction network \((X, R)\) is sign-ergodic and the system \((S_A, e_1, e_f^T)\) is sign output controllable.

b) All the matrices in \(\mathcal{Q}(S_A)\) are sign Hurwitz stable.

c) The sign \(\text{sgn}(S_A)\) is Hurwitz stable.

d) The diagonal elements of \(\Sigma\) are negative and the directed graph \(G_{S_A} = (V, E)\) defined with

\[
\begin{align*}
V : &= \{1, \ldots, d\} \\
E : &= \{(m, n): e_m^T \Sigma e_n \neq 0, \ m, n \in V, \ m \neq n\}
\end{align*}
\]

is an acyclic directed graph.

B. Sign Output-Controllability of Unimolecular Networks

We have the following result.

Proposition 35: The following statements are equivalent:

a) The sign system \((S_A, e_1, e_f^T)\) is sign output-controllable.

b) For all \(A \in \mathcal{Q}(S_A)\), there exists a vector \(w \in \mathbb{R}^d_{\geq 0}\) verifying \(w^T e_1 > 0\) and \(w^T (A - \mu I_d) + e_f^T = 0\).

c) There exists a vector \(w \in \mathbb{R}^d_{\geq 0}\) and a scalar \(\mu \in \mathbb{R}_{\geq 0}\) verifying \(w^T e_1 > 0\) and \(w^T (\text{sgn}(A) - \mu I_d) + e_f^T = 0\).

Moreover, if all the matrices in \(\mathcal{Q}(S_A)\) are Hurwitz stable then the above statements hold with \(\mu = 0\).

Proof: The equivalence between the statements (a) and (b) follows from Proposition 2 and the definition of sign output controllability. The implication that (b) implies (c) is also immediate. To show the reverse direction, it is enough to notice that the output-controllability only depends on the location of the nonzero off-diagonal entry [see Proposition 2, (e)] and is therefore a structural property. The final statement follows from Proposition 2.

C. Sign Antithetic Integral Control of Unimolecular Networks

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

Theorem 36: Let us consider an open unimolecular reaction network \((X, R)\) with sign characteristic matrix \(S_A\) and sign offset vector \(S_0\). Assume further that the closed-loop reaction network \(((X, Z), R \cup R^c)\) is irreducible. Then, the following statements are equivalent:

a) The open-loop reaction network \((X, R)\) is sign ergodic and the system \((S_A, e_1, e_f^T)\) is sign output controllable.

b) There exist vectors \(v \in \mathbb{R}^d_{\geq 0}\) and \(w \in \mathbb{R}^d_{\geq 0}, w_1 > 0\) such that the conditions hold

\[
v^T \text{sgn}(S_A) < 0 \text{ and } w^T \text{sgn}(S_A) + e_f^T = 0. \tag{37}
\]

Moreover, when one of the above statements holds, then the closed-loop reaction network \(((X, Z), R \cup R^c)\) is sign ergodic and we have that \(\mathbb{E}[X(t)] \to \mu/\theta\) as \(t \to \infty\) for any values for the controller rate parameters \(\eta, k > 0\) and each \((A, b_0) \in \mathcal{Q}(S_A) \times \mathcal{Q}(S_b)\) provided that

\[
\frac{\mu}{\theta} > \frac{v^T b_0}{\alpha e_f^T v} \tag{38}
\]

where \(\alpha > 0\) and \(v \in \mathbb{R}^d_{\geq 0}\) verify \(v^T (A + c I) \leq 0\).

Proof: The equivalence between the statements (a) and (b) follows from Propositions 34 and 35. The conclusion follows from an adaptation of that of Theorem 10.

The above result naturally translates into the following linear program:

\[
\begin{align*}
\text{Find } & v: \mathbb{R}^d_{\geq 0}, \ w: \mathbb{R}^d_{\geq 0} \\
\text{s.t. } & w^T e_1 > 0, v^T \text{sgn}(S_A) < 0, w^T \text{sgn}(S_A) + e_f^T = 0 \tag{39}
\end{align*}
\]

which has the same complexity as in the nominal and the interval case.
 VII. STRUCTURAL RESULTS

Similarly as for the interval approach, the sign approach fails to be tight in the presence of conversion reactions. The structural approach is developed here to complement this.

