Abstract—We consider biochemical systems associated with a generalised class of Petri nets with possibly negative token numbers. We show that the existence of a structural polyhedral Lyapunov function for the biochemical system is equivalent to the boundedness of the associated Petri net evolution or, equivalently, to the finiteness of the number of states reachable from each initial condition. For networks that do not admit a polyhedral Lyapunov function, we investigate whether it is possible to enforce polyhedral structural stability by applying a strong negative feedback on some pinned nodes: in terms of the Petri net, this is equivalent to turning pinned nodes into black holes that clear any positive or negative incoming token. If such nodes are chosen so that the transformed Petri net has bounded discrete trajectories, then there exists a stabilising pinning control: the biochemical network becomes Lyapunov stable if a sufficiently strong local negative feedback is applied to the pinned nodes. These results allow us to structurally identify the critical nodes to be locally controlled so as to ensure the stability of the whole network.

I. INTRODUCTION AND MOTIVATION

Structural analysis investigates how several systems often encountered in nature enjoy important properties in view of their interconnection structure, regardless of parameter values. Here, we consider structural stability and stabilisation of biochemical networks [12], [18], [23], adopting piecewise-linear Lyapunov functions [8], [9], [10], which — along with the complementary piecewise-linear-in-rate Lyapunov functions [1], [2], [3], [9] that can be seen as their dual [11] — have proven effective in the stability analysis of chemical reaction networks. A recent contribution [4] shows that this type of functions can be very useful to detect, more in general, non-oscillatory behaviours.

Chemical reaction networks have been often analysed resorting to discrete-event frameworks, employing for instance Petri nets [3], [32]: a chemical reaction is seen as a process that assembles the needed number of reactant molecules and releases the proper number of product molecules.

In this paper, we show how the existence of a piecewise-linear Lyapunov function for the large class of unitary (bio)chemical networks can be interpreted as the boundedness of the evolution of a suitable generalised Petri net, which can have both positive and negative token numbers.

This generalisation of Petri nets has been widely investigated in the literature, e.g. under the name of lending Petri net [6] and negative tokens [32] have been also called anti-tokens [25], [36] or debit tokens [7], [28]. However, to the best of the authors’ knowledge, this is the first time that such a concept is associated with the stability of biochemical networks.

We also consider a structural pinning control problem. Pinning some nodes means applying a strong feedback to these nodes with the goal of controlling the whole network.

Pinning control has been extensively investigated in past years [29], [38], with one of the main driving questions being how many nodes to pin and which ones [33]. The approach has been used to address network control problems ranging from asymptotic convergence [21] and noise rejection [16] to consensus [17] and synchronisation [34]. Pinning techniques have been applied in different areas such as circuits [21], power grids [33], networked systems and gene regulatory networks [16]. Pinning control of a (bio)chemical reaction network system can be seen as equivalent to the conversion of the pinned nodes into black holes, which swallow any incoming token (either positive or negative), in the associated generalised Petri net.

The main contributions of this paper are summarised next.

• We formulate the structural stability problem for biochemical reaction networks (Section II) and we associate a biochemical network with a Generalised Petri Net (GPN), with possibly negative tokens (Section III).
• The GPN is fully determined by the network structure, and it does not depend on the (monotonic) reaction rate functions.
• The boundedness of all possible evolutions of the GPN is equivalent to the existence of a polyhedral Lyapunov function (PLF) for the biochemical system; such a PLF can be computed based on the efficient numerical procedure proposed in [8] (Section III-A).
• The equivalence with the GPN suggests more efficient stopping criteria for the numerical procedure (Section III-C).

For networks that do not admit a PLF, we study how to convert some nodes into black holes that swallow any incoming token (Section III-D), so as to ensure the stability of the network.

• We show that converting some nodes into black holes is equivalent to pinning them, i.e. virtually fixing their state variables to imposed values (Section IV); after pinning appropriately chosen nodes, the network can admit a PLF.
• We illustrate our results by assessing the structural stability, possibly after pinning suitably chosen nodes, of some examples from the biochemical literature, including transcription and translation models (Section V).
II. Problem Formulation

Consider the general class of biochemical systems

\[ \dot{x}(t) = Sg(x(t)) + g_0, \tag{1} \]

where the state vector \( x(t) \in \mathbb{R}^n \) includes the concentrations of the involved biochemical species, \( S \in \mathbb{Z}^{n \times m} \) is the stoichiometric matrix, the vector function \( g : \mathbb{R}^n_+ \to \mathbb{R}^m \) represents reaction rates, and \( g_0 \in \mathbb{R}^n_+ \) is a vector of constant influxes. We make the following standing assumptions.

Assumption 1: System (1) admits the equilibrium \( \bar{x} \in \mathbb{R}^n_+ \), such that

\[ 0 = Sg(\bar{x}) + g_0. \tag{2} \]

Assumption 2: The network is unitary [8], namely, each of the entries of matrix \( S \) is either 1, 0 or −1.

Assumption 3: Function \( g_k(x) \) is nonnegative and strictly monotonic (either increasing or decreasing) in each of its arguments; it depends on variable \( x_i \) if and only if \( S_{ik} = -1 \), and it is zero if and only if one of its arguments is zero.

Remark 1: Unitary networks, as in Assumption 2, cannot include multi-molecular reactions, such as \( 2X_1 + X_2 \rightarrow X_3 \). However, multi-molecular reactions are known to occur in fact as chains of bi-molecular reactions (e.g., \( X_1 + X_2 \rightarrow X_4 \) and \( X_1 + X_4 \rightarrow X_3 \)), which do lead to a unitary network. Note also that Assumption 2 rules out autocatalytic reactions (e.g. of the form \( X_1 \rightarrow 2X_1 \)), for which structural stability could never be guaranteed.

As shown in [8], [10], [12], the variable shift \( z(t) = x(t) - \bar{x} \) allows us to write the system in the equivalent form

\[ \dot{z}(t) = BD(z(t))Cz(t), \tag{3} \]

where \( D \) is a diagonal matrix with positive diagonal entries,

\[ D(z) = \text{diag}\{D_1(z), D_2(z), \ldots, D_q(z)\}, \quad D_k(z) > 0. \]

Matrices \( B, D \) and \( C \) are derived from (1) as follows:

- The diagonal entries of \( D \) are related to the absolute values of the \( q \) nonzero partial derivatives \( \partial g_j / \partial x_i \), with \( j \in \{1, \ldots, m\}, i \in \{1, \ldots, n\} \), arbitrarily ordered.
- The \( k \)th column of \( B, B_k \), corresponding to \( D_k \) related to \( |\partial g_j / \partial x_i| \), is equal to the column \( S_i \) of \( S \).
- The \( k \)th row of \( C, C_k^\top \), corresponding to \( D_k \) related to \( |\partial g_j / \partial x_i| \), has a single nonzero entry, the \( i \)th, equal to the sign of \( \partial g_j / \partial x_i \).

The proof [10], [12] relies on the fact that the Jacobian of \( Sg(x) \) can be written as \( J(x) = BDC \), where the diagonal matrix \( \Delta \) includes the absolute value of all partial derivatives, and on the integral formula

\[ Sg(x) - Sg(\bar{x}) = \int_0^1 J(\bar{x} + \sigma (x - \bar{x}))d\sigma \]

\[ = B \left[ \int_0^1 \Delta(\bar{x} + \sigma (x - \bar{x}))d\sigma \right] C(x - \bar{x}) = BD(x)C(x - \bar{x}). \]

Structural stability (which needs to hold regardless of the numerical values and functional expressions within matrix \( D \), [8], [10], [12]) can be studied by absorbing system (3) in a differential inclusion

\[ \dot{z}(t) = BD(t)Cz(t), \tag{4} \]

where \( D(t) \) is a positive definite diagonal matrix of size \( q \).

