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Piecewise Linear in Rates Lyapunov Functions for Complex Reaction Networks

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Combinatorial and Algebraic Approaches to Chemical Reaction Networks
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Background

- Complex Reaction Networks (CRNs) is a multi-disciplinary area of research connecting engineering, mathematics, physics and systems biology.
- Large degree of uncertainty is a problem for the modelling of CRNs.
- Hence, analysis based solely on the structure is desirable, and shall be robust with respect to variations in the values of parameters, and reaction rates.
- Earlier work on asymptotic stability focused on the class of weakly reversible zero deficiency networks (Horn and Jackson 1972, Feinberg 1979).
- Angeli and Sontag (2008), Angeli et al. (2010) used monotonicity for establishing convergence of a class of CRNs.

Complex Reaction Networks

- A CRN is defined by a set of species $\mathscr{S} = \{X_1, .., X_n\}$, and a set of reactions $\mathscr{R} = \{\mathrm{R}_1, ..., \mathrm{R}_\nu\}$. Each reaction is denoted as:

$$\mathrm{R}_j : \quad \sum_{i=1}^{n} \alpha_{ij} X_i \longrightarrow \sum_{i=1}^{n} \beta_{ij} X_i, \; j = 1, .., \nu, \tag{1}$$

- The stoichiometry matrix is an $n \times r$ matrix which is defined as:

$$[\Gamma]_{ij} = \beta_{ij} - \alpha_{ij}.$$

ODE Forumalation

The dynamics of a CRN with n species and ν reactions are described by a system of ordinary differential equations (ODEs) as:

$$\dot{x}(t) = \Gamma R(x(t)),\ x(0) \in \bar{\mathbb{R}}_+^n \tag{2}$$

where $x(t)$ is the concentration vector evolving in the nonnegative orthant $\bar{\mathbb{R}}_+^n$, $\Gamma \in \mathbb{R}^{n \times \nu}$ is the stoichiometry matrix, $R(x(t)) \in \bar{\mathbb{R}}_+^\nu$ is the reaction rates vector.

In addition, the manifold $\mathscr{C}_{x_\circ} := (\{x(0)\} + \mathrm{Im}(\Gamma)) \cap \bar{\mathbb{R}}_+^n$ is forward invariant, and is called the stoichiometric compatibility class associated with $x_\circ$.

Reaction Rates

We assume that the reaction rate satisfies the following:

A1. it is a $\mathscr{C}^1$ function, i.e. continuously differentiable;

A2. $x_i = 0 \Rightarrow R_j(x) = 0$, for all i and j such that $\alpha_{ij} > 0$;

A3. it is nondecreasing with respect to its reactants, i.e

$$\frac{\partial R_j}{\partial x_i}(x) \begin{cases} \geq 0 & : \alpha_{ij} > 0 \\ = 0 & : \alpha_{ij} = 0 \end{cases} .$$

A4. The inequality in (6) holds strictly for all $x \in \mathbb{R}^n_+$.

Furthermore, we assume the following:

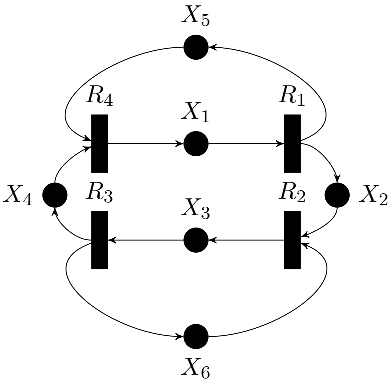
A6. There are no autocatalytic reactions.

A7. There exists $v \in \ker \Gamma$ such that $v \gg 0$.

Siphons

- Let the set of output reactions of P is denoted by $\Lambda(P)$.
- A conservation law is some $w \gg 0$ where $w^T\Gamma = 0$.
- A nonempty set $P \subset V_S$ is called a siphon (Angeli et al 2007) if each input reaction associated to P is also an output reaction associated to P.
- A siphon is a deadlock if $\Lambda(P) = V_R$.
- A siphon or a deadlock is said to be critical if it does not contain a set of species corresponding to the support of a conservation law.

