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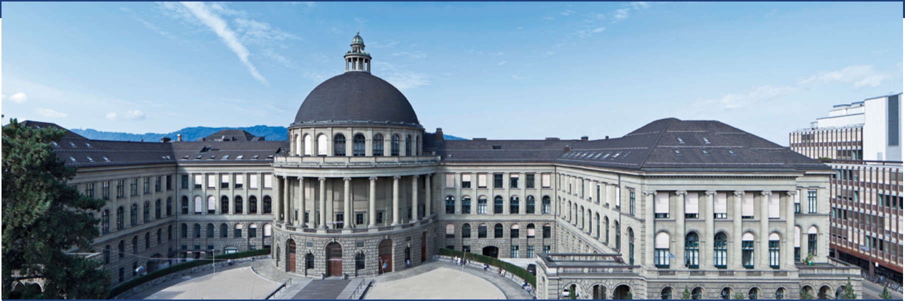

Robust and structural ergodicity of stochastic reaction networks

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Preliminaries

- Reaction network with d molecular species $\boldsymbol{X_1}, \ldots, \boldsymbol{X_d}$ that interacts through K reaction channels $\mathcal{R}_1, \ldots, \mathcal{R}_K$ defined as

$$\mathcal{R}_k : \sum_{i=1}^{d} \zeta_{k,i}^{l} \boldsymbol{X_i} \xrightarrow{\rho_k} \sum_{i=1}^{d} \zeta_{k,i}^{r} \boldsymbol{X_i}, \ k = 1, \ldots, K. \tag{1}$$

- $\rho_k \in \mathbb{R}_{>0}$ is the reaction rate parameter of reaction $\mathcal{R}_k$
- $\zeta_k := \zeta_k^r - \zeta_k^l \in \mathbb{Z}^d$ is the stoichiometric vector of $\mathcal{R}_k$
- Stoichiometric matrix is $S \in \mathbb{Z}^{d \times K}$ as $S := \begin{bmatrix} \zeta_1 \ldots \zeta_K \end{bmatrix}$
- We consider mass-action kinetics, so the propensity functions take the form

$$\lambda_k(x) = \rho_k \prod_{i=1}^{d} \frac{x_i!}{(x_i - \zeta_{k,i}^l)!}$$

- 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 $\mathbb{Z}_{\geq 0}^d$ [AK15]
- Such a system can be described by the Chemical Master Equation (CME) describing the evolution of the probability density function of the Markov process

Preliminaries

- We assume that the network $(\boldsymbol{X}, \mathcal{R})$ is at most bimolecular and that all the rates are independent of each other
- The propensity function vector can be then decomposed as

$$\lambda(x) = \begin{bmatrix} w_0(\rho_0) \\ W(\rho_u)x \\ Y(\rho_b, x) \end{bmatrix}, \quad \rho = \begin{bmatrix} \rho_0 \\ \rho_u \\ \rho_b \end{bmatrix} \quad \text{and} \quad S =: \begin{bmatrix} S_0 & S_u & S_b \end{bmatrix} \tag{2}$$

Definition

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

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

- $A(\rho_u)$ is Metzler (i.e. all the off-diagonal elements are nonnegative) for all $\rho_u \geq 0$

Ergodicity analysis

Definition

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

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Theorem (PLOS CB [GBK14])

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

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Corollary (PLOS CB [GBK14])

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

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- Let us decompose S_u as

$$S_u = \begin{bmatrix} S_{dg} & S_{ct} & S_{cv} \end{bmatrix} \tag{4}$$

where $S_{dg} \in \mathbb{R}^{d \times n_{dg}}$ is a matrix with nonpositive columns, $S_{ct} \in \mathbb{R}^{d \times n_{ct}}$ is a matrix with nonnegative columns and $S_{cv} \in \mathbb{R}^{d \times n_{cv}}$ is a matrix with columns containing at least one negative and one positive entry.

- Let us also decompose accordingly ρ_u as $\rho_u =: \mathrm{col}(\rho_{dg}, \rho_{ct}, \rho_{cv})$ and define

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

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

- So, we can alternatively rewrite the matrix $A(\rho_u)$ as $A(\rho_{dg}, \rho_{ct}, \rho_{cv})$

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- So, we can alternatively rewrite the matrix $A(\rho_u)$ as $A(\rho_{dg}, \rho_{ct}, \rho_{cv})$

Lemma

The following statements are equivalent:

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

(b) *The matrix*
$$A^+(\rho_{cv}) := A(\rho_{dg}^-, \rho_{ct}^+, \rho_{cv}) \tag{5}$$
is Hurwitz stable for all $\rho_{cv} \in \mathcal{P}_{cv}$.

Preliminaries

Lemma

Let us consider a parameter-dependent Metzler matrix $M(\theta) \in \mathbb{R}^{d\times d}$, $\theta \in \Theta \subset \mathbb{R}^N_{\geq 0}$, *where* Θ *is compact and connected. Then, the following statements are equivalent:*

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(b) *The coefficients of the characteristic polynomial of* $M(\theta)$ *are positive for all* $\theta \in \Theta$.