Example 1: Consider the biochemical reaction network \( 0 \xrightarrow{\beta V} X_1, X_1 \xrightarrow{\beta V} X_2 + X_3, X_1 + X_3 \xrightarrow{\beta V} \emptyset, X_2 \xrightarrow{\beta V} \emptyset \), admitting the graph representation in Fig. 1 left. The system evolution is described by the differential equations

\[ \begin{cases} \dot{x}_1 = u_1 - g_1(x_1) - g_13(x_1, x_3) \\ \dot{x}_2 = g_1(x_1) - g_2(x_2) \\ \dot{x}_3 = g_1(x_1) - g_13(x_1, x_3) \end{cases} \]

which can be recast in the form (3) with

\[ B = \begin{bmatrix} -1 & 0 & -1 \\ -1 & 0 & 0 \\ 0 & 1 & -1 \end{bmatrix}, \quad C = \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix}. \]

Remark 2: For unitary networks, satisfying Assumption 2, \( C_k^\top B_i = -1 \) for all \( i = 1, \ldots, q \).

Henceforth we work under an additional, mild assumption.

Assumption 4: There exist unknown bounds \( D_k^- > 0 \) and \( D_k^+ > 0 \) such that

\[ D_k^- \leq D_k \leq D_k^+, \quad k = 1, \ldots, q. \tag{5} \]

Definition 1: The system (3) under Assumptions 1, 4 is structurally stable if the differential inclusion (4) is Lyapunov stable (possibly marginally), while it is structurally asymptotically stable if (4) is asymptotically stable.

Remark 3: The purely technical Assumption 4 does not change the structural nature of our investigation. The upper bound \( D_k^+ \) ensures compactness and can be arbitrarily large. The arbitrarily small \( D_k^- \) ensures \( D_k \) to be bounded away from zero (cf. the \( \epsilon \)-perturbation in [4] Definition 2). For instance, the scalar system \( \dot{z}(t) = -D(t)z(t) \) is not necessarily asymptotically stable with the weaker bound \( D > 0 \) (e.g., if \( D(t) = \epsilon^{-t}, \dot{z} = -D(t)z(t) \), does not converge to 0), while stability is asymptotic if \( D(t) \geq D^- \).

III. Polyhedral Lyapunov Functions and Generalised Petri Net Boundedness

Definition 2: Given an uncertain dynamical system

\[ \dot{x} = f(x, w), \quad w \in W, \]

where \( W \) is a closed set, the positively homogeneous convex function \( V(x) \) is a Lyapunov function (LF) for the system \( \dot{x} = f(x, w) \) if, for some \( \beta \geq 0 \), the (generalised) Lyapunov derivative

\[ D^+ V(x, w) = \limsup_{h \to 0} \frac{V(x + hf(x, w)) - V(x)}{h} \leq -\beta V(x) \]

Fig. 1. Graph and GPN representation of the system in Example 1.
for all $x$ and $w \in \mathcal{W}$. The LF is weak if the inequality holds for $\beta = 0$, strong if $\beta > 0$. The LF $V(x)$ is polyhedral (PLF) if it can be written as

$$V(x) = \|Fx\|_\infty,$$

(6)

where matrix $F$ has full column rank, or

$$V(x) = \min\{\|p\|_1 : x = Xp\},$$

(7)

where matrix $X$ has full row rank. Polyhedral stability means that the system admits a PLF.

The procedure in [8] to generate a PLF for the system associates the original differential inclusion (4) with a discrete difference inclusion

$$y(k+1) = \Phi(k)y(k), \quad \Phi(k) \in F,$$

(8)

where

$$F = \{\Phi_i : \Phi_i = I + B_i C_i^T, \ i = 1, \ldots, q\}.$$

(9)

The procedure iterates over polyhedral sets, starting from the unit ball of the 1-norm: $Y^0 = \text{conv}\{[-I I]\}$, where conv denotes the convex hull.

Procedure 1: [8]

1. $Y^0 = I$, $Y^0 = \text{conv}\{[-Y^0 Y^0]\}$;
2. $Y^{k+1} := \{\Phi_1 \Phi_2 \ldots \Phi_q\}Y^k$;
3. $Y^{k+1} := \text{conv}\{[Y^{k+1} Y^{k+1}]\}$;
4. IF $Y^{k+1} = Y^k$, set $\hat{Y} = Y^k$ and STOP; ELSE go to step 2.

For a practical implementation, further stopping conditions should be added before the ELSE statement at step 4 of the procedure; otherwise, as currently stated, the procedure might fail to stop. Convergence issues are one of the aspects we will investigate: stopping criteria with a negative outcome (i.e., no structural PLF exists) will be discussed in Section III-C for numerical purposes.

If Procedure 1 stops, the polytope $\hat{Y} = Y^k$, with vertices $X = [-Y^k Y^k]$, is the unit ball of a PLF as in (7). If we apply the same procedure to the dual system $\dot{z} = C^*DB^Tz$, by considering $\Phi^*_i$, under convergence assumptions, we obtain the PLF in the dual form in (6) with $F = Y^T$, where $Y = [-Y^k Y^k]$. The efficient implementation of the procedure requires removing the redundant columns at each iteration $k$; see [8] for details.

The sequence $\tilde{Y}$ being formed by integer vectors drastically improves computability and provides efficient stopping criteria when the procedure fails to converge.

As proven in [8], the stability of the differential inclusion (4) is equivalent to the stability of (5); if (4) admits a (weak) PLF, then it is marginally stable, which implies that system (5), with $D(\tilde{z})$ continuous, is stable, and is asymptotically stable if and only if its Jacobian $BDC$ is structurally non-singular [10]. Moreover, if $C_i^*B_i = -1$, the stability of (4) is equivalent to the existence of a PLF for both (4) and (8), and also equivalent to the fact that Procedure 1 successfully stops in finite time. If $C_i^*B_i = -1$, systems (4) and (8) admit a structural (weak) Lyapunov function if and only if they admit a (weak) structural PLF. Hence, the existence of a PLF guarantees stability, and even asymptotic stability under structural non-singularity assumptions, as summarised in the following result.

**Theorem 1:** [10] Assume that system (4), under Assumptions (4) admits a (weak) PLF. Then, it is asymptotically stable if and only if matrix $BDC$ is non-singular for all possible matrices $D$ satisfying (5).

Asymptotic stability is shown to be exponential in [22].

**Remark 4:** Structural non-singularity is easy to check, as shown in [26]: it is equivalent to $\det[-BDC] > 0$ for all matrices $D$ on the vertices of the hyper-rectangle in [4].

### A. Generalised Petri net model

Procedure 1 can be interpreted as the evolution of a Generalised Petri Net (GPN), a discrete-event system that, albeit similar to a Petri net, does not work as a Petri net because the number of tokens at each node can be either positive or negative [32]. The integer vector $\tau(k)$ denotes the presence of $\tau_i(k)$ tokens in position $i$ at time $k$.

**Example 2:** The system in Example 1 can be associated with the difference inclusion $y(k+1) = \Phi(k)y(k)$, where, at each step $k$, $\Phi(k)$ is one of the following matrices:

$$\Phi_1 = \begin{bmatrix} 1 & 0 & 0 \\ 1 & 0 & 1 \\ 0 & 0 & 1 \end{bmatrix}, \ \Phi_2 = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 0 \end{bmatrix}, \ \Phi_3 = \begin{bmatrix} 0 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \ \Phi_4 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 1 & 0 \\ -1 & 0 & 1 \end{bmatrix}.$$