Example: Futile Cycle



$$
\begin{aligned}
X_1 &\longrightarrow X_2 + X_5, \\
X_2 + X_6 &\longrightarrow X_3, \\
X_3 &\longrightarrow X_4 + X_6, \\
X_4 + X_5 &\longrightarrow X_1,
\end{aligned}
$$

$$
\dot{x} = \begin{bmatrix} -1 & 0 & 0 & 1 \\ 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \\ 1 & 0 & 0 & -1 \\ 0 & -1 & 1 & 0 \end{bmatrix} \begin{bmatrix} R_1(x) \\ R_2(x) \\ R_3(x) \\ R_4(x) \end{bmatrix}
$$

Motivation

- Consider the following continuous PWL in Rate (PWLR) function:

$$V(x) = |R_1(x) - R_2(x)| + |R_2(x) - R_3(x)| + |R_3(x) - R_4(x)| + |R_4(x) - R_1(x)|$$

- If we are in the region $R_1(x) \geq R_2(x) \geq R_3(x) \geq R_4(x)$, then:

$$V(x) = 2(R_1(x) - R_4(x)).$$

- The time derivative can be written as:

$$\dot{V}(x) = 2\frac{\partial R_1}{\partial x_1}\dot{x}_1 - 2\frac{\partial R_4}{\partial x_4}\dot{x}_4 - 2\frac{\partial R_4}{\partial x_5}\dot{x}_5$$

- Note that in that region we have a determined sign pattern: $\dot{x}_1 < 0, \dot{x}_4 > 0, \dot{x}_5 > 0$.

Definition I

Definition

Given H with $\ker H = \ker \Gamma$, let

$$\{\mathcal{W}_k\}_{k=1}^{m} = \{r \in \mathbb{R}^\nu : \Sigma_k H r \geq 0\}$$

, and assume that $C = [c_1^T \, .. \, c_{m/2}^T]^T \in \mathbb{R}^{m/2 \times \nu}$. Then, $V : \mathbb{R}^n \to \mathbb{R}$ is said to be a Piecewise Linear in Rates (PWLR) function if it admits the representation $V(x) = \tilde{V}(R(x))$, where $\tilde{V} : \mathbb{R}^\nu \to \mathbb{R}$ is a continuous PWL function given as

$$\tilde{V}(r) = c_k^T r, \;\; r \in \mathcal{W}_k, k = 1, .., m/2, \qquad (3)$$

and $c_{k_2} = -c_{k_1}$ if $\Sigma_{k_1} = -\Sigma_{k_2}$.

Defintion II

Definition

Let C as above with $0 \ll v \in \ker C$. Then, $V : \mathbb{R}^n \to \mathbb{R}$ is said to be a convex PWLR function if it admits the representation $V(x) = \tilde{V}(R(x))$, where $\tilde{V} : \mathbb{R}^\nu \to \mathbb{R}$ is a a convex PWL given by

$$\tilde{V}(r) = \max_{1 \leq k \leq m/2} |c_k^T r| = \|Cr\|_\infty. \tag{4}$$

PWLR Lyapunov Function

Definition

Given (2) with initial condition $x_\circ := x(0) \in \bar{\mathbb{R}}^n_+$. Let $V : \bar{\mathbb{R}}^n_+ \to \bar{\mathbb{R}}_+$ be given as: $V(x) = \tilde{V}(R(x))$, where $\tilde{V}$ is the associated PWL function. Then V is said to be a PWLR Lyapunov Function if it satisfies the following for all $R \in \mathscr{K}_\Gamma$,

1. Positive-Definite: $V(x) \geq 0$ for all x, and $V(x) = 0$ if and only if $R(x) \in \ker \Gamma$.
2. Nonincreasing: $\dot{V}(x) \leq 0$ for all x.

The set of networks for which there exists a PWLR Lyapunov function is denoted by $\mathscr{P}$.

Lyapunov's Second Method I

Theorem (Lyapunov's Second Method)

Given (2) with initial condition $x_\circ \in \mathbb{R}^n_+$, and let $\mathscr{C}_{x_\circ}$ as the associated stoichiometric compatibility class. Assume there exists a PWLR Lyapunov function. and suppose that $x(t)$ is bounded,

1. *then the equilibrium set $E_{x_\circ}$ is Lyapunov stable.*
2. *If, in addition, V satisfies the LaSalle's Condition, then $x(t) \to E_{x_\circ}$ as $t \to \infty$ (meaning that the point to set distance of $x(t)$ to $E_{x_\circ}$ tends to 0). Furthermore, any isolated equilibrium relative to $\mathscr{C}_{x_\circ}$ is asymptotically stable.*

Lyapunov's Second Method II

If the boundedness of solution was known a priori, then the former Theorem can be strengthened to the following:

Corollary (Global Stability)

Consider a CRN in $\mathscr{P}$ that satisfies the LaSalle condition with a given $x_\circ$. Assume that all the trajectories are bounded. If there exists $x^* \in E_{x_\circ}$, which is isolated relative to $\mathscr{C}_{x_\circ}$ then it is unique, i.e., $E_{x_\circ} = \{x^*\}$. Furthermore, it is globally asymptotically stable equilibrium relative to $\mathscr{C}_{x_\circ}$.