A. Preliminary Result

The following result will play an instrumental role in proving the results in this section:

Lemma 37: Let $A(ρ_u) ∈ R^{d×d}$ be the characteristic matrix of some unimolecular network and $ρ_u ∈ P_u$. Then, the following statements are equivalent:

a) For all $ρ_{dg} ∈ P_{dg}$ and $ρ_{cv} ∈ P_{cv}$, the matrix $A(ρ_{dg}, ρ_{cv}, 0)$ is Hurwitz stable.

b) The matrix $A(I, ρ_{cv}, 0)$ is Hurwitz stable for all $ρ_{cv} ∈ P_{cv}$.

Proof: The proof that (a) implies (b) is immediate. To prove the reverse implication, we use contradiction and we assume that there exist a $ρ_{dg} ∈ P_{dg}$ and a $ρ_{cv} ∈ P_{cv}$ such that $A(ρ_{dg}, ρ_{cv}, 0)$ is not Hurwitz stable. Then, we clearly have that

$$A(ρ_{dg}, ρ_{cv}, 0) ≤ A(θI, ρ_{cv}, 0)$$

(40)

where $θ = min(ρ_{dg})$ and hence $A(θI, ρ_{cv}, 0)$ is not Hurwitz stable. Since $A(θI, ρ_{cv}, 0)$ is affine in $θ$ and $ρ_{cv}$, then we have that $θA(I, ρ_{cv}, θ, 0)$ and since $θ$ is independent of $ρ_{cv}$, then we get that the matrix $A(I, ρ_{cv}, 0)$ is not Hurwitz stable for some $ρ_{cv} ∈ P_{cv}$. The proof is complete.

B. Structural Ergodicity of Unimolecular Networks

We have the following result:

Proposition 38: Let us consider an open irreducible unimolecular reaction network $(X, R)$ with parameter-dependent characteristic matrix $A(ρ_u) , ρ_u ∈ P_u$. Then, the following statements are equivalent:

a) The reaction network $(X, R)$ is structurally ergodic.

b) The matrix $A(ρ_u)$ is Hurwitz stable for all $ρ_u ∈ R^{n_u>0}$.

c) There exists a polynomial vector $v(ρ_u) ∈ R^d$ of degree at most $d−1$ such that $v(ρ_u) > 0$ and $v^T A(ρ_u) < 0$ for all $ρ_u ∈ R^{n_u>0}$.

d) There exists a $ρ_u ∈ R^{n_u>0}$ such that the matrix $A(ρ_u)$ is Hurwitz stable and the polynomial $−1^d det(A(ρ_u))$ is positive for all $ρ_u ∈ R^{n_u>0}$.

e) For all $ρ_{dg} ∈ R^{n_{dg}>0}$ and $ρ_{cv} ∈ R^{n_{cv}≥0}$, the matrix $A_p := A(ρ_{dg}, ρ_{cv}, 0)$ is Hurwitz stable and we have that $θ(W_{A_p} A_p^{-1} S_{ct}) = 0$.

f) The matrix $A_{bg}(ρ_{cv}) := A(I, ρ_{cv}, 0)$ is Hurwitz stable for all $ρ_{cv} ∈ R^{n_{cv}≥0}$ and $θ(W_{A_p} A_{bg}(ρ_{cv})^{-1} S_{ct}) = 0$ for all $ρ_{cv} ∈ R^{n_{cv}≥0}$.

Moreover, when each column of $S_{ct}$ contains exactly one entry equal to $−1$ and one equal to $1$, then the above statements are also equivalent to

f) The matrix $A_{I} := A(I, I, 0)$ is Hurwitz stable and $θ(W_{A_I} A_{I}^{-1} S_{ct}) = 0$.

g) There exist vectors $v_c ∈ R^{d_{cv}>0}$, $v_d ∈ R^{d_{dg}>0}$, $w ∈ R^{d_{cv}>0}$ such that $v_c^T A_{I} < 0$ and $v_d^T (sgn(W_{A_{I}} A_{I}^{-1} S_{ct}) − I_d) < 0$.