We start from the unit ball of the 1-norm, $X^0 = [-I I] = [-v_1 -v_2 -v_3 v_1 v_2 v_3]$, and consider just the positive vertices (the evolution of the others can be immediately obtained, being the opposite). Vertex $v_1 = [1 0 0]^T$ is transformed into $\Phi_1 v_1 = [1 1 1]^T = v_4$, $\Phi_2 v_1 = \Phi_3 v_1 = [1 0 0]^T = v_1$, $\Phi_4 v_1 = [0 0 1]^T = -v_3$; vertex $v_2 = [0 1 0]^T$ is transformed into $\Phi_1 v_2 = \Phi_2 v_2 = \Phi_3 v_2 = [0 1 0]^T = v_2$, $\Phi_4 v_2 = [0 0 1]^T = v_3$; vertex $v_3 = [0 0 0]^T$ is transformed into $\Phi_1 v_3 = \Phi_2 v_3 = \Phi_3 v_3 = [-1 0 0]^T = -v_1$. The sole newly generated vertex is $v_4 = [0 1 1]^T$ (and its opposite). The procedure applied to $v_2$ gives $\Phi_1 v_2 = \Phi_2 v_2 = [0 1 1]^T = v_4$, $\Phi_3 v_2 = [0 0 0]^T = v_3$, $\Phi_4 v_2 = [-1 1 0]^T = v_5$. Applying the procedure to the only new vertex, $v_5 = [-1 1 0]^T$, gives $\Phi_1 v_5 = [0 0 -1]^T = -v_3$, $\Phi_2 v_5 = [-1 0 0]^T = -v_1$, $\Phi_3 v_5 = [-1 1 0]^T = v_5$, $\Phi_4 v_5 = [0 1 1]^T = v_4$. No new vertices are generated at this step, hence the procedure stops successfully: the system admits a PLF having unit ball $\text{conv}\{[-X X]\}$, with $X = [v_1 v_2 v_3 v_4 v_5]$. The evolution of the discrete-time system in the numerical Procedure 1 can be related to the evolution of a particular discrete-event system, in which the initial conditions represent an initial marking $\tau(0)$, assigning an integer number of tokens to each node (associated with each of the chemical species), and a transition (associated with each of the black rectangles in Fig. 1 right, i.e. with each of the reactions occurring in the network) is enabled whenever at least one of the starting nodes of the transition contains a non-zero number of tokens. When either the number of tokens in the starting node is positive, or the starting nodes are two and the number of tokens in position in at least one of them, then the transition takes tokens from the starting node(s) and moves them to the arrival node(s), if explicitly present (otherwise, they simply disappear). When either the starting node is one only and the number of tokens therein is negative,
When a transition is enabled, and performed, all the tokens are
moved until one of the starting nodes has zero tokens. If one
token number is negative and the other positive, their effects
are superposed.

**Example 3:** For the system in Examples 1 and 2 the GPN
evolution is shown in Fig. 2 on the left side, the initial
marking is illustrated (enabled transitions are in green, non-
enabled transitions in red); on the right side, the new marking
generated by the action of each of the enabled transitions is
illustrated. Reaction I corresponds to the evolution matrix
$\Phi_1$ (and generates the same outcome for the same initial
conditions), reaction II corresponds to matrix $\Phi_2$ (and again
generates the same outcome for the same initial conditions),
while reaction III corresponds to matrices $\Phi_3$ and $\Phi_4$. In this
latter case, the outcome of (at least) one of the two evolution
matrices is the same as that of the transition related to reaction
III in the discrete-event evolution, while the outcome of the
other (if different) is always the unchanged input vertex.
Interestingly, the evolution is the very same as that of the
numerical procedure, and the same new vertices are generated
at each iteration.

**Proposition 1:** If $C_i^T B_i = -1 \forall i = 1, \ldots, q$, the
sequence generated by the discrete-time switching system (8)-
(9) uniquely corresponds to the evolution of a GPN discrete-
event system if the initial vector $y(0) = \tau(0)$ has integer
components.

**Proof:** To keep the notation simple, we assume that all
reactions are functions of at most two variables. The integer
operator $\Phi_h$ corresponds to the $i$th non-zero derivative, say
$\partial g_i/\partial x_j$. Consider the $i$th reaction $X_j + X_w \xrightarrow{h} X_t$. Then,

$$
\Phi_h = I + B_h C_h^T = I + S_i e_j^T
$$

where $S_i$ is the $i$th column of $S$ and $e_j^T$ is the $j$th canonical
row vector. Hence, $\Phi_h$ has all columns equal to the identity
matrix excluding the $j$th column. Column $j$ has the same entries as
$B_h = S_i$, excluding the diagonal entry $(i, j)$ which is 0 (see
Example 2). Operator $\Phi_h$ applied to any integer vector $\tau$ as
$\tau^+ = \Phi_h \tau$, a shorthand notation for $\tau(k + 1) = \Phi_h \tau(k)$,
corresponds to the following transition $T_h$ performed on the
Petri net:

1) $\tau^+_j = 0$ (remove $\tau_j$, i.e. all, tokens from node $j$);
2) $\tau^+_{\ell} = \tau_{\ell} + B_{\ell j} \tau_j = \tau_{\ell} + \tau_j$ (add $\tau_j$ tokens to node $\ell$);
3) $\tau^+_{w} = \tau_{w} + B_{w j} \tau_j = \tau_{w} - \tau_j$ (remove $\tau_j$ tokens from $w$).

This defines a one-to-one correspondence between matrix
$\Phi_h$ applied on integer vectors and the corresponding transition
$T_h$ (such that $\tau^+ = T_h \tau$).

Henceforth, we denote by $\Phi(h)$, $h = 0, 1, \ldots$, the generic
matrix sequence $\Phi(h) \epsilon \{\Phi_1, \Phi_2, \ldots, \Phi_q\} = F$. The family of
all their products,

$$
\Pi(F) \equiv \left\{ \prod_{h=0}^{K} \Phi(h), \ K \geq 0, \ \Phi(h) \in F \right\}, \quad (10)
$$

is an algebraic semigroup under the multiplication operation,
i.e., if both $P_1$ and $P_2$ are in $\Pi(F)$, then also $P_1 P_2 \epsilon \Pi(F)$.

**Theorem 2:** If $C_i^T B_i = -1 \forall i = 1, \ldots, q$, the following
statements are equivalent:

(i) for any initial integer token distribution vector $\tau(0) = \tau_0$,
the set of possible evolutions of the GPN $\tau(k+1) = T_k \tau(k)$, 
\[ \mathcal{R}(\tau_0) = \{\tau = T_\ell \circ T_{\ell-1} \cdots \circ T_0 \mid \tau_0, \ell \geq 0, T_\ell \text{ arbitrary}\}, \]
i.e. the reachable set from $\tau_0$, is finite. 
(ii) The semigroup $I(\mathcal{F})$ in (10) is finite.  
(iii) Procedure 1 stops in finite time. 

Proof: (i) ⇒ (ii): If the GPN generates a finite number of configurations given any initial token distribution $\tau(0)$, then from Proposition 1 for any integer $y(0)$, the number of states reached by $y(k+1) = \Phi(k)y(k)$, is finite, hence bounded. Since the generic trajectory given $y(0)$ has the form 
\[ y(k) = \Phi(k)y(0), \]
this implies that the products in the set $I(\mathcal{F})$ are uniformly bounded by some constant $\mu > 0$: $\|\prod_{h=0}^{k} \Phi(h)\| \leq \mu$. Then (ii) follows because all these products are integer matrices. (ii) ⇒ (iii): Procedure 1 does stop in finite time, because all the columns of the matrices $\mathcal{Y}^k$ are generated as $\prod_{h=0}^{k} \Phi(h)Y^0$, which are in a finite number.  
(iii) ⇒ (i): If Procedure 1 stops in finite time, the matrix family $\mathcal{F}$ admits the PLF induced by the final set $\mathcal{Y}$. Hence, for any integer initial condition $y(0)$ the sequence $y(k)$ is bounded and, being integer, it is finite. Statement (i) then follows from Proposition 1. 

B. Interpretation of the results 

Theorem 2 has an interesting biochemical interpretation, where tokens can be seen as molecules. The transition operators $T_k$ defined in the proof of Proposition 1 remove the tokens (if any) from some nodes (associated with species) so as to generate tokens at other nodes. The existence of a PLF is equivalent to the fact that no (infinite) sequence of these transitions can drive the token count to infinity at some node.  

Consider the important special case of mono-molecular reaction networks, where all the internal reactions have the form $X_i \xrightarrow{g_i} X_j$. Any transition just moves all tokens in a node (possibly a negative number) to another node leaving unchanged the total amount. For instance, if we initialise the network with just a token at node $0$, the set of all possibly reached states corresponds to a single token at some node. All mono-molecular reaction networks are associated with bounded GPNs: indeed they are nonlinear compartmental systems, well known to be structurally stable [30].  