The LaSalle's condition can be verified via a certain graphical algorithm.

Checking Candidates: First Representation

- Recall that $\mathcal{W}_k = \{r | \Sigma_k H r \geq 0\}$.
- To ensure nonnegativity, the coefficient vector should have the representation: $c_k^T = \xi_k^T \Sigma_k H$, $\xi_k > 0$.
- The continuity constraint can be verified by requiring the existence of $\eta_{kj} \in \mathbb{R}$ for every pair of neighboring regions $\mathcal{W}_k, \mathcal{W}_j$ such that

$$c_k - c_j = \eta_{kj} h_{s_{kj}}.$$

- The nondecreasingness condition is met if
  1. $\mathrm{sgn}(c_{kj_1})\,\mathrm{sgn}(c_{kj_2}) \geq 0$ for any pair of reactions $\mathrm{R}_{j_1}, \mathrm{R}_{j_2}$ sharing a reactant S_i. Denote $\nu_{ki} = \mathrm{sgn}(c_{kj})$.
  2. There shall exist $\lambda^{(ki)} \in \mathbb{R}^p$, with $\lambda^{(ki)} \geq 0$ such that

$$-\nu_{ki} \gamma_i^T = {\lambda^{(ki)}}^T \Sigma_k H,$$

Checking Candidates: Second Representation

- Recall the representation $V(x) = \|CR(x)\|_\infty$.
- The nonnegativity and continuity constraints are automatically satisfied.
- The nonnedecreasingness condition can be similarly stated where there shall exist $\lambda^{(ki)} \in \mathbb{R}^m$, with $\lambda^{(ki)} \geq 0$ such that

$$-\nu_{ki}\gamma_i = \sum_{\ell=1}^{m} \lambda_\ell^{(ki)}(c_k - c_\ell),$$

Constraints on the Possible Sign Patterns

- For simplicity, assume the system has no inflow reactions.
- Recall the time-derivative in each region $\mathcal{W}_k$:

$$\dot{V}(x) = \sum_{j \in J_k} \sum_{i \in I_k} c_{kj} \frac{\partial R_j}{\partial x_i} \dot{x}_i \leq 0$$

  Since the sign of $\dot{x}_i$'s is known, this induce a sign constraints vector $b_k \in \{\pm 1, 0\}^r$ on the coefficient vector c_k.

- Hence, The orthogonality condition is to require existence of $\zeta_k > 0$ such that

$$\zeta_k^T \, \text{diag}\,(b_k) u_s = 0$$

  for all $0 < u_s \in \ker \Gamma$.

Constraints on the Possible Sign Patterns II

Using the previous necessary condition, a simple graphical test for the nonexistence of a PWLR Lyapunov function can be derived. It can be stated as follows:

Corollary

Given Γ. If there exists a critical deadlock, then $\mathscr{N}_\Gamma \notin \mathscr{P}$.

Property of the Jacobian of $\mathscr{P}$ Networks

- We have shown that networks in $\mathscr{P}$ with bounded trajectories and satisfying the LaSalle's condition cannot have multiple isolated stoichiometrically compatible equilibria.
- Recall that a matrix is P_0 if all its principal minors are nonnegative, Hence:

Theorem

Given Γ. *If* $\mathscr{N}_\Gamma \subset \mathscr{P}$, *then the jacobian* $-\Gamma \frac{\partial R}{\partial x}(x)$ *is a* P_0 *matrix for all* x, *and for all networks in* $\mathscr{N}_\Gamma$.

- It is known that a map is injective if its jacobian matrix is P. In our case, the Jacobian matrix being P_0 implies that the network cannot admit multiple nondegenerate positive equilibria, where no assumption on boundedness is needed (Banaji & Pantea 2014).