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(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 following conditions hold:*

- (c1) *there exists a* $\theta^* \in \Theta$ *such that* $M(\theta^*)$ *is Hurwitz stable, and*
- (c2) *for all* $\theta \in \Theta$ *we have that* $(-1)^d \det(M(\theta)) > 0$.

- The first two statements come from the theory of linear positive systems
- The equivalence with the third one follows from the connectedness of the set, the continuity of eigenvalues and the Perron-Frobenius theorem.
- (c1) is easily checked by randomly choosing a point in $\mathcal{P}_{cv}$ while (c2) can be checked using optimization-based methods based e.g. on the Handelman's Theorem (LP) or Putinar's Positivstellensatz (SDP)

Unimolecular networks

Theorem

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

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

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

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

- Checking (c) amounts to solving two problems: (i) construct a $\rho_{cv} \in \mathcal{P}_{cv}$ s.t. the matrix $A^+(\rho_{cv})$ is Hurwitz stable and (ii) checking whether a polynomial is positive on a compact set
- Checking (d) may be difficult (infinite dimensional LP) but methods exist (e.g. SOS, Handelman)

Bimolecular networks

Proposition

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

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

$$v(\rho_u) > 0,\ v(\rho_u)^T S_b = 0 \text{ and } v(\rho_u)^T A(\rho_u) < 0 \tag{7}$$

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

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

$$\tilde{v}(\rho_{cv})^T S_b^{\perp} > 0 \text{ and } \tilde{v}(\rho_{cv})^T S_b^{\perp} A^{+}(\rho_{cv}) < 0 \tag{8}$$

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

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

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A preliminary result

Lemma

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

(a) *For all $\rho_{dg} \in \mathbb{R}^{n_{dg}}_{>0}$ and a $\rho_{cv} \in \mathbb{R}^{n_{cv}}_{>0}$, the matrix $A(\rho_{dg}, \rho_{cv}, 0)$ is Hurwitz stable.*

(b) *The matrix $A(\mathbb{1}, \rho_{cv}, 0)$ is Hurwitz stable for all $\rho_{cv} \in \mathbb{R}^{n_{cv}}_{>0}$.*

- Proof by contraposition using rescaling of the (independent) parameters and exploiting linearity of the matrix

The main one (unimolecular case)

Theorem

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

(a) *The matrix* $A(\rho_u)$ *is Hurwitz stable for all* $\rho_u \in \mathbb{R}^{n_u}_{>0}$.

(b) *There exists a polynomial vector* $v(\rho_u) \in \mathbb{R}^d$ *of degree at most* $d-1$ *such that* $v(\rho_u) > 0$ *and* $v(\rho_u)^T A(\rho_u) < 0$ *for all* $\rho_u \in \mathbb{R}^{n_u}_{>0}$.

(c) *There exists a* $\rho_u^s \in \mathbb{R}^{n_u}_{>0}$ *such that the matrix* $A(\rho_u^s)$ *is Hurwitz stable and the polynomial* $(-1)^d \det(A(\rho_u))$ *is positive for all* $\rho_u \in \mathbb{R}^{n_u}_{>0}$.

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(d) *For all $\rho_{dg} \in \mathbb{R}^{n_{dg}}_{>0}$ and a $\rho_{cv} \in \mathbb{R}^{n_{cv}}_{>0}$, the matrix $A_\rho := A(\rho_{dg}, \rho_{cv}, 0)$ is Hurwitz stable and we have that $\varrho(W_{ct} A_\rho^{-1} S_{ct}) = 0$*

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(e) *The matrix $A_n(\rho_{cv}) := A(\mathbb{1}, \rho_{cv}, 0)$ is Hurwitz stable for all $\rho_{cv} \in \mathbb{R}^{n_{cv}}_{>0}$ and $\varrho(W_{ct} A_n(\rho_{cv})^{-1} S_{ct}) = 0$ for all $\rho_{cv} \in \mathbb{R}^{n_{cv}}_{>0}$.*

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(e) *The matrix $A_n(\rho_{cv}) := A(\mathbb{1}, \rho_{cv}, 0)$ is Hurwitz stable for all $\rho_{cv} \in \mathbb{R}^{n_{cv}}_{>0}$ and $\varrho(W_{ct} A_n(\rho_{cv})^{-1} S_{ct}) = 0$ for all $\rho_{cv} \in \mathbb{R}^{n_{cv}}_{>0}$.*

Moreover, when each column of S_{cv} contains exactly two nonzero entries, one being equal to -1 and one being equal to 1, then the above statements are also equivalent to

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

Contents

SIR Model

- Let us consider the open stochastic SIR model described by the matrices

$$A = \begin{bmatrix} -\gamma_s & 0 & k_{rs} \\ 0 & -(\gamma_i + k_{ir}) & 0 \\ 0 & k_{ir} & -(\gamma_r + k_{rs}) \end{bmatrix}, \quad S_b = \begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix} \tag{9}$$

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

$$\tilde{v}^T S_b^{\perp} A < 0 \Leftrightarrow \tilde{v}^T \begin{bmatrix} -(\gamma_i + k_{ir}) & k_{rs} \\ k_{ir} & -(\gamma_r + k_{rs}) \end{bmatrix} < 0. \tag{10}$$

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

$$\tilde{v}^T \begin{bmatrix} -(\gamma_i + k_{ir}) & k_{rs} \\ k_{ir} & -(\gamma_r + k_{rs}) \end{bmatrix} = \begin{bmatrix} -\gamma_i & -\gamma_r \end{bmatrix} < 0 \tag{11}$$

from which the same result follows.