Proof: The equivalence between the three first statements has been proved in Proposition 30. Let us prove now that (c) implies (d). Assuming that (c) holds, we get that the existence of a $ρ_u = col(ρ_{dg}, ρ_{cv}, ρ_{ct})$ such that the matrix $A(ρ_u)$ is Hurwitz stable immediately implies that the matrix $A_p := A(ρ_{dg}, ρ_{cv}, 0)$ is Hurwitz stable since we have that $θ ≤ A(ρ_{dg})$ and, therefore $λ_{PF}(A_p) ≤ λ_{PF}(A(ρ_{dg})) < 0$. Using now the determinant formula, we have that

$$det(A(ρ_u)) = det(I + D(ρ_u) W_{ct} A_p^{-1} S_{ct})$$

(41)

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

$$det(I + D(ρ_u) W_{ct} A_p^{-1} S_{ct}) > 0$$

(42)

for all $ρ_u ∈ R^{n_u>0}$. Since the matrices $W_{ct}, S_{ct}$ are nonnegative, the diagonal entries of $D(ρ_u)$ are positive and $A_p^{-1}$ is nonpositive (since $A_p$ is Metzler and Hurwitz stable), then it is necessary that all the eigenvalues of $W_{ct} A_p^{-1} S_{ct}$ 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 $A_p$ is Hurwitz stable, then $A_p + ϵ S_{ct} W_{ct}$ remains Hurwitz stable for some sufficiently small $ϵ > 0$. This proves the existence of a $ρ_u ∈ R^{n_u>0}$ such that the matrix $A(ρ_u)$. 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 37 and the fact that the sign-pattern of the inverse of a Hurwitz stable Metzler matrix is uniquely defined by its sign-pattern (see [14]).

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

$$A_{22}(ρ_{dg}, ρ_{cv}) := \begin{bmatrix} 0 & I \\ I & A(ρ_{dg}, ρ_{cv}, 0) \end{bmatrix}$$

(43)

is Hurwitz stable for all $(ρ_{dg}, ρ_{cv}) ∈ R^{n_{dg}>0} × R^{n_{cv}≥0}$. Note that this is a necessary condition for the matrix $A(ρ_{dg}, ρ_{cv}, 0)$ to be Hurwitz stable for all rate parameters values. Hence, this means that the stability of the matrix $A_p$ is equivalent to the Hurwitz stability of $A_{I} := A(I, I, 0)$. Finally, since $A_{22}(ρ_{dg}, ρ_{cv})$ is Hurwitz stable, then we have that $I_d^T A_{22}(I, I) < 0$.

Finally, the equivalence between (f) and (g) follows from Proposition 1 and the fact that the nonnegative matrix $W_{ct} A_{I}^{-1} S_{ct}$ has a zero spectral radius if and only if all its diagonal elements are zero and its directed graph is acyclic [14]. This is equivalent to say that the matrix $sgn(W_{ct} A_{I}^{-1} S_{ct})$ satisfies the same conditions or, equivalently that $sgn(W_{ct} A_{I}^{-1} S_{ct}) − I_d$ is Hurwitz stable. The conclusion then follows.
C. Structural Output Controllability
of Unimolecular Networks

We have the following result.

**Proposition 39.** The following statements are equivalent:

a) The parameter-dependent system \( (A(\rho_u), e_1, e_T^f) \), \( \rho_u \in \mathcal{P}_u^\infty \), is structurally output-controllable.

b) For all \( \rho_u \in \mathcal{P}_u^\infty \), there exist a vector-valued function \( w : \mathcal{P}_u^\infty \to \mathbb{R}_{d_0}^2 \) and a function \( \mu : \mathcal{P}_u^\infty \to \mathbb{R}_{>0} \) verifying

\[
w(\rho_u)^T e_i > 0 \quad \text{and} \quad w(\rho_u)^T(A - \mu(\rho_u)I_d) + e_T^f = 0.
\]

c) There exists a vector \( w \in \mathbb{R}_{d_0}^2 \) and a scalar \( \mu \in \mathbb{R}_{>0} \) verifying \( w^T e_i > 0 \) and \( w^T (\text{sgn}(A) - \mu I_d) + e_T^f = 0 \).

Moreover, if all the matrices in \( \{A(\rho_u) : \rho_u \in \mathcal{P}_u^\infty\} \) are Hurwitz stable then the above statements hold with \( \mu \equiv 0 \).