Construction of PWLR Lyapunov Functions for a Given Partition

- A generic partitioning matrix is given as: $H = [\Gamma^T \hat{H}^T]^T$.
- Consider sign regions $\{\mathcal{S}_\ell\}$ which are generated by Γ. Denote $q(.) : k \mapsto \ell$ if $\mathcal{W}_k \subset \mathcal{S}_\ell$.
- A linear program can be stated as:

$$\begin{aligned}
\text{Find} \quad & c_k, \xi_k, \zeta_k \in \mathbb{R}^\nu, \eta_{kj} \in \mathbb{R}, k = 1, .., \tfrac{m}{2}; j \in \mathcal{N}_k, \\
\text{subject to} \quad & c_k^T = \xi_k^T \Sigma_k H, \\
& c_k^T = \zeta_k^T \,\text{diag}\,(b_{q_k}), \\
& c_k - c_j = \eta_{kj} \sigma_{k s_{kj}} h_{s_{kj}}, \\
& \xi_k \geq 0, \mathbf{1}^T \xi_k > 0, \\
& \zeta_{kj} \geq 0, j \in \{1, .., \nu\} \backslash \mathcal{I}.
\end{aligned}$$

Remark

- A natural candidate for the partition matrix is $H = \Gamma$. Hence, we can write

$$V(x) = c_k^T R(x) = \xi_k^T \Sigma_k \Gamma R(x) = \| \operatorname{diag}(\xi_k) \dot{x} \|_1, R(x) \in S_k.$$

- If we have additional constraint that for all k, $\xi_k = \mathbf{1}$, then the Lyapunov function considered by Maeda et al [1978]:

$$V(x) = \|\dot{x}\|_1,$$

can be recovered as a special case.

- However, there are classes of networks for which $H = \Gamma$ does not induce a PWLR Lyapunov function, while there exists a partitioning matrix $\hat{H}$ which does.

Iterative Algorithm for Convex PWLR Functions

- Recall that for the representation $V(R(x)) = \|CR(x)\|_\infty$, the main condition is nondecreasingness.
- If we start with an initial matrix C_0, then we devise an algorithm to append rows to C_0 to satisfy the condition.
- Define the active region and the permissible region:

$$\mathcal{W}_0(c_k) := \{r \in \mathbb{R}^\nu : c_k^T r \geq c_j^T r, -m_0 \leq k \leq m_0, k \neq 0\}$$
$$\mathcal{P}(c_k) := \{r \in \mathbb{R}^\nu : \nu_{ki}\gamma_i^T r \leq 0, i \in I_k\}$$

- Append rows so that $\mathcal{W}_1(c_k) \subset \mathcal{P}(c_k)$. The new rows can be define as

$$c_{m_0+i} := c_k + \nu_{ki}\gamma_i, i \in I_k.$$

- If Algorithm 1 terminates after finite number of iterations, then we have the reqiured function.

Special Constructions

Theorem

Consider the network family $\mathscr{N}_\Gamma$. Suppose the following properties are satisfied:

1. $\dim(\ker\Gamma) = 1$,
2. $\forall X_i \in V_S$, *there exists a unique output reaction,*

Then,

- *the following is a PWLR function for the network family $\mathscr{N}_\Gamma$:*

$$V(x) = \max_{1\leq j\leq \nu} \frac{1}{v_j} R_j(x) - \min_{1\leq j\leq \nu} \frac{1}{v_j} R_j(x), \tag{5}$$

  where $v = [v_1 \ldots v_\nu]^T \in \ker(\Gamma), v \gg 0$.
- *If the network is conservative, then it is persistent, i.e, $\omega(x_0) \cap \partial\mathbb{R}^n_+ = \emptyset$ for all $x_\circ$. Furthermore, if there exists an isolated equilibrium, then it is a unique globally asymptotically stable equilibrium with respect to $\mathscr{C}_{x_\circ}$.*

Illustrative Example I

1. Consider the following network given by Feinberg in 1979:

$$X_1 \leftrightharpoons 2X_2,$$
$$X_1 + X_3 \leftrightharpoons X_4 \longrightarrow X_2 + X_5 \longrightarrow X_1 + X_3$$

- The network has a critical deadlock $\{X_1, X_2, X_4\}$, therefore it does not admit a PWLR Lyapunov function.
- The deficiency-zero theorem can be applied with Mass-Action kinetics to show that the interior equilibrium is asymptotically stable despite the existence of boundary equilibria.

Illustrative Example II

2. On the other hand, consider the following CRN for a given integer $n \geq 1$:

$$
\begin{array}{l}
X_1 + E_1 \longrightarrow E_1 X_1 \longrightarrow X_2 + E_1,\ X_2 \longrightarrow X_1 \\
X_2 + E_2 \longrightarrow E_2 X_2 \longrightarrow X_3 + E_2,\ X_3 \longrightarrow X_2 \\
\vdots \\
X_n + E_n \longrightarrow E_n X_n \longrightarrow X_{n+1} + E_n, X_{n+1} \longrightarrow X_n,
\end{array}
$$

which has a deficiency n. For every n, there exists a PWLR Lyapunov function for such CRN. This shows that there is no clear relationship between our results and the notion of deficiency.