Circadian clock model

- Let us consider the circadian clock-model of Vilar et al. which is described by the matrices

$$A = \begin{bmatrix} -\delta_{M_A} & 0 & 0 & 0 & 0 \\ \beta_A & -\delta_A & 0 & 0 & 0 \\ 0 & 0 & -\delta_{M_R} & 0 & 0 \\ 0 & 0 & \beta_R & -\delta_R & \delta_A \\ 0 & 0 & 0 & 0 & -\delta_A \end{bmatrix}, \quad S_b = \begin{bmatrix} 0 \\ -1 \\ 0 \\ -1 \\ 1 \end{bmatrix} \tag{12}$$

- As in the previous example, the condition reduces to

$$\tilde{v}^T S_b^{\perp} A < 0 \Leftrightarrow \tilde{v}^T \begin{bmatrix} -\delta_{M_A} & 0 & 0 & 0 \\ \beta_A & -\delta_A & 0 & 0 \\ 0 & 0 & -\delta_{M_R} & 0 \\ 0 & 0 & \beta_R & -\delta_R \end{bmatrix} < 0 \text{ where } \tilde{v} > 0. \tag{13}$$

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- Using the last statement of the main result we get that $A_{\mathbb{1}} = -I$,

$$W_{ct} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix} \quad \text{and} \quad S_{ct} = \begin{bmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}^T, \text{ hence } W_{ct} A_{\mathbb{1}}^{-1} S_{ct} = 0 \tag{14}$$

which proves that the system is structurally stable. Alternatively, the triangular structure of the matrix would also lead to the same conclusion.

Toy example

- Let us consider here the following toy network where

$$A = \begin{bmatrix} -(\gamma_1 + \alpha_1) & 0 & k_1 \\ k_2 & -(\gamma_2 + \alpha_2) & 0 \\ 0 & k_3 & -k_1 \end{bmatrix}. \tag{15}$$

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

$$A_{\mathbb{1}} = \begin{bmatrix} -2 & 0 & 1 \\ 1 & -2 & 0 \\ 0 & 1 & -1 \end{bmatrix} \tag{16}$$

is Hurwitz stable and hence that the matrix is structurally stable.

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- If we assume now that $\alpha_1 = \alpha_2 = 0$, then we get

$$A_{\mathbb{1}} = \begin{bmatrix} -1 & 0 & 1 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix} \text{ (Hurwitz stable)} \quad \text{and} \quad A_{\mathbb{1}}^{-1} = \begin{bmatrix} -1 & 0 & -1 \\ 0 & -1 & 0 \\ 0 & 0 & -1 \end{bmatrix} \tag{17}$$

- We have $W_{ct} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix}$, $S_{ct} = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}^T$ and hence $\varrho(W_{ct}A_{\mathbb{1}}^{-1}S_{ct}) = \varrho\left(\begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}\right) = 1$. Hence, the matrix is not structurally stable.

Toy Model

- Define now

$$A^{+}(k_1) = \begin{bmatrix} -\gamma_1^- & 0 & k_1 \\ k_2^+ & -\gamma_2^- & 0 \\ 0 & k_3^+ & -k_1 \end{bmatrix}. \tag{18}$$

- Using a perturbation argument, we can prove that the 0-eigenvalue of $A^{+}(0)$ locally bifurcates to the open right-half plane for some sufficiently small $k_1 > 0$ if and only if $k_2^+ k_3^+ - \gamma_1^- \gamma_2^- < 0$.

Toy Model

- Define now

$$A^+(k_1) = \begin{bmatrix} -\gamma_1^- & 0 & k_1 \\ k_2^+ & -\gamma_2^- & 0 \\ 0 & k_3^+ & -k_1 \end{bmatrix}. \quad (18)$$

- Using a perturbation argument, we can prove that the 0-eigenvalue of $A^+(0)$ locally bifurcates to the open right-half plane for some sufficiently small $k_1 > 0$ if and only if $k_2^+ k_3^+ - \gamma_1^- \gamma_2^- < 0$.
- Hence, there exists a $k_1 > 0$ such that $A^+(k_1)$ is Hurwitz stable if and only if $k_2^+ k_3^+ - \gamma_1^- \gamma_2^- < 0$. Noting now that

$$\det(A^+(k_1)) = k_1(k_2^+ k_3^+ - \gamma_1^- \gamma_2^-) < 0 \quad (19)$$

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

Contents

Concluding statements

Conclusion

- Exact characterization of robust Hurwitz stability for Metzler matrices
- Exact characterization of structural Hurwitz stability for Metzler matrices
- More complex that previously obtained approximate condition but can be checked using optimization techniques
- Previous conditions are encompassed in those results

Thank you for your attention
Any questions?

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