Besides reactions of the form $X_i \xrightarrow{g_i} X_j$, let us consider internal reactions of the form $X_h + X_r \xrightarrow{g_{hr}} 0$ and $X_w \xrightarrow{g_w} 0$. The former new reaction introduces operators such that, if $x_h$ tokens are present at node $X_h$, they are removed ($x_h = 0$) and the opposite amount appears at node $X_r$, $x_r^+ = x_r - x_h$. The latter new reaction removes all the tokens present at node $X_w$ ($x_w^+ = 0$). Although the total amount of tokens now is not conserved, it cannot increase: hence, these GPNs are also bounded and the corresponding networks are structurally stable, in agreement with [8]. 

As a simple unbounded case, consider the reactions $\emptyset \xrightarrow{u_{X_1}} X_1, X_1 \xrightarrow{g_1} X_1 + X_2, X_2 \xrightarrow{g_2} X_1, X_3 \xrightarrow{g_3} X_1, X_2 \xrightarrow{g_2} 0$, $X_3 \xrightarrow{g_3} \emptyset$, associated with 
\[ \begin{align*} 
\dot{x}_1 &= u_1 - g_1(x_1) + g_2(x_2) + g_3(x_3) \\
\dot{x}_2 &= g_1(x_1) - g_2(x_2) - g_3(x_2) \\
\dot{x}_3 &= g_1(x_1) - g_3(x_3) \\
\end{align*} \]
The corresponding Petri net is not bounded. Start with just one token at $X_1$. Then $\partial g_1/\partial x_1$ can act producing two tokens, one at $X_2$ and one at $X_3$. Then $g_2$ and $g_3$ can both act to transfer the two tokens back at $X_1$. Repeating the argument, we see an unbounded increase of tokens at node 1. Indeed, the Jacobian $J = BDC$, where 
\[ B = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 \\
1 & -1 & 0 & 1 & 0 \\
0 & 1 & 0 & 1 & 0 \\
0 & 0 & 1 & 1 & 1 \\
0 & 0 & 0 & 0 & 0 \\
\end{bmatrix}, \quad C = \begin{bmatrix} 1 & 0 & 0 \\
0 & 1 & 0 \\
0 & 0 & 1 \\
0 & 0 & 0 \\
0 & 0 & 0 \\
\end{bmatrix}, \]
is not structurally Hurwitz: $\det[-J] = D_1(D_4D_5 - D_2D_3)$, the constant term of the characteristic polynomial, can be negative. 

Remark 5: (Stoichiometric compatibility class.) If the network evolves in a proper stoichiometric compatibility class, namely $\sigma^T S = 0$ for some vector $\sigma \neq 0$, so that $\sigma^T B = 0$, we have a conservation law: $\dot{\sigma^T z}(t)$ is constant. This property is preserved by the discrete operators $\Phi_h$: $\sigma^T y^+ = \sigma^T [I + B_hC_h^0] y = \sigma^T y$. For our analysis, we can reduce the system by applying a state transformation that turns $BDC$ into $T^{-1} BDCT \equiv \hat{BDC}$ and then neglecting some of the variables (see Example 7); the key condition $C_h^0 B_h = C_h^0 \hat{B}_h = -1$ is invariant. Therefore, if $T$ and its inverse are integer matrices, as usually happens, the proposed theory applies without changes. 

Interestingly, the convergence of Procedure 1 (i.e., the fact that the procedure stops in finite time) implies that the joint spectral radius [27] of the matrix family $\mathcal{F}$ is equal to one: 
\[ \sigma(\mathcal{F}) \doteq \lim_{k \to 0} \max_{\Phi(\cdot) \in \mathcal{F}} \|\Phi(1)\Phi(2)\Phi(3)\cdots\Phi(k)\|^\frac{1}{k} = 1. \]
Indeed, the convergence of Procedure 1 implies the boundedness of the trajectories, hence $\sigma(\mathcal{F}) \leq 1$. Conversely, since $C_h^0 B_h = C_h^0 \hat{B}_h = -1$, matrix $I + B_hC_h$ admits 1 as an eigenvalue, hence the spectral radius cannot be smaller than 1. 

Boundedness of the GPN evolution is equivalent to polyhedral stability, and the GPN evolves according to an asynchronous mechanism: hence, the different time scales of the system components play no role in defining its stability properties. To formalise this concept, we modify system (1) as 
\[ \Theta \dot{x} = S g(x) + g_0, \tag{11} \]
where $\Theta = \text{diag}\{\theta_1, \theta_2, \ldots, \theta_n\} \succ 0$ is a diagonal matrix of positive time constants. 

Proposition 2: Structural polyhedral stability, guaranteed when Procedure 1 stops in finite time, implies the structural stability of system (11) for any arbitrary diagonal $\Theta \succ 0$.  

Proof: Scaling the state variable as $y = \Theta x$ turns equation (11) into $\dot{y} = \hat{S} g(\Theta^{-1} y) + g_0$. The proof follows immediately by noticing that matrices $B$ and $C$ are the same regardless of $\Theta$, while the derivatives are scaled as $\partial g_i/\partial y_j = \Theta_j^{-1} \partial g_i/\partial x_j$, which does not alter their sign. ■
C. Stopping criteria for Procedure 2

The procedure may fail to converge; in this case, the system does not admit any structural PLF. A possible stopping criterion, proposed in [3], is to interrupt the procedure when either the size of the region \(Y^k\) reaches a bound \(\mu\), or an assigned maximum number of steps, \(n_{\text{max}}\), is reached.

We discuss here other possible criteria. The procedure will never converge if, for some \(k\), \(Y^k\) includes the original region \(Y^0\) in its interior [13]. The inclusion of the initial polytope, with vertex matrix \([-I \ I]\), should be checked at each step; this can be done as follows.

**Proposition 3:** If the polytope \(Y = \text{conv}\{[-Y, Y]\}\) has a non-empty interior, then it includes \(Y^0 = \text{conv}\{[-I, I]\}\) in its interior if and only if

\[
\nu_i = \min\{||p_i||_1 : Y p_i = e_i\} < 1, \quad i = 1, 2, \ldots, n, \quad (12)
\]

where \(||p||_1 = \sum |p_i|\) is the 1-norm and \(e_i\) is the \(i\)th vector of the canonical basis.

**Proof:** From expression (7) we see that \(\nu_i = V_Y(e_i)\), where \(V_Y\) is the polyhedral norm with unit ball \(Y\). Vector \(e_i\) (along with its opposite \(-e_i\)) is in the interior of \(Y\) iff \(\nu_i = V_Y(e_i) < 1\). Moreover, \(Y^0 = \text{conv}\{[-I, I]\}\) is in the interior of \(Y\) iff it vertices, i.e., \(\pm e_i\), are in the interior. \(\blacksquare\)

Note that problem (12) can be solved via linear programming and allows to efficiently stop the procedure at an early stage when the system does not admit a structural PLF.

Another stopping criterion relies on eventually periodic matrices. A square matrix \(M\) is said **eventually periodic** if there exist a non-negative integer \(m\) and a positive integer \(p\) such that

\[
M^m = M^{m+kp} \quad \text{for all integer } k \geq 0. \quad (13)
\]

**Proposition 4:** If the square matrix \(M\) is eventually periodic, then its eigenvalues are either zero or roots of the unity.

**Proof:** Take the eigenpair \((\lambda, v)\), \(M v = \lambda v, v \neq 0\). If \(M\) is eventually periodic,

\[
(M^m - M^{m+kp})v = \lambda^m (1 - \lambda^{kp})v = 0.
\]

Then \(\lambda^m (1 - \lambda^{kp}) = 0\), i.e., \(\lambda\) must be either 0 or a root of the unity. \(\blacksquare\)

**Proposition 5:** The set \(\Pi(F)\) is a finite set only if each matrix in \(\Pi(F)\) is eventually periodic.

**Proof:** By contradiction, if a matrix in \(\Pi(F)\) is not eventually periodic, then its powers form an infinite sequence of different matrices, hence the set \(\Pi(F)\) is infinite. \(\blacksquare\).