Illustrative Example III

3. Consider

$$X_3 \xrightarrow{k_1} X_1,\ 0 \xrightarrow{k_2} X_2, X_1 + X_2 \xrightarrow{k_3} X_3,$$

- The three constructions presented yield a Lyapunov function, in particular (5) is a valid one.
- However, consider the network with Mass-Action Kinetics, and let $A = x_2(0) + x_3(0)$ be the parameter corresponding to the stoichiometric compatibility class. If $A > \frac{k_2}{k_3}$, then the system trajectories are bounded and the unique equilibrium $\left(\frac{k_2 k_3}{k_3 A - k_2}, A - \frac{k_2}{k_3}, \frac{k_2}{k_3}\right)$ is globally asymptotically stable.
- When $A \leq \frac{k_2}{k_3}$, there are no equilibria in the nonnegative orthant, solutions are unbounded and approach the boundary.

Illustrative Example IV

4. Consider the following network:

$$X_1 \xrightarrow{k_1} X_2,\ \ X_5 \xrightarrow{k_4} X_4,\ \ X_2 + X_4 \xrightarrow{k_2} X_3 \xrightarrow{k_3} X_1 + X_5$$

- The linear program with $H = \Gamma$ is infeasible, however, Algorithm 1 and the Special construction give rise to the PWLR function (5) with $v = \mathbf{1}$.
- Close examination indicates that if we use a partitioning matrix $\hat{H} = [1\,0\,0\ \ {-1}]$, then the linear program will be feasible.

Illustrative Example V

5. Consider the following network:

$$2X_1 + 3X_3 \xrightarrow{k_1} 0 \xrightarrow{k_3} 3X_1 + X_2 + 2X_3,\ X_1 + X_2 \xrightarrow{k_2} X_3$$

The special construction does not apply. Algorithm 1 does not terminate.
However, the linear program with $H = \Gamma$ gives the following convex PWLR Lyapunov function:

$$V(x) = \max\{|6R_1(x) + R_2(x) - 7R_3(x)|, |3R_2(x) - 3R_3(x)|, |6R_1(x) - 6R_3(x)|\}.$$

Biochemical Example I

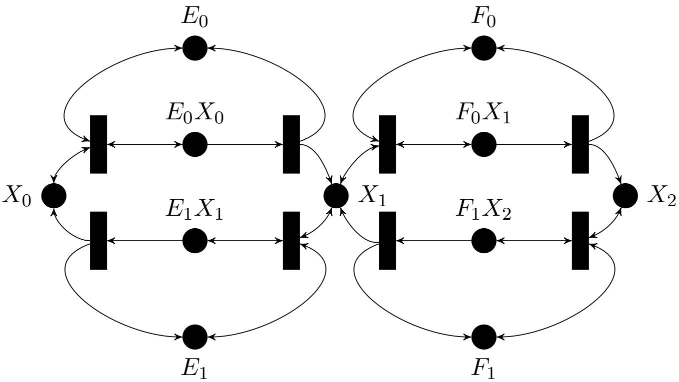


Figure: Double Futile Cycle with distinct enzymes.

Biochemical Example I

$$X_0 + E_0 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E_0X_0 \xrightarrow{k_2} X_1 + E_0,$$

$$X_1 + E_1 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} E_1X_1 \xrightarrow{k_4} X_0 + E_1,$$

$$X_1 + F_0 \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} F_0X_1 \xrightarrow{k_6} X_2 + F_0,$$

$$X_2 + F_1 \underset{k_{-7}}{\overset{k_7}{\rightleftharpoons}} F_1X_2 \xrightarrow{k_8} X_1 + F_1,$$

Biochemical Example II

- The PWLR function constructed can be represented as:

$$V(x) = \| \text{diag}(\xi)\dot{x}\|_1,$$

  where $\xi = [2\,2\,2\,1\,1\,1\,1\,1\,1\,1\,1]$ and species are ordered as $X_0, X_1, X_2, \ldots, F_1X_2$.

- Existing results in the literature does not apply to this network.

Conclusion

- A new type of Lyapunov functions have been introduced for network systems, and CRNs in particular.
- Results have been provided for checking candidate PWLR Lyapunov functions.
- Several methods were introduced for their construction.
- Future direction is develop more exact characterizations for CRNs admitting PWLR Lyapunov functions:
  - Investigate the persistence of $\mathscr{P}$ networks.
  - Develop control PWLR Lyapunov functions.

Thank you

Further details @ arxiv.org/abs/1407.0662