**Proof:** The equivalence between the statements (a) and (b) follows from Proposition 2 and the definition of sign output controllability. To show the equivalence with the statement (c), it is enough to notice that the output controllability only depends on the location of the nonzero off-diagonal entry [see Proposition 2, (e)] and is therefore a structural property. The final statement follows from Proposition 2.

D. Structural Antithetic Integral Control
of Unimolecular Networks

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

**Theorem 40.** Let us consider an open unimolecular reaction network \( (X, R) \) with parameter-dependent characteristic matrix \( A(\rho_u), \rho_u \in \mathcal{P}_u^\infty \) and parameter-dependent offset vector \( b_0(\rho_u), \rho_u \in \mathbb{R}_{d_0}^\infty \). Assume further that each column of \( S_{cv} \) contains exactly one entry equal to \(-1\) and one equal to \(1\) and that the closed-loop reaction network \( ((X, Z), R \cup R_c) \) is irreducible. Then, the following statements are equivalent:

a) The open-loop reaction network \( (X, R) \) is structurally ergodic and the system \( (A(\rho_u), e_1, e_T^f) \) is structurally output-controllable.

b) There exist vectors \( v_c \in \mathbb{R}_{d_0}^n, v_d \in \mathbb{R}_{d_0}^m, w \in \mathbb{R}_{d_0}^n \) such that the conditions hold

\[
v_c^T A_1 < 0, \quad v_T^f (\text{sgn}(W_{ct} A_1^1 S_{ct}) - I_d) < 0
\]
\[
w^T e_1 > 0, \quad w^T \text{sgn}(A) + e_T^f = 0
\]

Moreover, when one of the above statements holds, then the closed-loop reaction network \( ((X, Z), R \cup R_c) \) is structurally ergodic and we have that \( \mathbb{E}[X_i(t)] \to \mu/\theta \) as \( t \to \infty \) for any values for the controller rate parameters \( \eta, k > 0 \) and each \( (\rho_u, \rho_0) \in \mathcal{P}_u^\infty \times \mathbb{R}_{d_0}^\infty \) provided that

\[
\frac{\mu}{\theta} > \frac{v_T^f b_0(\rho_0)}{\alpha e_T^f v}
\]

with \( \alpha > 0 \) and \( v \in \mathbb{R}_{d_0}^m \) verify \( v^T (A(\rho_u) + \alpha I_d) \leq 0 \).

**Proof:** The equivalence between the two statements follows from Propositions 38 and 39. The concluding statement is an adaptation of that of Theorem 10.

VIII. Examples

A. SIR Model: Structural Ergodicity of a Bimolecular Network

Let us consider the open irreducible stochastic SIR model considered in [6] described by the matrices

\[
A = \begin{bmatrix}
-\rho_{ag} & 0 & \rho_{cv}^2 \\
0 & -\rho_{ag} + \rho_{cv}^1 & 0 \\
0 & \rho_{cv}^1 & -\rho_{ag} - \rho_{cv}^2
\end{bmatrix}, \quad S_b = \begin{bmatrix}
-1 \\
0 \\
0
\end{bmatrix}
\]

(46)

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

\[
\begin{bmatrix}
-\rho_{ag} + \rho_{cv}^1 \\
\rho_{cv}^2 \\
-\rho_{ag} - \rho_{cv}^2
\end{bmatrix} < 0.
\]

(47)

Since the entries are not independent, the corresponding sign-matrix is not sign-stable whereas this matrix is clearly structurally stable. Similarly, the associated interval matrix may fail to be interval stable even in the case when it would be robustly stable. The latter only holds if the diagonal entries are negative and bounded away from 0.

B. Antithetic Integral Control of an Uncertain Unimolecular Reaction Network

Let us consider an open unimolecular irreducible reaction network \( (X, R) \) with characteristic matrix \( A(\rho_u) \) given by

\[
\begin{bmatrix}
-\rho_{ag} & 0 & 0 & \rho_{ct}^3 \\
\rho_{cv}^1 & -\rho_{ag}^2 - \rho_{cv}^1 & 0 & 0 \\
\rho_{ct}^2 & 0 & -\rho_{ag} - \rho_{cv}^2 + \rho_{ct}^4 & \rho_{cv}^4 \\
0 & \rho_{ct}^2 & \rho_{cv}^4 & -\rho_{ag} - \rho_{cv}^4
\end{bmatrix}
\]

(48)

with \( \rho_u = (\rho_{ag}, \rho_{cv}, \rho_{ct}) \). The goal is to act on the first species to control the last one. Hence, we have \( b = e_1 \) and \( c = e_4 \). We also assume that the set \( \mathcal{P}_u \) is compact for simplicity. The following statements hold.