The previous condition is not sufficient; even if all matrices are eventually periodic, there can be an infinite sequence of products among them. Combining Propositions 4 and 5 yields the following corollary.

**Corollary 1:** If \(\Pi(F)\) includes a matrix whose eigenvalues are not either zero or roots of the unity, then it has infinite cardinality.

**Remark 6:** To check the condition, there is no need to compute all the products in \(\Pi(F)\). In fact,

- if \((I + B_1 C_1^T) \in F\), then \((I + B_1 C_1^T)^n = (I + B_1 C_1^T)\) for any positive integer \(n\). Indeed, since \(C_i^T B_i = -1\),
  \((I + B_1 C_1^T)^2 = I + 2B_1 C_1^T + B_1 (C_1^T B_1) C_1^T = I + B_1 C_1^T;\)
- if \(\Phi_1 = I + B_1 C_1^T\) and \(\Phi_2 = I + B_2 C_2^T\) with \(C_1 = C_2\),
  then \(\Phi_1 \Phi_2 = \Phi_2\), as it can be seen in a similar way.

Based on Corollary 1, an alternative stopping criterion is achieved by computing the sequence of products \(\Pi(F)\) of increasing order and stopping whenever one of them has an eigenvalue that is neither zero nor a root of the unity. This produces, in principle, an exponentially growing list of matrices. Yet, extensive numerical experiments have shown that, in most cases, the stopping condition is quickly reached.

D. Turning nodes into black holes

We introduce a new type of node, called black hole, in which any incoming token (either positive or negative) is cleared, so that the black hole contains zero tokens throughout the system evolution. If a node is replaced by a black hole, then the GPN associated with the reaction network is transformed and behaves differently.

**Example 4:** Consider the reaction network in Fig. 3, where \(\emptyset \rightarrow X_1, \emptyset \rightarrow X_2, X_1 + X_2 \rightarrow X_3 + X_4, X_4 \rightarrow X_2, X_1 + X_3 \rightarrow \emptyset\). The GPN associated with this network is unbounded, i.e., no structural PLF exists for the system. If we turn \(X_2\) into a black hole, then we virtually have \(X_2 := \emptyset\) and the transformed reaction network becomes: \(\emptyset \rightarrow X_1, X_1 \rightarrow X_3 + X_4, X_4 \rightarrow \emptyset, X_1 + X_3 \rightarrow \emptyset\). The GPN associated with the transformed network is bounded. Boundedness is achieved also if node \(X_4\) is turned into a black hole, instead of \(X_2\). Conversely, turning either node \(X_1\) or node \(X_3\) into a black hole does not yield boundedness.

As we show in the next section, replacing a node with a black hole can be regarded as applying a strong feedback to that node, thus enforcing a pinning control.

IV. PINNING CONTROL

Pinning control strategies control just some of the state variables, each by means of a (strong) local feedback, so as to stabilise the whole network. Without loss of generality, we split the state vector as \(z = [z_1^T \ z_2^T]^T\) and we assume that a feedback control action with \(\gamma > 0\) is applied to \(z_1\), the first \(p\) entries of \(z\):

\[
\dot{z}_1 = S_1 (g(x) - g(\bar{x})) - \gamma z_1,
\]
where \( S_1 \) contains the first \( p \) rows of \( S \). The system (3) can then be split as

\[
\begin{bmatrix}
\dot{z}_1 \\
\dot{z}_2 \\
\end{bmatrix} =
\begin{bmatrix}
B_1 D(z) C_1 - \gamma I & B_1 D(z) C_2 \\
B_2 D(z) C_1 & B_2 D(z) C_2
\end{bmatrix}
\begin{bmatrix}
z_1 \\
z_2 \\
\end{bmatrix},
\]

(14)

where \( B_1 \) and \( B_2 \) contain the first \( p \) and the last \( n - p \) rows of \( B \), respectively, while \( C_1 \) and \( C_2 \) contain the first \( p \) and the last \( n - p \) columns of \( C \).

We have a first main result.

**Theorem 3:** Under Assumptions [14] the following conditions are equivalent:

(i) The \((n - p)\)-dimensional subsystem

\[
\begin{bmatrix}
\dot{z}_1 \\
\dot{z}_2 \\
\end{bmatrix} = B_2 D(t) C_2 z_2(t)
\]

(15)

admits a structural PLF \( U(z_2) \), in the strong sense of Definition [2].

(ii) There exists a polyhedral function \( V(z) \) and \( \gamma > 0 \) such that \( V(z) \) is a structural strong LF for system (14) if \( \gamma \geq \bar{\gamma} \).

**Remark 7:** The structural result needs Assumption [4]. Consider the linear differential inclusion with matrix

\[
\begin{bmatrix}
-\gamma + D_1(t) & 1 \\
1 & -D_2(t)
\end{bmatrix}.
\]

No matter how large \( \gamma > 0 \) is, the system becomes unstable if \( D_1(t) > 0 \) diverges and/or \( D_2(t) > 0 \) converges to 0; conversely, under Assumption [4] a stabilising \( \gamma \) always exists, which depends on the bounds in [5].

**Proof of Theorem 3**

(iii) \( \Rightarrow \) (ii). Due to the compactness Assumption [4] the matrix family in system (14) is polytopic and we can write

\[
A(D, \gamma) = \begin{bmatrix}
B_1 D_{C_1} & B_1 D_{C_2}
B_2 D_{C_1} & B_2 D_{C_2}
\end{bmatrix} = \sum_{k=1}^{M} \lambda_k \begin{bmatrix}
A^{(k)}_{11} & A^{(k)}_{12}
A^{(k)}_{21} & A^{(k)}_{22}
\end{bmatrix},
\]

where \( \sum_{k=1}^{M} \lambda_k = 1, \lambda_k > 0 \), because each of the four matrix blocks in \( A(D, \gamma) \) can be expressed as a polytopic matrix \( \sum_{k=1}^{M} \lambda_k A^{(k)} \).

By assumption, system (15) admits a structural PLF, hence \( [A^{(k)}_{22}] X_2 = X_2 P^{(k)}_{22} \), where \( P^{(k)}_{22} \) is strictly column diagonally dominant and \( X_2 \) has full row rank [14, 15, 31]. Then we can take

\[
\dot{X} = \begin{bmatrix}
\rho I & 0 \\
0 & X_2
\end{bmatrix},
\]

where \( \rho > 0 \) is a parameter to be selected, and write the \( \gamma \)-parametrised equation

\[
\begin{bmatrix}
-\gamma I + A^{(k)}_{11} & A^{(k)}_{12}
A^{(k)}_{21} & A^{(k)}_{22}
\end{bmatrix} \dot{X} = \begin{bmatrix}
-\gamma I + A^{(k)}_{11} & A^{(k)}_{12} X_2 / \rho
A^{(k)}_{21} / \rho & P^{(k)}_{22}
\end{bmatrix} \dot{X} = \begin{bmatrix}
\dot{X}_1 \\
\dot{X}_2
\end{bmatrix},
\]

\[
\begin{bmatrix}
\dot{z}_1 \\
\dot{z}_2
\end{bmatrix} =
\begin{bmatrix}
F_{11} - \mu I & F_{12}
F_{21} & F_{22}
\end{bmatrix}
\begin{bmatrix}
z_1 \\
z_2
\end{bmatrix}
\]

(17)

for all \( \mu > 0 \). Then the intersection \( S_2 = \{ z \in S : z_1 = 0 \} \) is a C-set in the subspace \( \tilde{z}_1 = z_2 \) with \( z_1 = 0 \) and is positively invariant for the subsystem \( \dot{z}_2 = F_{22} z_2 \).

The proof of Lemma [1] is in the appendix.