(Obs1) The network is interval output-controllable if and only if \( \rho_{ag} - \rho_{cv}^1 > 0 \) or \( \rho_{ct}^2 - \rho_{cv}^2 > 0 \).

( Obs2) The network is robustly output-controllable under the same conditions.

( Obs3) The network is sign output-controllable.

( Obs4) The network is structurally output-controllable.

We now focus on the ergodicity property of the associated network. The ergodicity conditions given below also preserve the output-controllability of the network:

( Erg1) The network is interval ergodic if and only if the associated \( A^+ \) matrix is Hurwitz stable.
(Erg2) The network is robustly ergodic if and only if
\[ \rho_{dg}^1 \rho_{ce}^4 - \rho_{dt}^3 (\rho_{et}^4 + \rho_{ct}^2) > 0. \]
(Erg3) The network is sign ergodic if and only if \( \rho_{ct}^3 = \rho_{et}^4 = 0, \rho_{ct}^2 = 0. \)
(Erg4) The network is structurally ergodic if and only if \( \rho_{ct}^3 = \rho_{et}^4 = 0. \)

By mixing the different conditions, we then immediately obtain the associated conditions for the antithetic integral control of the reaction network.

References

[1] C. Briat, A. Gupta, and M. Khammash, “Antithetic integral feedback ensures robust perfect adaptation in noisy biomolecular networks,” Cell Syst., vol. 2, pp. 17–28, 2016.

[2] J. Goutsias and G. Jenkinson, “Markovian dynamics on complex reaction networks,” Phy. Rev. E, vol. 83, pp. 2099–2112, 2011.

[3] M. Thattai and A. van Oudenaarden, “Intrinsic noise in gene regulatory networks,” Proc. Nat. Acad. Sci., vol. 98, no. 15, pp. 8614–8619, 2001.

[4] M. B. Elowitz, A. J. Levine, E. D. Siggia, and P. S. Swain, “Stochastic gene expression in a single cell,” Sci., vol. 297, no. 5584, pp. 1183–1186, 2002.

[5] D. F. Anderson and T. G. Kurtz, Stochastic Analysis of Biochemical Systems, ser. Mathematical Biosciences Institute Lecture Series, vol. 1.2. Berlin, Germany: Springer Verlag, 2015.

[6] A. Gupta, C. Briat, and M. Khammash, “A scalable computational framework for establishing long-term behavior of stochastic reaction networks,” PLOS Comput. Biol., vol. 10, no. 6, 2014, Art. no. e1003669.

[7] C. Zechner, G. Seelig, M. Rullan, and M. Khammash, “Molecular circuits for dynamic noise filtering,” Proc. Nat. Academy Sci., vol. 113, no. 17, pp. 4729–4734, 2016.

[8] J. M. G. Vilar, H. Y. Kueh, N. Barkai, and S. Leibler, “Mechanisms of noise-resistance in genetic oscillator,” Proc. Nat. Acad. Sci., vol. 99, no. 9, pp. 5998–5992, 2002.

[9] J. Paulsson, O. G. Berg, and M. Ehrenberg, “Stochastic focusing: fluctuation-enhanced sensitivity in intracellular regulation,” Proc. Nat. Acad. Sci., vol. 97, no. 13, pp. 7148–7153, 2000.

[10] A. Gupta, B. Hepp, and M. Khammash, “Noise induces the population-level entrainment of incoherent, uncoupled intracellular oscillators,” Cell Syst., vol. 3, no. 6, 2016.

[11] D. Del Vecchio, A. J. Dy, and Y. Qian, “Control theory meets synthetic biology,” J. Roy. Soc. Interface, vol. 13, no. 120, 2016.