By assumption, \( S = \{ z : V(z) \leq 1 \} \), the unit ball of \( V(z) \), is an invariant set for system (14) for all \( \gamma \geq \bar{\gamma} \). Let us perturb system (14) and write it as

\[
\dot{z} = [A(D, \gamma) + \epsilon I] z = F_{\gamma}(D, \gamma) z,
\]

(18)

with \( \epsilon > 0 \) small enough to ensure that exponential stability is preserved: if \( D^+ V(z) \leq -\beta V(z) \), just take \( 0 < \epsilon < \beta \).

For any fixed \( D \), if \( \gamma \geq \bar{\gamma} \), \( S \) is invariant for the linear time invariant system with state matrix \( F_\gamma(D, \gamma) \). Take \( \mu = \gamma - \bar{\gamma} \) and apply Lemma [1]. The intersection \( S_2 = \{ z \in S : z_1 = 0 \} \), which is a polyhedral C-set in the \( 2_2 \)-space, is positively invariant for the system \( \dot{z}_2 = [A_{22}((D(t), \gamma)+\epsilon I) z_2 \) since this claim is true for any choice of \( D \), the C-set \( S_2 \) is robustly positively invariant for the differential inclusion \( \dot{z}_2 = [A_{22}(D(t), \gamma)+\epsilon I] z_2 \), which is thus at least marginally stable. As a consequence, \( \dot{z}_2 = A_{22}(D, \gamma) z_2 \) is exponentially stable, hence it admits a PLF (14), (15), (31).}

Although the same local feedback parameter \( \gamma \) is considered in Theorem 3 for all pinned nodes, different parameters \( \gamma_i \) could be adopted for the \( p \) nodes, provided that, for all \( i \), \( \gamma_i \geq \bar{\gamma} \) is large enough to ensure diagonal dominance of the first \( p \) columns in the last matrix in (16). Furthermore, the result easily extends to nonlinear feedback strategies \( k_i(z_i) z_i \), provided that \( k_i(z_i) \geq \bar{\gamma} \) for all \( z_i \).

We now need to face a technical issue. Procedure [1] can be adopted to find a structural PLF for system (15), and all the results in Section III including the stopping criterion, remain valid. Unfortunately, the procedure provides a weak structural PLF \( V(z) \), and not a strong one as required by Theorem 3. To fix the problem we consider three facts.

- In view of Theorem 3 if we find a weak PLF for the differential inclusion (15), we can claim its robust asymptotic stability if (and only if) matrix \( BDC \) is structurally non-singular.
- A classical result (14), (15), (31) ensures that, if (15) with compact bounds (5) (introduced exactly for this technical reason) is asymptotically stable, then it is also exponentially stable and it admits a strong PLF \( U(z) \).
- Hence, if we find \( V(z) \) and \( BDC \) is structurally non-singular, we know that a strong PLF \( U(z) \) exists. This allows us to apply Theorem 3, fortunately, we do not need to compute \( U(z) \).
Corollary 2: Assume that $V(z_2)$ is a weak structural PLF for (15) and that $\det(B_2DC_2) \neq 0$ for all $D$ in (5). Then, there exists $\gamma$ such that, for all $\gamma > \bar{\gamma}$, system (14) is structurally exponentially stable. Structural non-singularity of $BDC$ can be checked as discussed in Remark 4.

Remark 8: All the results presented in this section so far hold also for non-unitary networks: we do not need to assume $C_k^TB_k = -1$.

A. Lyapunov function for the free variables $z_2$

If we find a PLF for the $z_2$-subsystem of dimension $n - p$, and we have structural non-singularity of $BDC$, then the stability of the overall system is ensured for large enough $\gamma$, according to Corollary 2. How can we exploit the GPN to this aim?

Theorem 4: If $C_i^TB_i = -1 \forall i = 1, \ldots, q$, the following statements are equivalent:

i) The $z_2$-subsystem (15) admits a weak structural PLF.

ii) The evolution of the GPN where nodes $1, \ldots, p$ have been turned into black holes is bounded for any integer initial marking.

Proof: We show that a (weak) PLF exists for (15) if and only if a (weak) PLF exists for the differential inclusion

$$\dot{z}_2 = \begin{bmatrix} 0 & 0 & 0 \\ 0 & B_2D(t)C_2 & 0 \end{bmatrix} z_2.$$  (19)

Indeed, let $B_2DC_2 = \sum_{k=1}^q D_kB_{2,k}C_{2,k}$. A weak PLF for (19) exists if and only if the equation (14) holds with $X = [X_1^T X_2^T]^T$ full row rank and $P(k)$ weakly diagonally dominant. Hence, $X_2$ has full row rank and

$$A_{22}^{(k)}X_2 = X_2P_{22}^{(k)}$$  (21)

holds, which is equivalent to the existence of a weak PLF for the subsystem (15). Conversely, if (21) holds with $X_2$ full row rank and $P_{22}^{(k)}$ diagonally dominant, then (20) holds with $X$ and $P^{(k)}$ as follows

$$\begin{bmatrix} 0 & 0 & 0 \\ 0 & A_{22}^{(k)} & 0 \end{bmatrix} \begin{bmatrix} I \\ 0 \end{bmatrix} = \begin{bmatrix} I & 0 \\ 0 & X_2 \end{bmatrix} \begin{bmatrix} 0 & 0 \\ 0 & P_{22}^{(k)} \end{bmatrix}.$$  (22)

To complete the proof, note that, after having turned nodes $1, \ldots, p$ into black holes, the evolution of the GPN is represented by the integer operators

$$\Psi(k) = \begin{bmatrix} 0 & 0 \\ 0 & I + B_2,hC_{2,h}^T \end{bmatrix}.$$  

If we apply Procedure 1, initialised with $X_0 = [I, -I]$, we generate the matrices $X_k$

$$X_k = \begin{bmatrix} I & 0 \\ 0 & I \end{bmatrix} - \begin{bmatrix} 0 & 0 \\ 0 & -I \end{bmatrix} \quad \text{and} \quad X_k = \begin{bmatrix} 0 & X_k^T \end{bmatrix}, \quad k > 0$$

where the first $p$ rows are zero, while the remaining $n - p$ rows are exactly those we get by applying the procedure to subsystem (15). On the other hand, Procedure 1 applied to the original system with the pinned nodes converges if and only if a (weak) structural PLF exists for (15), as shown in [8].

The conditions of Theorem 4 are equivalent to the fact that Procedure 1 converges after having zeroed the rows of $B$ and the columns of $C$ corresponding to the pinned nodes. From a computational standpoint, however, applying the procedure on the subsystem (15) is more convenient, because the system size is reduced and the stopping criteria discussed in Section II-C remain valid for the restricted subspace, while they are no longer valid for the original state space.

Remark 9: (Strong convergence.) According to Theorem 4, the differential inclusion can be reduced as in (19). If matrix $B_2DC_2$ is structurally non-singular, then pinning the first $p$ nodes makes the differential inclusion strongly convergent, according to the definition in [22].

It is worth stressing that a dual procedure can be adopted as well. We can derive a Lyapunov function (if it exists) defined in terms of planes, as in [5]. As shown in [8], [9], this is equivalent to applying the Procedure 1 to the dual system $\dot{w}(t) = C^TD(t)B^T(t)w(t)$. In view of duality properties [11], [14], [31], a PLF exists for the primal system if and only if it exists for its dual.

B. Arc pinning: Regulating the reactions

Node pinning means imposing a strong feedback to some nodes. By arc pinning, we mean that a strong feedback is imposed to some flows, hence

$$g_j(x) := g_j(x) - \gamma(g_j(x) - \bar{r}_j),$$

so that, roughly speaking, the flow is forced to have a prescribed nominal value.