[12] C. Briat and M. Khammash, “Robust ergodicity and tracking in antithetic integral control of stochastic biochemical reaction networks,” in Proc. 55th IEEE Conf. Decis. Control, 2016, pp. 752–757.

[13] C. Briat and M. Khammash, “Robust and structural ergodicity analysis of stochastic biomolecular networks involving synthetic antithetic integral controllers,” in Proc. 20th IFAC World Congress, 2017, pp. 4051–4101.

[14] C. Briat, “Sign properties of Metzler matrices with applications,” Linear Algebra Appl., vol. 515, pp. 53–86, 2017.

[15] R. E. Moore, R. B. Kearfott, and M. J. Cloud, Introduction to Interval Analysis, Philadelphia, PA, USA: SIAM, 2009.

[16] C. Jeffries, V. Kle, and P. van den Driessche, “When is a matrix sign stable?” Can. J. Math., vol. 29, pp. 315–326, 1977.

[17] R. A. Brualdi and H. J. Ryser, Combinatorial Matrix Theory, Cambridge, UK: Cambridge Univ. Press, 1991.

[18] M. Cooper and B. Ghosh, “Stability of bounded subsets of metzler sparse matrix cones,” Linear Algebra Appl., vol. 421, pp. 544–547, 2004.

[19] J. W. Helton, V. Katsnelson, and I. Klep, “Sign patterns for chemical reaction networks,” J. Math. Chem., vol. 47, pp. 403–429, 2010.

[20] G. Giordano, C. Cebrian, E. Franco, and F. Blanchini, “Computing the structural influence matrix for biological systems,” J. Math. Biol., vol. 72, pp. 1927–1958, 2016.

[21] W. M. Haddad and V. Chellaboina, Stability and dissipativity theory for nonnegative dynamic systems: A unified analysis framework for biological and physiologic systems, Nonlinear Anal.: Real World Appl., vol. 6, pp. 35–65, 2005.

[22] D. Anderson and T. G. Kurtz, “Continuous time Markov chain models for chemical reaction networks,” in Design and analysis of biomolecular circuits—Engineering Approaches to Systems and Synthetic Biology, H. Koeppl, D. Dennismore, G. Setti, and M. di Bernardo, Eds. Berlin, Germany: Springer Science+Business Media, 2011, pp. 3–42.

[23] S. P. Meyn and R. L. Tweedie, “Stability of Markovian processes III: Foster-Lyapunov criteria for continuous-time processes,” Adv. Appl. Prob., vol. 25, pp. 518–548, 1993.

[24] A. Gupta and M. Khammash, “Computational identification of irreducible state-spaces for stochastic reaction networks,” SIAM J. Appl. Dyn. Syst., vol. 17, no. 2, pp. 1213–1266, 2018.

[25] A. Berman and R. J. Plemmons, Nonnegative Matrices in the Mathematical Sciences. Philadelphia, PA, USA: SIAM, 1994.

[26] W. Mitkowski, “Remarks on stability of positive linear systems,” Control Cybern., vol. 29, no. 1, pp. 295–304, 2000.

[27] D. Handelman, “Representing polynomials by positive linear functions on compact convex polyhedra,” Pacific J. Math., vol. 132, no. 1, pp. 35–62, 1988.

[28] C. Briat, “Robust stability and stabilization of uncertain linear positive systems via integral linear constraints - L1- and L∞-gains characterizations,” J. Robust Nonlinear Control, vol. 23, no. 17, pp. 1952–1954, 2013.

[29] M. Putinar, “Positive polynomials on compact semi-algebraic sets,” Indiana Univ. Math. J., vol. 42, no. 3, pp. 969–984, 1993.

[30] P. Parrilo, “Structured semidefinite programs and semialgebraic geometry methods in robustness and optimization,” Ph.D. dissertation, California Institute of Technology, Pasadena, California, 2000.

[31] J. B. Lasserre, “Global optimization with polynomials and the problem of moments,” SIAM J. Optim., vol. 11, no. 3, pp. 796–817, 2001.

[32] J.-B. Lasserre, Moments, Positive Polynomials and Their Applications. London, U.K.: Imperial College Press, 2010.

[33] C. Briat, “Sign properties of Metzler matrices with applications,” Linear Algebra Appl., vol. 515, pp. 53–86, 2017.

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