This dual arc-pinning problem can be solved by writing the system in reaction coordinates, as in [11], [2], [3], and then adopting the EDF-decomposition [9]. If $\bar{x}$ is an equilibrium point of the system, under suitable conditions, we can define a transformation from concentration coordinates $(x_i)_{i=1}^n$ to reaction coordinates $(r_j)_{j=1}^m$ as $r(x(t)) = g(x(t)) - g(\bar{x})$. After this transformation, the system becomes

$$\dot{r}(t) = \left[ \frac{\partial g}{\partial x} \right] S r(t).$$  (22)

A procedure similar to the BDC-decomposition [9] transforms system (22) into the linear differential inclusion

$$\dot{r}(t) = E D(t) F r(t),$$  (23)

where $D$ is a diagonal matrix with positive diagonal entries. The theory remains completely unchanged. Pinning reactions $1, \ldots, p$ is equivalent to zeroing the first $p$ rows of $E$ and the first $p$ columns of $F$.

C. Periodic forcing input

Assume that $g_0(t)$ is a periodic input [19], [24], [35] and $x_p(t)$ is a periodic target trajectory, having the same period as $g_0(t)$, corresponding to $g_0(t)$. Let $x(t)$ be any other trajectory. Then, we can write

$$\dot{x}(t) = S g(x(t)) + g_0(t) \quad \text{and} \quad \dot{x}_p(t) = S g(x_p(t)) + g_0(t).$$
Denoting \( z(t) = x(t) - x_p(t) \), the BDC-decomposition leads to the dynamical system

\[
\dot{z}(t) = BD(z(t), t)Cz(t).
\]

Since our analysis considers a differential inclusion with arbitrary time-varying \( D(\cdot) \), the stability – or stabilisation via pinning control – of such a differential inclusion implies \( z(t) \to 0 \), hence the stability – or stabilisation – of the periodic trajectory.

V. PINNING CONTROL OF REACTION NETWORKS

Pinning control, as mentioned, consists in applying strong local feedback actions to some nodes (or arcs) with the aim of regulating the whole network. How can one select the node(s) to be pinned in order to achieve the control objective?

Based on our results, we can re-formulate the question as: Which are the nodes that, if converted into black holes, ensure global boundedness of the GPN evolution, hence leading to Lyapunov stability of the overall system once they are subject to a sufficiently strong local feedback?

We provide here some examples of chemical reaction networks: the readers are invited to have a preliminary look at the network graphs (shown in Figures 4 and 5) and see if they can spot immediately which nodes are the most important ones to be governed so as to rule all the others; the authors of this paper often failed to guess these nodes in advance.

Example 5: For the network in Fig. 4 Procedure 1 does not converge, hence the system does not admit a structural polyhedral Lyapunov function. However, if we pin any of the nodes \( X_2, X_4 \) or \( X_5 \), the procedure converges, hence the system is structurally stabilised by enforcing a sufficiently strong local feedback on any of these nodes. Conversely, the procedure does not converge even if we pin node \( X_1 \) or node \( X_3 \). This fact is explained by noticing that pinning \( X_2, X_4 \) or \( X_5 \) cuts the loop \( X_2 \to X_4 \to X_5 \to X_2 \), and tokens repeatedly circulating in this loop continue depleting \( X_1 \) or filling up \( X_3 \).

Example 6: The network in Fig. 5 does not admit a structural PLF: Procedure 1 does not converge. If we pin node \( X_3 \), then the procedure converges. This node is then the most crucial one in the network: pinning any one of the other nodes does not yield convergence.

Example 7: (A translation model.) The complete translation model proposed in [20] includes the chemical reactions:

\[
\begin{align*}
X_1 + X_2 \xrightarrow{\gamma_{12}} & X_3 \xrightarrow{\gamma_3} X_4 + X_2, \\
X_4 \xrightarrow{\gamma_4} & X_5 \xrightarrow{\gamma_5} X_6 \xrightarrow{\gamma_6} X_7 \xrightarrow{\gamma_7} X_8 + X_9, \\
X_8 \xrightarrow{\gamma_8} & X_1, \quad X_9 \xrightarrow{\gamma_9} X_{10} \xrightarrow{\gamma_{10}} \emptyset.
\end{align*}
\]

The stability of the reduced order model

\[
X_1 + X_2 \xrightarrow{\gamma_{12}} X_3 \xrightarrow{\gamma_3} X_4 + X_2 + X_4, \quad X_4 \xrightarrow{\gamma_4} \emptyset
\]

is considered in [3], where the system is shown to admit a piecewise-linear Lyapunov function in rates.

We consider here the complete model associated with the reaction network (24), corresponding to the system of equations

\[
\begin{bmatrix}
\dot{x}_1 \\
\dot{x}_2 \\
\dot{x}_3 \\
\dot{x}_4 \\
\dot{x}_5 \\
\dot{x}_6 \\
\dot{x}_7 \\
\dot{x}_8 \\
\dot{x}_9 \\
\dot{x}_{10}
\end{bmatrix} =
\begin{bmatrix}
-g_{12}(x_1, x_2) + g_3(x_3) + g_8(x_8) \\
-g_{12}(x_1, x_2) + g_3(x_3) + g_4^*(x_4) \\
g_{12}(x_1, x_2) - g_3(x_3) - g_4^*(x_4) \\
g_3^*(x_3) - g_4(x_4) \\
g_4(x_4) - g_5(x_5) \\
g_5(x_5) - g_6(x_6) \\
g_7(x_7) - g_8(x_8) \\
g_7(x_7) - g_9(x_9) \\
g_9(x_9) - g_{10}(x_{10})
\end{bmatrix}
\]

We do not consider the last two equations: if the subsystem associated with the variables \( x_1 \cdots x_8 \) converges to an equilibrium, and in particular \( x_7 \to x_7^* \), then also \( x_9 \) and, in turn, \( x_{10} \) converge to an equilibrium.

It is apparent that \( \dot{x}_1 + \dot{x}_3 + \dot{x}_4 + \dot{x}_5 + \dot{x}_6 + \dot{x}_7 + \dot{x}_8 \equiv 0 \) and \( \dot{x}_2 + \dot{x}_4 \equiv 0 \), hence the sums of concentrations \( x_1 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 = w_1 \) and \( x_2 + x_4 \equiv w_2 \) remain constant, thus forming a stoichiometric compatibility class, which is bounded because \( x \geq 0 \). Hence, an equilibrium indeed exists [12]. We can then replace variables \( x_1 \) and \( x_2 \) by \( w_1 \) and \( w_2 \), and keep all the other variables. This is equivalent to considering the state transformation \( T^{-1}x = w \) and the transformed system

\[
\dot{w} = T^{-1}BDCTw,
\]

with

\[
T^{-1} =
\begin{bmatrix}
1 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & 1 & 1 \\
0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}
\]
and then neglecting the first two rows of $B$, which are of course zero because $w_1$ and $w_2$ are both constant, as well as the first two columns of $C$. The resulting reduced 6-dimensional system admits the $BDC$-decomposition with

$$B = \begin{bmatrix} 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and

$$C = \begin{bmatrix} -1 & -1 & -1 & -1 & -1 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

where $C_i^T B_i = -1$, for all $i$, as expected (cf. Remark 5). Procedure [1] converges, yielding a structural PLF with 42 vertices, and matrix $BDC$ passes the structural non-singularity test: this proves asymptotic stability of the complete system.

**Example 8: (A transcription model.)** The complete transcription model proposed in [20] is

$$X_1 g_1 \overset{g_2}{\rightarrow} X_2 g_3 \overset{g_5}{\rightarrow} X_3,$$

$$X_3 + X_4 \overset{g_{64}}{\rightarrow} X_5 g_5 \overset{g_6}{\rightarrow} X_6 g_7 \overset{g_8}{\rightarrow} X_7,$$

$$X_7 g_9 \overset{g_{10}}{\rightarrow} X_8 g_9 \overset{g_{10}}{\rightarrow} X_9 g_{10} \overset{g_{11}}{\rightarrow} X_{11} + X_{12},$$

$$X_7 g_9 \overset{g_{11}}{\rightarrow} X_{11}, \quad X_{12} g_9 \overset{g_{12}}{\rightarrow} 0.$$ Again, [20] also proposed a reduced-order model

$$X_1 + X_2 g_{12} \overset{g_3}{\rightarrow} X_3 g_3 \overset{g_5}{\rightarrow} X_4 + X_5, \quad X_3 g_3 \overset{g_5}{\rightarrow} X_1, \quad X_4 g_{12} \overset{g_9}{\rightarrow} 0,$$

for which a piecewise-linear Lyapunov function in rates is known to exists [3].

We consider the system of differential equations associated with the complete reaction network (25), which is

$$\begin{align*}
\dot{x}_1 & = -g_1(x_1) + g_2(x_2) + g_{11}(x_{11}) \\
\dot{x}_2 & = g_1(x_1) - g_2(x_2) - g_3(x_3) + g_{31}(x_{13}) \\
\dot{x}_3 & = g_2(x_2) - g_3(x_3) - g_{34}(x_{34}) + g(x_5) \\
\dot{x}_4 & = -g_{34}(x_{34}) + g(x_5) + g_6(x_6) \\
\dot{x}_5 & = g_{34}(x_{34}) - g(x_5) - g_5(x_5) \\
\dot{x}_6 & = g_5(x_5) - g_6(x_6) \\
\dot{x}_7 & = g_6(x_6) - g_7(x_7) \\
\dot{x}_8 & = g_7(x_7) - g_8(x_8) \\
\dot{x}_9 & = g_8(x_8) - g_9(x_9) \\
\dot{x}_{10} & = g_9(x_9) - g_{10}(x_{10}) \\
\dot{x}_{11} & = g_{10}(x_{10}) - g_{11}(x_{11})
\end{align*}$$

We can neglect the additional equation $\dot{x}_{12} = g_{12}(x_{12}) - g_{12}(x_{12})$, because once we prove that the 11-order system is stable and converges to an equilibrium, convergence of $x_{12}$ to an equilibrium immediately follows. For this system, matrices $B$ and $C$ are

$$B = \begin{bmatrix} -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & -1 & -1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix},$$

and

$$C = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \end{bmatrix}. $$

Note that, given that the corresponding derivatives add up to zero, the following sums of concentrations are constant: $x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} = w_1$ and $x_4 + x_5 + x_6 = w_2$ for all $t$. Along with $x \geq 0$, this ensures boundedness of the stoichiometric compatibility class, hence the existence of an equilibrium [12]. Again, we replace $x_1$ and $x_2$ by $w_1$ and $w_2$, for which $w_1 = 0$ and $w_2 = 0$, and the corresponding equations are removed.

For this system, Procedure [1] does not converge, hence we cannot prove structural stability. However, according to [20], a negative regulatory action can be present, due to a repressor signal acting on variable $x_1$ (the DNA promoter). To investigate the case in which $x_1$ is under a feedback action, we can pin node $x_4$: then, Procedure [1] converges, providing a PLF whose unit ball has 54 vertices (the function in the reduced space has 52 vertices).

**VI. CONCLUDING DISCUSSION**

The main contribution of this paper is twofold. First, we have shown that, for dynamical systems associated with unitary chemical reaction networks, the existence of a polyhedral Lyapunov function is equivalent to the finiteness of the reachable set of an associated generalised Petri net, with possibly negative token numbers. Second, we have shown that applying a pinning control to some nodes is structurally equivalent to converting the corresponding nodes of the generalised Petri net into black holes that swallow any incoming token.

Pinning a node means applying a strong local feedback that keeps the node variable constant. For a biochemical reaction network, enforcing actions that keep the concentration of a species constant seems indeed a viable control approach, which we conjecture is actually used in natural systems to stabilise important cellular processes. In many cases, when a species is far more abundant than all the other chemical species involved in the reaction network, its concentration can be regarded as constant, because it is essentially unchanged by the process, while other concentrations are subject to ample fluctuations: this can already be seen as an “embedded” pinning control action.

Future research directions along these lines include considering more general types of structural feedback laws. Another aspect we leave for the future is how to fit this framework in a stochastic setting in which the transitions are probabilistic, going beyond the worst case structural analysis provided here.

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APPENDIX

PROOF OF LEMMA 1

The set $S$ is positively invariant for (17) for any large $\mu > 0$. Consider the modified set

$$S_\nu = \{ z \in S : \| z_1 \| \leq \nu \},$$

which corresponds to the portion between the cyan planes in Fig. 6. For any $\nu > 0$ (no matter how small) there exist $\mu$ such that $S_\nu$ becomes positively invariant for $\mu \geq \mu$. Indeed,

$$z_1 = F_{11}z_1 - \mu z_1 + F_{12}z_2, \quad z_2 = F_{22}z_2,$$

where both $F_{12}z_2$ and $F_{11}z_1$ are bounded terms, because $S_\nu$ is a compact set. Therefore, we can write $|z_1^T F_{12}z_2| \leq \alpha$ and $|z_1^T F_{11}z_1| \leq \beta$ for suitable positive coefficients $\alpha$ and $\beta$.

Consider the candidate Lyapunov function $W(z_1) = \frac{1}{2}\|z_1\|^2$ and the ball $\|z_1\|^2 \leq \nu^2$. Then

$$\dot{W}(z_1) = z_1^T F_{11}z_1 - \mu z_1^T z_1 + z_1^T F_{12}z_2 \leq -\mu z_1^T z_1 + \alpha + \beta,$$
hence $\dot{W}(z_1) < 0$ for $\|z_1\|^2 > \nu^2$ provided that $\mu \geq \hat{\mu} = (\alpha + \beta)/\nu^2$.

Therefore, assume that $\|z_1\| \leq \nu$, $\mu \geq \hat{\mu}$. Take the initial condition $z_1(0) = 0$ and $\hat{z}_2 = \tilde{z}_2(0)$ on the boundary of $S_2$.

By contradiction, assume that the solution $\tilde{z}_2(t)$ of $\dot{\tilde{z}}_2 = F_{22}\tilde{z}_2$ leaves the set $S_2$. Consider this solution in the extended $z$-space, $\ddot{z}(t) = [0 \tilde{z}_2(t)]^\top$. There exists a time instant $T$ such that $\dot{z}(T) = [0 \tilde{z}_2(T)]^\top$ is outside the compact $\mathcal{S}$ and there exists a neighbourhood $\mathcal{U}$ (the ball in Fig. 6) centred at $\ddot{z}(T)$, which has no intersection with $\mathcal{S}$. Note that $\ddot{z}(T)$ does not depend on $\mu$.

Now, consider the solution $\ddot{z}(t)$ of the full system (which depends on $\mu$) with the same initial condition $\ddot{z} = [0 \tilde{z}_2(T)]^\top$.

We complete the proof by showing that $\ddot{z}(T)$ gets arbitrarily close to $\ddot{z}(T)$ if $\mu$ is large enough. The first component satisfies $\|\ddot{z}_1\| \leq \nu$. The second component satisfies $\dot{\tilde{z}}_2 = F_{22}\tilde{z}_2 + F_{21}\ddot{z}_1$. Then, the difference $\hat{z}_2(t) - \tilde{z}_2(t)$ satisfies

$$\frac{d}{dt}[\hat{z}_2 - \tilde{z}_2] = F_{22}[\hat{z}_2 - \tilde{z}_2] + F_{21}\ddot{z}_1, \quad \|\ddot{z}_1(t)\| \leq \nu, \quad \forall t$$

with $\hat{z}_2(0) - \tilde{z}_2(0) = 0$. Hence

$$\|\hat{z}_2(T) - \tilde{z}_2(T)\| \leq \left\| \int_0^T e^{F_{22}(T-t)} F_{21}\ddot{z}_1(t) dt \right\| \leq \|\nu\| \left\| \int_0^T e^{F_{22}(T-t)} F_{21} dt \right\|.$$ 

Given any small $\rho > 0$, we may ensure $\|\hat{z}_2(T) - \tilde{z}_2(T)\| \leq \rho$ by forcing a small enough $\nu$. Since both $\nu$ and $\rho$ can be arbitrarily small, we get that $\ddot{z}(T) \in \mathcal{U}$, hence it is outside $\mathcal{S}$, against the invariance assumption. We have reached a contradiction, which completes the proof.

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